TOWARDS A BETTER UNDERSTANDING OF THE PATHOPHYSIOLOGY AND CLINICAL MANAGEMENT OF IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

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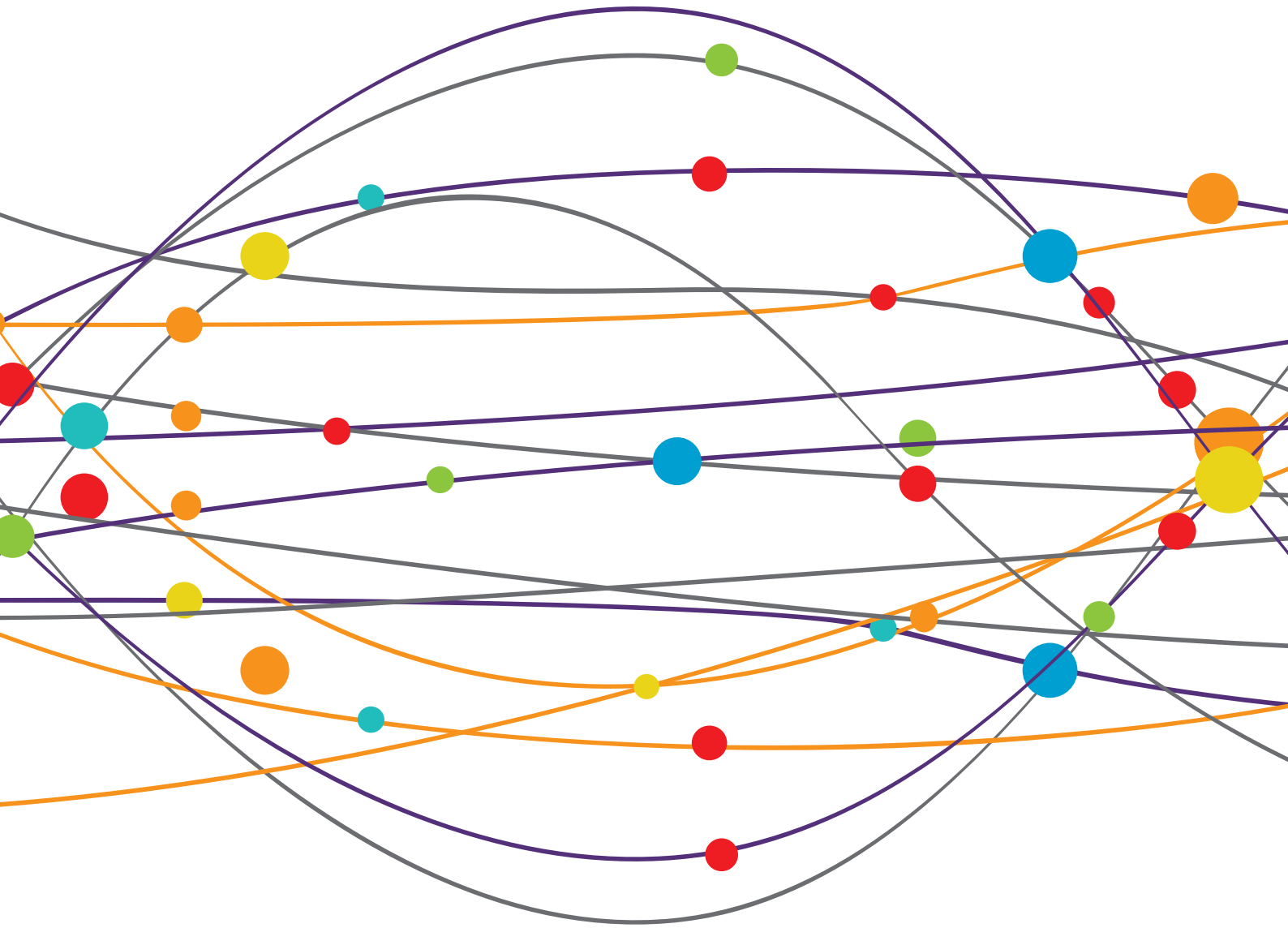

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TOWARDS A BETTER UNDERSTANDING OF THE PATHOPHYSIOLOGY AND CLINICAL MANAGEMENT OF IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

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Editorial: Toward a better understanding of the pathophysiology and clinical management of idiopathic normal pressure hydrocephalus

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Editorial on the Research Topic
Toward a better understanding of the pathophysiology and clinical management of idiopathic normal pressure hydrocephalus

Considering the broad spectrum of unsolved problems in the understanding of iNPH, the authors contributing to this Research Topic have addressed very diverse research interests. This illustrates the significant deficiencies in research on this subject.

Although not strictly defined as clinically applied pathophysiology, two studies explore this subject. Jeppsson et al. explore related vascular pathology and Martinoni et al. examine some mechanisms in late-onset idiopathic aqueductal stenosis (LIAS), a condition similar to iNPH.

Jeppsson et al. performed a comparative biomarker study on patients with iNPH and subcortical small vessel disease(SSVD). In searching for pathophysiological similarities and differences, the authors selected biomarkers reflecting APP metabolism (subcortical damage and remodeling), neurofilament light protein (subcortical neural degeneration), glial fibrillary acidic protein (astroglial response), myelin basic protein (demyelination), and matrix metalloproteinases for subcortical tissue remodeling. By examining CSF biomarkers in patients with iNPH and SSVD, and in healthy controls (HC), they found similarities in the biomarker pattern of iNPH and SSVD, and differences with HC. This may indicate some common features in the underlying pathophysiology of iNPH and SSVD. The interrelation of these two pathological conditions might render iNPH "less idiopathic" and "more vascular" related.

Martinoni et al. prospectively evaluate an important differential diagnostic entity, LIAS, which may manifest with similar symptoms to iNPH but is treated primarily by endoscopic third ventriculostomy (ETV) instead of a shunt. A detailed anatomical visualization of the aqueduct with membrane identification by MRI is key for diagnosis. LIAS detection is

important since ETV is more physiological than a shunt and avoids the mechanical complications of an implantable device. Postoperative neuro-cognitive improvement was seen mainly in attentive and executive functions, visuo-spatial memory, verbal executive functions, and behavioral and affective domains. With its pathophysiological insight, this study can help the understanding of some more common, broader mechanisms to iNPH CSF dynamics and contribute to differential diagnosis.

The majority of the papers directly investigate clinical diagnostic advancements and post-operative assessment. Clinical diagnosis refinement is the focus of articles by Kameda et al., Rydja et al., Wesner et al., and Kazui et al..

Kameda et al. attempt to improve the value of the tap test (TT) by refining the evaluation after it. For this purpose, they utilized the Functional Gait Assessment (FGA) and Global Rating of Change (GRC) scales. FGA and GRC demonstrated much higher sensitivity for TT predictive effectiveness than the 3-m Timed Up and Go test (TUG). It is found to be more justifiable to exclude FGA and GRC negative patients from surgery than the TUG negative patients.

Rydja et al. focus on postoperative motor function recovery in iNPH patients after shunting. They assess short-distance walking, functional exercise capacity, functional strength, and variables of activity and sleep, and evaluate the effect of a physical exercise program in the first 6 months after shunting. Both "exercise" and control groups improved at 3 and 6 months after shunting without significant differences between them. Remarkably, short-distance walking improvement is weakly correlated with voluntary walking, indicating that improved physical capacity does not directly translate to increased physical activity. Therefore, behavioral factors and participation of other frontal lobe mechanisms are important for motor recovery too.

Wesner et al. sought an empirically-based index to determine if iNPH patients show significant cognitive improvement after TT in a commonly used cognitive test, the Montreal Cognitive Assessment (MoCA). They compare various methods for estimating reliable change indices (RCIs) for MoCA in suspected iNPH patients undergoing TT or ELD. RCIs have already been applied as a strong empirically-based approach to improve clinical decision-making and cognitive changes in Parkinson's disease, stroke, and concussion patients (1). The study used estimated reliable change thresholds for MoCA in a population of older adults with suspected iNPH after the CSF drainage procedure (TT/ELD) and a subset of them with shunt surgery. The study obtains clinically applicable practical empirical standards for potential cognitive improvement following CSF drainage.

Kazui et al. explore ways for better cooperation between dementia specialists and neurosurgeons and evaluate, through a questionnaire, the network of specialized dementia institutions in Japan. They conclude that medical care for possible iNPH patients may be improved by dementia specialists performing CSF tap tests and sharing indications for shunt surgery with neurosurgeons. Certainly, better management of comorbidity in dementia patients can improve overall success.

Kikuta et al., Eide et al., and Keong et al. investigate an important current focus of iNPH research: patho-physiologically based imaging methods.

Kikuta et al. examine CSF diffusion along perivascular spaces, exploring the potential role of the glymphatic system in view of current pathophysiological theories. A number of studies show reduced perivascular flow in iNPH, and its improvement with CSF drainage. The authors explore the effect of CSF shunting (LPS) on this phenomenon. By applying the "Analysis along the perivascular space" index as an MRI technique, they compare patients before and after shunting, as well as responders and non-responders. Shunting and positive clinical response are shown to be associated with index increase, improved water diffusion, and better assumed glymphatic clearance.

Eide et al. perform a prospective observational study on 95 iNPH patients by evaluating recently introduced imaging biomarkers of CSF dynamics and glymphatic enhancement. They compare different intrathecal doses of gadobutrol (MRI contrast agent), aiming at the lowest reasonable, diagnostically informative dose. They find that tracer enrichment of subarachnoid CSF spaces (cisterna magna, vertex, and velum interpositum), ventricular reflux of tracer, and glymphatic tracer enrichment are dose-dependent. A reduction to 0.25 mmol gadobutrol concentration improves safety margins while remaining diagnostically informative on CSF homeostasis and glymphatic failure in iNPH.

Keong et al. attempted to reduce interpretation complexity of the diffusion tensor imaging (DTI) profiles of white matter disruption in hydrocephalic and non-hydrocephalic patients. The final investigated dataset was comprised of mild traumatic brain injury, NPH, and Alzheimer's disease patients vs. controls. By mapping tissue signatures included into the created "periodic table of DTI elements," they rapidly characterized cohorts by their differing patterns of injury. The novel strategy with this "periodic table" interpretation allows distinguishing between the different cohorts along the spectrum of brain injury.

By paying attention to the effect of comorbidities, a multinational team (Goh et al.) from Malaysia, Singapore and the UK (Edinburgh and Oxford) evaluate clinical responses after ventriculo-peritoneal shunting in a cohort with coexisting NPH and neurodegenerative disease. They defined two categories patients with iNPH: Classic and Complex (Parkinson's, Alzheimer's diseases or vascular dementia comorbidity). They conducted follow ups with them for over one year and complete a retrospective pilot study and cohort analysis. They stratified the degree of comorbidity in the pilot study to criteria of probable or possible iNPH. After exclusions, 12 patients completed the pilot and 32 patients the retrospective study. The study concludes that the presence of neurodegenerative comorbidity should not preclude CSF tap/drainage tests, and further definition of comorbidity

cohorts can provide better specialized treatment protocols for these patients.

Yamada et al., Kamo et al., and Kajimoto et al. investigate the outcome optimization of post-operative shunt management in iNPH patients.

Yamada et al. explore optimal pressure adjustment early and late after shunting. Residual symptoms may worsen again after several years, even when there is initial improvement after early optimal valve pressure setting. Because of the possibility of insufficient CSF drainage, valve pressure should be reduced by one step (2–4 cmH_2O) 6 months to a year after shunting to maximize symptom improvement, followed by a head CT scan a month later.

Kamo et al. identify shunt malfunction with significant weight change and correct it with valve adjustment: in weight gain there was under-drainage and in weight loss, over-drainage. In the study, there were five cases of weight-related shunt malfunction with pressure environment assessment before, through and after the shunt malfunction, four cases of under drainage worsened gait disturbance with an average weight gain of 6.8 kg, and one over-drainage patient had an asymptomatic chronic subdural hematoma (CSDH) with a weight loss of 10 kg. For the weight-gain patients, intra-cranial and intra-abdominal pressures increased by 8.8 and 4.8 mmHg, respectively, and the ICP decrease was 5 mmHg for the weight-loss patient. Valve pressure re-adjustments led to the complete recovery of all patients, indicating the need for attention in patients with significant weight changes.

Kajimoto et al. investigate whether an early intervention has potential benefits and define a "prodromal" iNPH stage (TUG $\leq$ 13.5 s and MMSE $\geq$ 24). They evaluate 12 such cases over 4 years from the pool of treated patients at their institution with the iNPH Grading Scale, Frontal Assessment Battery, intermittent gait disturbances, social participation status, and development of comorbidities. Early intervention in the prodromal iNPH stage maintained good cognition, mobility, and social participation ability in the long term. The maintenance of long-term cognitive function suggests a preventive effect on dementia. Early intervention for iNPH will require the application of earlier diagnostic protocols.

The Research Topic is complemented by the mini-review of Langheinrich et al. on cognitive presentations of iNPH for clinicians, a useful adjunct for clinical practice.

The present collection is the next step toward a better understanding of iNPH. We are still seeking to establish the specific pathophysiology of this condition with the co-existing structural changes at all levels, from molecular to macroscopic, and the continuity of such diverse exploration of iNPH will be crucial for achieving a breakthrough on this subject.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Reconsidering Ventriculoperitoneal Shunt Surgery and Postoperative Shunt Valve Pressure Adjustment: Our Approaches Learned From Past Challenges and Failures

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Treatment for idiopathic normal pressure hydrocephalus (iNPH) continues to develop. Although ventriculoperitoneal shunt surgery has a long history and is one of the most established neurosurgeries, in the 1970s, the improvement rate of iNPH triad symptoms was poor and the risks related to shunt implantation were high. This led experts to question the surgical indication for iNPH and, over the next 20 years, cerebrospinal fluid (CSF) shunt surgery for iNPH fell out of favor and was rarely performed. However, the development of programmable-pressure shunt valve devices has reduced the major complications associated with the CSF drainage volume and appears to have increased shunt effectiveness. In addition, the development of support devices for the placement of ventricular catheters including preoperative virtual simulation and navigation systems has increased the certainty of ventriculoperitoneal shunt surgery. Secure shunt implantation is the most important prognostic indicator, but ensuring optimal initial valve pressure is also important. Since over-drainage is most likely to occur in the month after shunting, it is generally believed that a high initial setting of shunt valve pressure is the safest option. However, this does not always result in sufficient improvement of the symptoms in the early period after shunting. In fact, evidence suggests that setting the optimal valve pressure early after shunting may cause symptoms to improve earlier. This leads to improved quality of life and better long-term independent living expectations. However, in iNPH patients, the remaining symptoms may worsen again after several years, even when there is initial improvement due to setting the optimal valve pressure early after shunting. Because of the possibility of insufficient CSF drainage, the valve pressure should be reduced by one step (2–4 cmH_2O) after 6 months to a year after shunting to maximize symptom improvement. After the valve pressure is reduced, a head CT scan is advised a month later.

Keywords: idiopathic normal pressure hydrocephalus (iNPH), ventriculoperitoneal shunt (VP shunt), ventricles, cerebrospinal fluid (CSF), pressure adjustment and management, CSF tap test, DESH, preoperative simulation

INTRODUCTION

Ventriculoperitoneal (VP) shunt surgery has a long history and is one of the most established neurosurgeries. The purpose of VP shunt surgery is to divert an accumulation of cerebrospinal fluid (CSF) from the cerebral ventricles to the abdominal cavity. The first VP shunt surgery was performed in 1905 by Kausch et al. but was unfortunately unsuccessful (1). The first clinically successful case used a shunt valve system to divert CSF from the ventricles to the jugular vein (2).

The Codman Company is a manufacturer of neurosurgical devices that began selling shunt valve devices for the treatment of hydrocephalus in the 1950s. Until the 1970s, however, several fixed differential pressure valves had been used in patients with idiopathic normal pressure hydrocephalus (iNPH), but the improvement rate of symptoms was poor and the risk of CSF over-drainage was extremely high. This led experts to question the surgical need for iNPH, and, for the next 20 years, CSF shunt surgery for iNPH was rarely performed. However, the Codman-Hakim Programmable Valve (CHPV) was developed in collaboration with Dr. Salomón Hakim, a Colombian neurosurgeon known to have named iNPH in the 1980s (3), and has been in use since 1992. Developments in shunt valve systems with programming pressure have dramatically reduced the problems of CSF over- and under-drainage and increased shunt effectiveness in elderly patients with iNPH (4–15). Nowadays, numerous patients with iNPH are treated with shunt surgery, according to the Japanese and international guidelines for the management of iNPH (16–21). This review was conducted to examine the history and current outcome of VP shunt surgery with recent shunt valve systems for iNPH patients. The latest knowledge of current surgical outcomes highlights the next issue to be addressed. The intention was to avoid repeating negative history of VP shunt surgery and to lead to the future of surgical intervention in elderly patients who require long-term care.

SELECTION OF PATIENTS

Evaluation of Symptoms

The best way to get better surgical outcomes is accurate diagnosis and careful selection of patients who are likely to improve with shunt surgery. The guidelines for the management of iNPH have consistently recommended to be used as some subjective evaluation scales along with objective and quantitative methods such as the 3-meter Timed Up & Go test (TUG) and Mini-Mental State Examination (MMSE) (18, 19, 21). As subjective evaluations, the grading scales for the severity of gait disturbance, cognitive impairment, and urinary incontinence and the modified Rankin scale have been used. In addition, as the pathological gait features specific to iNPH, small-step gait (short length of stride), broad-based gait (increasingly large step intervals), instability, difficulty in changing directions, frozen gait (no first step taken), and shuffle (dragging of feet and decreased elevation), are evaluated, respectively (21–24). However, it is known that different countries use different scales for these subjective assessments (25–29), and scale ratings do not match even among experts (23). Therefore, symptoms should be evaluated objectively using quantitative tests as much as possible. As reliable quantitative tests in patients with iNPH, TUG is widely used for assessment of gait and balance (14, 30, 31), and MMSE is for cognitive impairment (32). In addition, The European iNPH multicenter study adopted the Grooved Pegboard test and Stroop test as relatively simple neuropsychological tests (6, 29).

The CSF tap test is known as an invasive test useful for the diagnosis of iNPH before surgery (6, 13, 33–35), although it's also known to be a test with low sensitivity, that is, a high false negative rate. In a systematic review (36), the sensitivity was reported 58% (range: 26–87%) and the specificity was 75% (33–100%). Therefore, the CSF tap test is shifting its significance to a test for predicting the postoperative improvement of symptoms rather than for the diagnosis of iNPH (15, 37). There is no difference in the positive detection rate, sensitivity, and specificity with respect to the amount of CSF removed, in the range of 30 to 50 ml (38). Instead, the evaluation method and timing of assessing changes in clinical symptoms are more important (39). The time on TUG in the CSF tap test was proposed to be a reliable quantitative measure for predicting gait improvement after shunt surgery. The Japanese SINPHONI study showed that the patients whose TUG time shortened by $\geq$5 s at the CSF tap test had an almost 40% expectation of $\geq$10 s improvement on TUG time at 12 months after shunt surgery and an almost 65% expectation of $\geq$5 s improvement (14). In addition, the same study group recently showed that the iNPH patients whose MMSE improved by $\geq$3 points at the CSF tap test had an almost 50% expectation of $\geq$6 points improvement on MMSE at 12 months after shunt surgery, whereas the patients whose MMSE does not worsen at the CSF tap test had an almost 60% expectation of $\geq$3 points improvement on MMSE at 12 months after shunt surgery (32). However, the TUG time and MMSE were also found to be unsuitable for iNPH patients with mild symptoms.

To establish an internationally unified objective and quantitative evaluation of symptoms, a simple and accurate measurement method using modern smart devices owned by many people all over the world is suitable. By using an inertial gyroscope in a commercial smartphone, movements during the TUG can be automatically segmented into stand up, go forward, turn, go back, turn, and sit down (31). In addition, the chronological changes of acceleration of the trunk in three axial directions, forward-and-backward longitudinal acceleration, upward-and-downward vertical acceleration, and left-and-right horizontal acceleration can be precisely measured by using an accelerometer in a smartphone (40). For the iNPH patients with mild gait disturbance, the volume of 95% confidence ellipsoid for the tracks of the chronological changes of three dimensional (3D) acceleration during the TUG is a more important index for assessing gait severity than the time on TUG. Based on the results, we created the iTUG score, which simultaneously reflects both the iTUG time and the 3D acceleration volume. An iTUG score of 0 or less indicates inability to walk, and an iTUG score of 100 or more indicates healthy walking and no risk of falling (40). As an iPhone application that automatically calculates the

iTUG score and automatically segments the six actions during TUG, Hacaro–iTUG (Digital Standard Co., Ltd., Osaka, Japan) can be freely downloaded from the Apple store (https://itunes.apple.com/us/app/hacaro-itug/id1367832791?l=ja&ls=1&mt=8). In addition, Hacaro–StroopTest (Digital Standard Co., Ltd.) is also available as a free download from the Apple Store (https://apps.apple.com/us/app/hacaro-strooptest/id1447081813) as a simplified version of the Stroop test that has been used in the European iNPH multicenter study. We recommend the iTUG score calculated by Hacaro–iTUG and the time measured by Hacaro–StroopTest as the next-generation international scales for assessing gait and cognitive dysfunction.

Image Evaluation

The finding of ventricular enlargement on CT or MRI is essential for the diagnosis of iNPH. Although the etiology of ventricular enlargement in iNPH has not yet been elucidated, the total amount of intracranial CSF volume increases due to CSF malabsorption (41). The historically used Evans index >0.3 is defined as the maximum width of both frontal horns of the lateral ventricles divided by the maximum intracranial width on the same slice on CT or MRI. However, the lateral ventricles in iNPH are usually enlarged to the vertex direction rather than horizontal direction, because the Sylvian fissure is simultaneously enlarged by sandwiching the lateral ventricle from both sides. Therefore, the z-Evans index (42) which indicate the z-axial expansion of the bilateral ventricles is appropriate for evaluating ventricular enlargement and shunt effectiveness in iNPH, rather than the Evans index (43–48). By this simultaneous expansion of the ventricles and Sylvian fissure toward the top of the head, the high convexity and medial parts of the brain and subarachnoid spaces just above the lateral ventricles are compressed. This morphological characteristic of CSF distribution specific to iNPH has been called as Disproportionately Enlarged Subarachnoid-Space Hydrocephalus (DESH) (49, 50). As quantitative indicators of DESH, the callosal angle defined as the angle of the roof of the bilateral ventricles on the coronal plane at the posterior commissure (PC) level (51) and brain per ventricle ratios (BVRs) defined as the maximum width of the brain just above the lateral ventricles divided by the maximum width of the lateral ventricles on the coronal planes at the at the anterior commissure (AC) and PC levels (52) are useful not only for preoperative evaluation but also for comparison before and after shunt surgery (53, 54).

A state-of-the-art artificial intelligence technology is already able to automatically, accurately, and instantly segment the ventricles and subarachnoid spaces. Therefore, in the near future, it is expected that the diagnostic imaging of iNPH will become more accurate as the three-dimensional index of DESH such as convexity subarachnoid space per ventricle ratio (CVR) defined as the volume of the convexity subarachnoid space divided by the total ventricular volume (54) can be measured more easily.

Surgical Indication

Only about half of the patients diagnosed with probable iNPH based on the image finding of DESH and response to the CSF tap test undergo shunt surgery (55, 56). Even if a patient is diagnosed with probable iNPH, the advantages (symptom improvement) and disadvantages (complications) of having shunt surgery should be evaluated individually for each patient. The major reasons why surgical indications are divided among neurosurgeons are patient's age and comorbid conditions such as Alzheimer's disease, stroke, and diabetes mellitus; heavy drinking, which increase the surgical risk and reduce improvement rates; and environmental factors including living alone without any caregivers or in domiciliary care or care homes. The majority of neurosurgeons may decide that the shunt surgery is not indicated, if a patient with probable iNPH has no decision-making ability and the cooperation of relatives cannot be obtained (57). The prediction of symptom improvement and surgical risks require consensus among the patients, neurosurgeons and referring physicians. Based on the evidence (10, 11, 49), neurosurgeons estimate that shunt surgery will improve only 20% of symptoms in 60–80% of iNPH patients, and a complete improvement of iNPH-related symptoms is very rare, even with the correct diagnosis of iNPH and perfect surgery and postoperative management (15). In addition, neurosurgeons are concerned about unexpected surgical complications and co-existence of comorbid degenerative diseases that worsen symptoms after shunting. Super-seniors aged 85 years old or over had the higher comorbidity rate of stroke and dementia, and these comorbidities are known to be the cause of diminished effectiveness of shunting and shortened sign improvement period. In addition, super-seniors diagnosed with iNPH often have a decreased walking speed, decreased physical activity, and muscle weakness, so then they already meet the criteria for frailty at the time of iNPH diagnosis, and are vulnerable to external stress. Super-seniors with frailty syndrome have a risk of being unable to maintain their preoperative living functions due to hospitalization or shunt surgery. In addition, the risk of shunt infection increases due to the deterioration of the skin's protective function and immunity due to aging, and if a shunt infection should occur, there will be a period during which the patient cannot stand or walk, and the symptoms will remain worse than before surgery at the discharge. In addition, because the super-seniors usually have their cerebral atrophy, the risk of chronic subdural hematoma is also increased due to CSF overdrainage and falls. Therefore, surgical intervention should be considered after fully explaining to the patient and their caregiver that the possibility of exacerbation is not unexpected.

SURGICAL TECHNIQUES AND POSTOPERATIVE CLINICAL MANAGEMENT

Lateral Ventricle Approach

The lateral ventricles are C-shaped cavities at the center of the cerebrum divided into the frontal (or anterior), occipital (or posterior), and temporal (or inferior) horns; the trigone (or atrium); and the body. In general, access to the lateral ventricles is by the frontal, occipital, or parietooccipital approach. The frontal approach is the most frequently used in this procedure. The coronal point, which is located 1–2 cm anterior to the coronal suture and 3–4 cm lateral from the midline, is the most

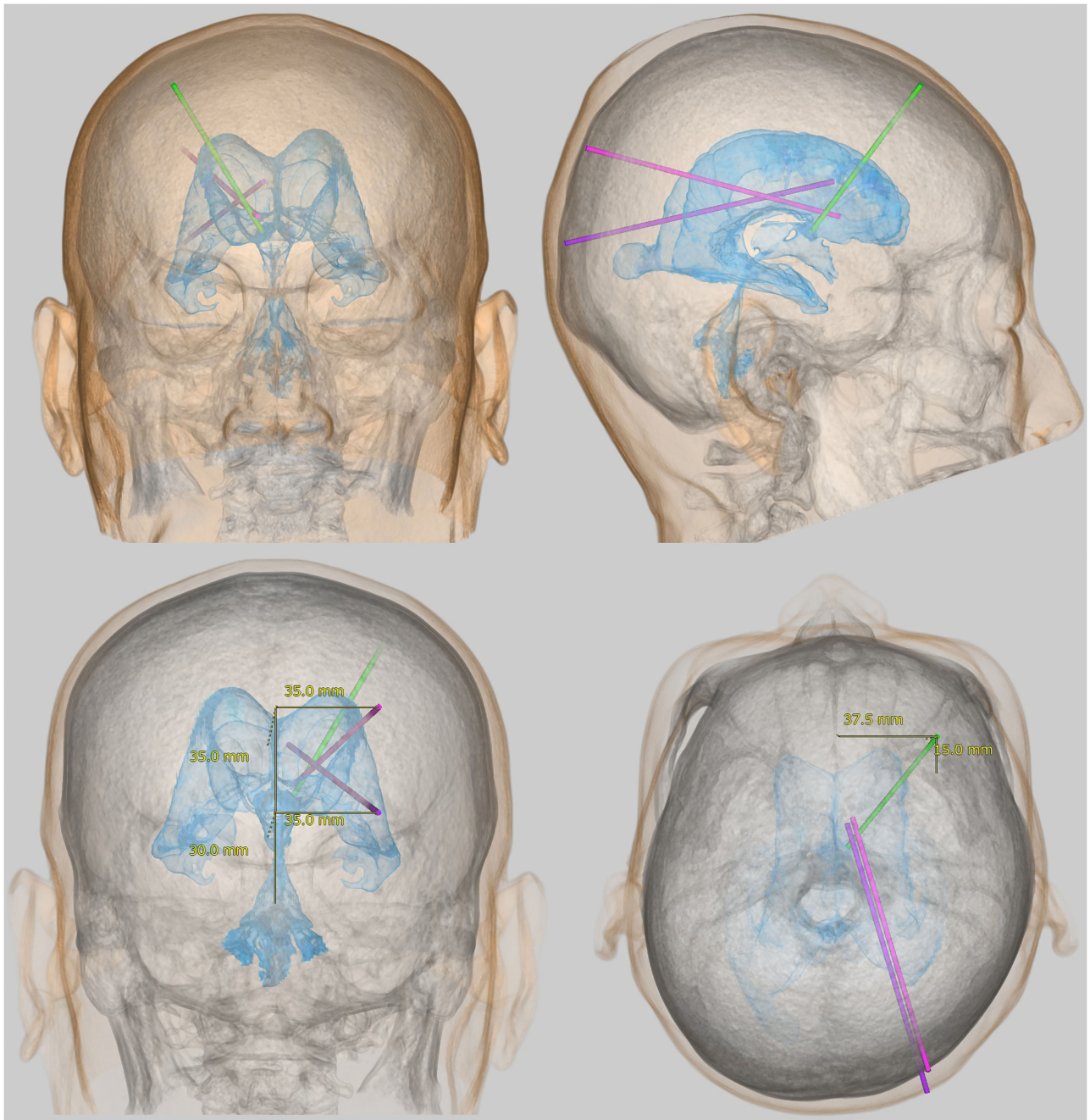

FIGURE 1 | Representative approaches for placement of a ventricular catheter in the lateral ventricle. The light green bar indicates the root for the frontal approach from the coronal point, the purple bar indicates the root for the occipital approach from Dandy's point, and the pink bar indicates the root for the parietooccipital approach from Frazier's point.

common site for ventricular puncture (**Figure 1**), and the eyes, nose, and ears can be used as surface anatomical landmarks. However, the frontal approach in VP shunting requires the head to rotate because the silicone tube passes under the scalp behind the ear. This makes entry to the frontal horn of the ipsilateral lateral ventricle difficult, compared to the external ventricular drainage in which the head position is maintained in the median position (58). In addition, patients with iNPH sometimes exhibit smaller lateral ventricles, especially the frontal horn due to the enlargement of Sylvian fissure and basal cistern (42, 45, 49, 52, 59). The occipital and parietooccipital approaches are thought to make entry into the ipsilateral lateral ventricle more difficult. Using the occipital approach, the nearest entry point from the occipital horn of the lateral ventricle is Dandy's point, located 3 cm above and 2 cm lateral to the external occipital protuberance (inion). In the parietooccipital approach, Frazier's point is the

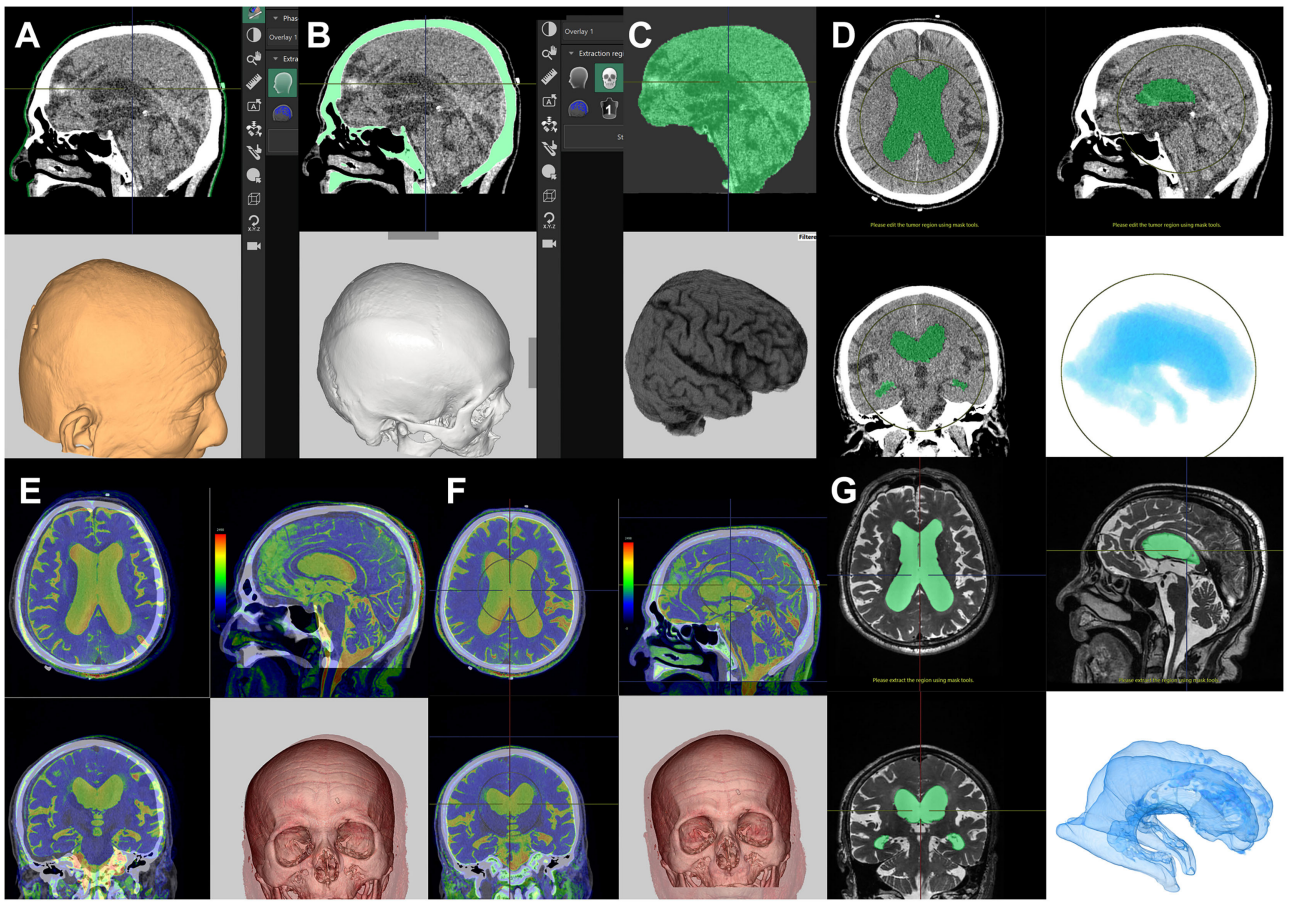

FIGURE 2 | Preparation for computational virtual simulation of ventricular puncture. Screenshots of the Craniotomy/Tensor Analysis application on the SYNAPSE 3D workstation. Clicking the buttons causes the following three imaging components to be extracted automatically from the plain head CT scan: scalp **(A)**, skull **(B)**, and brain **(C)**. After the automated extraction, the lateral ventricle images were manually extracted from the brain **(D)**. If the patient has had a 3D-MRI for iNPH diagnosis, the T2-weighted 3D MRI is superimposed on the CT scan **(E)**. The CT and superimposed MRI images are automatically aligned with a single click **(F)**. The lateral ventricle images from T2-weighted 3D-MRI images **(G)** are easier and clearer to read than CT images **(D)**.

most suitable entry point. This is located 6 cm above and 4 cm lateral to the inion. While Frazier's point is further from the ventricle, it provides easier catheter insertion into the body of the ipsilateral lateral ventricle than Dandy's point, as shown in **Figure 1**. However, ventricular puncture from Dandy's point in the occipital approach provides easier catheter insertion into the temporal horn of the lateral ventricle. With entry through both Dandy's point and Frazier's point, the ears and inion are the useful superficial landmarks. Therefore, while these points offer a cosmetic advantage but a higher risk of inappropriate catheter placement than the coronal point for the frontal approach. If the puncture point moves for any reason, there is the possibility of accidental puncture of the venous sinus. In particular, Dandy's point has a higher risk of bleeding than Frazier's point because it is close to both the superior sagittal sinus and the transverse sinus. However, using the preoperative simulation described below, the parietooccipital approach from Frazier's point can more accurately place the ventricular catheter in the optimal position than the frontal approach in VP shunt surgery.

Preoperative Simulation for Ventricular Catheter Placement

Although VP shunt surgery is considered a relatively simple operation, few neurosurgeons are confident in their ability to position a ventricular catheter correctly with the first puncture. Misdirected brain puncture risks damaging functionally important locations such as the thalamus, basal ganglia, and corona radiata. In addition, inappropriate catheter placement, for example, with the ventricular catheter tip inserted into the brain, significantly increases the risk of shunt malfunction (58, 60–62). Therefore, it is necessary to pay special attention to the appropriate placement of the ventricular catheter in VP shunt surgery. Recent studies have found that the success rate of the frontal approach with the free-hand technique is only 44–64% (58, 60, 63–65), whereas that of the occipital or parietooccipital approach is 67–71% (62, 66). Because the possibility of inappropriate placement is significant in all free-hand approaches, ventricular catheter placement should not be performed by free-hand puncture. Some neurosurgeons

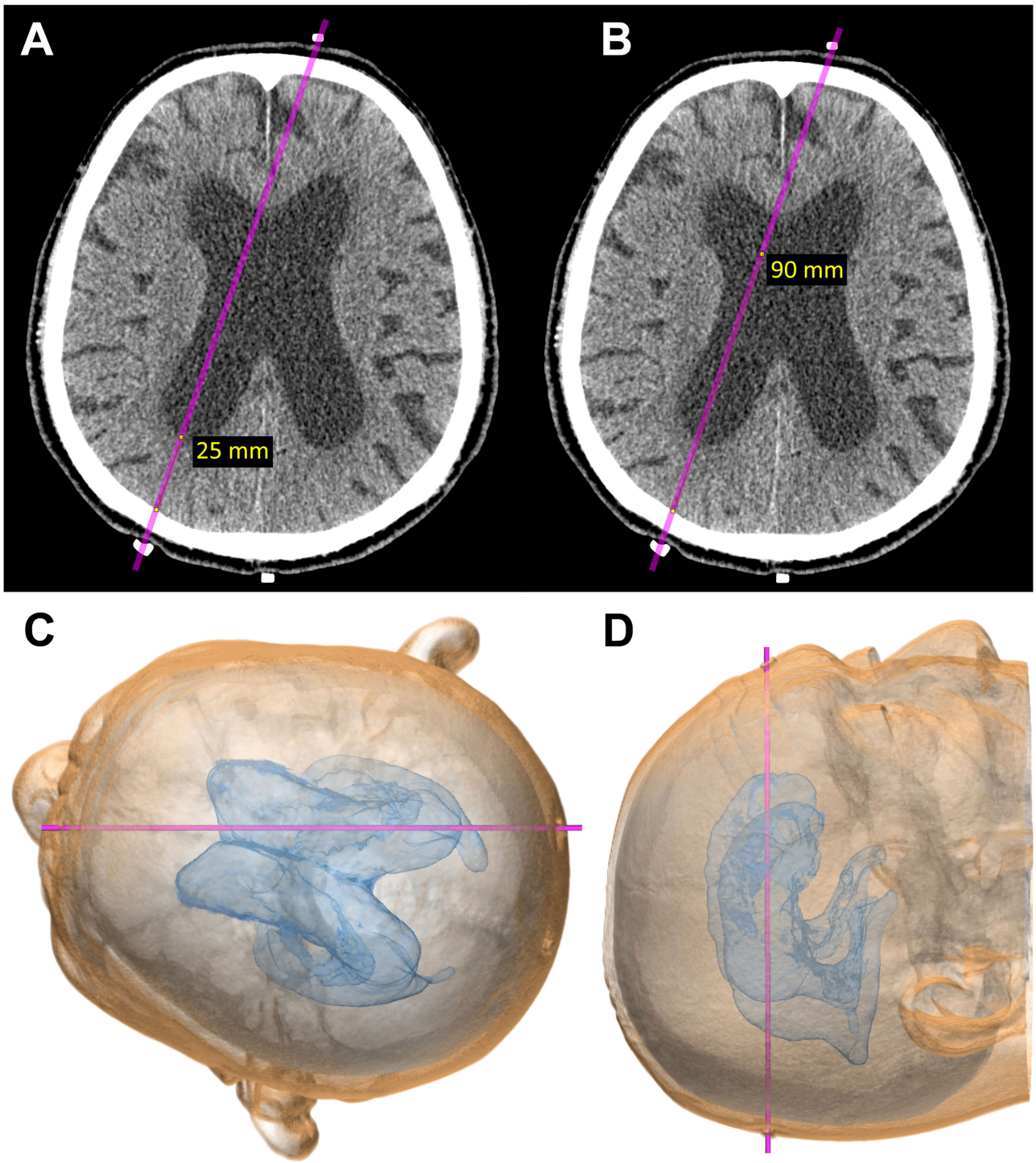

FIGURE 3 | Computational virtual simulation of ventricular puncture in parietooccipital approach from Frazier's point. The depth from the brain surface to the entry point of the posterior horn of the lateral ventricle **(A)** and the length planned for ventricular catheter placement **(B)** were measured on the CT images. The virtual head position for surgery, setting the entry–target line parallel to the horizontal plane, was observed from the vertex angle **(C)**, and from above, perpendicular to the horizontal plane **(D)**.

prefer to use intraoperative imaging guidance instruments, such as ultrasonography, stereotaxy, and neuro-navigation. These have been shown to provide significantly greater accuracy than free-hand puncture (58, 62, 64, 65, 67, 68). An alternative to intraoperative imaging is preoperative simulations to determine the entry point, direction, and depth of puncture. With a frontal approach from the coronal point, it is not possible to determine the target on the scalp by using preoperative simulation, whereas a parietooccipital or occipital approach allows accurate determination of the scalp target. Thus, a posterior ventricular puncture using preoperative simulation has a higher success rate due to accurate determination of the entry and target points.

We have described as concretely as possible so that many neurosurgeons can utilize our method, preoperative 3D simulation of ventricular catheter placement using the parietooccipital approach from Frazier's point.

We usually perform the computational simulation twice using a 3D workstation (Synapse 3D; Fujifilm Medical Systems, Tokyo, Japan) before shunt surgery (**Supplementary Video 1**). The first simulation is to determine the optimal route and entry and target points, and the second is to confirm the measurement points where the markers have been placed.

Using the application tool Craniotomy/Tensor Analysis on the Synapse 3D workstation (https://healthcaresolutions-us.fujifilm.com/enterprise-imaging/synapse-3d), images of the scalp, skull, and brain can be automatically extracted from a plain helical CT scan within a few minutes (**Figures 2A–C**). A helical CT scan provides higher detectability of the scalp and skull than a 3D MRI. After automatic extraction of brain images, ventricle images can be obtained using techniques such as cutting, threshold extraction, and user-steered live-wire segmentation in the same application (**Figure 2D**). The extraction of images of CSF spaces using a simple threshold algorithm is preferential as these images can be superimposed on T2-weighted 3D MRI (**Figures 2E–G**), which provides clearer imaging of the boundary between the brain and the CSF than a CT scan. The annotation bar, with a diameter of 2 mm and a length of 180–200 mm, is useful for deciding the optimal direction for placement of the ventricular catheter (**Figure 3**). The priority in making this decision is to find the shortest pathway of brain penetration and the longest pathway in the ipsilateral ventricle. The entry and target points on the scalp are set to pass through the annotation bar on the scalp. The ideal target point in the brain is the genu of the corpus callosum and the anterior median wall of the bilateral ventricles. Therefore, the target point on the scalp is typically located 3–5 cm superior to the contralateral inner eye angle, using the nasion as a facial landmark.

A rubber eraser is the best marker for CT scans because it creates fewer artifacts and is easy to see even if it is small. To confirm the measured points for entry and target before shunt surgery, patients undergo a CT scan after setting three markers made using the tip of a rubber eraser, as shown in **Figure 3**. The first marker is placed at the planned entry point, the second at the planned target point on the scalp, and the third marker at the occipital midline, 6–8 cm superior to inion. This third marker is useful for the correction of the entry point.

During the second simulation to confirm the marker locations (**Figure 3**), the direction for ventricular catheter placement can be corrected if it is not ideal. It is preferable to correct the frontal marker rather than the occipital marker because the frontal marker has more facial landmarks, including the eyes and nose that help to guide the direction and find the midline. However, the third marker at the occipital midline is useful for the correction of the entry point. After determination of the entry point and the optimal direction for ventricular catheter placement, the depth from the brain surface to the entry point of the posterior horn of the lateral ventricle (**Figure 3A**) and the length planned for ventricular catheter placement (**Figure 3B**) are measured. In the final part of the preoperative simulation, the patient's head is virtually rotated to the surgical position, with the entry–target line parallel to the horizontal plane (**Figure 3C**) and observed from a top view perpendicular to the horizontal plane (**Figure 3D**).

Shunt Valve Selection

All pressure-controlled shunt valves are manufactured to operate within a specific pressure range. As the history of iNPH treatments has shown, CSF shunt surgery using fixed-pressure valves for iNPH produces poor prognoses. However, some previous studies have found that fixed-pressure valves are still used more frequently than programmable-pressure shunt valves (5, 69, 70). Elderly patients who use the medium pressure valve have a high shunt revision rate due to issues with over-drainage (subdural hematoma) or under-drainage (less effective than expected). Brain plasticity in elderly patients with iNPH seems to be lower than that seen in young patients with secondary NPH. Since the therapeutic effects of iNPH have been recognized since the development and distribution of programmable-pressure shunt valves, it seems obvious that this type of shunt valve should be used for the treatment of iNPH. It is possible that the preference for fixed-pressure valves is due to financial constraints, but when the costs of re-operation are taken into account, it is cheaper to use a programmable-pressure shunt valve (12, 71). Programmable-pressure valves allow the neurosurgeon to choose a pressure setting before surgery and easily change them afterward based on the needs of the patient. Until 2015, our iNPH patients used the CHPV (Integra LifeSciences Corp., USA), which has 18 operating pressure settings in 10 mmH_2O increments from 30 to 200 mmH_2O (3). In 2015, the Codman CERTAS Plus Programmable Valve (Integra LifeSciences Corp., USA) was developed. This is an MRI-resistant programmable valve with seven operating pressure levels from 36 to 238 mm H_2O and "virtual off (8)," which sets the valve pressure consistently above 400 mmH_2O (72). Considering the easy adjustment and confirmation of valve pressure, there is no need for re-adjustment after 3Tesla MRI, and the virtual off function offers greater advantages for iNPH patients than does the fine pressure setting in CHPV. Therefore, the CERTAS valve has been the first choice for our VP shunt surgery since 2015. In addition, to prevent over-drainage related to body posture, we routinely use the Siphonguard Anti-Siphon Device (Integra LifeSciences Corp., USA). This is an automatic hydrodynamic

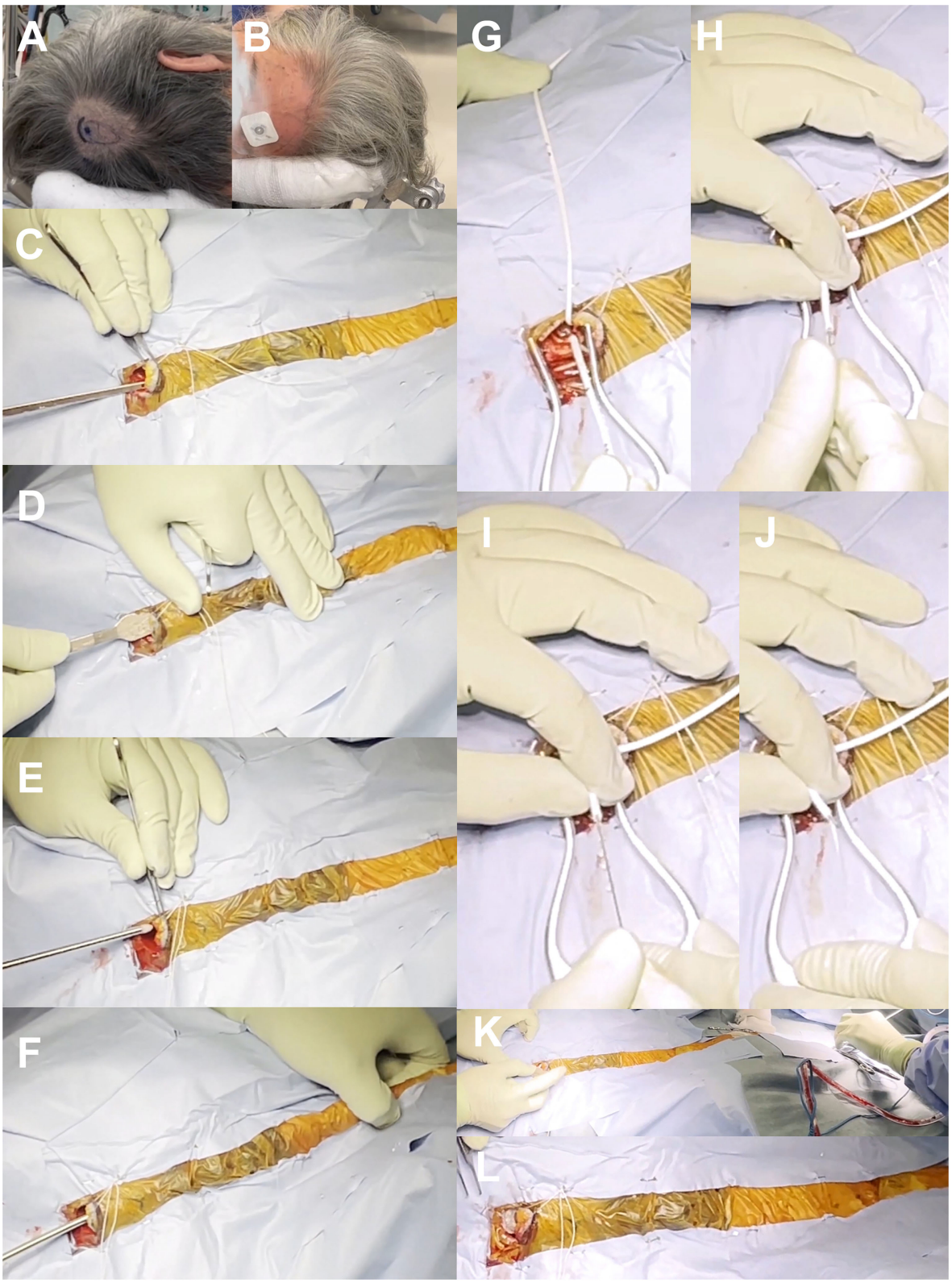

FIGURE 4 | Surgical photographs. Marking of skin incision and valve placement position **(A)**, putting electrocardiogram sticker on the target point of scalp **(B)**, subcutaneous tunnel using spatula-shaped passer **(C,D)** and long cylindrical passer **(E,F)**, insertion of ventricular catheter **(G–J)**, and placement of shunt valve **(K,L)**.

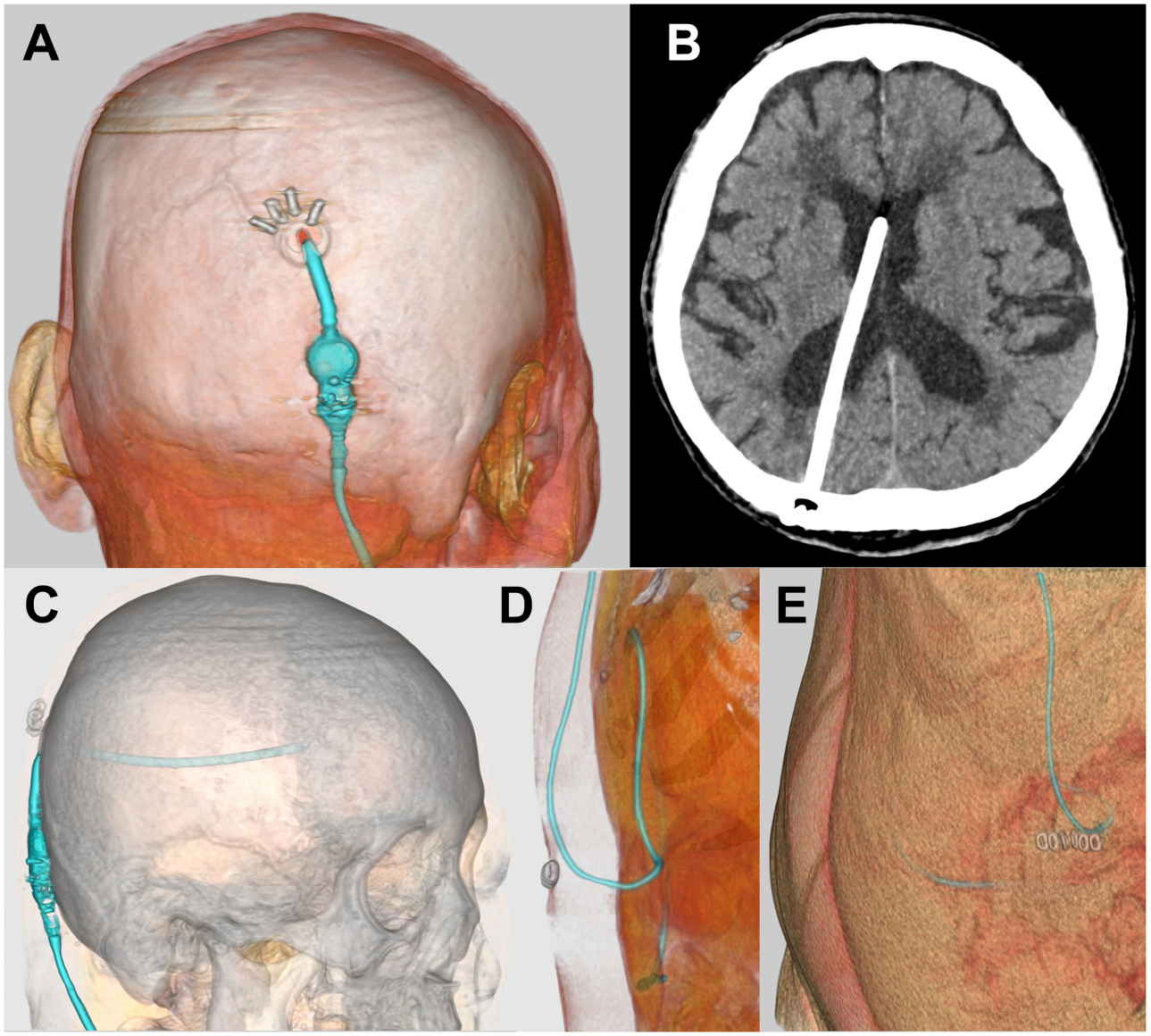

FIGURE 5 | Postoperative CT images. Postoperative head CT images **(A–C)** and abdominal CT images **(D,E)** created by SYNAPSE 3D workstation were confirmed.

switch that increases resistance to reduce the CSF drainage rate below 0.4 ml/min when it rises above 0.6 ml/min (73).

Surgical Procedure

As described above, the first choice for our VP shunt surgery is a right-side parietooccipital approach (**Figure 4A**). Patients are placed with a pillow under the right shoulder and a slightly arched back to ensure shallow abdominal depth. The patient's head is carefully placed so that the entry–target line is horizontal to the ground in the same way as in the preoperative 3D simulation. An electrocardiogram sticker is placed on the left side of the forehead at the measured scalp target (**Figure 4B**). The right parietooccipital scalp is incised at the entry point, at ∼2 cm on the slightly curved protrusion toward the vertex, and the periosteum is retracted (**Supplementary Video 2**). A skin incision is then made ∼2 cm above the right rectus abdominis muscle. The subcutaneous tunnel is passed from the cranial side to the abdominal side using two types of passers (**Supplementary Video 3**). The first short spatula-shaped passer is placed subcutaneously from the scalp incision to just above the collarbone (**Figures 4C,D**). This is then changed to a long cylindrical passer to the abdominal incision without a relay incision to prevent infection (**Figures 4E,F**). During tunneling, the passer is carefully positioned to prevent deep insertion, particularly under the collarbone, checking the tip position visually and by touch. A small hole is drilled in the skull, and a cross is incised on the dura. A ventricular catheter with an inlet stylet is then directly punctured without a trial puncture

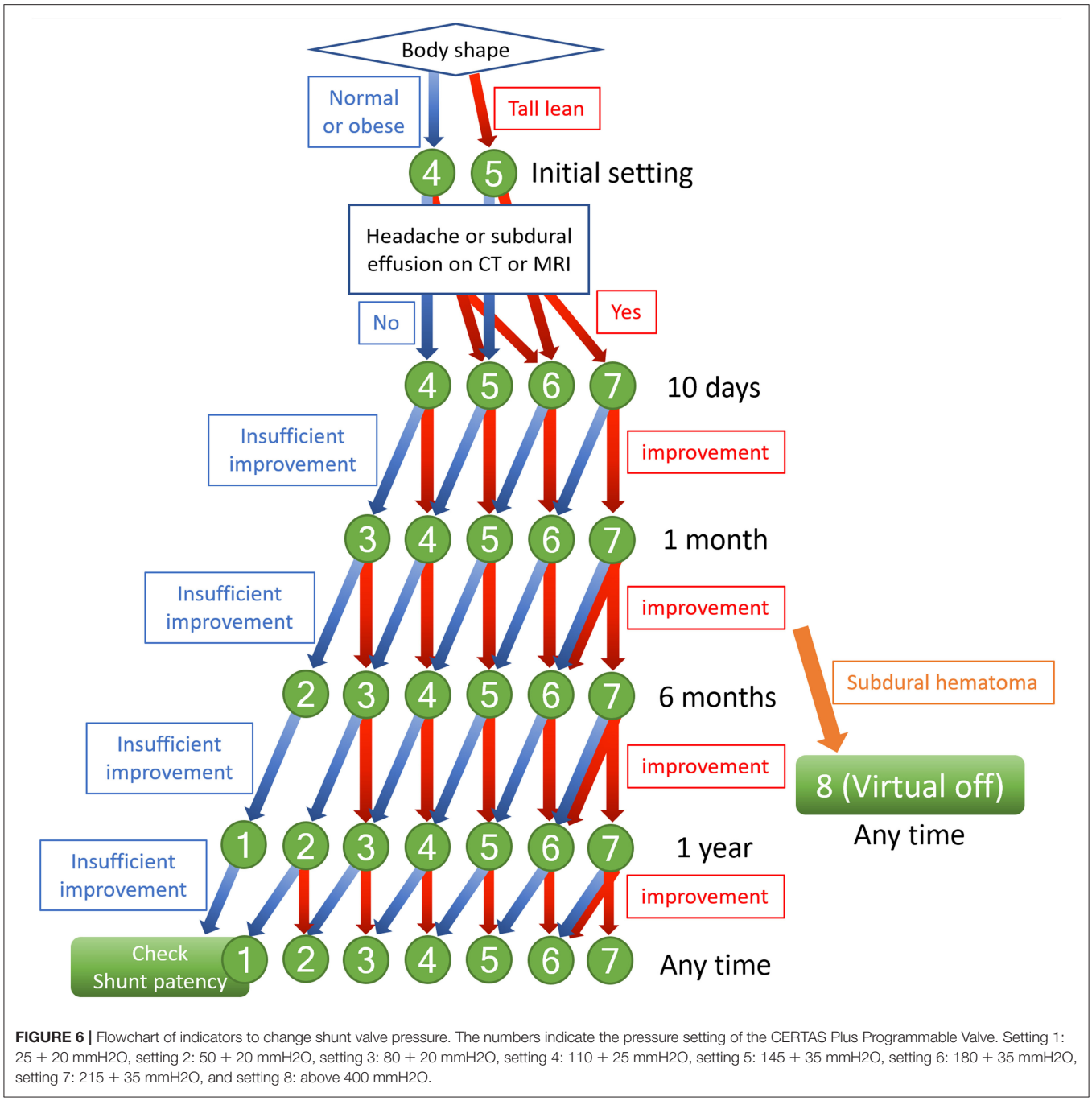

FIGURE 6 | Flowchart of indicators to change shunt valve pressure. The numbers indicate the pressure setting of the CERTAS Plus Programmable Valve. Setting 1: 25 ± 20 mmH2O, setting 2: 50 ± 20 mmH2O, setting 3: 80 ± 20 mmH2O, setting 4: 110 ± 25 mmH2O, setting 5: 145 ± 35 mmH2O, setting 6: 180 ± 35 mmH2O, setting 7: 215 ± 35 mmH2O, and setting 8: above 400 mmH2O.

using a metal puncture needle (**Supplementary Video 3**). A ventricular catheter is inserted horizontally to the ground while considering the direction toward the target from the top viewpoint (**Figure 4G**). When the ventricular catheter is inserted into the posterior horn of the lateral ventricle, a small amount of CSF leaks through the side of the inlet stylet. After confirming the clear CSF droplet, the ventricular catheter is slowly advanced to the simulated length, and the inlet stylet is removed (**Figures 4H–J**). The catheter is placed in the anterior horn or body of the ipsilateral ventricle to avoid choroid plexus involvement. After confirming smooth CSF drainage, the ventricular catheter is cut to an adequate length and connected with the shunt valve system. Finally, the patency of the shunt valve system is confirmed by pushing the shunt reservoir (**Figures 4K,L**). After the operation, the position of the shunt valve system is confirmed by a CT scan (**Figure 5**).

Initial Setting of Shunt Valve Pressure

Over-drainage is most likely to occur early after CSF shunt surgery, so it is safer to set the initial pressure higher than the estimated optimal pressure. However, this can prevent sufficient improvement of the patient's symptoms due to under-drainage.

If the valve pressure is initially set low to drain sufficient CSF, the symptoms may improve early after the shunt surgery, but the risk of over-drainage is also increased.

Miyake et al. have produced a quick reference table that uses the patient's height and weight (body mass index) to estimate the optimal initial pressure setting (74). This quick reference table was adopted in a Japanese study of iNPH on neurological improvement (SINPHONI) in which 100 patients with iNPH underwent VP shunt surgery using the CHPV. They observed relatively good outcomes and a low complication rate, but they were unable to prove that the quick reference table is superior to other methods because this was a single-arm study (11, 49, 75).

Because NPH is defined as "normal pressure" chronic hydrocephalus, it is widely believed that valve pressure fixed at medium (normal range pressure of human CSF) is sufficient for iNPH. In a prospective, double-blind, randomized controlled study using a CHPV, iNPH patients were divided into two groups (9). The first group underwent a monthly reduction of the valve pressure in steps of 40 mmH_2O from an initial pressure of 200 mmH_2O to a final pressure of 40 mmH_2O over 4 months. The second group had valve pressure set and maintained at 120 mmH_2O. In the first group, the improvement rate 6 months after VP shunt surgery was 88%, while that in the second group was 62%. However, the complication rate due to over-drainage was significantly higher in the second group with a consistent valve setting of $\leq$120 mmH_2O. A second report by the same authors found improvement rates in quantitative assessments of steps taken during a 10 m walk, Stroop tests, and Grooved Pegboard tests but with no significant differences between the two groups (76). Therefore, they recommended setting the initial shunt valve pressure at 120 mmH_2O and not reducing it lower than 120 mmH_2O.

Since 2015, we have routinely used the CERTAS Plus Programmable Valve with Siphonguard Anti-Siphon Device in VP shunt surgery with our iNPH patients. The initial shunt valve pressure is set at medium pressure (4: 110 $\pm$ 25 mmH_2O) for iNPH patients with normal body shape but optionally set one level higher (5: 145 $\pm$ 35 mmH_2O) for tall lean patients. Within 10 days of VP shunting, the optimum valve pressure for each patient is determined by increasing one or two levels in those presenting with postural headaches or asymptomatic subdural effusion on a CT scan, as shown in flowchart of **Figure 6**. One month after VP shunting, the symptoms were not sufficiently improved or worsen, the valve pressure should be carefully decreased one level. We believe that this pressure setting protocol for the CERTAS Plus Valve can improve patients' symptoms early after shunt surgery, although we have not compared it with other protocols.

Long-Term Shunt Valve Pressure Reduction After Initial Optimal Setting

Many studies have examined the optimal initial pressure setting of programmable-pressure shunt valves and adjustments early after shunting, but none have focused on long-term changes of the valve pressure more than half a year after shunting. In patients with severe symptoms, the remaining symptoms often worsen after several years following surgery, even when symptoms are initially improved by setting the optimal valve pressure early after shunting. In such patients, it is recommended that the valve pressure is reduced one level as the cause is likely to be under-drainage. However, it would be preferable if such patients could be identified in advance and the valve pressure lowered before the worsening of symptoms. Therefore, we postulate that the optimal pressure in the early period after shunting might not be the same as the optimal pressure in the medium to long-term. Compared to secondary NPH subsequent to subarachnoid hemorrhage (77), iNPH may have a longer period from CSF accumulation to the appearance of symptoms (45). It may take some time for normal CSF distribution and brain formation to return (54). Based on this evidence, if the expected improvement in symptoms and radiological findings are not observed 6 months after shunting, the shunt valve pressure should be reduced one level from the initial optimal valve pressure 6 months to 1 year after shunting (**Figure 6**). When the valve setting is reduced, patients should be checked for symptoms of over-drainage and subdural effusion or hematoma on a CT scan within 1 month. Using this aggressive long-term pressure-lowering strategy, we have experienced many patients who have improved beyond expectations and few adverse events such as re-over-drainage. We hope to confirm the effectiveness of these aggressive pressure-lowering approach in future clinical studies.

Surgical Complication

The adverse events associated with VP shunt surgery in iNPH are listed as shunt malfunction (shunt pathway obstruction and mechanical failure), subdural hematomas, infection, cerebral hemorrhage around the ventricular puncture route, and symptoms of intracranial hypotension (e.g., headache, nausea, vomiting, dizziness, and tinnitus). In a systematic review of papers published before 2000, the mean complication rate of was 38% (range, 5–100%), and 22% (range, 0–47%) of patients required additional surgery (78). However, a systematic review of 28 studies published from 2006 to 2010 reported that the shunt revision rate was 13% and the rate of other surgical complications including subdural hematomas and infection was 8.2% (79). In the recent multicenter prospective cohort studies, the rate of serious adverse events had been reported to be 15–22% (9, 11), and 10–16% in the community-based retrospective studies (56, 80). Therefore, the complications of VP shunt surgery in iNPH have steadily decreased in recent years due to improvement in shunt technology and surgical techniques. However, the complication rate is still over 10%, which is too high for surgery aimed at improving the function of the elderly patients with an average age of 75 years. Since the surgical complications leads to the unfortunate outcomes that the symptoms do not improve as expected, neurosurgeons need to seriously improve the technique of VP shunt surgery to further reduce complications.

DISCUSSION

Delays in the diagnosis and treatment of progressive diseases are harmful to patients. The effects of CSF tap test or spinal

drainage test for the iNPH diagnosis are transient, and symptoms return after a while (15). The effects of the CSF tap test has been reported to be associated with the duration since the onset of symptoms, and the effect diminishes as the disease duration increases (37). Therefore, even if the CSF tap test is repeated palliatively every time the symptom worsens, the same effect as the first one is not obtained, and there is a high possibility that the symptoms gradually progress and the timing of treatment is missed. For early diagnosis and early intervention, there is a need for widespread awareness that gait disturbance, cognitive impairment, and urinary incontinence or urgency is typical symptoms of iNPH in the elderly. Recently, Andrén et al. reported that delays in the surgical planning of shunting for iNPH patients create 2.57 times higher risk of mortality than early treatment (81). Crude mortality rates of 4 years occurred in 39.4% of patients waiting for shunt surgery for 6–24 months (mean: 13 months) and 10.1% in the patients treated within 3 months. In addition, iNPH patients are known to be at increased risk of falls due to imbalance and gait disturbance. The Idiopathic Normal Pressure Hydrocephalus Comorbidity and Risk Factors Associated with Hydrocephalus (iNPH-CRasH) study by the Swedish Hydrocephalus Quality Registry reported that the frequency of recurrent falls decreases from 67% before shunting to 35% after shunting, although this is still higher than the 11% risk in the general population (82). They also reported that iNPH patients feared falling more often than the general population even after shunting. The reduction of quality of life and independent living expectations due to fear of falling leads to frailty, social withdrawal, and impaired healthy life expectancy. Therefore, patients should be provided with additional interventions such as rehabilitation exercises and home safety care education after shunting. Especially, patients who had a complication of lower limb disuse syndrome and an impaired daily life due to moderate or severe gait disturbance are recommended actively perform rehabilitation even if the hospitalization period is extended, rather than being discharged as soon as possible after CSF shunting. It is expected that a better quality of life will continue even after discharge, if the patients are discharged after recovering until living their daily life without needing assistance at home and until the fear of falling disappears.

In conclusion, patients diagnosed with iNPH are referred to the hospital with the expectation that "dementia, gait disturbance, and urinary incontinence will be cured." However, elderly iNPH patients with frailty syndrome, especially those with a history of stroke or comorbidity of Alzheimer's disease, may not get the therapeutic benefits they expect. Surgical intervention should be considered after fully explaining to the patient and their caregiver that the possibility of exacerbation is not unexpected. We should treat iNPH patients with the following points in mind: early detection, accurate diagnosis, consideration of surgical indications by a neurosurgeon experienced in iNPH treatment, the best treatment for each patient (including surgical method and adequate adjustment of shunt valve pressure), and post-shunting rehabilitation and long-term follow-up. We hope to work together in the future with specialists in the departments of neurosurgery, neurology, psychiatry, and rehabilitation to further develop and improve treatments for iNPH patients.

AUTHOR CONTRIBUTIONS

SY: conception and design. MI, MN, and KN: critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.798488/full#supplementary-material

Supplementary Video 1 | Preoperative simulation.

Supplementary Video 2 | Setting position.

Supplementary Video 3 | Operation.

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Water Diffusivity Changes Along the Perivascular Space After Lumboperitoneal Shunt Surgery in Idiopathic Normal Pressure Hydrocephalus

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Background: The aim of this study was to evaluate the water diffusivity changes along the perivascular space after lumboperitoneal shunt (LPS) surgery in idiopathic normal pressure hydrocephalus.

Methods: Nine patients diagnosed with idiopathic normal pressure hydrocephalus (iNPH; three men and six women, mean age ± SD = 75.22 ± 5.12 years) according to the guidelines for iNPH in Japan were included in the study. Post-LPS surgery, six patients with iNPH who exhibited improvement in symptoms were defined as responder subjects, while three patients with iNPH who did not were defined as non-responder subjects. We calculated the mean analysis along the perivascular space (ALPS) index of the left and right hemispheres and compared the differences between pre- and post-LPS surgery mean ALPS indices in iNPH patients. In the responder or non-responder subjects, the mean ALPS indices in the pre- and post-operative iNPH groups were compared using Wilcoxon signed-rank tests. Next, correlation analyses between pre- and post-operation changes in the mean ALPS index and clinical characteristics were conducted.

Results: The mean ALPS index of the post-operative iNPH group was significantly higher than that of the pre-operative iNPH group ($p = 0.021$). In responder subjects, the mean ALPS index of the post-operative iNPH group was significantly higher than that of the pre-operative iNPH group ($p = 0.046$). On the other hand, in the non-responder subjects, the mean ALPS index of the post-operative iNPH group was not significantly different compared to the pre-operative iNPH group ($p = 0.285$). The mean ALPS index change was not significantly correlated with changes in the Mini-Mental State Examination (MMSE) score ($r = -0.218$, $p = 0.574$), Frontal Assessment Battery (FAB) score ($r = 0.185$, $p = 0.634$), Trail Making Test A (TMTA) score ($r = 0.250$, $p = 0.516$),

and Evans' index ($r = 0.109$, $p = 0.780$). In responder subjects, the mean ALPS index change was significantly correlated with Evans' index in pre-operative patients with iNPH ($r = 0.841$, $p = 0.036$).

Conclusion: This study demonstrates the improved water diffusivity along perivascular space in patients with iNPH after LPS surgery. This could be indicative of glymphatic function recovery following LPS surgery.

Keywords: idiopathic normal pressure hydrocephalus, ALPS index, lumboperitoneal shunt surgery, glymphatic system, diffusion-weighted imaging, cerebrospinal fluid, interstitial fluid

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is accompanied by gait dysfunction, cognitive impairment, and urinary incontinence in the elderly (1). The prevalence of iNPH varies between populations and can be as high as between 1.3 and 2.1% for a population aged between 65 and 79, and 8.9% for those above 80 years of age (2, 3). iNPH is characterized by dilation of the cerebral ventricles, normal cerebrospinal fluid (CSF) pressure, and mostly symptomatic improvement after CSF diversion procedures (4). In a prospective study of iNPH, shunt surgery efficacy was reported to be approximately 80% in cases diagnosed with one or more of these symptoms (5). Besides, lumboperitoneal shunt (LPS) surgery is a minimally invasive approach and a popular treatment option for patients with iNPH in Japan (6, 7). Nagajima et al. (7) reported that the treatment efficacy of LPS against iNPH was not different from what is obtained following ventriculoperitoneal shunting. However, without treatment, the disease progresses, symptoms worsen and the probability of favorable outcomes from shunt surgery diminishes (8).

Characteristic features of iNPH that can be identified in imaging include dilatation of the Sylvian fissure, narrowing of the CSF space in the parietal region, and callosal angle. The effectiveness of shunt placement for the treatment of iNPH has been evaluated using CT or MRI. Kitagaki et al. (9) showed that in five patients with iNPH, the mean post-operative CSF volumes were significantly decreased in the Sylvian space and in the ventricle, marginally decreased in the basal cistern, and significantly increased in the suprasylvian space as compared with the pre-operative volumes. Anderson et al. (10) reported that the ventricular volumes of 10 (91%) out of 11 patients with iNPH who underwent shunt surgery were decreased, with a mean change rate of 39%. Hiraoka et al. (11) found that the decrease in ventricular volumes had a significant correlation to clinical improvement after shunt surgery.

In iNPH, the accumulation of amyloid-β is known to be one of the causes of impairment in cognitive symptoms. The accumulation of interstitial amyloid-β is a characteristic feature of both iNPH and Alzheimer's disease (AD). Typically, compared to patients with AD who have increased production of amyloid-β, patients with iNPH are believed to have impaired CSF absorption and excretion, thereby resulting in the accumulation of amyloid-β in the brain (9). However, there is also iNPH with AD pathology, the symptom is more complicated. The accumulation of interstitial amyloid-β is a pathological feature that correlates with poor shunt responsiveness in patients with iNPH (10). Therefore, studies on clearance pathways of waste products in iNPH are very important for the development of more effective treatments for these patients. There exist some gaps in our understanding of the mechanisms of the clearance system by CSF dynamics in iNPH.

Recently the glymphatic system hypothesis has been put forward to help to evaluate the elimination of waste solutes, such as amyloid-β and tau protein, in the brain parenchyma (12). The glymphatic system is essential for tissue homeostasis and is mediated by the CSF-interstitial fluid (ISF) exchange pathway (13). The exchange of fluids and their solutes between the CSF and ISF is dominated by convection and diffusion. Convection is characterized by solutes following the movement of their solvent (bulk flow). Diffusion is driven mainly by Brownian motion and characterized by solute movement being symmetric from a higher to a lower concentration. Aquaporin-4 water channels on astrocytic end-feet have been proposed to support perivascular fluid and solute movement along the glymphatic system (12). The glymphatic system is believed to be involved in AD, Parkinson's disease, diabetes, Meniere's disease, traumatic cerebral damage, iNPH, and various other diseases (13). Iliff et al. (14) demonstrated in mice using labeled CSF *via* injection of a fluorescent tracer into the cisterna magna that the CSF enters the brain along the cortical pial arteries. Several studies have assessed CSF dynamics primarily using tracers through intrathecal or intravenous injection of a gadolinium-based contrast agent (GBCA) and observations using MRI (15–19). As a part of MRI tracer studies using stable isotopes to evaluate CSF motion, the analysis of $H_2{}^{17}O$ has also been reported. Kudo et al. (20) utilized dynamic steady-state sequences to detect the T2-shortening effect by $H_2{}^{17}O$.

Taoka et al. (21) introduced the analysis along the perivascular space (ALPS) method, which is calculated using diffusion-tensor imaging as a non-invasive tool to evaluate the glymphatic system of living humans. This method assumes that diffusion may have an essential role in fluid transport in the brain parenchyma. Their study showed that in AD, the ALPS index was positively correlated with the Mini-Mental State Examination (MMSE) score (21). ALPS method was also reported to be robust under fixed imaging method and parameters even when different scanners were used (22). Subsequently, there have been reports of the use of the ALPS method for the assessment of different conditions in living patients, such as AD (21), iNPH (23, 24),

diabetes (25), hypertension (26), Parkinson's disease (27–29), stroke (30), multiple sclerosis (31), and tumor-associated brain edema (32, 33). Interestingly, recently Zhang et al. (34) using intrathecal administration of gadolinium in patients with small vessel disease ($r = -0.772$ to -0.844, $p < 0.001$) demonstrated that the ALPS index is significantly associated with glymphatic clearance. This study strongly supports the clinical use of the ALPS index as a glymphatic biomarker. Furthermore, to our knowledge, there are only two studies that have explored the glymphatic function in patients with iNPH, using the ALPS method (22, 23). Yokota et al. (22) showed that ALPS indices were lower in both pseudo-iNPH and iNPH patients than in healthy controls. Bae et al. (23) also reported the ALPS index to be significantly lower in iNPH patients compared to controls ($p < 0.0001$). The ALPS index was also significantly lower in the iNPH group, which did not show a treatment response that could be detected by diagnostic CSF drainage (lumbar puncture of 50 cc) as opposed to the group, which showed symptomatic improvement ($p < 0.0001$). These reports indicate that patients with iNPH exhibit lower water diffusivity in the direction of the perivascular space in the living human brain than healthy subjects. Bae's study examined patients with iNPH who only underwent the diagnostic CSF drainage (23); however, changes of diffusivity in the direction of the perivascular space post-shunt surgery have not been evaluated yet. Hence, this study aimed to evaluate post-LPS surgery changes in the ALPS index in patients with iNPH.

METHODS

Study Participants

Nine patients diagnosed who were with iNPH (three men and six women, mean age ± SD = 75.22 ± 5.12 years) according to the guidelines for iNPH in Japan were included in this study (35). The following inclusion criteria were adopted: (1) patients aged between 60 and 85 years; (2) the presence of the triad of symptoms, which were measurable on the iNPH grading scale (35); (3) both ventriculomegaly with an Evans' index >0.3 and high-convexity and medial subarachnoid space tightness on coronal MR images; and (4) the absence of disorders known to produce ventriculomegaly. The exclusion criteria were as follows: (1) complications with locomotor disorders (bone and joint disorders, etc.), visceral disorders (heart failure, etc.), and other psychiatric disorders; (2) complications with a hemorrhagic predisposition, abnormal blood coagulation, or hemorrhagic disease (cerebral hemorrhage, subarachnoid hemorrhage, and active peptic ulcer); (3) patients with hepatic dysfunction that may affect the clinical symptoms of iNPH, such as hepatic coma (aspartate transaminase [AST] or alanine aminotransferase [ALT] 100 U/L or more within 3 months of consent date); and (4) patients with renal dysfunction that required artificial dialysis (serum creatinine ≧2.0 mg/dl within 3 months of consent date). Evans' index, MMSE, Frontal Assessment Battery (FAB), and Trail Making Test A (TMTA) were conducted in patients with iNPH for pre- and post-LPS surgery. The clinical and MRI data of patients' post-LPS surgery were obtained within 1 year of surgery. **Table 1** shows the demographic characteristics of the subjects.

TABLE 1 | Demographic characteristics of subjects.

	Pre-operation iNPH group	Post-operation iNPH group	Pre-operation vs. Post-operation *P*-values
Sex (Men / Female)	3/6		
Age	75.22 ± 5.12		
Evans' index	0.33 ± 0.03	0.31 ± 0.03	0.012
MMSE	24.11 ± 3.48	25.67 ± 2.40	0.228
FAB	12.78 ± 3.67	14.00 ± 3.12	0.392
TMTA	104.78 ± 31.74	91.11 ± 34.93	0.351
Fazekas scale			
PVH	2.33 ± 0.50	2.33 ± 0.50	1
DSWMH	2.33 ± 0.50	2.33 ± 0.50	1

MMSE, Mini-Mental Statement Examination; FAB, Frontal Assessment Battery; TMTA, Trail Making Test A; PVH, Periventricular hyperintensity; DSWMH, Deep and subcortical white matter hyperintensity.

MRI Acquisition

All MRI data were acquired using a 3T MRI scanner (Achieva Quasar Dual; Philips Medical Systems, Best, The Netherlands). We performed fluid-attenuated inversion recovery (FLAIR) imaging. A magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence was collected as a high resolution, three-dimensional structural image. Diffusion-weighted imaging (DWI) with 32 non-collinear directions was acquired using a single-shot spin-echo echo-planar imaging sequence. Echo-planar images were acquired using a b value of 1,000 s/mm² along 32 isotropic diffusion gradients in the anterior-posterior phase-encoding direction. Each DWI acquisition was completed with a b = 0 image. We also acquired standard and reverse phase-encoded blipped images with no diffusion weighting (blip-up and blip-down) to correct for magnetic susceptibility-induced distortions related to the echo-planar image acquisitions. Within ∼1 year of shunting, the second MRI scan was performed on each participant. The acquisition parameters of FLAIR, MPRAGE, and DWI are presented in **Table 2**. Periventricular hyperintensity and deep white matter hyperintensity evaluations using the Fazekas scale (36) and Evans' index based on axial FLAIR imaging were conducted by an experienced neuroradiologist (JK).

DWI Processing

Diffusion-weighted imaging data were processed using FMRIB Software Library (FSL; Oxford Center for Functional MRI of the Brain, Oxford, UK; www.fmrib.ox.ac.uk/fsl;) version 6.0 (37). The DWI data were corrected for susceptibility-induced geometric distortions, eddy current distortions, and inter-volume subject motion using EDDY and TOPUP toolboxes (38). Diffusivity maps of each subject in the direction of the x-axis (right-left; *Dxx*), y-axis (anterior-posterior; *Dyy*), and z-axis (inferior-superior; *Dzz*) were obtained. Fractional anisotropy (FA) maps of all participants were also created and aligned into the FMRIB58_FA standard space using FSL's linear and non-linear registration tools.

TABLE 2 | Acquisition parameters for MPRAGE, DWI, and FLAIR.

Imaging sequence	MPRAGE	DWI	FLAIR
TR (ms)	15	3,000	10,000
TE (ms)	3.52	80	120
Slice thickness (mm)	0.86	5	5
Voxel size (mm^3)	0.8125 × 0.8125 × 0.86	2 × 2 × 5	0.72 × 1.13 × 5
FOV (mm)	260 × 260	256 × 256	230 × 200
b-values (s/mm^2)		0, 1,000	
Acquisition time (min:s)	5:14	2:43	2:40

DWI, Diffusion-weighted image; FOV, Field of view; MPRAGE, Magnetization-prepared rapid acquisition gradient-echo; TR, Repetition time; TE, Echo time.

Region of Interest (ROI) Placement and ALPS Index Calculation

Using each subject's color-coded FA map, 5-mm-diameter ROIs were manually placed in the projection and association areas at the level of the right and left lateral ventricles (**Figure 1A**). These ROIs were registered to the same FA template.

The diffusivity values in the *x*-, *y*-, and *z*-axes within ROIs were obtained from each participant (**Figure 1B**). The ALPS index was calculated as a ratio of the mean of the x-axis diffusivity in the projection area (*Dxxproj*) and association area (*Dxxassoc*) to the mean of the y-axis diffusivity in the projection area (*Dyyproj*) and the z-axis diffusivity in the association area (*Dzzassoc*) as follows (21): $ALPS\ index = \frac{(Dxxproj + Dxxassoc)}{(Dyyproj + Dzzassoc)}$.

An ALPS index close to 1.0 reflects minimal diffusion along the perivascular space, whereas higher values indicate greater diffusivity. The left and right ALPS indices and the mean ALPS index of the left and right hemispheres were calculated.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 27.0 (IBM Corporation, Armonk, NY, USA). Age, sex, Evans' index, MMSE scores, FAB scores, and TMTA scores in the pre-operative iNPH group were compared to those in the post-operative group using Fisher's exact tests or Wilcoxon signed-rank tests. Moreover, age, sex, disease duration, Evans' index, MMSE scores, FAB scores, and TMTA scores for the responder group were compared to those for the non-responder group using Fisher's exact tests or Mann–Whitney U tests. Next, the mean ALPS indices in the pre- and post-operative iNPH groups were compared using the Wilcoxon signed-rank tests. For the responder or non-responder subjects, the mean ALPS indices in the pre- and post-operative iNPH groups were compared using the Wilcoxon signed-rank tests. Besides, both pre-operation and post-operation, the mean ALPS indices between the responder and non-responder groups were compared using Mann–Whitney U tests. A value of $p < 0.05$ was considered statistically significant (two-tailed). The effect sizes were calculated using Cohen's d to evaluate the statistical power of the relationships that were determined based on inter-group comparisons. Effect sizes of 0.2, 0.5, and 0.8 were classified as small, medium, and large, respectively (39). *Post-hoc* statistical power was calculated based on the sample and observed effect sizes. In addition, changes in the mean ALPS index, Evans' index, MMSE scores, FAB scores, and TMTA scores between the pre- and post-operative iNPH groups were calculated. Then, the association between the mean ALPS index and Evans' index changes, the mean ALPS index and MMSE score changes, the mean ALPS index and FAB score changes, and the mean ALPS index and TMTA score changes were evaluated using Spearman correlation coefficients. Moreover, for the responder subjects, the association between the mean ALPS index change and Evans' index for the pre-operative iNPH group was evaluated using Spearman correlation coefficients.

RESULTS

Table 1 summarizes patient characteristics and all measurements. Evans' index for the post-operative iNPH group was significantly lower than that of the pre-operative iNPH group. However, age, sex, disease duration, MMSE scores, FAB scores, and TMTA scores of the post-operative iNPH group were not significantly different from those of the pre-operative group.

Table 3 shows the demographic characteristics of the responder and non-responder groups. Mori (40) reported that among the symptoms of iNPH, the symptoms of gait disturbance are most likely to occur, and the rate of improvement by shunt surgery is also high. For this reason, six patients with iNPH (one man and five women, mean age ± SD = 75.17 ± 5.04 years) who exhibited an improvement in at least the symptom of gait dysfunction following LPS surgery were defined as responder subjects. On the other hand, three iNPH (one man and two women, mean age ± SD = 75.33 ± 7.37 years) patients who did not exhibit improvement in any symptoms following LPS surgery were defined as non-responder subjects. Age, sex, Evan's index, MMSE scores, FAB scores, and TMTA scores pre-operation in the responder group were not significantly different from those of the non-responder group.

The mean ALPS index of the post-operation group was significantly higher than that of the pre-operation group ($p = 0.021$, Cohen's d = 1.51, statistical power = 0.85; **Figure 2A**). Additionally, for the responder subjects, the mean ALPS index of the post-operation group was significantly higher than that of the pre-operation group ($p = 0.046$, Cohen's d = 1.71, statistical power = 0.76; **Figure 2B**). On the other hand, in the non-responder subjects, the mean ALPS index of the post-operation group was not significantly different compared to that of the pre-operation group ($p = 0.285$, Cohen's d = 0.99, statistical power = 0.16; **Figure 2C**). Besides, the mean ALPS indices of the responder group were not significantly different compared to those of the non-responder group in both the pre-operation ($p = 0.548$, Cohen's d = 0.99, statistical power = 0.16) and post-operation groups ($p = 0.548$, Cohen's d = 0.99, statistical power = 0.16; **Figure 2D**).

Figure 3 illustrates the correlations of the mean ALPS index change with MMSE score change, FAB score change, TMTA score change, and Evans' index change. The mean ALPS index change was not significantly correlated with MMSE score change ($r =$

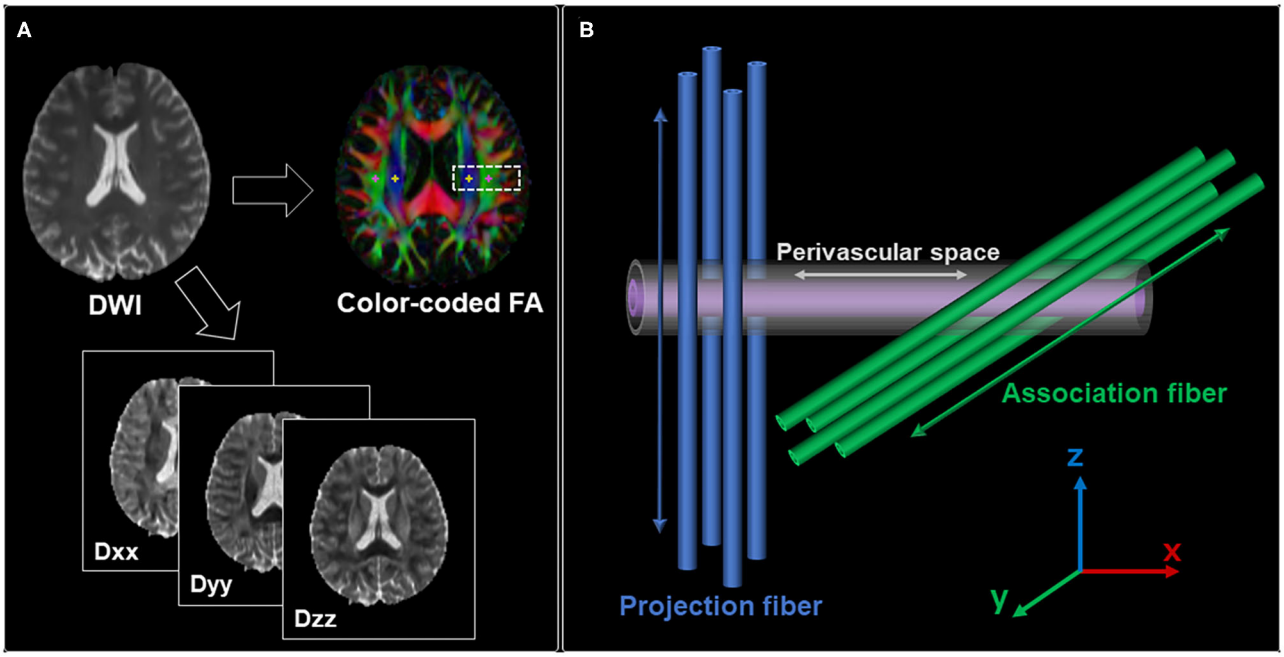

FIGURE 1 | (A) Region of interest (ROI) placement for the calculation of the ALPS index. ROIs with a size of 5 × 5 mm² were manually placed in the projection area (yellow) and association area (pink). **(B)** Schematic indicating the relationship between the direction of the perivascular space and the directions of the fibers. It shows that the direction of the perivascular space is perpendicular to both projection and association fibers.

TABLE 3 | Demographic characteristics of the responder and non-responder groups.

	Responder group	Non-responder group	Responder vs. Non-responder *P*-values
Number	6	3	
Sex (Men / Female)	1/5	1/2	1
Age	75.17 ± 5.04	75.33 ± 7.37	1
Disease duration (year)	1.5 ± 1.64	4.3 ± 2.08	0.095
Evan index (pre-ope)	0.33 ± 0.02	0.35 ± 0.03	0.167
MMSE (pre-ope)	23.33 ± 4.08	25.67 ± 1.15	0.714
FAB (pre-ope)	12.83 ± 3.82	12.67 ± 4.16	0.905
TMTA (pre-ope)	106.83 ± 38.78	100.67 ± 15.18	1
Fazekas scale			
PVH	2.50 ± 0.55	2	0.464
DSWMH	2.50 ± 0.55	2	0.464

MMSE, Mini-Mental Statement Examination; FAB, Frontal Assessment Battery; TMTA, Trail Making Test A; PVH, Periventricular hyperintensity; DSWMH, Deep and subcortical white matter hyperintensity.

−0.218, $p = 0.574$), FAB score change ($r = 0.185$, $p = 0.634$), TMTA score change ($r = 0.250$, $p = 0.516$), and Evans' index change ($r = 0.109$, $p = 0.780$). However, in responder subjects, the mean ALPS index change was significantly correlated with Evans' index in pre-operative iNPH patients ($r = 0.841$, $p = 0.036$).

DISCUSSION

This is the first reported study to have evaluated ALPS index change following LPS surgery in iNPH subjects. Our results demonstrate that the mean ALPS index of post-operative iNPH subjects was significantly higher than that of pre-operative iNPH subjects. This may be indicative of glymphatic function recovery following LPS surgery. In the responder subjects, the mean ALPS index of the post-operative iNPH group was significantly higher than that of the pre-operative iNPH group. On the other hand, in the non-responder subjects, the mean ALPS index of the post-operative iNPH group was not significantly different from that of the pre-operative group. Besides, the mean ALPS indices of the responder group were not significantly different from those of the non-responder group both pre-operation and post-operation. Notably, in the responder subjects, mean ALPS index change was significantly correlated with Evans' index in pre-operative iNPH patients. This result possibly indicates that the mean ALPS index recovered remarkably in progressive iNPH patients in the responder subjects. However, the mean ALPS index change after LPS surgery was not significantly correlated with Evans' index, MMSE score, FAB score, and TMTA score changes.

This study showed that water diffusivity in the direction of the perivascular space was improved following LPS surgery and could indicate the improvement of CSF-ISF dynamics. Several

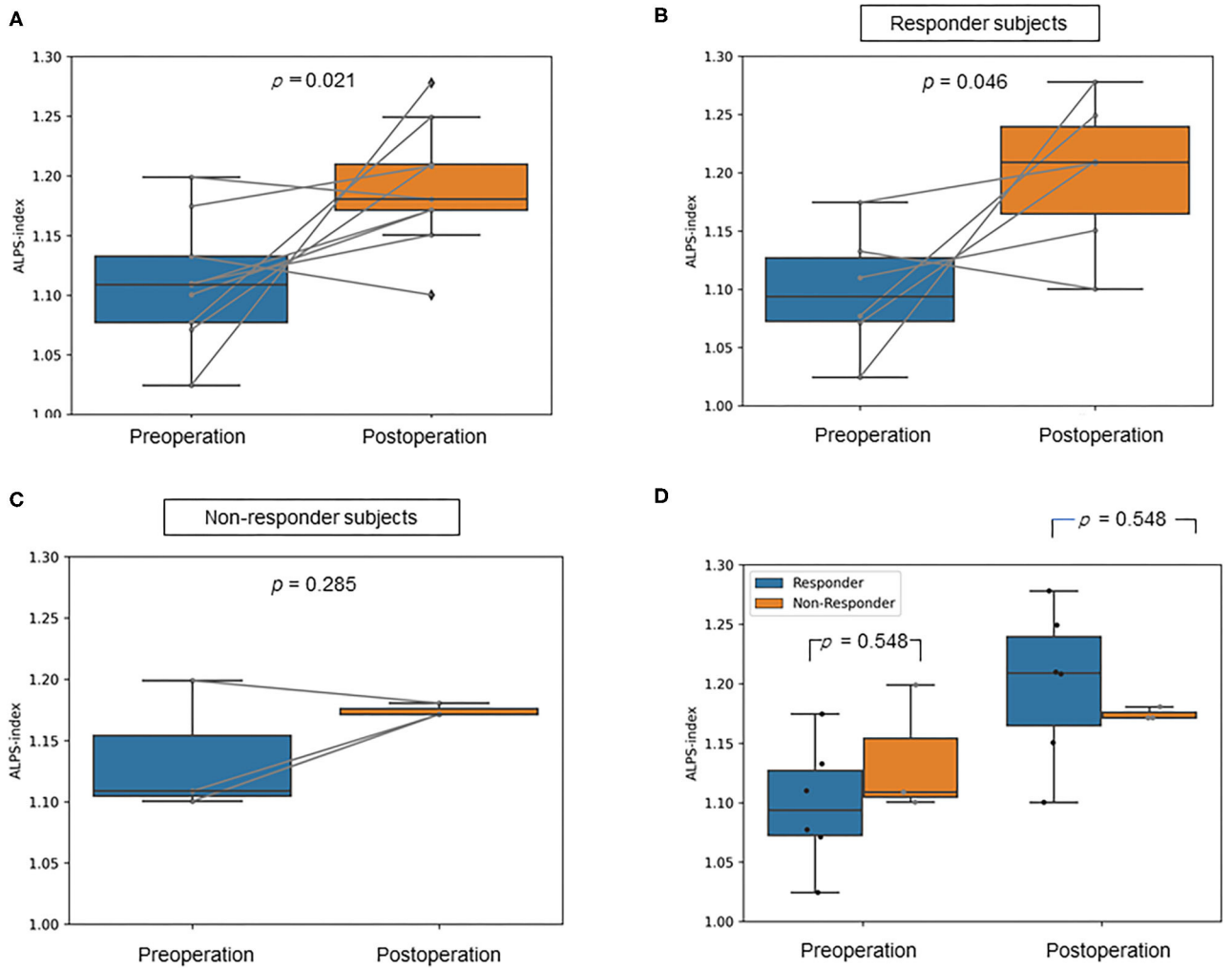

FIGURE 2 | Box plots show **(A)** the difference in the mean analysis along the perivascular space (ALPS) index between the pre-operative and post-operative idiopathic normal pressure hydrocephalus (iNPH) groups, **(B)** the difference in the mean ALPS index between the pre-operative and post-operative iNPH groups in responder subjects, **(C)** the difference in the mean ALPS index between the pre-operative and post-operative iNPH groups in non-responder subjects, **(D)** the difference in the mean ALPS index between the responder and non-responder group in pre- and post-operation.

effects of shunt surgery have been previously established, such as alterations in CSF dynamics (41, 42), which can lead to secondary changes in cerebral blood flow and metabolism (43, 44) and CSF components (45, 46). Nocun et al. (47) reported that cerebral perfusion is promptly recovered after shunt surgery in about 60% of patients with iNPH. Kawamura et al. (46) have reported that CSF amyloid-β oligomers were eliminated by LPS surgery. Thus, the insertion of a shunt could dramatically alter the CSF turnover and hydrodynamic properties of the cranio-spinal system. Assessment of the role of CSF dynamics is particularly important for the treatment of patients with iNPH. Notably, LPS surgery is less invasive, and is increasingly being performed in patients with iNPH. This study provides useful and substantial information regarding improvement in CSF-ISF dynamics following LPS surgery. Moreover, this study supports the use of the ALPS method as a potential neuroimaging marker of the glymphatic system and as a method to evaluate the effect of LPS surgery in iNPH.

In the responder subjects, the mean ALPS index in the post-operative group was significantly higher than that in the pre-operative group. On the other hand, in non-responder subjects, the mean ALPS index in the post-operative group was not significantly different from that in the pre-operative group. The brain parenchyma is stretched and compressed by mechanical pressure from ventricular enlargement in patients with iNPH, resulting in neural fibers stretching and normal brain tissue compression, such as blood vessels. Since LPS surgery releases normal tissue obstruction, perfusion and pulsatility may be improved and affect the ALPS index. Besides, responders improved the gait disturbance after LPS surgery and could

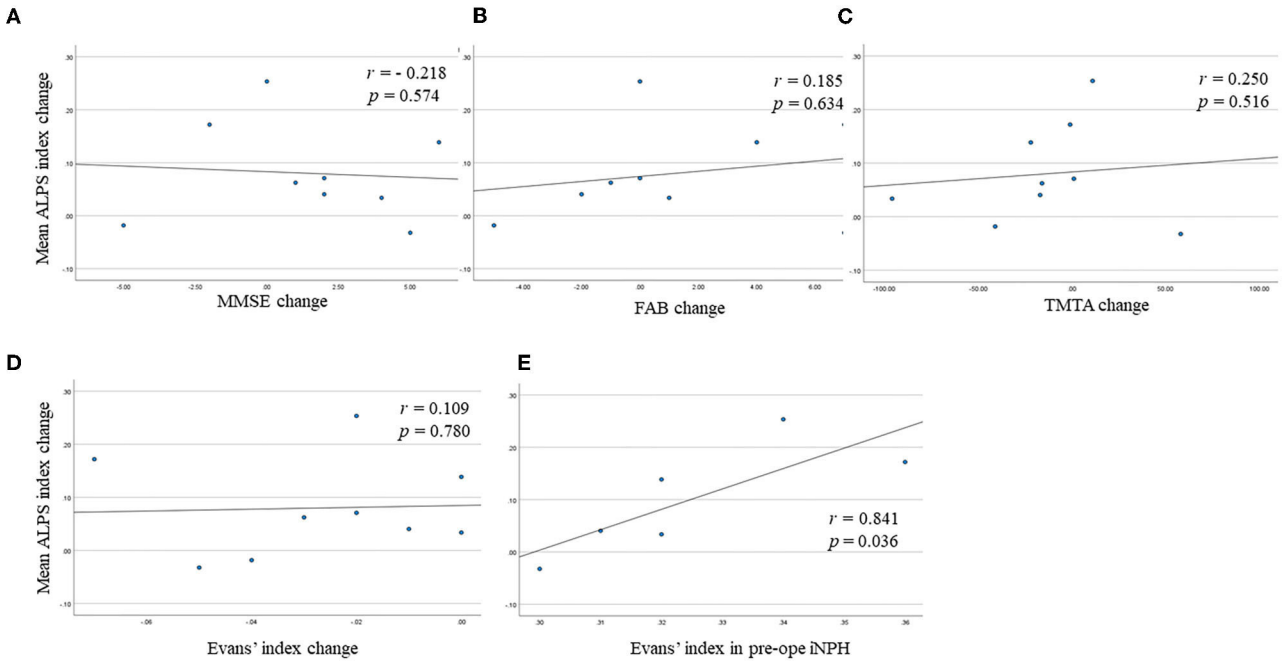

FIGURE 3 | Scatter plots show **(A)** the correlation between the mean analysis along the perivascular space (ALPS) index change and Mini-Mental Statement Examination (MMSE) score change, **(B)** the correlation between the mean ALPS index change and Frontal Assessment Battery (FAB) score change, **(C)** the correlation between the mean ALPS index change and Trail Making Test A (TMTA) score change, **(D)** the correlation between the mean ALPS index change and Evans' index change, **(E)** the correlation between the mean ALPS index change and Evans' index in pre-operative idiopathic normal pressure hydrocephalus (iNPH) group in responder subjects.

increase their physical activity; thereby, cerebral pulsatility and blood perfusion might have changed. Mohammadi et al. (48) reported that cerebral pulsatility was reduced after walking. Then, the change of cerebral pulsatility and blood perfusion could influence the measurement of ALPS index and glymphatic clearance (26, 34).

In this study, two participants had decreased mean ALPS index after LPS surgery. One participant was a responder, and another was a non-responder. MMSE scores in both participants were also decreased after LPS surgery. These iNPH participants could have had Alzheimer's pathology. For that reason, both fluid transport and cognitive impairments did not improve even after LPS surgery. Interstitial amyloid-β accumulation is a pathological feature that correlates with poor shunt responsiveness in patients with iNPH (10). Thus, further study on the relationship between ALPS index and amyloid-β accumulation degree, such as in amyloid PET examination, is expected. Additionally, the mean ALPS index was not significantly different between responders and non-responders after LPS surgery. It could be difficult to expect whether the subject is a responder or a non-responder only based on mean ALPS indices in the pre-operative and post-operative states.

In this study, mean ALPS index change was significantly correlated with Evans' index in pre-operative iNPH patients, particularly, in responders. This finding indicates that water diffusivity along perivascular space change of the brain parenchyma with iNPH, especially in responders, recovered in cases of larger ventricular enlargement (6). The brain parenchyma is stretched and compressed by mechanical pressure from ventricular enlargement in patients with iNPH, resulting in normal brain tissue compression, such as blood vessels. A larger ventricular enlargement may increase normal tissue compression in the brain. LPS surgery releases normal tissue compression, and an improvement of mean ALPS index accompanied by normal tissue recovery may be more pronounced in cases with larger ventricular enlargement.

This study has several limitations. First, only a small number of participants were included in this study. Therefore, it is necessary to increase the number of participants to evaluate the glymphatic function of patients with iNPH. Second, 5-mm slice thickness for DWI acquisition in ALPS index measurement in this study was thicker than in some previous papers (21, 34). In the projection area, nerve fibers run in the inferior-superior direction, and it is considered that slice thickness degree is not affected by the accuracy of placing ROIs onto specific fiber tracts. However, in the association area, nerve fibers run in the anterior-posterior direction; thereby, the ROIs placed on the association fiber may be affected by the partial volume effect of other tracts traveling nearby, such as the corpus callosum and the insular cortex. Finally, the ALPS method is not yet a well-established non-invasive tool to measure glymphatic system in living humans. Hence, further studies are needed to establish the correlation between the ALPS index and the ISF excretion function.

CONCLUSION

This study demonstrates the improved water diffusivity along perivascular space in patients with iNPH post-LPS surgery. This could be indicative of glymphatic function recovery following the LPS surgery.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Juntendo University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JK, KKam, TT, and CAn conceived and designed the analysis, analyzed and interpreted the data, drafted, and revised the manuscript for intellectual content. KT, WU, YS, and MN performed data acquisition, analyzed and interpreted the data, and revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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Shared CSF Biomarker Profile in Idiopathic Normal Pressure Hydrocephalus and Subcortical Small Vessel Disease

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Introduction: In this study, we examine similarities and differences between 52 patients with idiopathic normal pressure hydrocephalus (iNPH) and 17 patients with subcortical small vessel disease (SSVD), in comparison to 28 healthy controls (HCs) by a panel of cerebrospinal fluid (CSF) biomarkers.

Methods: We analyzed soluble amyloid precursor protein alpha (sAPPα) and beta (sAPPβ), Aβ isoforms −38, −40, and −42, neurofilament light protein (NFL), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), matrix metalloproteinases (MMP −1, −2, −3, −9, and −10), and tissue inhibitors of metalloproteinase 1 (TIMP1). Radiological signs of white matter damage were scored using the age-related white matter changes (ARWMC) scale.

Results: All amyloid fragments were reduced in iNPH and SSVD ($p < 0.05$), although more in iNPH than in SSVD in comparison to HC. iNPH and SSVD showed comparable elevations of NFL, MBP, and GFAP ($p < 0.05$). MMPs were similar in all three groups except for MMP-10, which was increased in iNPH and SSVD. Patients with iNPH had larger ventricles and fewer WMCs than patients with SSVD.

Conclusion: The results indicate that patients with iNPH and SSVD share common features of subcortical neuronal degeneration, demyelination, and astroglial response. The reduction in all APP-derived proteins characterizing iNPH patients is also present, indicating that SSVD encompasses similar pathophysiological phenomena as iNPH.

Keywords: biomarkers, cerebrospinal fluid, cerebral small vessel disease, hydrocephalus, normal pressure

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a potentially reversible disorder and one of the very few treatable forms of dementia as shunt surgery improves around 80% of the patients (1, 2). The prevalence may be as high as 0.5–2.9% in people aged 65 or above (3–5). However, only 20–30% of patients are treated (5–8), largely due to underdiagnosis. There are no specific diagnostic markers available, diagnosis is presently based on clinical and radiological assessments in combination with cerebrospinal fluid (CSF) dynamic tests (9). Patients with iNPH exhibit impaired gait, balance and motor performances, reduced bladder control, and a fronto-subcortical cognitive and conative impairment with reduced volition, executive dysfunction, and memory loss (10). MRI studies have revealed that, apart from the hallmark of ventricular enlargement, periventricular and deep white matter hyperintensities (PVH and DWMH, respectively), markers of small vessel disease, are common in iNPH (11). iNPH patients with PVH and DWMH have been shown to respond well to shunting (12), but some studies have found the improvement of patients with signs of cerebrovascular disease (CVD) to be less pronounced than in those without (13, 14).

Patients with subcortical small vessel disease (SSVD), sometimes also referred to as Binswanger's disease, exhibit a fronto-subcortical cognitive impairment similar to iNPH and may show similar patterns of gait, balance, and urinary dysfunction (15). Furthermore, PVH and DWMH are hallmarks of SSVD, and enlargement of the brain ventricular system may be present, at least in later stages of the disease, partly due to brain atrophy. Adding to the complexity, it has been suggested that patients fulfilling the diagnostic criteria for SSVD can improve after shunt surgery (16). Moreover, a negative CSF tap test cannot be used to exclude patients with iNPH from shunt surgery (17, 18). Hence, to distinguish between iNPH and SSVD and to identify patients that might experience symptom relief following shunt surgery constitutes a major challenge.

Several studies have reported on both MRI and CSF biomarkers of possible differential diagnostic value for iNPH and SSVD. However, none of these have proven useful in the clinical setting (11, 19–23). A number of CSF biomarkers have been introduced to assess different aspects of neurodegeneration, for example, in Alzheimer's disease (AD) [for a review see ref. (24)]. Putative CSF biomarkers reflecting brain changes in SSVD have been reviewed by Wallin et al. (25). We have reported that a combination of CSF biomarkers reflecting amyloid metabolism (where in iNPH all APP fragments are reduced), cortical neuronal degeneration, and astrocyte activation could separate iNPH from movement and cognitive disorders (26), such as vascular dementia, with good sensitivity and specificity, and is thought to distinguish the pathophysiology in iNPH from these disorders.

To analyze similarities and differences, the biomarkers chosen in this study were soluble amyloid precursor protein alpha (sAPPα) and beta (sAPPβ), Aβ isoforms −38, −40, and −42 (Aβ38, Aβ40, and Aβ42, reflecting APP metabolism), neurofilament light protein (NFL, reflecting subcortical neural degeneration), glial fibrillary acidic protein (GFAP, reflecting astroglial response), myelin basic protein (MBP, reflecting demyelination), matrix metalloproteinases (MMP −1, −2, −3, −9, and −10, reflecting subcortical tissue remodeling), and tissue inhibitors of metalloproteinase 1 (TIMP1).

The aim of this study was to explore differences and similarities in CSF biomarkers between iNPH and SSVD. As the subcortical picture is overlapping in iNPH and SSVD, we included a biomarker panel reflecting subcortical damage and remodeling, comprising biomarkers reflecting amyloid pathology, subcortical neuronal degeneration, myelin damage, astroglial response, and extracellular matrix remodeling in search for pathophysiological similarities and differences. CSF from healthy controls (HCs) was examined as a reference.

MATERIALS AND METHODS

Subjects

The study included 52 patients diagnosed with iNPH (aged 72; 68–79 (median; IQR) years; 29 men and 23 women), 17 patients diagnosed with SSVD (aged 72; 66–76 years; 5 men and 12 women) and 28 HCs (aged 67; 66–71; 18 men and 10 women).

The patients with iNPH were diagnosed between 2007 and 2012 at the Hydrocephalus Research Unit, Sahlgrenska University Hospital, Gothenburg, Sweden according to international guidelines (9).

The patients with SSVD, recruited between 2001 and 2012, were part of the Gothenburg mild cognitive impairment (MCI) study, comprising middle-aged to young elderly individuals with self-observed or informant-reported cognitive decline assessed by the physician as significant and without an obvious underlying causes, such as brain tumor, subdural hematoma, and major stroke (27). SSVD was diagnosed using the Erkinjuntti criteria (28). More specifically, the patients were required to have white matter changes [WMCs; mild, moderate, or severe according to Fazekas classification (28)] and predominant fronto-subcortical symptoms, such as mental slowness, executive dysfunction, and extrapyramidal motor signs, without pronounced memory loss. If WMCs were only mild, SSVD was diagnosed only if parietotemporal lobe syndromes, i.e., dysphasia, dyspraxia, dysgnosia, and loss of memory, were not marked (in which case mixed dementia, i.e., AD plus SSVD was indicated). Neither patients with mixed AD/SSVD dementia nor those with specific non-vascular neurodegenerative disorders with gait deficits, such as progressive supranuclear palsy and Parkinson's disease, were included in the study.

Healthy controls were primarily recruited through senior citizens organizations, e.g., at information meetings on dementia, and a small proportion were relatives of patients, also as part of the Gothenburg MCI study (27). To be regarded as healthy, the controls should not have experienced or exhibited any cognitive decline or have had diseases known to cause cognitive impairment at the time of inclusion.

CSF Analyses

Lumbar CSF was obtained from the patients with iNPH prior to surgery and from SSVD and HC at the time of medical examination according to a standardized protocol. All

lumbar punctures were performed in the morning to avoid any influence of possible diurnal fluctuations in biomarker levels and with the patient in a recumbent position. CSF samples were drawn at the lumbar vertebrae L3/L4 or L4/L5 interspace; the first portion of CSF was discarded to avoid blood contamination. The CSF was collected in polypropylene tubes and centrifuged at 2,000× g at room temperature for 10 min. The ensuing supernatant was aliquoted in screw-cap polypropylene tubes and stored at −80°C pending biochemical analyses.

The concentrations of the amyloid-beta (Aβ) peptides −38, −40, and −42 and sAPP-α and -β, MMP −1, −2, −3, −9, −10, and TIMP1 were measured using single- or multiplex electrochemiluminescent immunoassays (Meso Scale Discovery, Rockville, MD, USA), following the instructions of the manufacturer with minor modifications. The neurofilament light chain (NFL) ELISA (NF-light®, UmanDiagnostics, Umeå, Sweden) analysis was performed according to a previously established protocol (29), with minor modifications. GFAP concentration was measured using a previously described in-house ELISA method (30). The analysis of MBP was performed with an ELISA (Active® MBP, Diagnostic Systems Laboratories Inc., Webster, TX, USA), according to the instructions of the manufacturer. Intra- and inter-assay coefficients of variation were below 15% for all assays. All CSF analyses were performed batchwise in one round of experiments by laboratory technicians who were blinded to the clinical data.

Radiological Evaluation

To stage subcortical damage by extent and distribution of WMCs, scans from iNPH patients and SSVD patients were evaluated by the age-related white matter changes (ARWMC) scale, which can be used for both CT and MRI images (28). WMCs were defined as bright lesions ≥5mm on transverse relaxation (T2), proton density (PD), or fluid-attenuated inversion recovery (FLAIR) sequences on MRI or as hypodense areas of ≥5mm on CT. Ratings were made in five different brain regions: frontal, parieto-occipital, temporal, basal ganglia, and infratentorial. In each region, the left and right hemispheres were rated separately, giving a total of ten regions. In each region, the ARWMC was rated from 0 to 3 (0 = no lesions; 1 = focal lesions; 2 = beginning confluence of lesions, and 3 = diffuse involvement of the entire region). Evans' index (EI) was determined on transaxial images as the ratio between the maximum diameter of the frontal horns and the maximum inner skull diameter and used as a measure of ventricular enlargement. All patients with iNPH and SSVD were rated by the same observer (AJ). MRI or CT images were lacking for one iNPH and three patients with SSVD.

Statistics

Non-parametric statistical methods were used in all analyses due to non-symmetrical distributions and/or substantial differences in variances between groups (generally larger among patients than among controls). The Kruskal-Wallis one-way analysis of ranks (KW) was used to compare all three groups at once. The Wilcoxon-Mann-Whitney *U*-test was used for *post-hoc* analysis and for comparisons between pairs of groups. As the number of participants was few and the authors wished to avoid type 2 errors, no correction for the multiple comparisons was made. Alpha was set at $p < 0.05$. All analyses were performed in SPSS version 25.0 for Windows (IBM Corp, Armonk, NY, USA. Released 2014).

TABLE 1 | Age, sex, and mini-mental state examination (MMSE) in idiopathic normal pressure hydrocephalus (iNPH), subcortical small vessel disease (SSVD), and controls.

	iNPH *n* = 52	SSVD *n* = 17	Controls *n* = 28
Age, median (IQR)	72 (68–79)[#]	72 (66–76)	67 (66–71)
Female, *n* (%)	23 (44 %)	12 (71 %)	10 (36 %)
MMSE, median (IQR)	24 (22–27) [###]	27 (25–28)[&&&]	30 (29–30)

Age in years and mini-mental state examination (MMSE) are presented as median and interquartile range (IQR). Significance testing was made by Wilcoxon-Mann-Whitney U-test and shown as [#]$p < 0.05$, [###]$p < 0.001$ (iNPH vs. controls), [&&&]$p < 0.001$ (SSVD vs. controls).

Ethics

Participants (patients and/or their close relatives and HC) gave their written informed consent for participating in the study and for future results being published, in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the Swedish Ethical Review Authority in Gothenburg, Sweden.

RESULTS

There was no difference in age or MMSE scores between patients with iNPH and SSVD, but the SSVD group had a higher percentage of women. Compared to controls, patients with iNPH were older, there were more women in the SSVD group and both groups had lower MMSE scores (**Table 1**).

CSF Biomarkers

All APP-derived proteins were lower in iNPH than in SSVD and controls and lower in SSVD patients than in controls. Markers of WMCs, subcortical neuronal degeneration (NFL), demyelination (MBP), and astroglial response (GFAP), were increased in iNPH and in SSVD compared to controls. Of the markers of extracellular matrix remodeling, MMP-10 was increased in iNPH and SSVD in comparison to controls **Table 2**, **Figures 1**, **2**).

Imaging Measures

On the group level, both iNPH and SSVD patients exhibited dilated ventricles, as indicated by an EI > 0.3, although patients with iNPH had more pronounced ventricular enlargement. Of the 14 patients with SSVD who were included in the radiological evaluation, 9 patients had an EI of 0.3 or above (64.3%). ARWMC scores were higher in SSVD than in patients with iNPH (**Table 3**).

TABLE 2 | Cerebrospinal fluid (CSF) biomarker concentrations in iNPH, SSVD, and healthy controls.

	iNPH *n* = 52	SSVD *n* = 17	Controls *n* =28
sAPPα	384 (303–593)$^{\#\#\#,\S\S}$	683 (475–847)$^{\&}$	850 (694–1207)
sAPPβ	227 (170–325)$^{\#\#\#,\S\S}$	417 (232–458)$^{\&\&\&}$	516 (446–664)
Aβ38	1,333 (823–1,928)$^{\#\#\#,\S\S}$	2,196 (1,749–2,505)$^{\&\&}$	2,855 (2,266–3,261)
Aβ40	3,541 (2,206–5,648)$^{\#\#\#,\S\S}$	5,428 (4,678–6,838)$^{\&}$	7,009 (5,570–7,814)
Aβ42	361 (232–496)$^{\#\#\#}$	474 (320–558)$^{\&\&}$	693 (510–931)
NFL	1,592 (1,012–2,519)$^{\#\#\#}$	1,638 (1,150–3,149)$^{\&\&\&}$	889 (694–1,072)
GFAP	876 (659–1,146)$^{\#\#\#}$	820 (472–976)$^{\&}$	559 (381–718)
MBP	1,997 (1,407–2,503)$^{\#\#\#}$	1,691 (1,461–2,351)$^{\&\&}$	1,446 (1,228–1,632)
MMP−1	26 (16–47)	34 (20–54)	24 (19–33)
MMP-2	21,190 (18,965–23,600)	22,244 (21,146–25,104)	21,317 (18,423–23,549)
MMP-3	221 (162–322)	250 (186–372)	238 (201–344)
MMP-9	160 (114–205)	163 (107–193)	129 (89–160)
MMP-10	49 (38–67)$^{\#}$	63 (40–76)$^{\&}$	42 (31–49)
TIMP-1	99,329 (87,306–113,161)	105,464 (87,590–142,345)	86,094 (78,696–107,987)

CSF biomarker concentrations in pg/ml shown as medians and interquartile ranges (IQR). Wilcoxon-Mann-Whitney U-test. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ *(iNPH vs. controls);* $^{\S\S}p < 0.01$, *(iNPH vs. SSVD);* $^{\&}p < 0.05$, $^{\&\&}p < 0.01$, $^{\&\&\&}p < 0.001$ *(SSVD vs. controls). iNPH, idiopathic normal pressure hydrocephalus; SSVD, subcortical small vessel disease. sAPP, soluble amyloid precursor protein; Aβ, amyloid-beta; NFL, neurofilament light chain; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.*

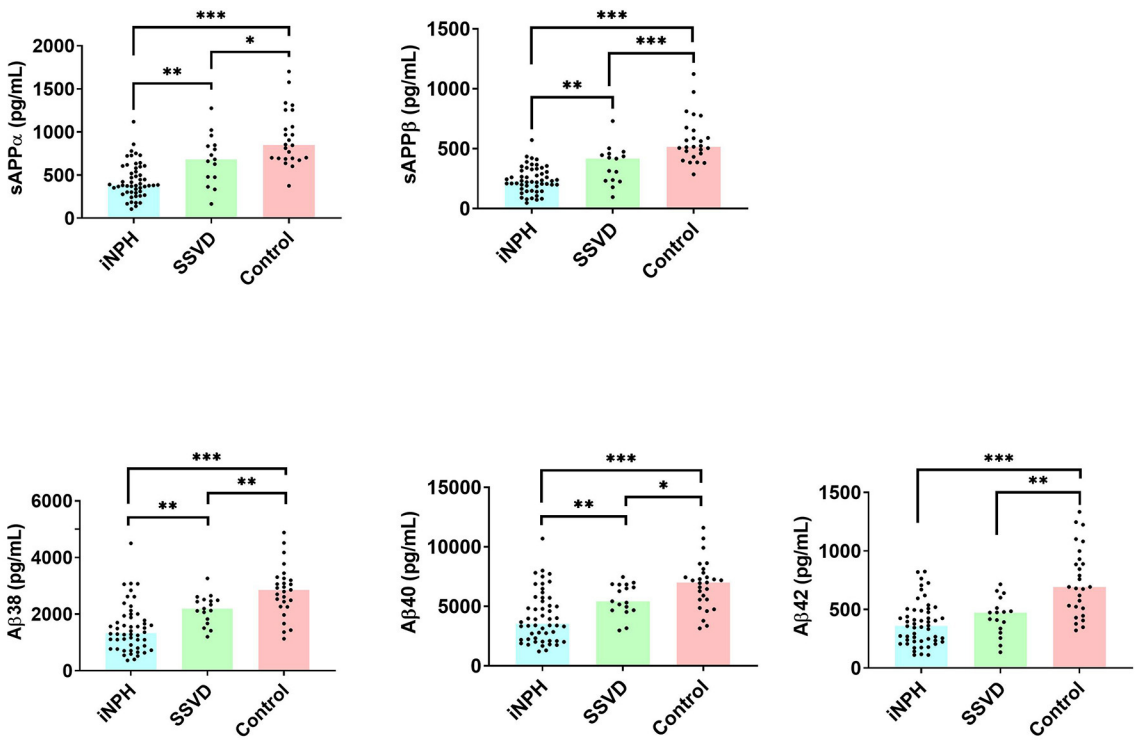

FIGURE 1 | APP-derived cerebrospinal fluid (CSF) proteins in 52 patients with idiopathic normal pressure hydrocephalus (iNPH), 17 patients with subcortical small vessel disease (SSVD), and 28 controls. Concentration is plotted as individual values. Bars indicate median values. Only significant values are marked. iNPH, idiopathic normal pressure hydrocephalus; SSVD, subcortical small vessel disease; sAPP, soluble amyloid precursor protein; Aβ, amyloid-beta. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

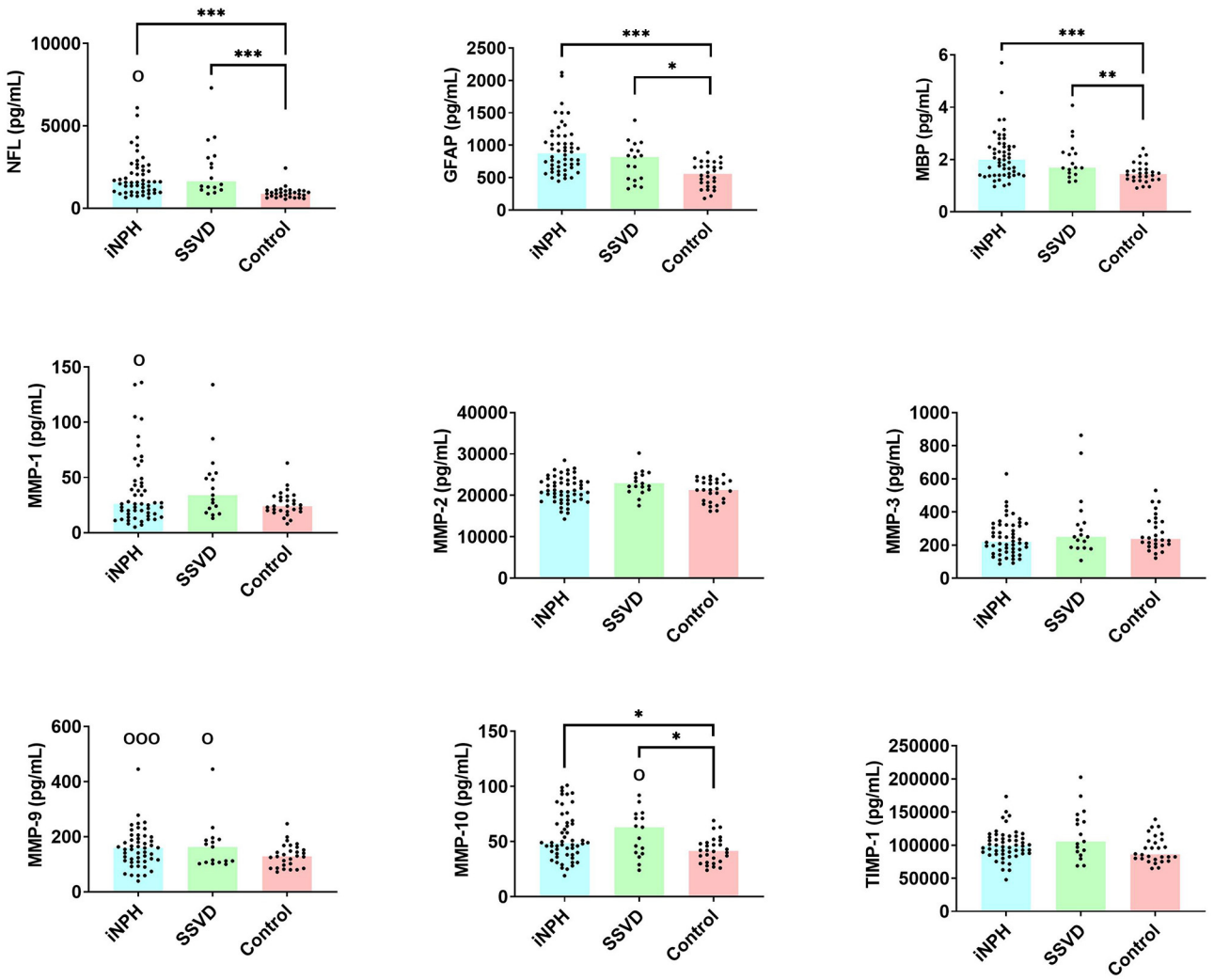

FIGURE 2 | Cerebrospinal fluid (CSF) biomarkers of white matter damage, astroglial response, and extracellular matrix remodeling in 52 patients with iNPH, 17 with SSVD, and 28 controls. Concentration is plotted as individual values. Bars indicate median values. Only significant values are marked. iNPH, idiopathic normal pressure hydrocephalus; SSVD, subcortical small vessel disease; NFL, Neurofilament light protein; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; MMP, matrix metalloproteinases; TIMP, tissue inhibitors of metalloproteinases. O indicates values outside the axis.

DISCUSSION

In this study, we show that all APP-derived proteins were lower in both iNPH and SSVD compared to controls, patients with iNPH exhibited a more pronounced reduction than patients with SSVD, while biomarkers related to white matter damage and astroglial response were increased in both disorders. Further, radiological WMCs were more pronounced in SSVD than in iNPH, whereas patients with INPH had more pronounced ventricular enlargement.

APP-Derived Biomarkers

A reduction of all measured APP-derived proteins in CSF has been shown repeatedly in iNPH and thus, this study corroborates earlier results (31–35). It has also been shown in iNPH that CSF concentrations of amyloid precursor protein-like protein (APLP) and its derivatives, processed by the same enzymatic machinery, are not affected in the same manner as APP-derived proteins, which points to a specific disturbance of APP-metabolism in iNPH, possibly due to decreased periventricular metabolism (36). An additional proposed mechanism is a reduced clearance of these proteins from the interstitial fluid to the CSF (37). The pattern of reduction of all APP proteins in SSVD reported here is similar to that in iNPH, albeit deviating less from the concentrations in CSF of controls. Lower Aβ42 in iNPH than in SSVD has been reported previously (38).

Biomarkers of Neuronal Degeneration, Myelin Damage, and Astroglial Response

Neurofilament protein is the dominant protein of the axonal skeleton and as a CSF biomarker, it reflects neuronal death

TABLE 3 | Age-related white matter changes (ARWMC) scores and Evans' Index in patients with iNPH and SSVD.

Brain region	iNPH $n = 51$	SSVD $n = 14$
Frontal		
R	1 (1–2)	2 (2–3)
L	1 (1–2)	2 (2–3)
Parietal-occipital		
R	1 (1–2)	2.5 (1–3)
L	1 (1–2)	2.5 (1–3)
Temporal		
R	0 (0–1)	0 0–0)
L	0 (0–1)	0 (0–0.25)
Basal ganglia		
R	0 (0–1)	1 (0–2.25)
L	0 (0–0)	1 (0–2.25)
Infratentorial		
R	0 (0–1)	1 (0–2)
L	0 (0–1)	0.5 (0–2)
Total	**7 (4–11)**	**12 (8–22)****
Evans' Index	0.4 (0.37–0.44)	0.31 (0.27–0.38)***

*ARWMC scores are presented for each sub-region, right (R) and left (L) hemisphere separately, and as total scores. Values are given as median and interquartile ranges. **$p < 0.01$, ***$p < 0.001$.*

and axonal degeneration (39, 40). In iNPH and SSVD, multiple studies have shown an increase of NFL in CSF, corroborating the results on NFL reported here (31, 34, 38, 41), the similarly increased NFL levels implying a comparable degree or mechanism of axonal degeneration in these disorders.

Increment of MBP, a constituent of the myelin sheath and marker of damage to oligodendroglia, reported here for iNPH and SSVD, is in line with the periventricular and deep white matter damage and has previously been shown to be increment in both iNPH (31) and SSVD (42). We also show that GFAP, indicative of reactive astrocytes and astroglial response, is increased in iNPH and SSVD patients alike, which has been reported earlier (19, 43, 44). Again, levels are similar, indicating similar degrees of astroglial response in these disorders. These similarities in white matter degeneration, hinted at by the NFL, MBP, and GFAP concentrations, are contradicted by the difference in radiological WMCs as indicated by the higher ARWMC score in patients with SSVD. These findings are in line with the findings of Abu-Rumeileh et al., who found no correlation between increased levels of CSF and ARWMC rating (34).

Matrix Metalloproteinases

To our knowledge, CSF levels of MMPs or TIMPs have not earlier been reported in iNPH in relation to HC or SSVD. Other studies have shown that ECM proteins, MMPs, and their substrates increase iNPH following shunt surgery (45). MMPs are believed to be activated by ischemic conditions and to play a major role in neuro-inflammation by, e.g., disruption of the blood brain barrier (BBB) and degradation of substances in the extracellular matrix (ECM), promoting ECM turnover (46). Inhibition of the MMPs is primarily regulated by TIMPs that are also thought to have independent biological actions. Here, increased CSF levels of MMP-9 and TIMP1 (at trend level), together with increased NFL and MBP, are in agreement with earlier suggestions of what characterizes a subcortical CSF profile and with earlier findings in patients with SSVD (42). This again indicates corresponding pathophysiological processes in the two disorders, albeit more pronounced in iNPH. Although interesting from a pathophysiological standpoint, this study does not support the use of these MMPs for diagnosing iNPH.

Patients with SSVD had more abundant WMCs on MRI or CT than patients with iNPH, why we expected the CSF biomarkers reflecting white matter damage, NFL and MBP, to be higher in SSVD. This, however, was not the case. The reason for this discrepancy between the biochemical similarity and radiological differences could be a more active degeneration of white matter in iNPH and thus augmented leakage to the CSF, despite less radiological evidence at standard sequences in CT or MRI. Alternatively, the pathophysiology in iNPH is more dynamic, with potentially reversible functional changes, whereas SSVD is characterized by more static and irreversible changes of the white matter, which the CSF biomarker pattern might suggest. Another radiological approach, e.g., perfusion- or diffusion-weighted MR imaging, could probably give an even better estimate of qualitative differences in the PVH and DWMH.

A possible interpretation of our results is that SSVD is affected by the same pathophysiological process as iNPH although to a lesser degree. In earlier reports, we have proposed that SSVD with ventricular enlargement may represent one form of hydrocephalus (11) and that iNPH pathology may induce periventricular vascular changes (47) or, alternatively, that severe vascular pathology may cause a CSF dynamic disturbance in itself (16). We speculate that the ventricular dilatation in SSVD, with 64% showing EI > 0.3, could be both related to CVD-related atrophy and secondary to a CSF dynamic disturbance similar to that seen in iNPH.

Idiopathic normal pressure hydrocephalus is characterized by disturbed CSF dynamics. CSF is absorbed through the periventricular capillaries and perfusion is reduced in the periventricular tissue (48, 49) which in turn leads to oxygen deprivation of the vulnerable glial cells. In SSVD, the WMCs are regarded as secondary to an arteriolar dysfunction and the reduced ability of the vessels to supply the highly perfused subcortical tissue (50). Vascular risk factors, such as hypertension, diabetes, and hyperlipidemia, are important in both iNPH and SSVD (15, 51, 52) and are likely the causes of arteriolar dysregulation. The deep white matter is affected in both diseases as indicated by the ARWMC rating reported here, but the ventricles are, at a group level, larger in iNPH. The ventriculomegaly in iNPH is considered secondary to the CSF dynamics whereas the enlargement in SSVD is supposedly due to atrophy, with loss of white matter, but, as discussed earlier, a certain element of disturbed CSF flow could be expected in SSVD. Our results further enhance the similar affection of subcortical structures in the two disorders.

The overlap of clinical, radiological, and biochemical characteristics is considerable and stresses the delicate questions facing the diagnosing clinician. It has been shown that patients with iNPH and extensive WMC can respond to shunt treatment (16, 53). A double-blind placebo-controlled study showed that iNPH patients with the heavy burden of vascular pathology and a negative CSF tap test can benefit from shunt surgery (16). It has even been proposed that the iNPH state may induce periventricular vascular changes or, alternatively, that severe vascular pathology may cause a CSF dynamic disturbance (11, 47). Our results indicate that the overlap is also evident in CSF biomarkers reflecting subcortical damage. As such, these biomarkers do not seem to hold any clear differential diagnostic value.

The similarities point to the importance of considering a CSF dynamic disturbance also in patients with SSVD and enlarged ventricles. Therefore, the next step should be to further examine which patients with SSVD might be diagnosed with iNPH and considered eligible for shunt surgery. Further, in future studies, it would be of interest to prospectively study the development of iNPH and SSVD to gain an understanding of the progression of pathophysiological events in iNPH and SSVD, and how these events are reflected in the biomarker changes.

There are some limitations that need to be addressed. We have tried to select as clear-cut patient groups as possible, diagnosing patients at specialized clinics for iNPH, and SSVD using up-to-date diagnostic criteria. The diagnoses are, however, clinical and without post-mortem verification. Given the similarities of these disorders and potential overlap between diagnostic criteria, we cannot rule out the possibility that patients with SSVD with enlarged ventricles could have been diagnosed as iNPH or vice versa. Moreover, as patients with abnormal Aβ42/Aβ40 ratio were not sought for and excluded, the inclusion of some cases of comorbid iNPH or SSVD and preclinical AD cannot be fully ruled out. The patients included reflect the routine clinical setting and we believe that the results reported here are representative and mirror true pathophysiological characteristics of iNPH and SSVD. One limitation is the rather small group sizes, especially the SSVD group, and HC, which may have caused more subtle differences in biomarker concentrations to be undetected due to low statistical power. Studies comparing larger groups are therefore warranted.

Patients with iNPH and SSVD have parts of the cognitive profile in common. MMSE was used to grade the severity of cognitive decline but is a rather crude tool for cognitive staging, and therefore, might underestimate differences between the groups. The radiological rating of WMC was done using the ARWMC scale because some patients had undergone MRI and some CT. A weakness of this scale is that it does not differ between periventricular and deep white matter changes.

CONCLUSION

By examining CSF biomarkers in patients with iNPH and SSVD and in HCs, we show that there are some similarities in the CSF biomarker pattern of iNPH and SSVD and that this pattern is different from that of HC. Patients with iNPH exhibit greater deviations from HC regarding APP-derived proteins than patients with SSVD, but these changes, along with increased markers of white matter damage and astroglial response, are also evident in patients with SSVD. Radiologically, patients with SSVD display more extensive WMCs. We argue that the underlying pathophysiology in iNPH and SSVD might share common features. The presumable overlaps and divergences in pathology deserve further investigation; expanding the knowledge of how vascular small vessel disease and CSF dynamic disturbances are interrelated might render idiopathic NPH less idiopathic.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Swedish Ethical Review Authority in Gothenburg, Sweden. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AJ participated in the design of the study, coordinated the study, statistical analysis, the interpretation of data, and drafted the manuscript for intellectual content. MB, KB, and HZ participated in the design of the study, laboratory analyses, interpretation of data, and revised the manuscript for intellectual content. PH and PK participated in the interpretation of data and drafted the manuscript for intellectual content. CW and MT participated in the design of the study, coordination of the study, interpretation of data, and drafted the manuscript for intellectual content. AW participated in the design of the study, interpretation of data, and drafted the manuscript for intellectual content. All authors read and approved the article for submission.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Evaluation of the Effectiveness of the Tap Test by Combining the Use of Functional Gait Assessment and Global Rating of Change

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Background: Although the tap test for patients with suspected idiopathic normal pressure hydrocephalus (iNPH) is still often performed as part of the preoperative evaluation, it is true that some studies have reported the limitations of the tap test, claiming that it does not provide the additional information for appropriate patient selection for surgery. We aimed to determine whether a better method of pre- and post-tap test assessment could lead to appropriate patient selection for shunting.

Methods: We performed the tap test as part of the preoperative evaluation in all 40 patients who underwent lumboperitoneal shunt surgery for iNPH from April 2021 to September 2021. We retrospectively analyzed the patient data. We examined whether a comprehensive evaluation of the effect of the tap test using the Functional Gait Assessment (FGA) and Global Rating of Change (GRC) scales would identify a wider range of patients who would benefit from shunt surgery than the 3-m Timed Up and Go test (TUG) alone.

Results: Assuming a prevalence of 1% for iNPH, the TUG had a sensitivity of 0.23, specificity of 0.71, positive likelihood ratio of 0.79, and negative likelihood ratio of 1.09. When improvement in either the FGA or the GRC was used as a criterion for the validity of the tap test, the sensitivity was 0.88, specificity was 0.17, positive likelihood ratio was 1.06, and negative likelihood ratio was 0.71.

Conclusion: Improvement in either the FGA or the GRC is a more sensitive criterion for the effectiveness of the tap test for the gait aspect than the TUG. Since the negative likelihood ratio is lower than that for the TUG alone, it is more appropriate to exclude patients with neither FGA nor GRC improvement from surgical indications than to exclude surgical indications based on a negative TUG.

Keywords: idiopathic normal pressure hydrocephalus, functional gait assessment, global rating of change scale, Timed Up and Go test, sensitivity and specificity

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a syndrome that presents as gait disturbance, incontinence, and cognitive impairment in patients with ventricle dilatation under normal cerebrospinal fluid (CSF) pressure. The causes of iNPH are unknown, and the prevalence of iNPH in Japanese residents over 65 years old is ∼1.1% (1). iNPH is recognized as a treatable disease because it can be improved by shunt surgery (efficacy rate: 60–70%) (2, 3). In addition, previous reports have shown that shunt surgery for iNPH is cost-effective (4–6). To maximize the therapeutic effect of shunting for iNPH, appropriate patient selection is important.

In daily practice, patients with symptoms characteristic of iNPH, such as gait disturbance, and imaging findings characteristic of iNPH, such as Evans index >0.3 and disproportionately enlarged subarachnoid space hydrocephalus (DESH), are considered candidates for shunt surgery.

It is true that some studies have reported the limitations of the tap test, claiming that it does not provide the additional information needed to distinguish between patients who respond to shunting and those who do not (7, 8). In the Japanese Guidelines for the Management of Idiopathic Normal Pressure Hydrocephalus (3rd edition), the tap test is not always necessary anymore if there are typical imaging findings such as DESH findings. In spite of this, the tap test remains a standard preoperative evaluation method in shunt surgery. This may be because the tap test mimics shunting surgery, and confirms that symptoms will improve after the CSF is drained (1, 2, 6). Therefore, it is important to develop a method of evaluation before and after the tap test that can lead to appropriate patient selection for shunting surgery.

The 3-m Timed Up and Go test (TUG) (9) is often used to determine the effect of the tap test on the gait aspect. A previous report showed that an improvement of 5 s is a useful threshold of the TUG time at the tap test for improvement after shunt surgery, rather than the percent improvement in TUG time. However, only 37% of patients had a TUG time improvement of 5 s or more after the tap test. In addition, few patients with minor gait disturbance improved more than 5 s (10). Therefore, the TUG has the disadvantage of low sensitivity, especially in evaluating mild gait disturbance (10, 11). Several reports have attempted to analyze gait movement after the tap test in order to detect more minor changes in gait disturbance (11–17).

In this study, we report that a comprehensive evaluation of the effect of the tap test using the Functional Gait Assessment (FGA) and Global Rating of Change (GRC) scales (18, 19) can lead to more appropriate patient selection for shunting than the evaluation of the effects of TUG alone.

MATERIALS AND METHODS

Eligible Patients

Forty patients were treated with lumboperitoneal (LP) shunt from April 2021 to September 2021 at Osaka Medical and Pharmaceutical University Hospital. Based on the Japanese iNPH guideline (1, 6), all patients underwent the tap test which involved 30 mL removal of CSF via a lumbar tap for preoperative evaluation as possible iNPH patients. All 40 patients were included in this study. This study was reviewed and approved by the ethics committee of Osaka Medical and Pharmaceutical University.

TUG

The TUG measures, in seconds, the time taken by an individual to stand up from a standard armchair, walk a distance of 3 m, turn, walk back to the chair, and sit down again (9). TUG values after the tap test that were at least 10% less than those before the tap test were considered tap test positive. Since it has been reported that the risk of falling is higher if the TUG time is more than 13.5 s (20), patients with TUG scores <13.5 s before the tap test were classified into the "mild gait disturbance group," and patients with TUG scores of 13.5 s or more before the tap test were classified into the "severe gait disturbance group." In this study, the TUG was conducted as a basic evaluation method before and after the tap test to determine the effect of the tap test on the gait aspect. The TUG after the tap test was performed from immediately after the tap test until 2 weeks after the tap test. If the tap test was performed as an inpatient investigation, the TUG assessment after the tap test was mainly performed 1 or 3 days after the tap test. If the tap test was performed as an outpatient investigation, the TUG after the tap test was performed immediately after the tap test and at the next outpatient visit up to 2 weeks later. If TUG was evaluated multiple times after the tap test, the best one was used as the result of TUG after the tap test for statistical analysis. The TUG was assessed by the rehabilitation staff or the neurosurgeon.

Functional Gait Assessment (FGA)

The Functional Gait Assessment (FGA) is a 10-item gait assessment. The FGA consists of 10 tasks, including gait level surface, change in gait speed, gait with horizontal head turns, gait with vertical head turns, gait and pivot turn, step over obstacle, gait with a narrow base of support, gait with eyes closed, ambulating backwards, and steps, and is evaluated with 0 to 3 points for each task, totaling 30 points (21). The FGA was performed as an inpatient investigation and assessed by the rehabilitation staff before and 1 or 3 days after the tap test.

Global Rating of Change (GRC)

Following the tap test, patients were asked to indicate whether they thought there was a change in their gait using a Global Rating of Change (GRC) scale. This is a visual scale with ratings ranging from −5 to +5 whereby −5 is labeled very much worse, 0 is labeled no change, and +5 is labeled complete improvement. Patients were instructed that complete improvement means their symptoms had resolved while very much worse meant that their symptoms had become unmanageably worse (19). If the tap test was performed as an inpatient investigation, The GRC was evaluated 1 or 3 days after the tap test. If the tap test was performed as an outpatient examination, GRC assessment was performed on consecutive days after the tap test, and the mean value was calculated at the next outpatient visit to determine the efficacy. In cases where patients were unable to evaluate GRC

by themselves due to cognitive problems, GRC was evaluated by their families or facility staff who were caring for them.

INPH Grading Scale (GS)

The iNPH grading scale (GS) examines three aspects: gait disturbance, dementia, and urinary incontinence. Gait disturbance is defined as 0, normal; 1, unstable but independent gait; 2, walking with one cane; 3, walking with two canes or a walker frame; and 4, walking not possible. Dementia is defined as 0, within the normal range; 1, no apparent dementia but apathetic; 2, socially dependent but independent at home; 3, partially dependent at home; and 4, totally dependent. Urinary incontinence is defined as 0, absent; 1, absent but with pollakiuria or urinary urgency; 2, present sometimes only at night; 3, present sometimes even during the day; and 4, frequent. The grades of gait disturbance, dementia, and urinary incontinence were summated to obtain the total grade, which ranged from 0 to 12 (6). Patients were evaluated by iNPHGS before shunting and at 1, 3, and 6 months after shunting. The iNPHGS was assessed by the neurosurgeon together with the patient's interview during the consultation and the results of the TUG for the gait aspect and the MMSE for the cognitive aspect, if available.

Measurement Parameters

We retrospectively obtained the following measurement parameters: age, sex, iNPHGS, TUG, FGA, GRC, MMSE, medical history and surgical procedure. The improvement ratio of the TUG before and after the tap test [= 1 - (TUG after tap test/TUG before tap test)], the reduction time in the TUG before and after the tap test (= TUG time before tap test—TUG time after the tap test), and the improvement score of the FGA before and after the tap test (FGA after tap test—FGA before tap test) were measured.

LP Shunt Surgery

Patients with a positive tap test who showed some improvement in any of the three symptoms of gait, urinary incontinence, and cognitive function after the tap test were determined to be eligible for LP shunt. In addition, patients with a negative tap test but DESH findings were identified as having a high probability of iNPH and were considered eligible for LP shunt.

Statistical Analysis

Data are presented as mean (standard deviation: SD). The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of each assessment method as well as the combination of multiple assessment methods were examined with a prevalence of iNPH as 1% (1). Spearman correlation was utilized to calculate the relationships among the improvement ratio of the TUG, the improvement score of the FGA, and the GRC score. Data analyses were performed using JMP 10 or IBM SPSS ver28.

RESULTS

Overall Results

The 40 patients consisted of 21 males and 19 females. The mean age at surgery was 78.8 years (SD 5.2). The most common background of patients was underlying hypertension. Some patients were on medical therapy for Alzheimer's disease or dementia with Lewy bodies (DLB), and 3 patients were transitioned from asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM) to iNPH (**Table 1**).

Due to the prevalence of COVID-19, the tap test could not be performed as an inpatient investigation in all patients, which is why homogeneous preoperative evaluation could not be performed. However, despite the differences between inpatient and outpatient investigations, all patients were evaluated for gait disturbance by TUG, although there were variations in the timing of evaluation after the tap test. As a result, FGA was performed in 24 patients and GRC in 28 patients. The effectiveness of the tap test was determined on the basis of the TUG and also by taking into account the FGA and GRC data collected for some patients.

As for the FGA score, 20 patients (83%) showed an improvement of 1 or more after the tap test. As for the GRC, 20 patients (71%) reported an improvement in gait disturbance after the tap test.

Thirty-seven patients had a positive tap test and exhibited some improvement in gait, urinary, or cognitive function symptoms, and three patients had a negative tap test but disproportionately enlarged subarachnoid space hydrocephalus on magnetic resonance imaging. These 40 patients were treated with LP shunt as probable iNPH patients. Subsequently, 32 patients (80%) had improvement in the iNPHGS after shunting and were diagnosed with definite iNPH.

The forty patients in this study were divided into the severe gait disturbance group (19 patients; 47.5%) and the mild gait disturbance group (21 patients; 52.5%), in which the TUG before the tap test was 13.5 s or more and <13.5 s, respectively. Of these 40 patients, only 10 (25%) showed an improvement of 10% or more in the TUG. Only one of these 10 patients (10%) was in the mild gait disorder group. Although three of the 40 patients (8%) had an improvement of 5 s or more in the TUG, none of them were in the mild gait disorder group. Although cutoff values such as an improvement ratio of the TUG by more than 10% or a reduction in TUG time by more than 5 s are often used to judge the effect of the tap test, these cutoff values were found to be less sensitive, especially in the mild gait disturbance group.

TUG vs. FGA

In addition to the TUG, 24 patients were also evaluated by FGA before and after the tap test to determine the effect of the tap test on the gait aspect. Based on the TUG before the tap test, 10 patients (42%) were included in the severe gait disturbance group and 14 patients (58%) were included in the mild gait disturbance group. Four patients (17%) showed a more than 10% improvement in the TUG, and all of them were in the severe gait disorder group. In addition, one patient (4%) showed an improvement of more than 5 s in the TUG, and this patient was in the severe gait disturbance group. The improvement ratio of

TABLE 1 | Patient characteristics ($n = 40$).

Age	78.8 (SD 5.2)	
Sex	Male, Female (19, 21)	
Hypertension (*n*, %)	19, 47.5	
Hyperlipidemia (*n*, %)	14, 30	
Diabetes mellitus (*n*, %)	5, 12.5	
Dementia with Lewy bodies (*n*, %)	1, 2.5	
Alzheimer's disease (*n*, %)	6, 15	
Transition to iNPH after AVIM (*n*, %)	3, 7.5	
Pre tap test evaluation		
	TUG	15.3 (SD 5.7)
	FGA	17.3 (SD 5.8)
	MMSE	24.5 (SD 4.6)
Post tap test evaluation		
	TUG	14.2 (SD 5.1)
	FGA	20.2 (SD 5.6)
	GRC for gait aspect	1.5 (SD 1.3)
	MMSE	24.5 (SD 4.9)
Preoperative iNPHGS (total)	5.2 (SD 2.4)	
Preoperative iNPHGS for gait aspect	1.8 (SD 0.9)	
Postoperative iNPHGS (total)	3.4 (SD 2.4)	
Postoperative iNPHGS for gait aspect	1.2 (SD 1.0)	
TUG after shunt surgery	12.8 (SD 4.6)	
MMSE after shunt surgery	25.5 (SD 4.3)	

the TUG after the tap test in the mild gait disturbance group was 4.4%, and it was thus considered difficult to find an improvement that exceeds these cutoff values (reduction of TUG time by more than 10% or more than 5 s) when the gait disturbance is mild.

In contrast, for the FGA, 20 of 24 patients (83%) showed FGA improvement of 1 or more after the tap test. Eighteen patients (75%) improved the gait aspect of the iNPHGS after shunt surgery. In the group of 14 patients with mild gait disturbance, 12 patients (86%) had an FGA improvement of 1 or more after the tap test, and 10 patients (71%) improved their gait aspect of the iNPHGS after shunt surgery. Therefore, FGA appeared to be more useful than the TUG in identifying patients who would respond to shunting.

The indications for shunt surgery were determined by referring to the improvement of other parameters, such as urinary incontinence and cognitive function as well as gait function after the tap test. A total of 21 of the 24 patients (88%) who were evaluated by the FGA and TUG had an improvement in the total score of the three parameters of the iNPHGS after shunt surgery.

Sensitivity Specificity, Positive Likelihood Ratio, and Negative Likelihood Ratio of the TUG, FGA, and GRC for Improvement of Gait Score in the Post-shunt INPHGS

In 26 out of 40 patients, an improvement of the gait score in the iNHPGS was observed.

TUG

Of the 10 patients who showed an improvement of 10% or more in the TUG, six showed improvement of gait score in the post-shunt iNHPGS. Of the 30 patients who did not show an improvement of 10% or more in the TUG, 20 showed improvement of gait score in the post-shunt iNPHGS. The sensitivity and specificity were thus 0.23 [95%CI: 0.14–0.32] and 0.71 [95%CI: 0.54–0.87], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 0.79 and the negative likelihood ratio was 1.09 (**Table 2**).

FGA

Of the 20 patients who showed improvement by the FGA, 15 also showed improvement by the iNHPGS. Of the four patients who did not show improvement by the FGA, three showed improvement by the iNPHGS. The sensitivity and specificity were thus 0.83 [95%CI: 0.79–0.92] and 0.17 [95%CI: 0.03–0.44], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 1.00 and the negative likelihood ratio was 1.00.

GRC

Of the 20 patients who showed improvement by the GRC, 14 showed improvement of gait score in the post-shunt iNHPGS. Of the eight patients who did not show improvement by the GRC, six showed improvement of gait score in the post-shunt iNPHGS. The sensitivity and specificity were thus 0.70 [95%CI: 0.63–0.81] and 0.25 [95%CI: 0.08–0.52], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 0.93 and the negative likelihood ratio was 1.20.

Sensitivity Specificity, Positive Likelihood Ratio, and Negative Likelihood Ratio of the FGA, and GRC for Improvement of Gait Score in the Post-shunt INPHGS in the Mild Gait Disturbance Group

As for the 14 patients in the mild gait disturbance group, of the 12 patients who showed improvement by the FGA, 8 showed improvement by the iNHPGS. Of the two patients who did not show improvement by the FGA, both showed improvement by the iNPHGS. The sensitivity and specificity were thus 0.80 [95%CI: 0.80–0.92] and 0 [95%CI: 0.00–0.31], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 0.80 and the negative likelihood ratio was infinite (**Table 3**).

As for the 16 patients in the mild gait disturbance group, of the 11 patients who showed improvement by the GRC, 7 showed improvement by the iNHPGS. Of the 5 patients who did not show improvement by the GRC, 4 showed improvement by the iNPHGS. Therefore, the sensitivity and specificity were 0.64 [95%CI: 0.56–0.79] and 0.20 [95%CI: 0.04–0.54], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 0.80 and the negative likelihood ratio was 1.80.

As shown above, all indices were worse when only the mild gait disturbance group was evaluated as compared to when all 40 patients were evaluated.

TABLE 2 | Sensitivity specificity, positive likelihood ratio, and negative likelihood ratio of the TUG, FGA, and GRC for improvement of gait score in the post-shunt iNPHGS.

	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
TUG	0.23	0.71	0.79	1.09
FGA	0.83	0.17	1.00	1.00
GRC	0.70	0.25	0.93	1.20

TABLE 3 | Sensitivity specificity, positive likelihood ratio, and negative likelihood ratio of the FGA, and GRC for improvement of gait score in the post-shunt iNPHGS in the mild gait disturbance group.

	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
FGA	0.80	0.00	0.80	Infinite
GRC	0.64	0.20	0.80	1.80

Evaluation Method for the Effectiveness of the Tap Test Combined With the FGA and GRC

The GRC score exhibited the strongest correlation with the improvement score of the FGA ($r = 0.577$), followed by the improvement ratio of TUG time ($r = 0.401$) whereas the improvement score of the FGA and the improvement ratio of TUG time exhibited almost no correlation ($r = 0.110$).

We investigated whether the combination of the FGA and GRC as well as the TUG could be used to identify patients who would benefit from shunt surgery but who could not be picked up by the TUG, and to determine the effectiveness of the tap test (**Figure 1**).

Improvement in Either FGA or GRC

Among the 23 patients with both FGA and GRC data, 20 (87%) showed improvement in either the FGA or GRC, and the iNPHGS gait scale improved in 15 patients (75%). In the remaining three patients, the iNPHGS gait scale improved in two patients. The sensitivity and specificity were thus 0.88 [95%CI: 0.84–0.96] and 0.17 [95%CI: 0.03–0.39], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 1.06 and the negative likelihood ratio was 0.71.

Improvement in Both FGA and GRC

Among the 23 patients for whom both FGA and GRC data were available, 19 patients showed an improvement of at least 1 in the FGA, and 15 of them showed improvement in gait disturbance in the GRC. Of the 15 patients who showed improvement in both the FGA and GRC, 11 (73%) showed improvement in the iNPHGS. Using this entry criterion (improvement in both FGA and GRC), eight patients were tap-negative, and 6 of these patients (75%) showed improvement in the iNPHGS. The sensitivity and specificity were thus 0.65 [95%CI: 0.57–0.76] and 0.33 [95%CI: 0.10–0.65], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 0.97 and the negative likelihood ratio was 1.06.

FGA Improvement of 4 or More

Patients who did not show improvement in the GRC showed an improvement of 3 or less in the FGA. In contrast, all patients with FGA improvement of 4 or more also reported improvement in the GRC, but only 6 (25%) of 24 patients had FGA improvement of 4 or more. Among the six patients with FGA improvement of 4 or more (all of which had GRC improvement), five (83%) showed improvement in the iNPHGS. Using this entry criterion (FGA improvement of 4 or more and GRC improvement), 18 patients were tap-negative, and 13 of these patients (72%) showed improvement in the iNPHGS. The sensitivity and specificity were thus 0.28 [95%CI: 0.17–0.32] and 0.83 [95%CI: 0.52–0.97], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 1.65 and the negative likelihood ratio was 0.87.

Improvement in Either the TUG or GRC

Twenty-one patients had an improved TUG or GRC, and 14 of them (66%) had an improved iNPHGS gait scale. Of the seven patients who did not show any improvement, six improved their iNPHGS gait scale. The sensitivity and specificity were thus 0.70 [95%CI: 0.66–0.81] and 0.13 [95%CI: 0.02–0.39], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 0.81 and the negative likelihood ratio was 2.31.

GRC Improvement of 2 or More

When the GRC score of 2 or more was judged to be positive for the tap test, 14 of 28 patients were positive for tap, and 9 of them improved their iNPHGS gait scale. A total of 14 patients were negative for tap, and 11 of them improved their iNPHGS gait scale. The sensitivity and specificity were thus 0.45 [95%CI: 0.36–0.56] and 0.38 [95%CI: 0.15–0.66], respectively. Based on a prevalence of 1% for iNPH, the positive likelihood ratio was 0.73 and the negative likelihood ratio was 1.45.

DISCUSSION

Idiopathic normal pressure hydrocephalus (iNPH) is a very complicated and easily misdiagnosed disease. Various studies have been conducted to determine which patients would benefit from surgery.

The tap test seems to be an attractive evaluation method because it actually mimics LP shunt surgery, as the spinal fluid is removed by lumbar puncture.

However, it has been reported that the tap test does not provide the necessary information to distinguish between patients who respond to shunting and those who do not (7), and this has led to research on the development of evaluation methods other than the tap test (22) or the combination of other tests in addition to the tap test (8) for more appropriate patient selection. In addition, there have been studies on what kind of gait evaluation method is effective after the tap test and the appropriate timing of evaluation after the tap test. It has

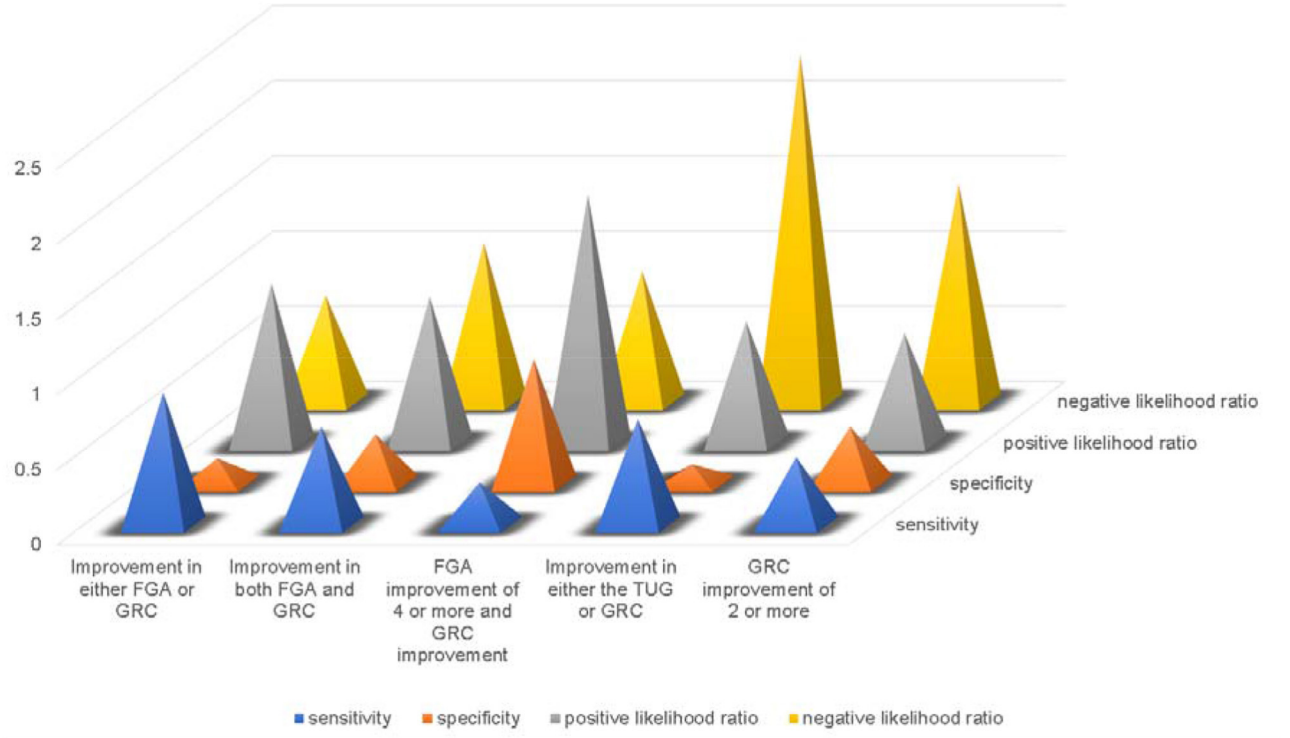

FIGURE 1 | Comparison of evaluation methods for the effectiveness of the tap test.

been reported that the time and the number of steps taken in a 10 m walk at free speed after the tap test correlate with the improvement of iNPH grading scale (23). Other reports suggest that the Tinetti Tool Assessment which involves different gait parameters is more effective at 72 h than at 24 h as the timing of evaluation after the tap test (24, 25).

In this study, we conducted TUG in all patients, which is the standard evaluation method in Japan. The disadvantage of TUG is its low sensitivity (26). Although cutoff values such as a reduction in time by more than 10% or a reduction in time by more than 5 s are often used to judge the effect, it is difficult to find an improvement that exceeds these cutoff values after the tap test when the gait disturbance is mild.

Our team has previously reported that the FGA score is an independent factor associated with the risk of falls associated with iNPH (17). In addition, we reported that the FGA may be suitable for distinguishing patients with mild iNPH who are more likely to fall from those who are less likely to fall (27), and that the FGA score can provide a more detailed representation of improvement after the tap test than the TUG, even in patients with mild gait disturbance (16).

Recently, there have been reports on the use of the GRC by patients or their families in addition to the TUG, Performance Oriented Mobility Assessment (Tinetti), and Berg Balance Scale (BBS) by medical professionals to determine the efficacy after the tap test (19, 28) or shunt surgery (29). Therefore, in this study, we investigated whether the FGA and GRC, as well as the TUG, could be combined to identify patients who are likely to benefit from shunt surgery but cannot be picked up by the TUG, and to determine the validity of the tap test.

It has been reported that the minimum detectable change of the GRC is 0.45 on an 11-point scale (18, 30). It has also been reported that the minimal clinically important change, which is the change most likely to be relevant to patients, is approximately half the standard deviation of the outcome measures (31). In the present study, the improvement in the FGA score ($n = 28$) was 2.78 (SD 1.93) and that in the GRC ($n = 23$) was 1.48 (SD 1.27). Thus, the minimally important differences (minimal clinically important change and minimal clinically important difference) of the improvement of the FGA score and GRC were 0.97 and 0.64, half of the SDs, respectively. Therefore, an improvement of 1 point or more in either the FGA or GRC is clinically meaningful and important. In addition, our group reported that, in order to produce an improvement of more than 2 points in the GRC after shunt surgery, the postoperative FGA needs to improve by more than 4 points compared to the preoperative FGA (16). Therefore, the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were also calculated for cutoff values, such as an improvement of GRC 2 points or more in addition to an improvement of GRC 1 point or more, and an improvement of FGA 4 points or more in addition to an improvement of FGA 1 point or more.

The higher the sensitivity or specificity, the larger the value of the positive likelihood ratio and the smaller the value of the

negative likelihood ratio. The larger the value of the positive likelihood ratio and the smaller the value of the negative likelihood ratio, the more useful they are as a criterion. As shown in section Sensitivity Specificity, Positive Likelihood Ratio, and Negative Likelihood Ratio of the TUG, FGA, and GRC for Improvement of Gait Score in the Post-Shunt iNPHGS, the TUG had a sensitivity of 0.23, specificity of 0.71, positive likelihood ratio of 0.79, and negative likelihood ratio of 1.09. In the present study, we calculated the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of various cutoff criteria by combining not only the TUG but also the FGA and GRC, and found no new criterion that was better than the TUG in both sensitivity and specificity. There were no new criteria that were superior to the TUG not only in sensitivity and specificity, but also in positive and negative likelihood ratios when calculated with a prevalence of 1%. Most of the cutoff criteria examined in this study were inferior to the TUG in all indices. However, when improvement in either the FGA or GRC was considered as a criterion for the effectiveness of the tap test, the sensitivity was 0.88, specificity was 0.17, positive likelihood ratio was 1.06, and negative likelihood ratio was 0.71, as shown in section Improvement in Either FGA or GRC. We thought that this criterion might be a candidate as an alternative cutoff criterion to the TUG.

When this criterion was used as the criterion for evaluating the effectiveness of the tap test, it was confirmed that the negative likelihood ratio was lower than that of the TUG alone. Therefore, it is more appropriate to exclude patients who do not show improvement in either the FGA or GRC. In addition, when improvement in either the FGA or GRC is used as a criterion for judging the efficacy of the tap test for the gait aspect, the sensitivity of the test is higher than that of the TUG alone, although the specificity is lower. This high sensitivity but low specificity may mean that there will be more patients who undergo surgery but do not benefit from the treatment. Nevertheless, in the present study, only 25% of patients were tap test positive when the TUG alone was used for patient selection, but with this criterion (improvement in either the FGA or GRC), the number of tap test–positive patients increased to 87%. Seventy-five percent of these patients improved in the iNPHGS gait scale with shunt surgery. In clinical practice, the effectiveness of the tap test is judged together with the improvement of symptoms other than gait, but we believe that excluding patients from shunting because of a negative TUG result, at least when the gait is evaluated only by TUG, does not adequately identify patients who would benefit from shunting.

One limitation of this study is that due to the prevalence of covid-19, preoperative evaluations were mixed between those performed in the inpatient setting and those performed in the outpatient setting, resulting in variations in the timing and method of evaluation. Another limitation is that the number of cases was not large and this was a retrospective study because all surgeries were performed at one institution during 6 months.

CONCLUSION

Improvement in either the FGA or GRC is a more sensitive criterion for the efficacy of the tap test for the gait aspect than the TUG. Since the negative likelihood ratio is lower than that of the TUG alone, it is more appropriate to exclude surgical indications in patients with neither FGA nor GRC improvement than to exclude surgical indications with no improvement in the TUG.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Osaka Medical and Pharmaceutical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MK, YK, and YN made substantial contributions to the conception and design of the study. All authors contributed to the acquisition, analysis, or interpretation of data for the study by patient management. MK wrote the draft. All authors revised the manuscript with critical comments and approved the final version.

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Physical Capacity and Activity in Patients With Idiopathic Normal Pressure Hydrocephalus

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Introduction: Most patients with idiopathic normal pressure hydrocephalus (iNPH) improve gait after surgery. However, knowledge on physical capacity and activity after shunt surgery is limited. One of the aims of this study was to evaluate the effect of shunt surgery in patients with iNPH on short-distance walking, functional exercise capacity, functional strength, and variables of activity and sleep, 3 and 6 months postoperatively. Another aim was to evaluate the effect of a physical exercise program. Additionally, we studied how changes in short-distance walking were correlated with functional exercise capacity and voluntary walking.

Methods: In total, 127 patients were consecutively included and randomized to the exercise group ($n = 62$) or the control group ($n = 65$). Participants in the exercise group underwent the supervision of a 12-week exercise program. All patients were assessed before surgery, at 3 and 6 months postoperatively with the 10-m walk test (10MWT), the 6-min walk test (6MWT), 30-s chair stand test (30sCST), and with the actigraphic recordings of activity variables measured for a total of 24 h/day for at least 3 days.

Results: All patients improved at 3 months postoperatively in the 10MWT ($p < 0.001$), 6MWT ($p < 0.001$), and 30sCST ($p < 0.001$). These results were maintained after 6 months. Actigraphic recordings for voluntary walking (steps per minute) were improved and nighttime sleep (%) increased after 6 months ($p = 0.01$, $p = 0.04$). There were no significant differences between the exercise group and the control group, except for the postoperative change in the proportion of daytime sleep after 3 months, which was slightly more reduced compared to baseline in the exercise group ($p = 0.04$). Changes after 3 months in the 10MWT and 6MWT were moderately correlated ($\rho = -0.49$, $p = 0.01$) whereas the correlation between the 10MWT and voluntary walking was weak ($\rho = -0.34$, $p = 0.01$).

Conclusion: Shunt surgery improved short-distance walking, functional exercise capacity, functional strength, and voluntary walking. An exercise program did not affect these outcomes. Short-distance walking was weakly correlated with voluntary walking, indicating improved physical capacity does not directly translate to increased physical activity. Further research should address how interventions should be tailored to promote physical activity after shunt surgery.

Trial Registration: clinicaltrials.gov, Id: NCT02659111.

Keywords: idiopathic normal pressure hydrocephalus, physical activity, exercise, actigraphy, gait, sleep

INTRODUCTION

The main symptoms of idiopathic normal pressure hydrocephalus (iNPH), caused by disturbance in the cerebrospinal fluid dynamics, are impaired gait and balance, along with cognitive impairment and/or incontinence (1, 2). The available treatment is a shunt insertion, and gait symptoms measured with a timed walking test will improve in approximately 80% of shunted patients (3–5).

We have limited knowledge about the overall activity level of patients before and after shunt surgery. After surgery, patients with iNPH have reported worse health-related quality of life in terms of mobility and daily activities than sex- and age-matched controls (6). A previous small study from our center used a body-worn triaxial accelerometer to measure the physical activity of patients with iNPH in daily life. In that study, patients were less active and took fewer steps with a lower total energy expenditure (TEE) than healthy individuals both before and after shunt surgery; however, no increase in physical activity was observed after surgery (7). Patients with iNPH improve gait as measured by timed short-distance walking tests (3–5), but it is unclear if they improve in terms of overall physical activity in daily life. The impact of shunt surgery on patients' physical capacity (strength and exercise capacity) and activity in daily life has not been thoroughly studied. The remaining questions to be answered are if these variables improve after surgery, and if short-distance walking correlates with exercise capacity and voluntary walking in daily life.

In a randomized clinical trial reported elsewhere (the iNPhys study), we evaluated the immediate and long-term effect of a 12-week high-intensity functional exercise program (HIFE) (8) compared to a control group of patients with iNPH receiving no intervention. The exercise group showed long-term effects on balance and achieved their stated goals to a higher extent than the controls; however, no effect was found on the primary outcome, the total iNPH scale score (9). In this study, we investigated secondary outcomes from the iNPhys study.

One of the aims of this study was to evaluate short-distance walking, functional exercise capacity, functional strength, and activity and sleep variables before, 3 and 6 months after shunt surgery in patients with iNPH. Another aim was to evaluate the effect of a physical exercise program on the same variables. Additionally, we studied how the changes from baseline in short-distance walking were correlated to the changes in functional exercise capacity and voluntary walking, respectively.

MATERIALS AND METHODS

Study Design and Inclusion of Participants

The iNPhys study (9) was a double-center trial conducted at Linköping University hospital in Linköping and Sahlgrenska University hospital in Gothenburg, Sweden. In total, 127 patients diagnosed with iNPH according to international guidelines (1), and planned for shunt surgery were consecutively enrolled between January 2016 and June 2018. Exclusion criteria were Mini-Mental State Examination (MMSE) <16, inability to walk with or without walking aids for >10 m, or suffering from other diseases making intensive exercises impossible. After the decision on surgery, eligible patients were included and randomized to either no intervention or a supervised highly intensive functional exercise intervention, the HIFE^{TM}-program (8), two times weekly for 12 weeks. Assessments were performed in the evaluation process before surgery, 3 and 6 months postoperation. All patients had a ventriculo-peritoneal shunt. More details are described in our previous publication (9).

The trial was approved by the medical ethical committee of Linköping, 2015/250-31, and the study protocol was registered in advance at clinicaltrials.gov, Id: NCT02659111. The study received ethical board approval and conforms with the World Medical Association Declaration of Helsinki, and all participants received oral and written information and gave written consent prior to the start of the study.

Outcome Measures

Short-Distance Walking

Short-distance walking was measured with the 10-m walk test (10MWT), in which patients walked 10 m between the two markings at their self-selected speed (10). The mean value in seconds from the two repeated tests was calculated. Patients were able to use their walking aids if needed.

Functional Exercise Capacity

Functional exercise capacity was measured with the 6-min walk test (6MWT) (11). To perform the test, patients were asked to walk as far as possible at a self-selected speed along a marked 30-m distance between the two cones for a period of 6 min. If

necessary, walking aids were allowed and, if needed, patients could stop and start the test again during the 6-min period. The assessor walked with patients and gave standardized information every minute. The total distance in meters walked for 6 min was noted.

Functional Lower Limb Strength

Functional lower limb strength was measured with the 30-s chair stand test (30sCST) (12). The test started with the patient seated in a chair without armrests. On a signal from the assessor, the patient stood upright and immediately sat down again until the back touched the backrest of the chair. This procedure was repeated as many times as possible in 30 s. The assessor stood close to the patient to avoid problems such as falls, but did not assist the patient in the test. The total number of full standings was noted.

Actigraphic Recordings

The overall daily activity was measured with an actigraphic recording using a SenseWear actigraph (BodyMedia, Inc., Pittsburg, PA, USA) worn on the dominant upper arm for 7 days. Patients were told to use the armband during the day and at night, and the recordings were divided into daytime, from 8.00 a.m. to 7.59 p.m., and nighttime from 8.00 p.m. to 7.59 a.m. The variables used in the analyses were the number of steps per minute reflecting voluntary walking, TEE, metabolic equivalent of task (MET), and proportions of time patients were asleep during daytime and nighttime. TEE is the total human energy cost, including the basal metabolic rate, the energy cost of digestion, and the energy cost of physical activity (13). MET is defined as the ratio between the energy expended for a certain activity and the energy used when sitting quietly. One MET is the energy expended sitting quietly and in a two-MET activity the person uses two times as much energy (14). To be included in the analysis, monitoring from at least 3 full days was required.

Statistical Analysis

The set of subjects included in the analyses were participants with at least one follow-up session after surgery. The normal distribution was tested with the Shapiro–Wilk test, and within-group differences were calculated with the related samples Friedmans two-way analysis of variance (ANOVA) by ranks. Significance values in within-group tests were adjusted by the Bonferroni correction for multiple tests. Differences between the exercise group and the control group were calculated with the Mann–Whitney U test for independent samples. Between-group differences in the baseline characteristics were calculated with the chi-squared test for categorical variables or the independent sample t-test for continuous variables. The correlation analyses were conducted using Spearman's ρ test or Pearson's correlation. Statistical analyses were performed with IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). A two-tailed p-value of ≤ 0.05 was considered as statistically significant.

RESULTS

Baseline Characteristics and Dropouts

In total, 127 patients were included in the study. Of these, 109 patients with at least one postoperative efficacy assessment were included in the data analysis (50 patients in the exercise group and 59 patients in the control group). At a follow-up after 6 months, data from 95 patients were available for the analyses (**Figure 1**). There were no significant differences in baseline characteristics between dropouts and participants included in the data analysis. Among included participants, 59.6% were male, the mean age was 73.7 $\pm$ 6.6 years, and the average MMSE result was 26.0 $\pm$ 3.0 points. The prevalence figures for comorbidities were: diabetes 31.2%, hypertension 65.1%, cardiovascular diseases 17.4%, stroke 8.3%, and atrial fibrillation 10.1%, and 11.3% of the participants were smokers (**Table 1**).

Postoperative Effects on Short-Distance Walking, Exercise Capacity, Strength, and Variables of Activity and Sleep

The time required to walk 10 m decreased significantly after surgery in a 3-month follow-up ($n = 94$; baseline median 13.0 s, interquartile range (IQR) 10.8–16.1; 3-month median 10.0 s, IQR 8.2–12.3, $p < 0.001$). Also, functional exercise capacity (distance in the 6MWT) increased after 3 months ($n = 90$; baseline median 265.0 m, IQR 171.5–328.5; 3-month median 344.5 m, IQR 243.5–420.0, $p < 0.001$). After 3 months, the functional strength improved as measured by the 30sCST (number of full standings) ($n = 92$; baseline median 6.0, IQR 2.0–8.8; 3-month median 9.0, IQR 6.0–12.0, $p < 0.001$). These results were maintained after 6 months with a trend of further improvement in the 6MWT and 30sCST, but without significant differences to the 3-month assessment (**Figure 2**). Details are presented in **Supplementary Table 1**.

The number of steps per minute and the proportion of nighttime sleep (8.00 p.m. to 7.59 a.m.) did not change significantly from baseline to a 3-month follow-up. However, after 6 months, both variables were significantly changed from baseline: steps per minute ($n = 49$; baseline median 1.2, IQR 0.4–3.4; 6-month median 2.4, IQR 0.6–5.7, $p = 0.01$) and the proportion of nighttime sleep ($n = 55$; baseline median 53.0%, IQR 43.0–61.6; 6-month median 53.4%, IQR 45.3–61.4, $p = 0.04$) (**Figure 2**; **Supplementary Table 1**).

Total energy expenditure, MET, and the proportion of time spent sleeping during daytime (8.00 a.m. to 7.59 p.m.) did not change significantly from baseline at any of the follow-up assessments (**Figure 2**, **Supplementary Table 1**).

None of the variables changed significantly between the 3- and 6-month assessments.

The gait velocity was calculated from the results of the 10MWT and 6MWT. The velocity results of the two tests were highly correlated at baseline ($r = 0.86$), at the 3- ($r = 0.86$), and at the 6-month follow-up ($r = 0.87$) (**Table 2**).

Effects of the Physical Exercise Program

There were no significant differences between the exercise group and the control group for any of the efficacy variables in changes

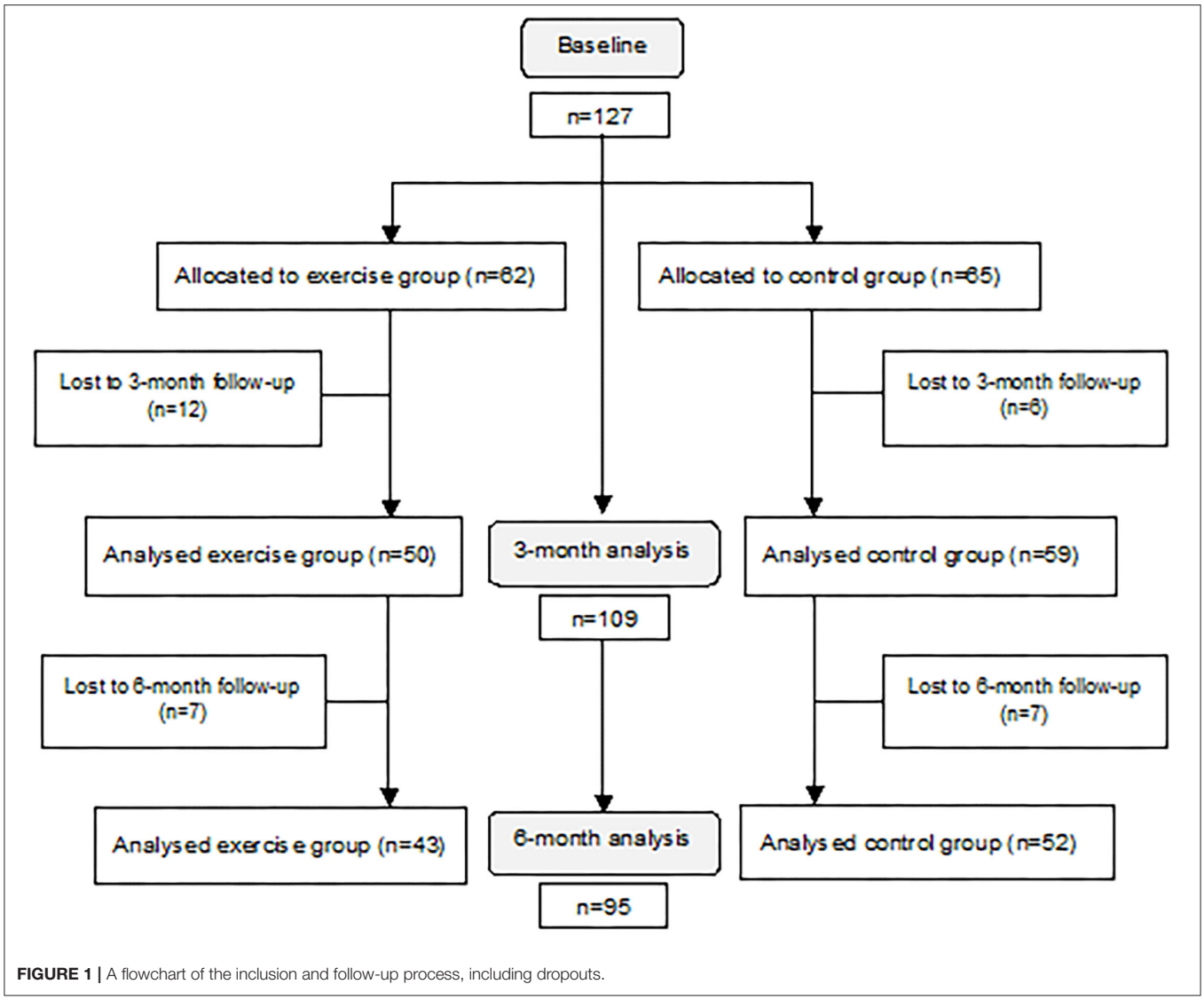

FIGURE 1 | A flowchart of the inclusion and follow-up process, including dropouts.

from baseline, except for the proportion of daytime sleep. Details are presented in **Supplementary Table 1**. At a 3-month follow-up, the exercise group decreased more from baseline in the proportion of daytime sleep ($n = 27$; median −1.2%, IQR −4.8–0.2), compared to the control group ($n = 32$; median 0%, IQR 1.3–3.0), $p = 0.04$. At a 6-month follow-up, the differences in changes with respect to baseline disappeared (exercise group: $n = 25$; median −1.0% IQR −4.1–2.3, and the control group: $n = 37$; median 0.3%, IQR −2.4–1.8, $p = 0.65$).

Correlations Between Postoperative Changes in Short-Distance Walking, Functional Physical Capacity, and Voluntary Walking

After 3 months, the changes with respect to baseline in the 10MWT and 6MWT showed a moderate negative correlation ($\rho = -0.49$, $p = 0.01$), i.e., the greater the improvement in the 10MWT, the longer the distance in 6MWT after 3 months. This result was maintained with a slightly stronger correlation after 6 months ($\rho = -0.54$, $p = 0.01$).

Weak negative correlations were seen between changes with respect to baseline in the 10MWT and voluntary walking (steps per minute) after 3 months ($\rho = -0.34$, $p = 0.01$) with an even weaker correlation after 6 months ($\rho = -0.21$, $p = 0.01$).

DISCUSSION

This study reports clear improvements in short-distance walking (10MWT), functional exercise capacity (6MWT), and functional strength (30sCST) 3 months after shunt surgery in iNPH with remaining results after 6 months. In actigraphic recordings, no significant differences from baseline were seen after 3 months, but voluntary walking (steps per minute) improved and the proportion of nighttime sleep increased after 6 months. Changes in the 10MWT and 6MWT were moderately correlated after 3 months, with a slightly stronger correlation at a 6-month

TABLE 1 | Characteristics of included participants and dropouts at baseline.

	Participants	Dropouts	*p*-value
	***n* = 109**	***n* = 18**	
Age (years)	73.7 ± 6.6	73.9 ± 7.4	0.87
Sex (male/female %)	59.6/40.4	50.0/50.0	0.44
BMI	26.6 ± 4.1	27.4 ± 3.8	0.94
MMSE (0–30)	26.0 ± 3.0	25.0 ± 3.0	0.11
Smoking (%)	11.3 ($n = 106$)	11.1	0.98
Diabetes (%)	31.2	22.2	0.44
Hypertension (%)	65.1	77.8	0.29
Cardiovascular disease (%)	17.4	22.2	0.63
Stroke (%)	8.3	5.5	0.69
Atrial fibrillation (%)	10.1	5.6	0.54

BMI, body mass index; MMSE, Mini Metal State Examination.
Continuous variables are presented with mean and standard deviation (SD) and categorical variables with proportions. Differences between the groups were tested with the independent sample t-test for continuous variables or chi-squared test for categorical variables.

follow-up. Correlations between the 10MWT and improvements in voluntary walking were weak at both the 3- and 6-month follow-up assessments.

The gait disturbance in iNPH has been described as broad-based, with short stride length and increased stride variability, and with decreased velocity and low foot to floor clearance (15–17). The gait function improves after shunt surgery (18), and timed short-distance walking tests are used in the evaluation of normal pressure hydrocephalus (NPH) (2, 19–24). However, large studies with a timed 10MWT before and after shunt surgery are scarce (25). The 10MWT performances among the 109 patients in our study were at baseline median 13 s, IQR 11–16, and, at a 3-month follow-up median of 10 s, IQR 8–12. These results partially correspond to a study with 429 patients describing the phenotype of iNPH (20). According to that study, the 10MWT results were slightly higher at baseline (median 15 s, IQR 12–20) and postoperatively (median 12 s, IQR 9–15), but with similar changes compared to our results (20). Gait velocity in the 10MWT at baseline (0.77 ± 0.26 m/s) agrees with the results in a study by Nikado et al. in which fall-related factors were evaluated in 63 patients with iNPH (0.74 ± 0.25 m/s) (21). Normal values in self-selected gait speed (50–79 years) are 1.31 ± 0.20 m/s for women and 1.41 ± 0.21 m/s for men (26). We did not differentiate between men and women, but even 6 months after shunt surgery the walking speed (1.05 ± 0.30 m/s) among patients with iNPH was low compared to healthy individuals (26).

The 10MWT and 6MWT are highly correlated among frail elderly with dementia ($r = 0.91$ $p < 0.001$) (27) and in patients with suspected NPH at baseline ($r = -0.80$, $p < 0.001$) (28). The moderate correlation in our study between changes in the 10MWT and 6MWT may have different causes. Variability in the gait pattern such as decreased velocity, step length and cadence has been reported according to the 6MWT (29). Gait variability may be an important aspect of the gait function in iNPH affecting long-distance walking, but knowledge on variability after 3 and 6 months is lacking. The results from both the 10MWT and 6MWT likely reflect improvements in postural control and gait pattern. However, endurance measured by the 6MWT may not be improved to the same degree after shunt surgery. Heart rate explains most of the variance in the 6MWT, and the motivation to maintain a high intensity during the test will influence the result (30). Heart rate measured in the 6MWT before and 7 days after shunt surgery was unchanged in a small sample of patients with iNPH although velocity increased after surgery (29). Patients with iNPH are used to performing low intensity activities for a long time and may not have the ability to increase intensity during testing in the postoperative period due to persistent poor overall physical condition. The fact that voluntary walking correlated weakly with changes in the 10MWT strengthens this hypothesis.

An interesting finding was the improvement in functional strength regardless of participation in the exercise program after shunt surgery. The 30sCST is intended to evaluate functional lower limb strength displayed when standing upright from a seated position (12). In this movement, the ability to maintain postural control has to be considered. Individuals with iNPH have higher backward–forward trunk sway in quiescent position than healthy individuals, but no significant improvements after shunt surgery have been demonstrated (31–33) although a reduced postoperative presence of retropulsion was reported by Agerskov et al. (20). However, patients with iNPH improve in sway area (34) and voluntary center-of-pressure movements after surgery (33) measured with a force platform. Lower limb strength may improve, but even increased postural control after surgery could have affected the outcome of the 30sCST. Lower limb strength is correlated with gait speed (35), and voluntary center-of-pressure movement is correlated with the gait function (33). The muscle strength of patients with iNPH before and after shunt surgery needs further investigation.

The intensity of daily physical activity does not increase postoperatively, which is confirmed by the nonsignificant changes in TEE and MET. That is, patients do not improve in daily activity levels despite improvements in the clinical assessments. In addition to the prolonged period of physical inactivity, the remaining executive dysfunction and mental behavioral symptoms, including reduced drive and the lack of initiatives (36), may explain these findings. However, an indication of altered behavior in voluntary walking was the improvement after 6 months reported here.

The proportion of nighttime sleep increased significantly after 6 months compared to baseline. This may be interpreted as an improved sleep quality after surgery. However, the differences were small and the result should be interpreted with caution. There are a few studies regarding sleep in iNPH (37, 38). Agerskov et al. showed that the need for sleep decreased after surgery (20). A postoperative improvement in daytime wakefulness has also been reported (39). In our study, there were no changes in the proportion of daytime sleep at any of the postoperative follow-up assessments.

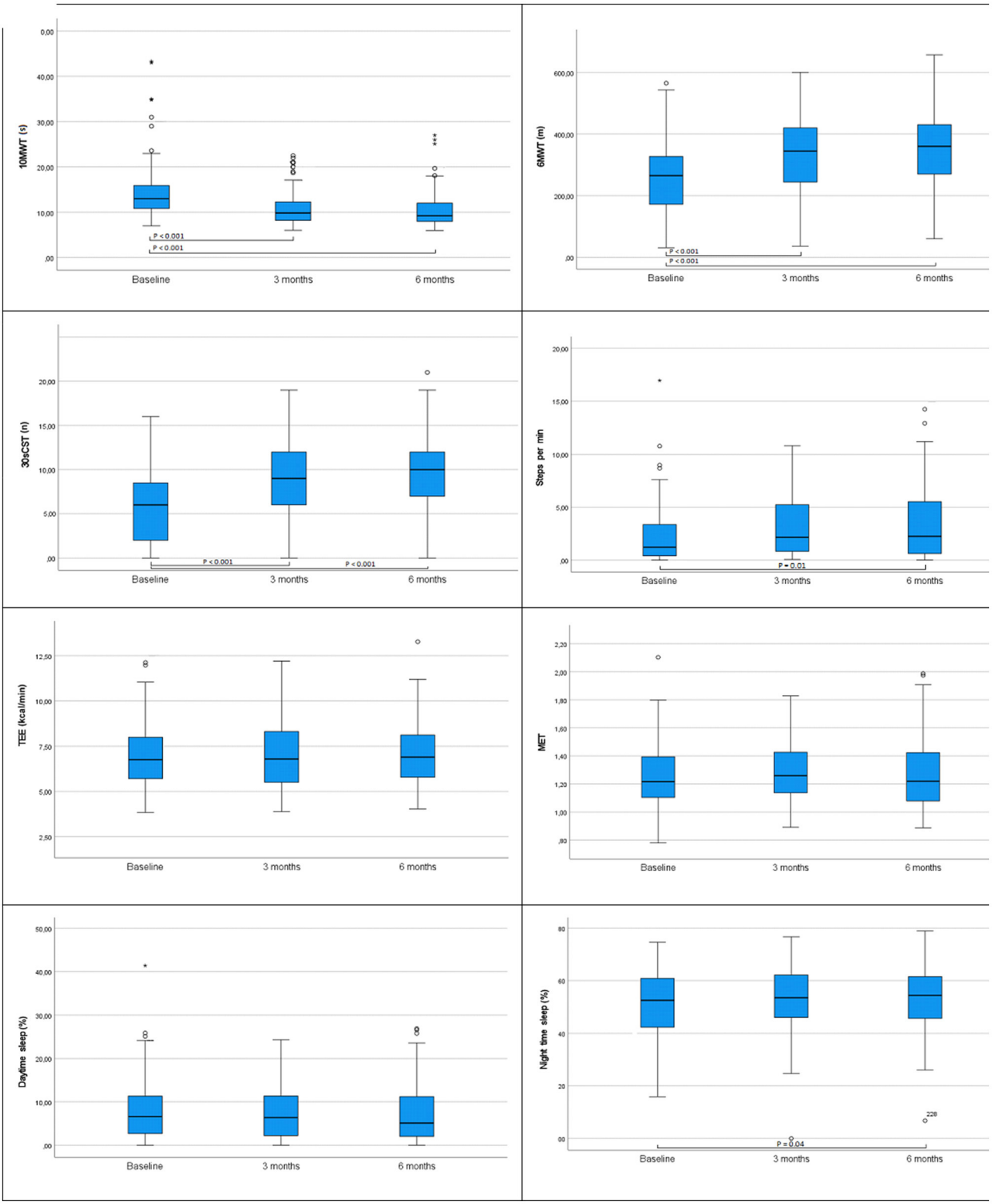

FIGURE 2 | Values at baseline, 3 and 6 months postoperatively for the variables in all patients: 10-m walk test (10MWT), 6-min walk test (6MWT), 30-s chair stand test (30sCST), total energy expenditure (TEE), metabolic equivalent of task (MET), daytime sleep, and nighttime sleep. Significant differences are presented in the figures, $p \leq 0.05$. Differences were tested with related samples Friedmans two-way analysis of variance (ANOVA) by ranks. Significance values are adjusted by the Bonferroni correction for multiple tests. N =109. In the figure of 10MWT, two extreme values are excluded.

TABLE 2 | Gait velocity calculated from the 10MWT and 6MWT at baseline and 3 and 6 months postoperatively.

	Gait velocity 10MWT m/s	Gait velocity 6MWT m/s	Correlation *r*
	***n* =109**	***n* = 109**	
Baseline	0.77 ± 0.26	0.71 ± 0.31 *n* = 106	0.86*
3 months postoperatively	1.00 ± 0.27 *n* = 107	0.92 ± 0.33 *n* = 104	0.86*
6 months postoperatively	1.05 ± 0.30 *n* = 95	0.95 ± 0.33 *n* = 94	0.87*

10MWT, 10-m walk test; 6MWT, 6-min walk test.
*Values are presented with mean and SD. Correlations are analyzed with Pearson's correlation. * $p < 0.001$.*

Tailored interventions with professional guidance and ongoing support have been suggested as facilitators to promote physical activity in older adults (40). Meaningful activities and social support, especially from family members, are motivators for maintaining physical activities (40, 41). In our study, the exercise intervention did not affect the measured outcomes. However, the intervention had a high attrition rate, entailing difficulties to detect differences between the exercise group and controls (9). The adoption and maintenance of new behaviors in daily life are complex, and established habits often persist strongly into long-standing behaviors. Habits are automated and trigged by associated cues. Contextual factors have to be considered to underpin behavioral changes and create new habits (42). Such behavioral factors may also explain why improved physical capacities after shunt surgery do not translate directly to improvements in daily physical activity. The lack of postoperative increase, in general, physical activity despite improvements in short-distance walking and physical exercise capacity indicate that patients with iNPH need guidance and motivation regarding meaningful physical activities to utilize the improved functions after surgery. Further research should address how interventions should be tailored to promote physical activity after shunt surgery.

This study has limitations. The outcomes are evaluated before and after surgery, but without a control group of healthy individuals. An additional limitation is that the total group contains a subgroup subjected to a rehabilitation intervention. We had dropouts from the follow-up assessments, and there were internal dropouts from the actigraphic recordings, resulting in small sample sizes.

CONCLUSION

Shunt surgery improved short-distance walking, functional exercise capacity, functional strength, and voluntary walking. An exercise program did not affect these outcomes. Short-distance walking was weakly correlated with voluntary walking, indicating that improved physical capacity does not directly translate to increased physical activity. Further research should address how interventions should be tailored to promote physical activity after shunt surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethical Committee of Linköping, Sweden 2015/250-31. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JR, LK, MT, and FL conceptualized and designed the study. MU analyzed the actigraphic recordings, JR, MT, and FL interpreted the results. JR reviewed and edited the manuscript for intellectual content. LK, MU, MT, and FL revised the manuscript and all authors approved the final version for submission. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.845976/full#supplementary-material

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Intrathecal Contrast-Enhanced Magnetic Resonance Imaging of Cerebrospinal Fluid Dynamics and Glymphatic Enhancement in Idiopathic Normal Pressure Hydrocephalus

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Idiopathic normal pressure hydrocephalus (iNPH) is a neurodegenerative disease, characterized by cerebrospinal fluid (CSF) flow disturbance. Today, the only available treatment is CSF diversion surgery (shunt surgery). While traditional imaging biomarkers typically assess CSF space anatomy, recently introduced imaging biomarkers of CSF dynamics and glymphatic enhancement, provide imaging of CSF dynamics and thereby more specifically reveal elements of the underlying pathophysiology. The biomarkers address CSF ventricular reflux grade as well as glymphatic enhancement and derive from intrathecal contrast-enhanced MRI. However, the contrast agent serving as CSF tracer is administered off-label. In medicine, the introduction of new diagnostic or therapeutic methods must consider the balance between risk and benefit. To this end, we performed a prospective observational study of 95 patients with iNPH, comparing different intrathecal doses of the MRI contrast agent gadobutrol (0.10, 0.25, and 0.50 mmol, respectively), aiming at the lowest reasonable dose needed to retrieve diagnostic information about the novel MRI biomarkers. The present observations disclosed a dose-dependent enrichment of subarachnoid CSF spaces (cisterna magna, vertex, and velum interpositum) with dose-dependent ventricular reflux of tracer in iNPH, as well as dose-dependent glymphatic tracer enrichment. The association between tracer enrichment in CSF and parenchymal compartments were as well dose-related. Intrathecal gadobutrol in a dose of 0.25 mmol, but not 0.10 mmol, was at 1.5T MRI considered sufficient

for imaging altered CSF dynamics and glymphatic enhancement in iNPH, even though 3T MRI provided better sensitivity. Tracer enrichment in CSF at the vertex and within the cerebral cortex and subcortical white matter was deemed too low for maintaining diagnostic information from a dose of 0.10 mmol. We conclude that reducing the intrathecal dose of gadobutrol from 0.50 to 0.25 mmol gadobutrol improves the safety margin while maintaining the necessary diagnostic information about disturbed CSF homeostasis and glymphatic failure in iNPH.

Keywords: idiopathic normal pressure hydrocephalus, cerebrospinal fluid, glymphatic function, magnetic resonance imaging, intrathecal gadobutrol, imaging biomarkers

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a neurodegenerative disease and a subtype of dementia comprising the symptoms of gait ataxia, urinary incontinence, and cognitive impairment in combination with disturbed cerebrospinal fluid (CSF) homeostasis. Today, the only effective treatment is CSF diversion (shunt) surgery that may improve symptoms, though it remains disputed which should be offered surgery (1). The American-European (2) and Japanese (3) diagnostic criteria are primarily based on the clinical picture and imaging signs of CSF space abnormality where imaging biomarkers address the morphology of the cerebral ventricles. Additionally, the lumbar CSF pressure should be normal to differentiate from other types of hydrocephalus. However, the fulfillment of the clinical and imaging criteria of "probable" or "possible" iNPH does not predict clinical response to shunt surgery (2, 4). To predict whether a symptomatic patient suffers "shunt-responsive iNPH", supplemental tests have included the assessment of clinical response to CSF drainage of short (Tap test) or long (extended lumbar drain) duration, measurements of the CSF pressure change following fluid infusion to the lumbar or ventricular CSF space (infusion tests) or long-term monitoring of static/pulsatile intracranial pressure (ICP) (4–8). Proper patient selection is worthwhile since shunt surgery may be accompanied by lasting symptom improvement in a substantial proportion of patients (9–11).

There is an increasing awareness that iNPH may be a rather common dementia subtype, possibly affecting more than 5% of individuals above 80 years (12, 13). It is a severe brain disease with high 5-year mortality (14, 15). With an aging population, there is a need for biomarkers that more precisely address the underlying pathophysiology. The established anatomic biomarkers Evan's index, callosal angle, and disproportional enlarged subarachnoid space hydrocephalus (DESH) provide morphological information about CSF space anatomy. However, their ability to predict clinical response to CSF diversion surgery remains disputed (16).

Abbreviations: CSF, Cerebrospinal fluid; DESH, Disproportional enlarged subarachnoid space hydrocephalus; GM, Gray matter; iNPH, Idiopathic normal pressure hydrocephalus; ICP, Intracranial pressure; MRI, Magnetic resonance imaging; MTA, Medial temporal atrophy; MMS, Mini-mental state; WM, White matter.

Adding to the established imaging biomarkers, we recently proposed functional imaging biomarkers for iNPH disease, based on imaging of CSF redistribution (degree of ventricular reflux), and imaging of CSF and glymphatic enhancement (17, 18). The association between neurodegeneration and impaired clearance of toxic metabolic by-products from CSF and the brain has recently emerged as a possible crucial mechanism behind iNPH disease (18). Furthermore, there is a clear histological overlap between iNPH and Alzheimer's diseases; both are characterized by deposition within the brain of toxic metabolites such as amyloid-β and tau (19, 20). Patients with positive CSF biomarkers of Alzheimer's, e.g., CSF levels of amyloid-β and tau, responded less to CSF diversion (21). Accordingly, impaired CSF clearance may be of particular significance since there are no known blood-brain-barrier (BBB) transporters for tau, and toxic isoforms of amyloid-β (e.g., pyroglutamate Aβ, pE3-Aβ) are primarily removed along extra-vascular pathways (22). The subarachnoid CSF space communicates directly with the brain interstitial space *via* the perivascular spaces (23, 24). Recently it was proposed that impaired glymphatic clearance of toxic metabolites is a common mechanism for dementia diseases, such as Alzheimer's disease (amyloid-β, tau), and Parkinson's disease (α-synuclein) (25).

The functional imaging biomarkers of CSF dynamics and glymphatic enhancement previously reported by our group (24, 26, 27) require an intrathecal injection of an MRI contrast agent. This may be considered a drawback since MRI contrast agents are used off-label and may be accompanied by neurotoxic effects (28). When new methods are introduced in medicine, there is always a need for determining the balance between risk and benefit to improve the therapeutic index, which also concerns intrathecal MRI contrast agents (29). For intrathecal contrast-enhanced MRI, macrocyclic chelates, e.g., gadobutrol, are preferable as they are more stable than the previous linear contrast agents. Toxic doses have not been reported for intrathecal gadobutrol in doses 1.0 mmol or below (28). We have used intrathecal gadobutrol in a dose of 0.5 mmol with good experience from a safety perspective (30, 31), but we have previously not determined the lowest dose needed to maintain the diagnostic information.

On this background, the present study was undertaken to examine the lowest sufficient dose of intrathecal gadobutrol needed to maintain adequate image quality for clinical assessment of MRI biomarkers of CSF dynamics and glymphatic

enhancement in patients with iNPH. Secondarily, we questioned the role of these biomarkers in iNPH pathophysiology.

MATERIALS AND METHODS

Approvals and Study Design

The Regional Committee for Medical and Health Research Ethics (REK) of Health Region South-East, Norway (2015/96), The Institutional Review Board of Oslo university hospital (2015/1868), and The National Medicines Agency (15/04932-7) approved the study. Participants were included after written and oral informed consent. The study was conducted according to ethical standards of the Helsinki Declaration of 1975 (and as revised in 1983).

The study design was prospective and observational, primarily comparing MRI biomarkers of CSF dynamics and glymphatic enhancement in patients with iNPH using different doses of intrathecal gadobutrol (Gadovist, Bayer Pharma AG, Berlin, Germany) as CSF tracer, and secondarily comparing how different MRI biomarkers associate.

Patients

The study included consecutive patients with iNPH undergoing intrathecal contrast-enhanced MRI and phase-contrast MRI, as part of their neurosurgical work-up within the Department of Neurosurgery at the Oslo University Hospital-Rikshospitalet, Norway, during the six-year period of October 2015 to October 2021. The patients fulfilled the criteria of "probable" iNPH (or "possible" iNPH if no ICP monitoring was performed in our department), according to the American-European guidelines (2). The severity of symptoms was graded according to previously described iNPH scoring of symptom severity, with scores spanning from worst (=3) to best (=15) scores, assessing the combined severity of gait disturbance, urinary incontinence, and dementia (5, 11). It was beyond the scope of this study to examine how MRI biomarkers predict the outcome of shunt surgery.

MRI

The MRI protocol was standardized, as previously described (24, 27). Sagittal 3D T1-weighted gradient-echo volume scans were obtained using a 3 Tesla (3T) Philips Ingenia MRI scanner (Philips Medical systems, Best, The Netherlands), or a 1.5T Aera Siemens MRI scanner (Siemens Erlangen, Germany). Imaging sequence parameters at 3T were: Repetition time (TR) = 'shortest' (typically 5.1ms), echo time (TE) = 'shortest' (typically 2.3 ms), flip angle (FA) = 8, and voxel size 1 mm^3. T1 imaging sequence parameters (T1 MPRAGE) at 1.5T were: TR = 1,900 ms, TE = 2.36 ms and inversion time (TI) = 900 ms, FA = 10 and with voxel size 1 mm^3. Equal MRI protocol settings were used at each scanner before (Baseline), and 24 and 48 h after the intrathecal injection of gadobutrol. At 3T, T1 imaging was also carried out after intrathecal contrast administration on Day 1. We first included patients who were examined in a 3T MRI scanner; they received intrathecal gadobutrol in a dose of 0.5 mmol only. Secondly, we included patients who were examined in a 1.5T MRI scanner; they received intrathecal gadobutrol in the alternating doses of 0.10, 0.25, or 0.5 mmol. For logistic reasons, 1.5T imaging at Day 1 after intrathecal gadobutrol was not feasible.

At both 3T and 1.5T, we also obtained 3D T2 fluid-attenuated inversion recovery (FLAIR) scans. The image parameters at 3T were: TR = 4,800 ms, TE = 'shortest' (typically 318 ms), TI = 1,650 ms, with voxel size 1 mm^3. Image parameters at 1.5T were: TR = 5,000 ms, TR = 337 ms, TI = 1,600, FA = 120 and with voxel size 1 mm^3. In the present study, FLAIR scans were used for assessing Fazeka's grade.

MRI Biomarkers of CSF Dynamics and Glymphatic Enhancement

The MRI biomarkers of CSF flow include two measures:

(a) Estimation of tracer clearance from CSF spaces 24 and 48 h after intrathecal contrast (gadobutrol) administration. For each time point, circular regions of interest (ROIs) were placed on 1 mm thick slices within the CSF of cisterna magna and within a cerebral sulcus underneath the vertex where partial averaging with brain tissue could be avoided, preferably the central sulcus. At the individual level, ROI positions were identical between time points. Measurements were done directly in the hospital Picture archiving and communication system (PACS) (Sectra IDS7, Sectra, Sweden), where each ROI provides the mean T1 signal intensity (in signal units) from the image greyscale. For comparison, we also included the CSF space of the velum interpositum, estimated from FreeSurfer software, which represents an approximately mid-level position between the vertex region and cisterna magna.

(b) We have previously introduced a grading of ventricular reflux of CSF tracer as a marker of pathological CSF redistribution (17, 18). From T1 weighted images, ventricular reflux was graded at 24 h after intrathecal MRI contrast agent administration as follows: Grade 0: No supra-aqueductal reflux. Grade 1: Any sign of transient supra-aqueductal reflux at Day 1. Grade 2: Transient enrichment of lateral ventricles at Day 1. Grade 3: Lasting enrichment of lateral ventricles Day 2 (but not isointense with subarachnoid CSF). Grade 4: Lasting enrichment of lateral ventricles at Day 2 (isointense with subarachnoid CSF). In the current imaging protocol, imaging was not obtainable post-contrast on Day 1 at 1.5T for logistic reasons. This was acceptable as we only consider grades 3–4 on Day 2 indicative of abnormal reflux in iNPH. Therefore, the assessment of grades 1–2 was not examined in this study.

The MRI biomarkers of glymphatic enhancement rely on estimating enrichment of the CSF tracer within extra-vascular brain parenchyma at defined time points after intrathecal CSF tracer administration, as previously described (27). In short, we applied FreeSurfer software (version 6.0) (http://surfer.nmr.mgh.harvard.edu/) for the segmentation, parcellation, and registration/alignment of the longitudinal data, and to determine the tracer-induced increase in T1 signal intensity (32). Using a hybrid watershed/surface deformation procedure (33), non-brain tissue is removed, followed by the segmentation of the subcortical white matter and deep gray matter structures (including the

TABLE 1 | Demographic and clinical information about the different treatment groups.

	Total material	Intrathecal gadobutrol dosage groups				
		1.5T MRI			3T MRI	Significance
		0.10 mmol	0.25 mmol	0.50 mmol	0.50 mmol	
N	95	18	25	19	33	
Sex (F/M; *N*)	36/59	6/12	14/11	7/12	9/24	ns
Age (years)	71.7 ± 5.8	72.3 ± 5.3	72.3 ± 6.2	71.7 ± 4.4	70.8 ± 6.5	ns
Body mass index (kg/m^2)	27.3 ± 4.6	27.5 ± 5.3	27.6 ± 5.3	27.4 ± 4.3	27.0 ± 4.2	ns
Clinical grade						
Symptom duration (years)	3.2 ± 2.6	3.4 ± 3.1	2.8 ± 2.0	3.2 ± 2.4	3.3 ± 2.8	ns
Pre-shunt NPH-score[a]	11 (6–14)	11 (9–12)	11 (6–14)	11 (9–13)	12 (8–14)	[b]P<0.05
Gait sub-score	3 (2–4)	4 (3–4)	3 (2–4)	3 (2–4)	4 (3–4)	ns
Incontinence sub-score	4 (1–5)	4 (3–4)	4 (1–5)	4 (3–5)	4 (2–5)	[c]P<0.05
Dementia sub-score	4 (2–5)	4 (3–4)	4 (2–5)	4 (3–5)	4 (3–5)	ns
Tests of cognitive function						
Mini-mental state (MMS)	27 (14–30)	26 (16–30)	28 (17–30)	27 (20–30)	27 (14–30)	ns

Categorical data presented as numbers; continuous data presented as mean ± standard deviation, NPH-scores and MMS presented as median (ranges in parentheses). Significant differences between dosage groups were determined by the Pearson Chi-square test for categorical data and by ANOVA with Bonferroni post-hoc tests for continuous data. [a]NPH-score refers to our previously published grading of NPH symptoms (5). [b]0 mmol/1.5T MRI and 0.25 mmol/1.5T MRI vs. 0.50 mmol/3T MRI. [c]0.10 mmol and 0.25 mmol vs. 3T MRI.50 mmol. Ns, Non-significant.

hippocampus, amygdala, caudate, putamen, and ventricles) (34, 35). The MR images of each patient were used to create a median template registered to the baseline (36), and for each patient, the MR images were registered to the corresponding template applying a rigid transformation (36). The registrations were checked manually to correct any registration errors. Adjustments for changes in the gray-scale between MRI scans were made by dividing the T1 signal unit for each time point by the T1 signal unit of a reference region of interest (ROI) for the respective time point placed within the posterior part of the orbit (37). This *normalized T1 signal unit* corrects for baseline changes of image greyscale due to automatic image scaling. For visualization, a median template image of each patient group was created for each time point, and a relative change in intensity from before intrathecal gadobutrol to 24 h after gadobutrol was computed. The image was constructed by using the median value of each segmented region, and subsequent using the median of the cohort.

Criteria for Assessing the Lowest Acceptable Dose of Intrathecal Gadobutrol

The criteria for the lowest possible dose of intrathecal gadobutrol refer to the lowest dose needed to maintain necessary diagnostic information: (1) Tracer enrichment in CSF at vertex was obligatory since tracer enrichment in CSF is a requirement for glymphatic enhancement. We previously reported a significant correlation between enrichment in CSF and nearby brain parenchyma (24, 26), and between CSF and nearby parasagittal dura (38). (2) Ventricular tracer enrichment allowing for reliable assessment of ventricular reflux grade. (3) Tracer enrichment in parenchyma allowing for reliable assessment of glymphatic enhancement in brain parenchyma.

MRI Biomarkers of CSF Space Morphology and Neuro-Degeneration

Following our standardized protocol, three MRI biomarkers of CSF space morphology were determined: (a) Evans' index was determined from T1-weighted axially reconstructed images in a plane parallel to a plane defined by a line between the anterior and posterior commissures (AC-PC plane), respectively (1 mm thickness), which is the dividend between the largest diameter of the frontal horns and the largest inner diameter of the cranium in the same slice (39). (b) The callosal angle was measured on T1-weighted coronal images perpendicular to the AC-PC plane, representing the angle between lateral ventricles at the level of the posterior commissure (40). (c) The DESH (disproportional enlarged subarachnoid space hydrocephalus) sign (41) was assessed on T1-weighted coronal images and scored as yes/no; the DESH sign is the combination of 1. Enlarged ventricles; 2. Widening of Sylvian fissure; 3. Tight sulci at upper/medial cerebral convexities.

Our routine further included the determination of three MRI biomarkers of neurodegeneration: (a) The Schelten's score (42) for medial temporal atrophy (MTA) is a visual rating of the width of the choroid fissure, the width of the temporal horn, and the height of the hippocampal formation [Score 0 (no atrophy), score 1 (only widening of choroid fissure), score 2 (also widening of the temporal horn of lateral ventricle), score 3 (moderate loss of hippocampal volume, decrease in height), and score 4 (severe volume loss of hippocampus)]. (b) The Fazeka's scale for white

TABLE 2 | MRI biomarkers of CSF dynamics, ventriculomegaly and neurodegeneration for the different treatment groups.

	Total material		Intrathecal gadobutrol dosage groups				
			1.5T MRI			3T MRI	Significance
			0.10 mmol	0.25 mmol	0.50 mmol	0.50 mmol	
CSF dynamics							
Ventricular reflux	Grade 0	3 (3%)	2 (13%)	–	1 (6%)	–	[a]$P = 0.01$
	Grade 1	2 (2%)	–	–	–	2 (6%)	
	Grade 2	1 (1%)	–	–	–	1 (3%)	
	Grade 3	46 (52%)	12 (80%)	13 (54%)	11 (65%)	10 (30%)	
	Grade 4	37 (42%)	1 (7%)	11 (46%)	5 (29%)	20 (61%)	
CSF space anatomy							
Evans index		0.38 ± 0.04	0.37 ± 0.03	0.38 ± 0.05	0.38 ± 0.03	0.38 ± 0.04	ns
Callosal angel		68.6 ± 20.1	63.2 ± 15.8	67.7 ± 18.2	68.1 ± 18.1	72.0 ± 24.2	ns
DESH (Present/Absent; %)		57/92 (62%)	10/15 (67%)	16/25 (64%)	14/19 (74%)	17/33 (52%)	ns
Neurodegeneration biomarkers							
Scheltens MTA	Grade 0	–	–	–	–	–	ns
	Grade 1	5 (5%)	1 (7%)	1 (4%)	1 (5%)	2 (6%)	
	Grade 2	58 (63%)	7 (47%)	14 (56%)	12 (63%)	25 (76%)	
	Grade 3	29 (32%)	7 (47%)	10 (40%)	6 (32%)	6 (18%)	
Fazekas scale	Grade 0	7 (7.6%)	–	1 (4%)	3 (16%)	3 (9%)	ns
	Grade 1	32 (34.8%)	4 (27%)	10 (40%)	8 (42%)	10 (30%)	
	Grade 2	33 (35.9%)	7 (47%)	10 (40%)	5 (26%)	11 (33%)	
	Grade 3	20 (21.7%)	4 (27%)	4 (16%)	3 (16%)	9 (27%)	
Entorhinal Cortex Thickness (mm)		2.1 ± 0.3	2.1 ± 0.3	2.2 ± 0.2	2.3 ± 0.3	2.0 ± 0.4	[b]$P<0.001$ [c]$P = 0.018$

CSF, Cerebrospinal fluid; DESH, Disproportional enlarged subarachnoid space hydrocephalus; ERC, entorhinal cortex; MRI, magnetic resonance imaging; MTA, medial temporal atrophy. Significant differences between groups were determined by Pearson Chi-square test for categorical data and by ANOVA with Bonferroni post hoc tests for continuous data: [a]0.1 mmol/1.5T MRI vs.0.25 mmol/1.5T MRI; [b]0.5 mmol/1.5T MRI vs. 0.5 mmol/3TMRI; [c]25 mmol/1.5T MRI vs. 0.50 mmol/3T MRI.

matter lesions (43) includes four scores and was assessed at FLAIR [Score 0: None or a single punctate white matter hyperintensity lesion. Score 1: Multiple punctate lesions. Score 2: The beginning confluence of lesions (bridging). Score 3: Large confluent lesions]. (c) Entorhinal cortex thickness was determined on coronally reconstructed T1 volume acquisitions with 1 mm slice thickness at the level of the hippocampal sulcus and measured from the entorhinal cortex surface to the gray/white matter interface, and midway between the tentative location of parasubiculum and perirhinal cortex, as previously described (26).

Statistical Analyses

Statistical analyses were performed using SPSS version 27 (IBM Corporation, Armonk, NY, USA) and Stata/SE 16.1 (StataCrop LLC, College Station, TX, USA).

Continuous data were presented as mean (SD) or mean (95% CI), as appropriate. Group difference between categorical or continuous data was assessed with Pearson Chi-square test or independent samples *t*-test, respectively. Repeated measurements were examined with linear mixed models by maximum likelihood estimation using a subject-specific random intercept. Using the estimated marginal mean from the statistical model, we tested the difference between the individuals with different intrathecal doses and 1.5T or 3T MRI at each time point. The normal distribution assumptions were assessed with descriptive statistics, boxplots, and histograms. It was also conducted for other data in both groups.

Statistical significance was accepted at the 0.05 level (two-tailed).

RESULTS

Patient Material

The study was performed from October 2015 to October 2021 and included 95 patients with iNPH who fulfilled the diagnostic criteria of "Probable" iNPH (or "Possible" iNPH if ICP was not measured in our department), according to the American-European guidelines (2). Demographic and clinical information about the patients is shown in **Table 1**. The patients who received different doses of intrathecal gadobutrol (1.5T MRI: 0.1 mmol, $n = 18$;0.25 mmol, $n = 25$; 0.50 mmol, $n = 19$. 3T MRI: 0.50 mmol, $n = 33$) were comparable, except for significant differences in iNPH scores between some groups (**Table 1**).

The MRI biomarkers of ventriculomegaly and neurodegeneration were comparable across the dosage groups (**Table 2**). Notably, the estimation of entorhinal cortex thickness differed between the groups examined in the 1.5T vs. 3T MRI scanners (**Table 2**), probably related to the higher signal-to-noise ratio in the 3T vs. the 1.5T MRI and thereby better distinction of the gray-/white matter interface.

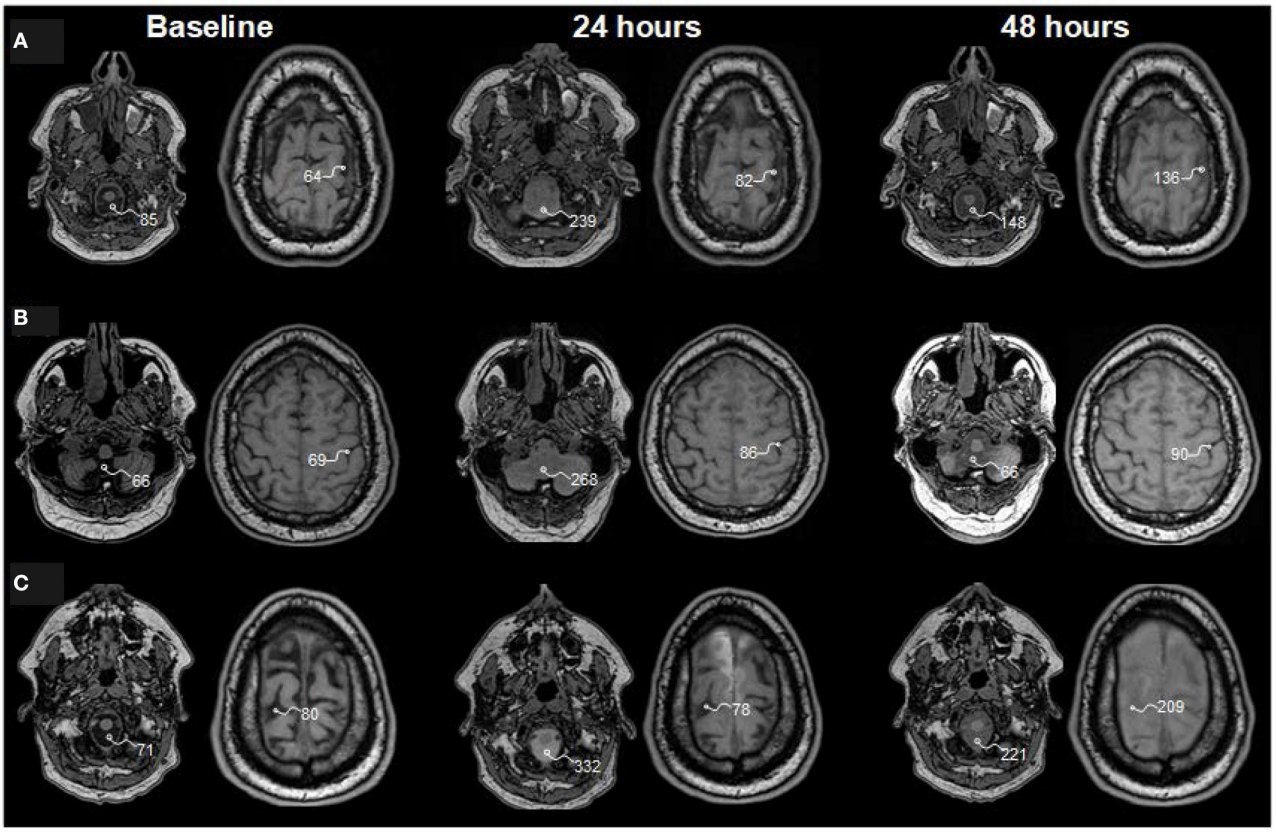

FIGURE 1 | Tracer enrichment within subarachnoid cerebrospinal fluid (CSF) spaces at baseline and 24 and 48 h after intrathecal injection of gadobutrol in doses of **(A)** 0.10 mmol, **(B)** 0.25 mmol, and **(C)** 0.50 mmol. Reconstructed axial T1 weighted images from three patients with idiopathic normal pressure hydrocephalus (iNPH) who were examined in a 1.5T MRI scanner. The T1 signal unit values within regions of interest in cisterna magna and at the vertex are shown and exemplify the strongest increase of T1 signal units after intrathecal gadobutrol in the dose of 0.5 mmol. For analysis of change in T1 signal units, we further normalize the T1 signal units against a region of interest placed within the posterior part of the orbit (not shown here), which provides normalized signal units (37). See **Tables 3**, **4**.

In this cohort of 95 patients with iNPH, it should be noted that ventricular reflux grade 3–4 was present in 83/89 (93%) of patients, an MTA score of 3 was seen in 29/92 (32%) of patients, and a Fazekas score of 3 in 20/92 (22%) of patients.

Tracer Enrichment Within the Subarachnoid CSF Space

Intrathecal gadobutrol enriched the CSF of the subarachnoid space, which is visualized as the increase in the T1 signal units. **Figure 1** shows in three patients with iNPH the changes in T1 signal units before normalization within CSF regions of interest at cisterna magna and vertex after different doses of intrathecal gadobutrol. The dose-dependent enrichment of CSF spaces is further presented in **Figure 2** as the percentage change in normalized T1 signal at 24 and 48 h within CSF of cisterna magna (**Figure 2A**), vertex (**Figure 2B**), and velum interpositum (**Figure 2C**). **Table 3** further presents for the different regions the signal units, as well as signal unit ratio and percentage change after 24 and 48 h from before contrast. The tracer enrichment in CSF at vertex after intrathecal gadobutrol in a dose of 0.10 mmol was deemed too low (**Figure 2C**). There were significant differences for the different doses of intrathecal gadobutrol (0.10, 0.25, or 0.50 mmol), and marked differences in tracer enrichment within CSF between 1.5T and 3T MRI scanners for the same dose of intrathecal gadobutrol (0.50 mmol) (**Figures 2D–F**).

Ventricular Reflux of Tracer

The grading of ventricular reflux of CSF tracer differed somewhat between groups receiving either 0.10 or 0.25 mmol (**Table 2**). How differences in ventricular reflux at 24 h are visualized for different doses of intrathecal gadobutrol are illustrated in **Figure 3**. The percentage increase in normalized T1 signal within ventricles at 24 h at the group level is shown in **Figure 4**; information about signal units and signal unit ratios are presented in **Table 3**. As further demonstrated in **Figures 5A–C**, there was a dose-dependent change in normalized T1 signal within ventricles at 24 h. Notably, all three doses of 0.10, 0.25, and 0.5 mmol were adequate for the visualization of ventricular reflux grade at 24 h (**Figures 5A–C**). The ventricular tracer enrichment differed markedly between the 1.5T and 3T MRI scanners (**Figures 5D–F**). Hence, the visualization of ventricular reflux assessment is affected by both dose and magnetic field strength, but the information about reflux grade is maintained by an intrathecal dose of 0.10 mmol gadobutrol.

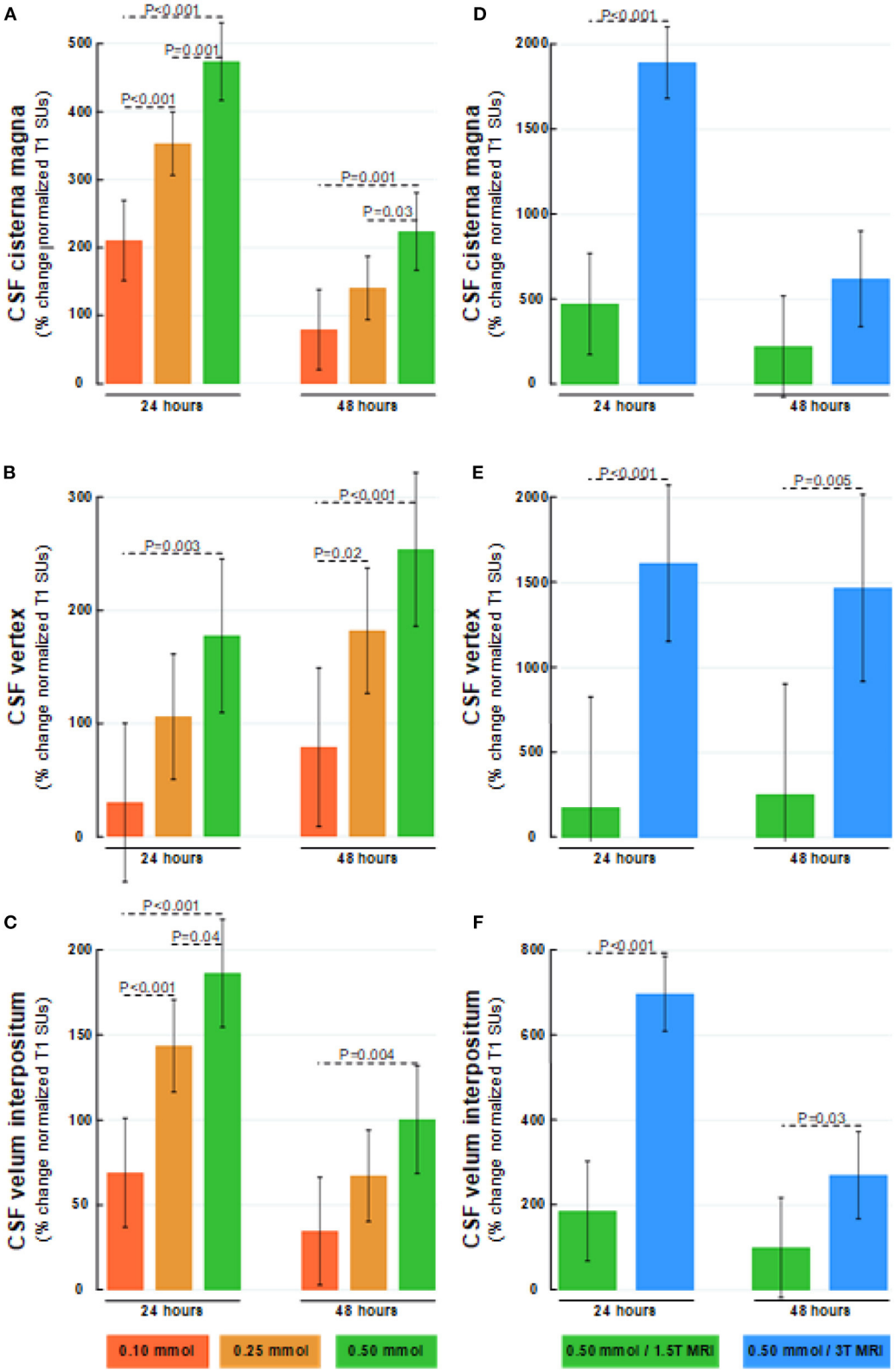

FIGURE 2 | Dose-dependent percentage changes in normalized T1 signal (1.5T MRI scanner) after 24 and 48 h are shown for **(A)** CSF of cisterna magna, **(B)** CSF at the vertex, and **(C)** CSF within velum interpositum calculated from FreeSurfer software following intrathecal gadobutrol in doses of 0.10 mmol (red bars), 0.25 mmol (orange bars), and 0.50 mmol (green bars). The normalized T1 signal at 24 and 48 h after intrathecal gadobutrol (0.50 mmol) within **(D)** CSF of cisterna magna, **(E)** CSF at the vertex, and **(F)** CSF within velum interpositum are shown for 1.5T (green bars) and 3T MRI scanners (blue bars). The bars show mean and 95% confidence intervals. Differences between groups were determined by mixed model analysis.

TABLE 3 | Dose-dependent change in T1 signal units and normalized T1 signal within some regions of interest.

	0.10 mmol/1.5T MRI										
	Pre			24 h				48 h			
Anatomical region	**ROI**	**REF**	**SU-ratio**	**ROI**	**REF**	**SU-ratio**	**%Change**	**ROI**	**REF**	**SU-ratio**	**%Change**
CSF cisterna magna	85 ± 17	386 ± 59	0.22 ± 0.04	253 ± 54	385 ± 56	0.67 ± 0.15	210 ± 89	156 ± 44	397 ± 61	0.39 ± 0.08	79 ± 41
CSF vertex	80 ± 19	386 ± 59	0.21 ± 0.04	101 ± 43	385 ± 56	0.26 ± 0.09	30 ± 50	144 ± 43	397 ± 61	0.36 ± 0.10	79 ± 47
CSF velum interpositum	128 ± 26	386 ± 59	0.33 ± 0.05	215 ± 50	385 ± 56	0.56 ± 0.12	70 ± 35	174 ± 32	397 ± 61	0.44 ± 0.08	35 ± 20
4th ventricle	100 ± 13	386 ± 59	0.26 ± 0.04	222 ± 46	385 ± 56	0.58 ± 0.11	125 ± 36	160 ± 34	397 ± 61	0.40 ± 0.07	57 ± 30
3rd ventricle	93 ± 11	386 ± 59	0.24 ± 0.02	206 ± 54	385 ± 56	0.54 ± 0.13	123 ± 123	150 ± 36	397 ± 61	0.38 ± 0.08	57 ± 33
Lateral ventricles	93 ± 11	386 ± 59	0.24 ± 0.02	182 ± 53	385 ± 56	0.47 ± 0.12	98 ± 50	140 ± 33	397 ± 61	0.35 ± 0.07	48 ± 32
Cerebral cortex	221 ± 27	386 ± 59	0.58 ± 0.05	240 ± 31	385 ± 56	0.63 ± 0.05	9 ± 7	241 ± 32	397 ± 61	0.61 ± 0.05	6 ± 4
Cerebral white matter	282 ± 35	386 ± 59	0.73 ± 0.05	289 ± 34	385 ± 56	0.76 ± 0.05	4 ± 4	297 ± 39	397 ± 61	0.75 ± 0.06	3 ± 3
	0.25 mmol/1.5T MRI										
CSF cisterna magna	80 ± 12	365 ± 44	0.22 ± 0.03	368 ± 77	382 ± 49	0.98 ± 0.22	353 ± 115	200 ± 44	389 ± 56	0.52 ± 0.12	141 ± 56
CSF vertex	69 ± 16	365 ± 44	0.19 ± 0.04	136 ± 80	382 ± 49	0.37 ± 0.24	106 ± 158	195 ± 63	389 ± 56	0.52 ± 0.20	182 ± 123
CSF velum interpositum	120 ± 18	365 ± 44	0.33 ± 0.05	304 ± 57	382 ± 49	0.81 ± 0.18	145 ± 53	211 ± 36	389 ± 56	0.55 ± 0.11	67 ± 32
4th ventricle	94 ± 14	365 ± 44	0.26 ± 0.03	334 ± 69	382 ± 49	0.89 ± 0.21	244 ± 76	202 ± 41	389 ± 56	0.53 ± 0.11	105 ± 42
3rd ventricle	87 ± 9	365 ± 44	0.24 ± 0.02	320 ± 73	382 ± 49	0.85 ± 0.22	252 ± 84	192 ± 42	389 ± 56	0.50 ± 0.12	108 ± 45
Lateral ventricles	86 ± 8	365 ± 44	0.24 ± 0.02	274 ± 61	382 ± 49	0.72 ± 0.17	210 ± 66	177 ± 39	389 ± 56	0.46 ± 0.10	96 ± 42
Cerebral cortex	200 ± 30	365 ± 44	0.55 ± 0.07	253 ± 29	382 ± 49	0.67 ± 0.08	23 ± 19	246 ± 28	389 ± 56	0.64 ± 0.07	17 ± 15
Cerebral white matter	260 ± 29	365 ± 44	0.71 ± 0.05	295 ± 28	382 ± 49	0.78 ± 0.06	9 ± 5	297 ± 32	389 ± 56	0.77 ± 0.06	8 ± 5
	0.50 mmol/1.5T MRI										
CSF cisterna magna	82 ± 16	382 ± 42	0.22 ± 0.03	475 ± 183	389 ± 42	1.21 ± 0.44	473 ± 222	276 ± 101	403 ± 43	0.69 ± 0.26	224 ± 127
CSF vertex	68 ± 11	382 ± 42	0.18 ± 0.03	188 ± 165	389 ± 42	0.47 ± 0.39	178 ± 223	250 ± 119	403 ± 43	0.62 ± 0.29	254 ± 159
CSF velum interpositum	121 ± 21	382 ± 42	0.32 ± 0.04	345 ± 139	389 ± 42	0.90 ± 0.38	186 ± 143	250 ± 82	403 ± 43	0.63 ± 0.22	100 ± 79
4th ventricle	102 ± 15	382 ± 42	0.27 ± 0.04	375 ± 160	389 ± 42	0.97 ± 0.42	269 ± 174	249 ± 88	403 ± 43	0.63 ± 0.23	136 ± 91
3rd ventricle	91 ± 8	382 ± 42	0.24 ± 0.01	359 ± 162	389 ± 42	0.93 ± 0.44	290 ± 191	235 ± 91	403 ± 43	0.59 ± 0.24	148 ± 105
Lateral ventricles	92 ± 14	382 ± 42	0.24 ± 0.03	313 ± 140	389 ± 42	0.81 ± 0.38	247 ± 175	214 ± 80	403 ± 43	0.54 ± 0.21	128 ± 96
Cerebral cortex	214 ± 28	382 ± 42	0.56 ± 0.05	265 ± 40	389 ± 42	0.68 ± 0.09	23 ± 24	272 ± 33	403 ± 43	0.68 ± 0.07	22 ± 19
Cerebral white matter	276 ± 30	382 ± 42	0.72 ± 0.05	301 ± 28	389 ± 42	0.78 ± 0.06	7 ± 8	319 ± 30	403 ± 43	0.79 ± 0.05	10 ± 8
	0.50 mmol/3T MRI										
CSF cisterna magna	14 ± 6	187 ± 89	0.07 ± 0.02	254 ± 125	185 ± 90	1.41 ± 0.48	1893 ± 844	131 ± 73	241 ± 130	0.59 ± 0.32	810 ± 584
CSF vertex	10 ± 5	187 ± 89	0.05 ± 0.02	146 ± 139	185 ± 90	0.79 ± 0.67	1616 ± 1741	165 ± 154	241 ± 130	0.70 ± 0.55	1295 ± 1157
CSF velum interpositum	32 ± 18	187 ± 89	0.17 ± 0.03	235 ± 127	185 ± 90	1.29 ± 0.43	698 ± 338	154 ± 78	241 ± 130	0.69 ± 0.26	328 ± 197
4th ventricle	18 ± 10	187 ± 89	0.10 ± 0.02	224 ± 117	185 ± 90	1.24 ± 0.46	1242 ± 583	114 ± 48	241 ± 130	0.53 ± 0.26	510 ± 333
3rd ventricle	20 ± 11	187 ± 89	0.10 ± 0.01	225 ± 122	185 ± 90	1.25 ± 0.48	1137 ± 528	117 ± 53	241 ± 130	0.55 ± 0.28	460 ± 313
Lateral ventricles	14 ± 8	187 ± 89	0.07 ± 0.02	168 ± 95	185 ± 90	0.94 ± 0.44	1534 ± 818	79 ± 41	241 ± 130	0.39 ± 0.25	556 ± 474
Cerebral cortex	59 ± 32	187 ± 89	0.31 ± 0.02	105 ± 52	185 ± 90	0.57 ± 0.12	86 ± 40	124 ± 67	241 ± 130	0.52 ± 0.12	67 ± 38
Cerebral white matter	106 ± 51	187 ± 89	0.56 ± 0.04	134 ± 64	185 ± 90	0.73 ± 0.08	30 ± 14	177 ± 92	241 ± 130	0.74 ± 0.11	30 ± 16

ROI, Region of interest for each anatomical region. REF, Reference region of interest within the posterior orbit. SU-Ratio, Signal unit ratio refers to signal unit within the particular region of interest (ROI) divided by the unit within the orbita serving as reference (REF). The percentage (%) change refers to the percentage change in signal unit ratio after 24 and 48 h relative to before contrast (Pre).

There was a close association between ventricular reflux grade and tracer enrichment within ventricles for intrathecal gadobutrol in doses of 0.10 or 0.50 mmol (**Figure 6**).

Furthermore, it should be noted that more pronounced ventricular reflux was accompanied by reduced callosal angle (ventricular reflux scores 0–2 vs. 3–4: 95 ± 40° vs. 67 ± 17°; $P = 0.001$; independent samples *t*-test).

Tracer Enrichment Within the Brain Parenchyma

As illustrated in **Figure 7**, the CSF tracer enrichment within the brain parenchyma, indicative of glymphatic enhancement, depended on the dose of intrathecal gadobutrol, as well as on the application of either 1.5T or 3T MRI. Intrathecal gadobutrol in a dose 0.10 mmol gave significantly less change in normalized

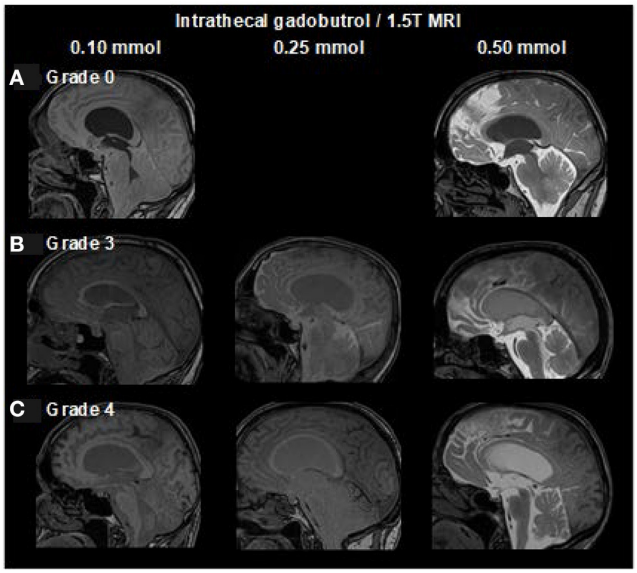

FIGURE 3 | Dose-dependent visualization of ventricular reflux of CSF tracer from sagittal reconstructed T1 weighted images (1.5T MRI) at 24 h after intrathecal gadobutrol in doses of 0.10, 0.25, and 0.50 mmol. Ventricular reflux is categorized into five categories: **(A)** Grade 0: No supra-aqueductal reflux. Grade 1: Sign of supra-aqueductal reflux Day 1. Grade 2: Transient enrichment of lateral ventricles Day 1. **(B)** Grade 3: Lasting enrichment of lateral ventricles Day 2 (not isointense with CSF subarachnoid). **(C)** Grade 4: Lasting enrichment of lateral ventricles Day 2 (isointense with CSF subarachnoid). At 1.5T, MRI was not obtained post-contrast at Day 1, which allowed for scoring of grades 0, 3, and 4 only. In iNPH, we only consider grades 3 to 4 Day 2 at 24 h as abnormal (18).

T1 signal within the cerebral cortex (**Figure 8A**) and cerebral white matter (**Figure 8B**). See also **Table 3**. An intrathecal dose of 0.10 mmol gadobutrol gave an average increase in normalized T1 signals below 10% in the cerebral cortex (**Figure 8A**) and below 5% in subcortical white matter (**Figure 8B**), which we deemed insufficient for assessment of glymphatic enhancement. After intrathecal gadobutrol in a dose of 0.50 mmol, the 1.5T MRI scanner gave markedly lower tracer enrichment in the cerebral cortex (**Figure 8C**) and cerebral white matter (**Figure 8D**) than the 3T MRI scanner. The same results were seen within various brain sub-regions, as further detailed in **Table 4**.

As shown in **Table 5**, there was a highly significant positive correlation between tracer enrichment within the CSF of subarachnoid spaces and tracer enrichment within the brain parenchyma, though correlations were strongest for intrathecal gadobutrol in a dose of 0.5 mmol. Furthermore, the location of measurements matters, with the strongest correlations between CSF tracer at vertex and enrichment in the cerebral cortex and the strongest correlations between CSF tracer at cisterna magna and enrichment within the entorhinal cortex.

Considering the entire material, we also note a significant relationship between entorhinal cortex (ERC) thickness and tracer enrichment within entorhinal cortex gray matter (**Figure 9A**) and entorhinal cortex white matter (**Figure 9B**). Thereby, reduced clearance of tracer from entorhinal cortex shown as higher tracer levels at 24 h was accompanied by the reduced thickness of the entorhinal cortex.

DISCUSSION

This study provides new insights about the utility of intrathecal gadobutrol to assess MRI biomarkers of CSF dynamics and glymphatic enhancement, where a reduction of dose from 0.50 to 0.25 mmol maintained necessary diagnostic information. We deemed a dose of 0.10 mmol insufficient because of too low tracer enrichment in CSF at the vertex and too low enrichment in the cerebral cortex and subcortical white matter. In iNPH, we found significant reflux of tracer toward ventricles (grades 3–4, indicative of marked ventricular re-direction of CSF flow), and a strong association between clearance of tracer from CSF and brain parenchyma, suggesting brain molecular clearance is dependent on CSF clearance. The modest tracer enrichment beneath the skull vertex indicates a minor role of arachnoid granulations in CSF efflux.

In previous studies, we have applied intrathecal gadobutrol in a dose of 0.5 mmol, which has been found safe (30, 31). A systematic review concluded that no severe complications have been shown for gadolinium-based contrast agents in doses of 1.0 mmol and lower, though toxic effects have been shown in doses above 1.0 mmol (28). The present study provides evidence that the diagnostic imaging information of intrathecal gadobutrol is maintained at 0.25 mmol, while a dose of 0.10 mmol seems too low at 1.5T. Moreover, 3T MRI seems preferable above 1.5T MRI, while the latter is sufficient for the biomarkers in question with a dose of 0.25 mmol. Intrathecal MRI contrast agents are presently used off-label, primarily because of potential neurotoxicity and concerns about deposition within the brain (44). However, the risk of deposition within the brain of gadobutrol when given in intrathecal doses of 0.25 or 0.50 mmol seems minor 0. After 4 weeks, we have not found changes in normalized T1 signals in any brain regions (27). After routinely intravenous administration, there is also the passage of contrast to the CSF in humans (45–47) as previously shown in animals (48). Gadobutrol is approved for intravenous use in dosage of 0.1–0.3 mmol/kg, which in a 80 kg adult represents 8–24 mmol body dose, i.e., 16–60 times higher than intrathecal doses of 0.25 and 0.50 mmol, respectively. Therefore, we consider that intrathecal gadobutrol in doses 0.25–0.50 mmol has an acceptable risk profile while the benefit is substantial, given the opportunity to retrieve unique information about disturbed CSF homeostasis. In our opinion, the therapeutic index (i.e., risk-benefit ratio) of intrathecal gadobutrol is acceptable, justifying its clinical application.

In this study, the increasing dose from 0.25 to 0.50 mmol at 1.5T provided only a modest signal increase in CSF spaces and brain tissue (**Figures 2**, **5**, **8**). At this magnetic field strength, it, therefore, seems reasonable to avoid doses higher than 0.25 mmol, while 0.10 mmol was deemed insufficient. It, therefore, seems that an intrathecal dose of 0.25 mmol is close to ideal for 1.5T. The effect on percentage signal increase in CSF and

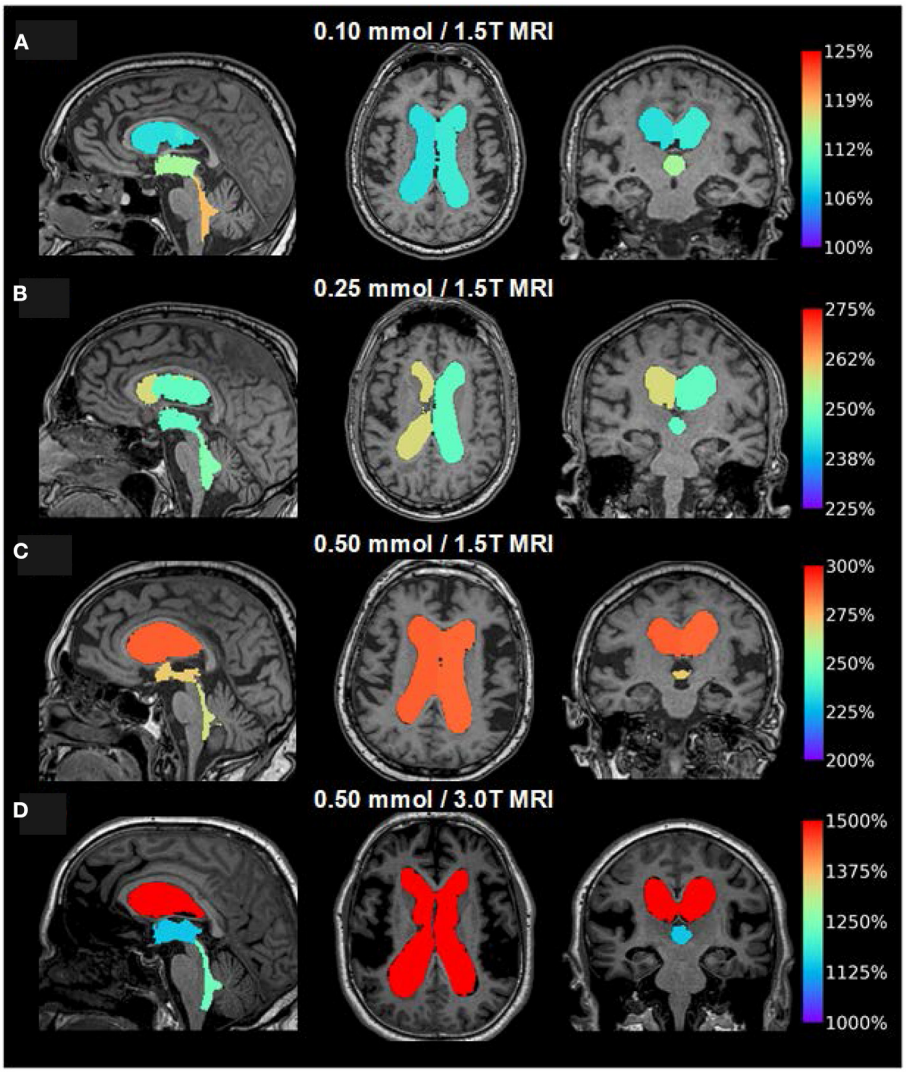

FIGURE 4 | Visualization of dose-dependent tracer enrichment at group level 24 h after intrathecal gadobutrol in the doses **(A)** 0.10 mmol (1.5T MRI; $n = 18$), **(B)** 0.25 mmol (1.5T MRI; $n = 25$), **(C)** 0.50 mmol (1.5T MRI; $n = 19$), and **(D)** 0.50 mmol (3T MRI; $n = 33$). The percentage change in a normalized T1 signal is indicated on the color bar to the right. It should be noted that the scale bar to the right differs for figures **(A–D)**.

brain tissue by increasing the magnetic field strength was, on the other side, much larger than the effect of increasing the contrast dose. We can therefore not rule out that 0.10 mmol may be sufficient at field strengths higher than 1.5T, and this could be explored in later studies. While the intrinsic signal-to-noise ratio (SNR) in MRI increases with field strength, signal unit change will also depend on the applied TR and TE, and the impact on using 3T at 0.1 mmol will therefore also depend on sequence parameters (49). It should also be noted that T1 signal increase in the MRIs is not necessarily proportional with the concentration of contrast agent, therefore the percentage change in normalized signal units is in this study used with the intention to illustrate by numbers how effects appear visually to a reader of MR images. To further increase sensitivity for the detection of contrast agents within the CSF spaces, other sequences might in future studies show to be of benefit, for instance, post-contrast FLAIR or T1 with blood suppression ("black blood"). Whether these techniques can maintain sufficient sensitivity for detection of enhancement within the brain remains to be seen.

We have previously shown that ventricular reflux of tracer characterizes iNPH disease (18). This study extends our previous observations showing ventricular reflux grades 3–4 in about 9/10 patients with iNPH. Estimation of tracer enrichment within ventricles using FreeSurfer software showed that tracer enrichment closely follows the categorical grading of reflux. Phase-contrast MRI supports the net retrograde aqueductal flow of CSF in iNPH (17, 50, 51). Others also reported

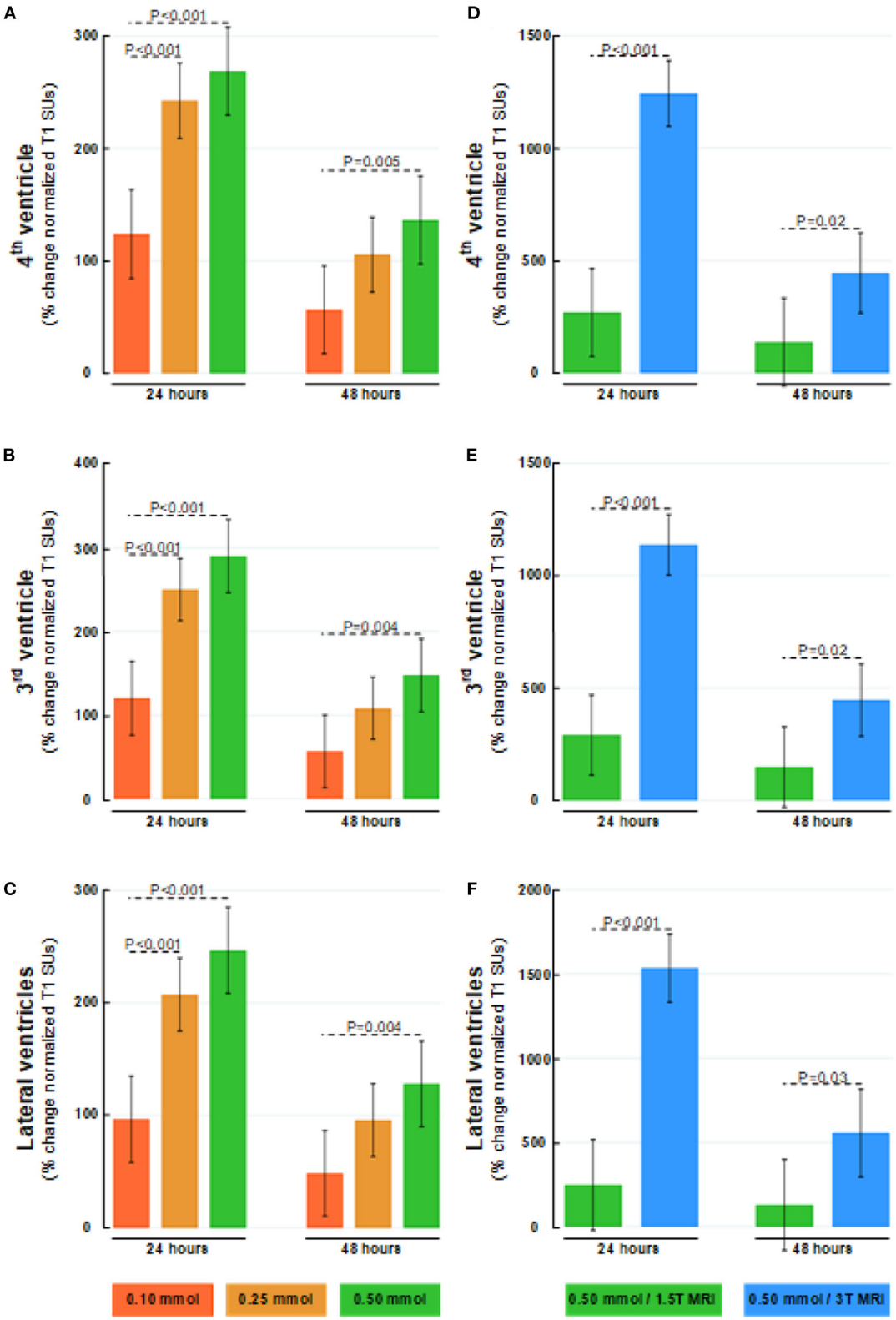

FIGURE 5 | Dose-dependent percentage changes in normalized T1 signal (1.5T MRI scanner) after 24 and 48 h are shown for **(A)** 4th ventricle, **(B)** 3rd ventricle, and **(C)** lateral ventricles following intrathecal gadobutrol in doses of 0.10 (red bars), 0.25 (orange bars), and 0.50 mmol (green bars). The percentage change in normalized T1 signal at 24 and 48 hours after intrathecal gadobutrol (0.50 mmol) within **(D)** 4th ventricle, **(E)** 3rd ventricle, and **(F)** lateral ventricles are shown for 1.5T (green bars) and 3T MRI scanners (blue bars). The bars show mean and 95% CIs. Differences between groups were determined by mixed model analysis.

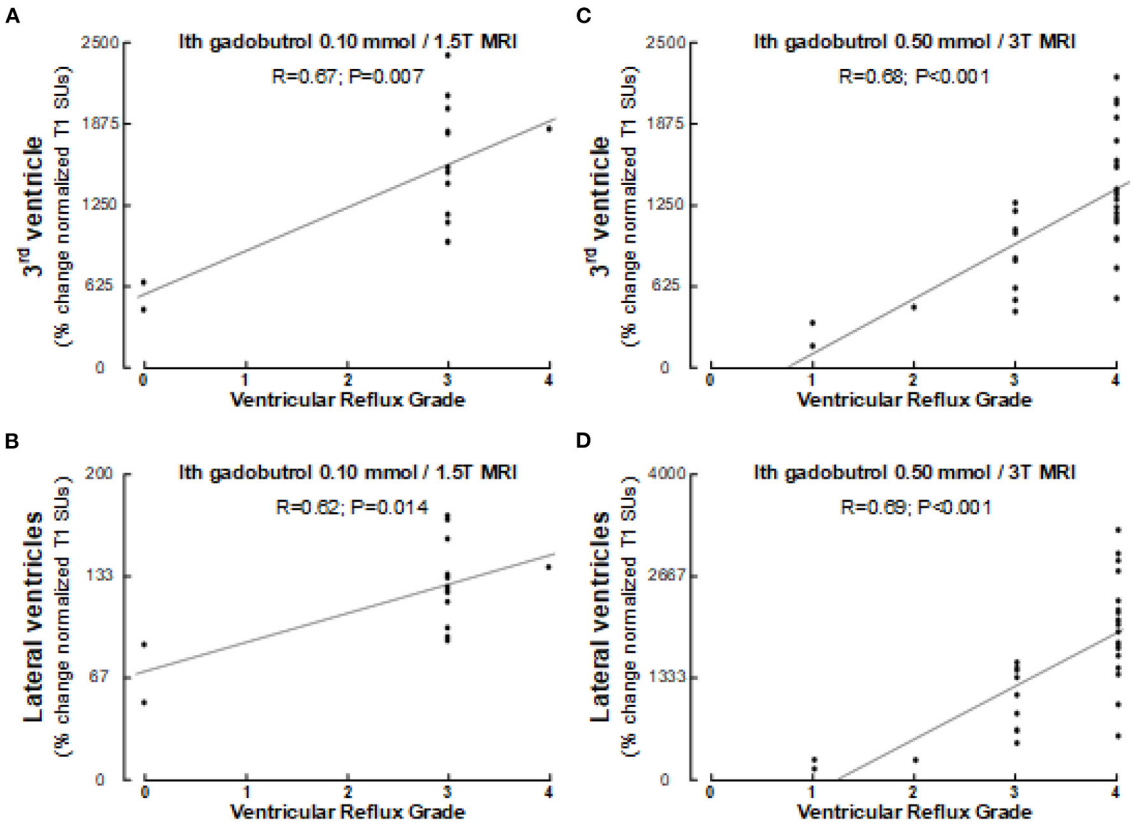

FIGURE 6 | Association between ventricular reflux grade and tracer enrichment 24 h after intrathecal gadobutrol.1 mmol (1.5T MRI) within **(A)** 3rd ventricle and **(B)** lateral ventricles, and between ventricular reflux grade and tracer enrichment 24 h after intrathecal gadobutrol 0.5 mmol (3T MRI) within **(C)** 3rd ventricle and **(D)** lateral ventricles. Pearson correlations with significance levels are shown. Of note, Pearson and Spearman's correlations were similar.

net retrograde CSF flow within the cerebral aqueduct in patients with communicating hydrocephalus (50, 52–56). On the contrary, other disease categories of CSF disturbance, e.g., idiopathic intracranial hypertension and spontaneous intracranial hypotension or brain cysts, demonstrated no ventricular reflux of tracer (17). Likewise, individuals without CSF disturbance showed no ventricular tracer reflux (17), or net retrograde aqueductal flow (51). The ventricular reflux grades 3–4 indicates net CSF flow from fourth to third to lateral ventricles, indicating redirection of CSF flow in iNPH disease. Accordingly, a pressure gradient toward the ventricles enables molecular passage via the cerebral aqueduct into the lateral ventricles and transependymal fluid transport to periventricular white matter. Efflux of CSF also seems to occur *via* the choroid plexus (57). It is of note that reflux grades 3–4 were accompanied by reduced callosal angle as compared with reflux grades 0–2. Hence, in iNPH, the inward pressure gradient, molecular reflux, and need for transependymal transport may underlie the particular ventricular shape characterized by reduced callosal angle and upward movement of the brain along the *z*-axis (58).

Whether reflux grade is predictive for shunt responsiveness was out of scope for this work. We have previously shown that patients with iNPH with reflux grades 3–4 also presented with increased pulsatile ICP during overnight ICP monitoring (18), which is highly predictive for shunt responsiveness in iNPH (5). This patient material only included patients with iNPH. With regard to ventricular reflux, only 6 individuals had reflux grades 0–2, in part since grades 1–2 could not be scored at exams performed at 1.5T due to the imaging routine. However, further studies are needed to address this.

Tracer enrichment at vertex peaked after 48 h for all doses, while enrichment in cerebral ventricles peaked at 24 h. In a previous study (59), we found that the time to peak concentration in blood of intrathecal gadobutrol (0.5 mmol) was 12.1 ± 3.8 h. Molecular egress from CSF to blood is therefore much faster than peak CSF concentration at a vertex. While the traditional view states that arachnoid granulations serve as a major route for CSF efflux (60), the present observations point to a minor role of this efflux route.

The brain-wide enrichment of tracer occurs in the extra-vascular space since the tracer is contained outside the blood

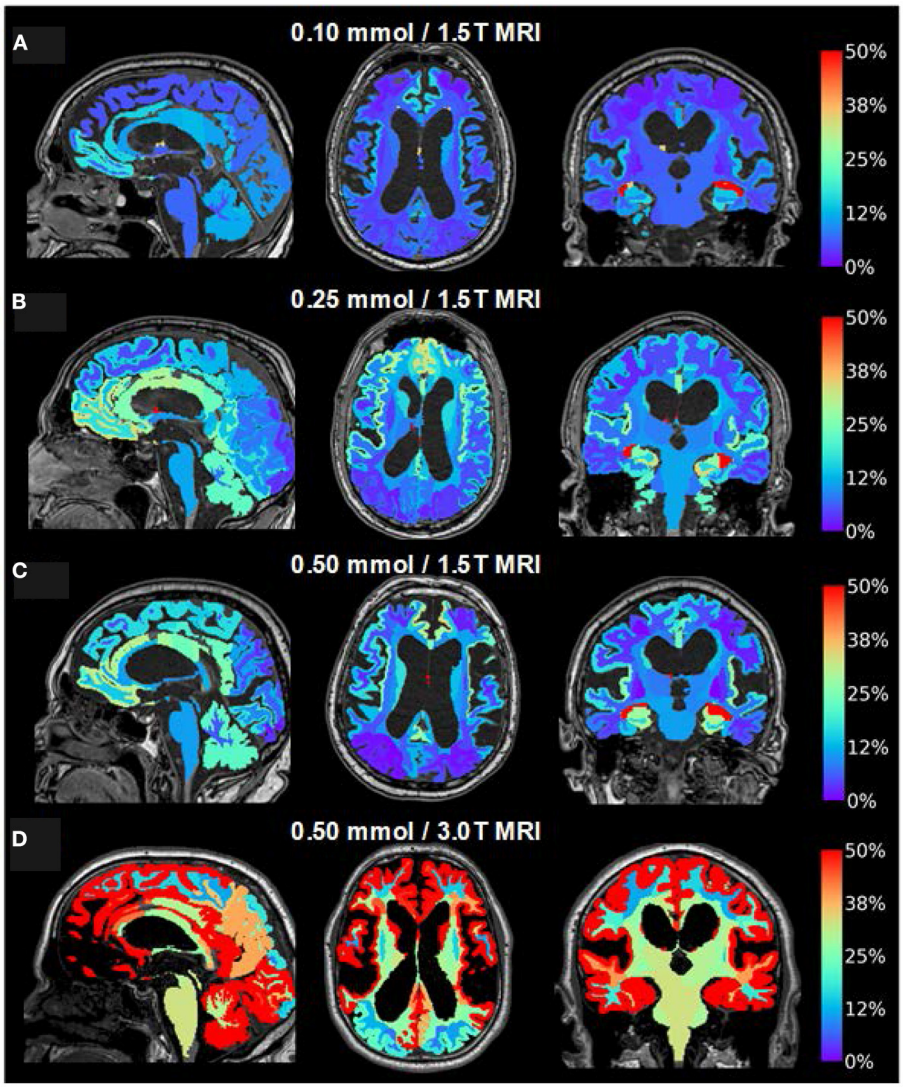

FIGURE 7 | Visualization of dose-dependent brain-wide tracer enrichment at group level 24 h after intrathecal gadobutrol in the doses **(A)** 0.10 mmol (1.5T MRI; $n = 18$), **(B)** 0.25 mmol (1.5T MRI; $n = 25$), **(C)** 0.50 mmol (1.5T MRI; $n = 19$), and **(D)** 0.50 mmol (3T MRI; $n = 33$). The percentage change in the normalized T1 signal is indicated on the color bar to the right.

vessels because of the blood-brain barrier. We refer to this as glymphatic enhancement since the tracer passes in the perivascular spaces and the interstitial tissue. Tracer enrichment is most pronounced in brain areas nearby large blood vessels, which may indicate a role of the forces created by the pulsatile arteries. The present observations indicate comparable tracer enrichment within brain parenchyma at 24 h for intrathecal gadobutrol in doses of 0.25 and 0.50 mmol, though tracer was far better visualized by 3T than 1.5T MRI, i.e., the effect of increasing magnetic field strength was larger on contrast dependent T1 signal increase.

It is reasonable to hypothesize that the transport of gadobutrol within the CSF and brain compartments mimics the transport of other molecules and metabolic by-products such as amyloid-β and tau. Intrathecal gadobutrol with a molecular weight of about 604 Da does not cross a healthy BBB and distributes in the brain via extra-vascular spaces (61). This contrast agent is highly hydrophilic with an estimated hydraulic diameter of <2 nm (27), enabling it to pass between the perivascular and interstitial space via astrocytic endfeet gaps of about 20 nm. In comparison, amyloid-β isomers and tau are cleared along extra-vascular pathways (22, 62); the outer diameter of amyloid-β oligomers is as well <20 nm (63). While there is no known BBB transporter for tau, some common amyloid-β isoforms have significant clearance over the BBB, even though some of the most toxic amyloid-β isoforms are clear *via* the extravascular pathways (64, 65). Therefore, clearance of gadobutrol from the brain may be a suitable surrogate marker for brain clearance of endogenous metabolites such as toxic amyloid-β isoforms and tau.

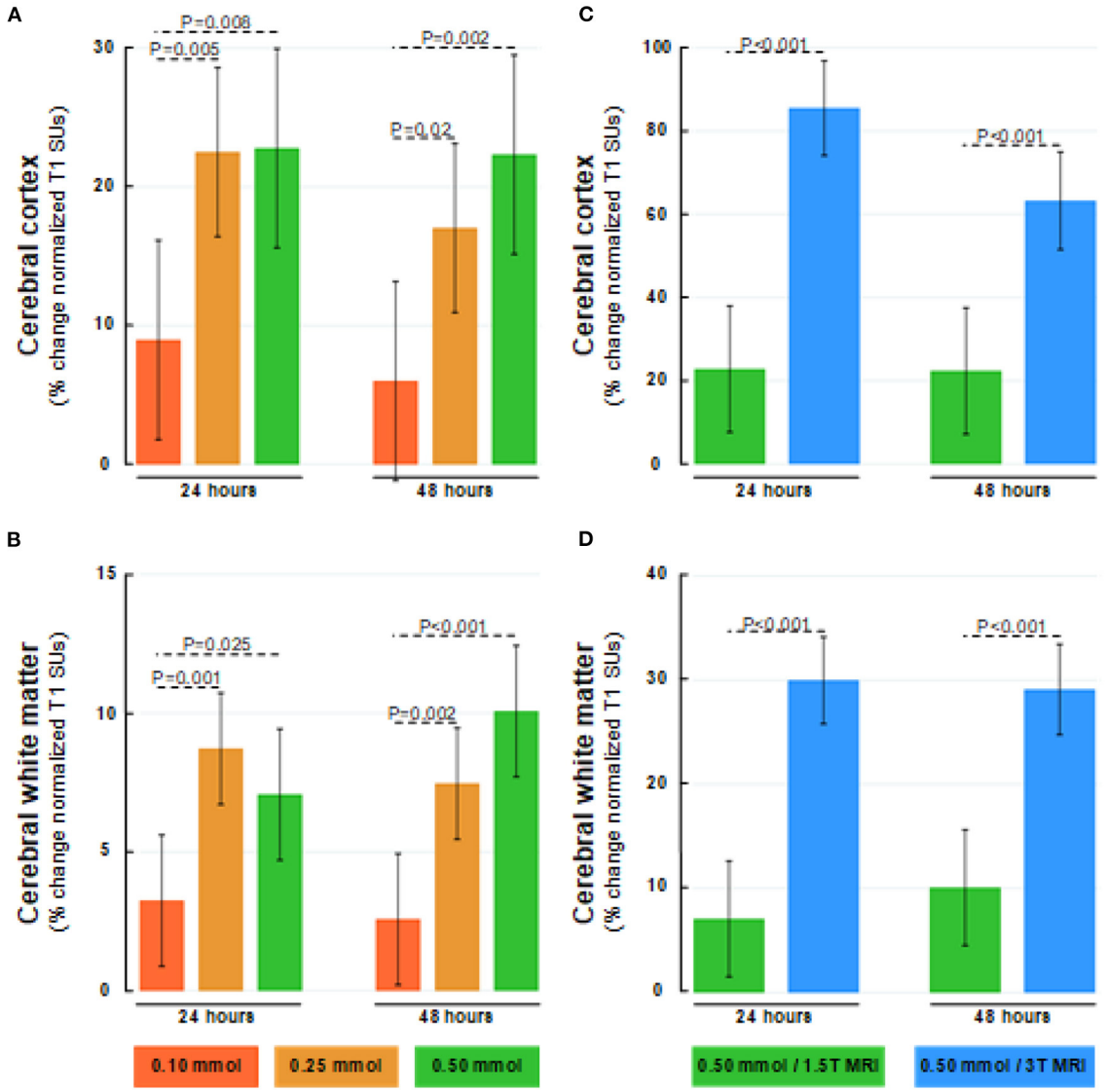

FIGURE 8 | Dose-dependent percentage changes in normalized T1 signal (1.5T MRI scanner) after 24 and 48 h within **(A)** cerebral cortex (gray matter), and **(B)** cerebral white matter after intrathecal gadobutrol in doses of 0.10 mmol (red bars), 0.25 mmol (orange bars), and 0.50 mmol (green bars). The percentage change in normalized T1 signal at 24 and 48 h after intrathecal gadobutrol (0.50 mmol) within **(C)** cerebral cortex (gray matter), and **(D)** cerebral white matter are shown for 1.5T (green bars) and 3T MRI scanners (blue bars). The bars show mean and 95% CIs. Differences between groups were determined by mixed model analysis.

Since dementia is an important part of iNPH disease, we have particularly addressed the alterations occurring within the entorhinal cortex. This region in the medial temporal lobe provides a major convergent neuronal input to the hippocampus after receiving direct projections from the neocortex. The entorhinal-hippocampal circuit plays a key role in learning and memories for locations and events (66–68). In Alzheimer's disease, neuronal degeneration within the entorhinal cortex occurs at an early time (69). Numerous studies have provided evidence of thinning of the entorhinal cortex visualized by MRI in mild cognitive impairment and dementia such as early Alzheimer's disease (70–74). Moreover, degeneration and thinning of the entorhinal cortex were accompanied by increased postmortem neurofibrillary tangle burden and amyloid-β (Aβ) load (75). We previously reported that patients with iNPH presented with reduced entorhinal cortex thickness, as compared with references (18). The present data extend previous observations by demonstrating a significant negative correlation between entorhinal cortex thickness and normalized T1 signal units at 24 h within the entorhinal cortex and entorhinal cortex white matter. Accordingly, higher tracer enrichment at 24 h, which is indicative of reduced molecular clearance, was accompanied by thinning of the entorhinal cortex. This supports the idea that reduced clearance of toxic metabolic by-products may be accompanied by neurodegeneration and hence reduced cortical thickness. The present data highlight that there may be

TABLE 4 | Dose-dependent change T1 signal units and normalized T1 within different brain regions after 24 h.

	0.10 mmol/1.5T MRI										
	Pre			24 h				48 h			
Anatomical region	**ROI**	**REF**	**Ratio**	**ROI**	**REF**	**Ratio**	**%Change**	**ROI**	**REF**	**Ratio**	**%Change**
Frontal cortex (GM)	214 ± 27	386 ± 59	0.56 ± 0.05	233 ± 30	385 ± 56	0.61 ± 0.06	10 ± 8	232 ± 30	397 ± 61	0.59 ± 0.04	6 ± 5
Frontal cortex (WM)	273 ± 35	386 ± 59	0.71 ± 0.06	280 ± 32	385 ± 56	0.73 ± 0.06	3 ± 4	287 ± 36	397 ± 61	0.73 ± 0.05	2 ± 3
Temporal cortex (GM)	228 ± 27	386 ± 59	0.59 ± 0.04	251 ± 32	385 ± 56	0.66 ± 0.06	11 ± 7	251 ± 34	397 ± 61	0.63 ± 0.05	7 ± 4
Temporal cortex (WM)	292 ± 38	386 ± 59	0.76 ± 0.05	303 ± 37	385 ± 56	0.79 ± 0.06	5 ± 4	312 ± 44	397 ± 61	0.79 ± 0.06	4 ± 3
Parietal cortex (GM)	221 ± 26	386 ± 59	0.58 ± 0.05	237 ± 31	385 ± 56	0.62 ± 0.05	8 ± 7	240 ± 34	397 ± 61	0.61 ± 0.06	6 ± 5
Parietal cortex (WM)	281 ± 34	386 ± 59	0.73 ± 0.06	287 ± 36	385 ± 56	0.75 ± 0.05	3 ± 4	294 ± 39	397 ± 61	0.75 ± 0.06	2 ± 3
Occipital cortex (GM)	231 ± 28	386 ± 59	0.60 ± 0.05	251 ± 35	385 ± 56	0.66 ± 0.05	9 ± 7	253 ± 37	397 ± 61	0.64 ± 0.05	7 ± 5
Occipital cortex (WM)	292 ± 35	386 ± 59	0.76 ± 0.06	302 ± 38	385 ± 56	0.79 ± 0.06	4 ± 5	309 ± 44	397 ± 61	0.78 ± 0.07	3 ± 4
Cerebellar cortex (GM)	238 ± 28	386 ± 59	0.62 ± 0.05	266 ± 32	385 ± 56	0.70 ± 0.07	13 ± 6	264 ± 38	397 ± 61	0.67 ± 0.06	8 ± 5
Cerebellar cortex (WM)	293 ± 35	386 ± 59	0.76 ± 0.06	301 ± 34	385 ± 56	0.79 ± 0.07	4 ± 5	310 ± 43	397 ± 61	0.78 ± 0.07	3 ± 4
Brainstem	281 ± 39	386 ± 59	0.73 ± 0.06	292 ± 40	385 ± 56	0.76 ± 0.08	5 ± 8	299 ± 46	397 ± 61	0.75 ± 0.06	4 ± 6
Basal ganglia	262 ± 31	386 ± 59	0.68 ± 0.06	273 ± 33	385 ± 56	0.71 ± 0.06	5 ± 4	278 ± 39	397 ± 61	0.70 ± 0.06	3 ± 3
Limbic structures	255 ± 31	386 ± 59	0.66 ± 0.05	282 ± 36	385 ± 56	0.74 ± 0.06	12 ± 5	277 ± 39	397 ± 61	0.70 ± 0.05	6 ± 3
	0.25 mmol/1.5T MRI										
Frontal cortex (GM)	194 ± 30	365 ± 44	0.53 ± 0.07	251 ± 27	382 ± 49	0.66 ± 0.08	26 ± 21	241 ± 27	389 ± 56	0.63 ± 0.07	19 ± 18
Frontal cortex (WM)	252 ± 29	365 ± 44	0.69 ± 0.05	287 ± 26	382 ± 49	0.76 ± 0.06	9 ± 5	290 ± 31	389 ± 56	0.75 ± 0.06	8 ± 6
Temporal cortex (GM)	208 ± 30	365 ± 44	0.57 ± 0.06	266 ± 29	382 ± 49	0.70 ± 0.08	24 ± 18	254 ± 28	389 ± 56	0.66 ± 0.06	16 ± 13
Temporal cortex (WM)	269 ± 32	365 ± 44	0.74 ± 0.06	309 ± 31	382 ± 49	0.82 ± 0.07	10 ± 6	309 ± 36	389 ± 56	0.80 ± 0.06	8 ± 5
Parietal cortex (GM)	199 ± 31	365 ± 44	0.55 ± 0.07	243 ± 33	382 ± 49	0.64 ± 0.08	18 ± 17	243 ± 31	389 ± 56	0.63 ± 0.08	16 ± 17
Parietal cortex (WM)	259 ± 28	365 ± 44	0.71 ± 0.05	289 ± 28	382 ± 49	0.76 ± 0.06	7 ± 5	292 ± 31	389 ± 56	0.76 ± 0.06	6 ± 6
Occipital cortex (GM)	210 ± 31	365 ± 44	0.58 ± 0.06	260 ± 33	382 ± 49	0.68 ± 0.08	19 ± 15	253 ± 30	389 ± 56	0.66 ± 0.06	14 ± 11
Occipital cortex (WM)	272 ± 30	365 ± 44	0.75 ± 0.05	308 ± 33	382 ± 49	0.81 ± 0.06	9 ± 6	305 ± 35	389 ± 56	0.79 ± 0.05	8 ± 5
Cerebellar cortex (GM)	224 ± 24	365 ± 44	0.62 ± 0.05	291 ± 32	382 ± 49	0.77 ± 0.09	25 ± 11	271 ± 30	389 ± 56	0.70 ± 0.06	14 ± 6
Cerebellar cortex (WM)	275 ± 30	365 ± 44	0.76 ± 0.05	311 ± 31	382 ± 49	0.82 ± 0.07	8 ± 6	308 ± 36	389 ± 56	0.80 ± 0.06	5 ± 4
Brainstem	267 ± 31	365 ± 44	0.74 ± 0.06	311 ± 33	382 ± 49	0.82 ± 0.08	11 ± 6	300 ± 38	389 ± 56	0.78 ± 0.07	6 ± 4
Basal ganglia	248 ± 27	365 ± 44	0.68 ± 0.04	287 ± 26	382 ± 49	0.76 ± 0.06	12 ± 6	282 ± 32	389 ± 56	0.73 ± 0.05	7 ± 4
Limbic structures	237 ± 27	365 ± 44	0.65 ± 0.05	303 ± 28	382 ± 49	0.80 ± 0.08	24 ± 11	280 ± 31	389 ± 56	0.72 ± 0.05	12 ± 6
	0.50 mmol/1.5T MRI										
Frontal cortex (GM)	207 ± 26	382 ± 42	0.54 ± 0.05	263 ± 43	389 ± 42	0.68 ± 0.09	26 ± 26	267 ± 35	403 ± 43	0.66 ± 0.07	24 ± 21
Frontal cortex (WM)	268 ± 29	382 ± 42	0.70 ± 0.05	294 ± 29	389 ± 42	0.76 ± 0.06	8 ± 9	312 ± 32	403 ± 43	0.78 ± 0.05	11 ± 9
Temporal cortex (GM)	221 ± 27	382 ± 42	0.58 ± 0.05	281 ± 45	389 ± 42	0.72 ± 0.10	26 ± 26	283 ± 33	403 ± 43	0.71 ± 0.07	23 ± 18
Temporal cortex (WM)	287 ± 32	382 ± 42	0.75 ± 0.05	318 ± 33	389 ± 42	0.82 ± 0.06	9 ± 9	335 ± 32	403 ± 43	0.84 ± 0.06	12 ± 9
Parietal cortex (GM)	213 ± 30	382 ± 42	0.56 ± 0.06	251 ± 33	389 ± 42	0.65 ± 0.08	17 ± 23	266 ± 32	403 ± 43	0.66 ± 0.07	20 ± 21
Parietal cortex (WM)	274 ± 30	382 ± 42	0.72 ± 0.05	292 ± 24	389 ± 42	0.75 ± 0.05	4 ± 6	311 ± 29	403 ± 43	0.78 ± 0.05	8 ± 7
Occipital cortex (GM)	226 ± 32	382 ± 42	0.59 ± 0.06	269 ± 36	389 ± 42	0.69 ± 0.08	17 ± 17	281 ± 33	403 ± 43	0.70 ± 0.07	19 ± 17
Occipital cortex (WM)	289 ± 32	382 ± 42	0.76 ± 0.06	312 ± 31	389 ± 42	0.81 ± 0.06	6 ± 7	329 ± 28	403 ± 43	0.82 ± 0.06	8 ± 8
Cerebellar cortex (GM)	236 ± 23	382 ± 42	0.62 ± 0.04	307 ± 52	389 ± 42	0.79 ± 0.12	28 ± 21	300 ± 35	403 ± 43	0.75 ± 0.09	22 ± 16
Cerebellar cortex (WM)	291 ± 28	382 ± 42	0.76 ± 0.05	318 ± 30	389 ± 42	0.82 ± 0.06	7 ± 8	332 ± 29	403 ± 43	0.83 ± 0.06	9 ± 8
Brainstem	282 ± 28	382 ± 42	0.74 ± 0.05	320 ± 35	389 ± 42	0.83 ± 0.07	12 ± 10	325 ± 33	403 ± 43	0.81 ± 0.07	9 ± 7
Basal ganglia	260 ± 23	382 ± 42	0.68 ± 0.04	291 ± 25	389 ± 42	0.75 ± 0.06	11 ± 10	300 ± 25	403 ± 43	0.75 ± 0.05	10 ± 8
Limbic structures	252 ± 25	382 ± 42	0.66 ± 0.04	320 ± 46	389 ± 42	0.83 ± 0.11	26 ± 19	309 ± 32	403 ± 43	0.77 ± 0.07	17 ± 12
	0.50 mmol/3T MRI										
Frontal cortex (GM)	56 ± 31	187 ± 89	0.29 ± 0.02	104 ± 52	185 ± 90	0.56 ± 0.12	96 ± 44	121 ± 66	241 ± 130	0.51 ± 0.12	74 ± 42
Frontal cortex (WM)	102 ± 50	187 ± 89	0.54 ± 0.04	129 ± 62	185 ± 90	0.70 ± 0.08	30 ± 14	173 ± 92	241 ± 130	0.73 ± 0.11	32 ± 17
Temporal cortex (GM)	57 ± 28	187 ± 89	0.30 ± 0.02	109 ± 52	185 ± 90	0.60 ± 0.13	97 ± 41	120 ± 63	241 ± 130	0.51 ± 0.13	71 ± 38
Temporal cortex (WM)	105 ± 47	187 ± 89	0.56 ± 0.04	142 ± 65	185 ± 90	0.78 ± 0.10	39 ± 17	179 ± 91	241 ± 130	0.76 ± 0.12	35 ± 18
Parietal cortex (GM)	64 ± 36	187 ± 89	0.34 ± 0.03	102 ± 50	185 ± 90	0.55 ± 0.12	65 ± 38	128 ± 69	241 ± 130	0.54 ± 0.11	60 ± 35
Parietal cortex (WM)	110 ± 56	187 ± 89	0.59 ± 0.04	133 ± 64	185 ± 90	0.72 ± 0.08	23 ± 13	178 ± 92	241 ± 130	0.75 ± 0.09	25 ± 15

(Continued)

TABLE 4 | Continued

	0.10 mmol/1.5T MRI										
	Pre			24 h				48 h			
Anatomical region	**ROI**	**REF**	**Ratio**	**ROI**	**REF**	**Ratio**	**%Change**	**ROI**	**REF**	**Ratio**	**%Change**
Occipital cortex (GM)	68 ± 38	187 ± 89	0.35 ± 0.03	108 ± 55	185 ± 90	0.58 ± 0.12	63 ± 35	132 ± 74	241 ± 130	0.55 ± 0.11	53 ± 32
Occipital cortex (WM)	112 ± 57	187 ± 89	0.59 ± 0.04	140 ± 69	185 ± 90	0.75 ± 0.09	27 ± 15	180 ± 96	241 ± 130	0.75 ± 0.10	23 ± 14
Cerebellar cortex (GM)	67 ± 32	187 ± 89	0.36 ± 0.03	129 ± 63	185 ± 90	0.71 ± 0.13	98 ± 35	139 ± 70	241 ± 130	0.59 ± 0.11	64 ± 25
Cerebellar cortex (WM)	113 ± 52	187 ± 89	0.61 ± 0.04	148 ± 74	185 ± 90	0.80 ± 0.08	32 ± 13	182 ± 96	241 ± 130	0.76 ± 0.09	25 ± 10
Brainstem	118 ± 57	187 ± 89	0.63 ± 0.04	156 ± 76	185 ± 90	0.84 ± 0.07	34 ± 12	188 ± 101	241 ± 130	0.78 ± 0.09	23 ± 11
Basal ganglia	94 ± 47	187 ± 89	0.50 ± 0.04	126 ± 61	185 ± 90	0.68 ± 0.07	42 ± 18	156 ± 83	241 ± 130	0.65 ± 0.08	29 ± 15
Limbic structures	86 ± 41	187 ± 89	0.46 ± 0.03	148 ± 69	185 ± 90	0.81 ± 0.12	82 ± 27	158 ± 81	241 ± 130	0.67 ± 0.11	48 ± 23

ROI, Region of interest for each anatomical region. REF, Reference region of interest within the posterior orbit. SU-Ratio, Signal unit ratio refers to signal unit within the particular region of interest (ROI) divided by the signal unit within the orbita serving as reference (REF). The percentage (%) change refers to the percentage change in signal unit ratio after 24 and 48 h relative to before contrast (Pre).

TABLE 5 | Correlations between tracer enrichment within subarachnoid CSF spaces and brain parenchyma.

	24 h after ith gadobutrol			48 h after ith gadobutrol		
	CSF cisterna magna	**CSF vertex**	**CSF velum interpositum**	**CSF cisterna magna**	**CSF vertex**	**CSF velum interpositum**
1.5T MRI						
Ith gadobutrol 0.10 mmol						
Cerebral cortex (GM)	$R = 0.32$; ns	$R = 0.65$; $P = 0.009$	$R = 0.06$; ns	$R = 0.33$; ns	$R = 0.53$; $P = 0.041$	$R = -0.13$; ns
Cerebral white matter	$R = 0.22$; ns	$R = 0.47$; ns	$R = 0.10$; ns	$R = 0.30$; ns	$R = 0.50$; ns	$R = -0.26$; ns
Entorhinal cortex (GM)	$R = 0.54$; $P = 0.040$	$R = 0.55$; $P = 0.034$	$R = -0.03$; ns	$R = 0.51$; $P = 0.054$	$R = 0.44$; ns	$R = 0.07$; ns
Entorhinal cortex (WM)	$R = 0.44$; ns	$R = 0.47$; ns	$R = 0.04$; ns	$R = 0.62$; $P = 0.013$	$R = 0.39$; ns	$R = -0.09$; ns
Ith gadobutrol 0.25 mmol						
Cerebral cortex (GM)	$R = 0.38$; ns	$R = 0.28$; ns	$R = 0.82$; $P < 0.001$	$R = 0.42$; $P = 0.041$	$R = 0.55$; $P = 0.005$	$R = 0.24$; ns
Cerebral white matter	$R = 0.43$; $P = 0.036$	$R = 0.49$; $P = 0.015$	–	$R = 0.27$; ns	$R = 0.58$; $P = 0.003$	$R = 0.36$; ns
Entorhinal cortex (GM)	$R = 0.61$; $P = 0.002$	$R = 0.08$; ns	$R = 0.30$; ns	$R = 0.59$; $P = 0.002$	$R = 0.43$; $P = 0.035$	$R = 0.33$; ns
Entorhinal cortex (WM)	$R = 0.67$; $P < 0.001$	$R = 0.25$; ns	$R = 0.43$; $P = 0.035$	$R = 0.46$; $P = 0.025$	$R = 0.35$; ns	$R = 0.36$; ns
Ith gadobutrol 0.50 mmol						
Cerebral cortex (GM)	$R = 0.60$; $P = 0.015$	$R = 0.75$; $P = 0.001$	$R = 0.52$; $P = 0.029$	$R = 0.73$; $P = 0.001$	$R = 0.63$; $P = 0.009$	$R = 0.60$; $P = 0.008$
Cerebral white matter	$R = 0.63$; $P = 0.009$	$R = 0.58$; $P = 0.02$	$R = 0.78$; $P < 0.001$	$R = 0.76$; $P = 0.001$	$R = 0.50$; $P = 0.049$	$R = 0.81$; $P < 0.001$
Entorhinal cortex (GM)	$R = 0.81$; $P < 0.001$	$R = 0.59$; $P = 0.016$	$R = 0.78$; $P < 0.001$	$R = 0.90$; $P < 0.001$	$R = 0.54$; $P = 0.030$	$R = 0.88$; $P < 0.001$
Entorhinal cortex (WM)	$R = 0.73$; $P = 0.001$	$R = 0.55$; $P = 0.026$	$R = 0.82$; $P < 0.001$	$R = 0.78$; $P < 0.001$	$R = 0.47$; ns	$R = 0.88$; $P < 0.001$
3T MRI						
Ith gadobutrol 0.50 mmol						
Cerebral cortex (GM)	$R = 0.53$; $P = 0.002$	$R = 0.67$; $P < 0.001$	$R = 0.38$; $P = 0.032$	$R = 0.80$; $P = 0.006$	$R = 0.70$; $P = 0.023$	$R = 0.44$; ns
Cerebral white matter	$R = 0.56$; $P = 0.001$	$R = 0.61$; $P < 0.001$	$R = 0.40$; $P = 0.025$	$R = 0.77$; $P = 0.009$	$R = 0.73$; $P = 0.017$	$R = 0.40$; ns
Entorhinal cortex (GM)	$R = 0.74$; $P < 0.001$	$R = 0.49$; $P = 0.005$	$R = 0.48$; $P = 0.005$	$R = 0.88$; $P = 0.001$	$R = 0.60$; ns	$R = 0.57$; ns
Entorhinal cortex (WM)	$R = 0.70$; $P < 0.001$	$R = 0.50$; $P = 0.004$	$R = 0.51$; $P = 0.003$	$R = 0.94$; $P < 0.001$	$R = 0.69$; $P = 0.026$	$R = 0.46$; ns

Pearson correlations were determined from percentage change in tracer enrichment (normalized T1 signal units) after 24 and 48 h as Pearson correlation coefficients with the significance level.

some differences when estimating entorhinal cortex thickness from 1.5T and 3T MRI, this is probably an effect of increased SNR at 3T MRI and thereby better ability to discriminate the cortical boundaries.

One important observation supporting our previous findings (24, 26) is that tracer enrichment within the brain, here exemplified by the cerebral cortex and entorhinal cortex, is strongly correlated with tracer enrichment in CSF. The correlation was strongest for nearby CSF and parenchymal regions. Since diffusion may be an important mechanism behind molecular transport in the brain (76), the concentration within the CSF may as well be crucial for molecular brain enrichment

from CSF. In patients with iNPH, molecular clearance from subarachnoid spaces is impaired (24); the present data further show that clearance of tracer from the subarachnoid CSF spaces was dose-dependent. Concerning glymphatic function, the role of CSF *per se* has received less attention. For a particular molecule, its glymphatic transport probably is affected by the concentration within the subarachnoid CSF spaces. In this regard, it may be proposed that the meningeal lymphatic vessels play a key role in molecular egress from CSF spaces.

The presently described imaging biomarkers provide some information about the pathophysiology behind iNPH, which is further summarized in **Figure 10**. (1) In iNPH, the flow of CSF is redirected toward the ventricles where transependymal transport of the water and molecular components of CSF may be an essential component. (2) Given the protracted and limited enrichment at a vertex, CSF absorption via arachnoid granulations to the superior sagittal sinus may play a minor role. (3) Delayed clearance from CSF may be instrumental for glymphatic failure. (4) Glymphatic failure affecting the entorhinal cortex may be partaking in the cognitive decline of iNPH patients. (5) In iNPH, defective meningeal lymphatic clearance may be a common cause behind the impaired CSF turnover and glymphatic failure characterizing the disease. Several lines of evidence suggest a crucial role of meningeal lymphatic CSF drainage for removal of cerebral waste products in age-related cognitive decline and Alzheimer's disease (82–84). Experimental data suggest that defective meningeal lymphatic clearance may impair the clearance of neurotoxic metabolites from CSF (85). The meningeal lymphatic drainage capacity becomes impaired with increasing age (83). In humans, the intrathecal MRI contrast agent serving as a CSF tracer passes from subarachnoid CSF to parasagittal dura (38) and to extra-cranial lymph nodes (86).

Some limitations of this study should be noted. At intrathecal enhanced MRI, contrast-induced T1 signal increase is an expression of an increased amount of contrast agent, but necessarily not proportional to changes in concentration. For that, T1 maps would have been necessary, which was beyond the scope of this study. In addition to different magnetic field strengths at 1.5T and 3T, respectively, the T1 gradient echo also differed. Regarding ventricular reflux grading, the imaging routine at 1.5T did not allow for categorizing patients into grades 1 or 2, however, did 9/10 iNPH have grades 3–4 at 1.5T and 3T combined. Furthermore, the study does not incorporate observations from using doses of 0.10 mmol and 0.25 mmol at 3T, and particularly the utility of reducing the dose to 0.10 mmol at 3T may be further explored in later assessments. It should also be noted that we at this stage do not adjust intrathecal dose for specific patient characteristics, such as age, height, or weight. Such adjustments seem meaningful for further dose optimization, and preferably dose reduction. Furthermore, the present data included both individuals with "possible" and "probable" iNPH. Theoretically, there might be differences between these diagnosis sub-categories. However, the one aspect differentiating these categories are the demonstration of normal CSF pressure. It is unlikely that any of our individuals with "possible" iNPH had non-recognized high CSF pressure (i.e., high-pressure hydrocephalus). In addition, the current classification has limitations making distinct differentiation between the possible and probable categories difficult (87).

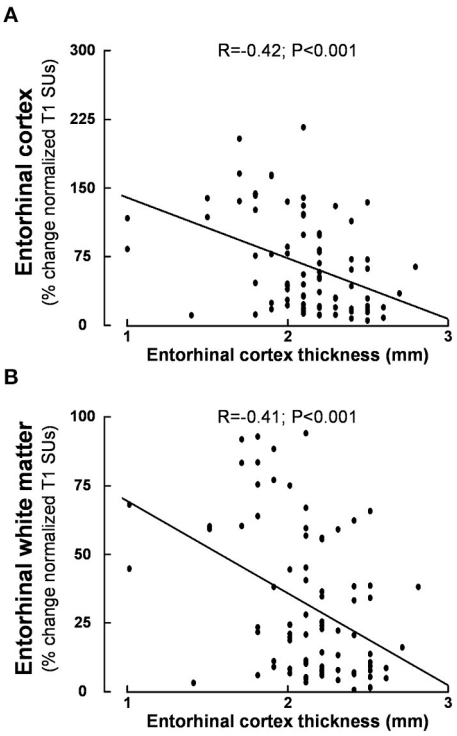

FIGURE 9 | Association between entorhinal cortex thickness and tracer enrichment at 24 h within **(A)** entorhinal cortex and **(B)** entorhinal white matter. Higher values of normalized T1 signal units are indicative of reduced parenchymal clearance of the tracer. Pearson correlations with significance levels are shown. Of note, Pearson and Spearman's correlations were similar. This plot is based on 84 patients.

CONCLUSIONS

Intrathecal gadobutrol can be utilized to trace extra-vascular molecular clearance from the brain and CSF and provide diagnostic information about impaired CSF flow at the brain surface in parallel. A dose of 0.25 mmol maintains adequate diagnostic information about dynamic CSF flow biomarkers (i.e., ventricular reflux grade and glymphatic enhancement) at 1.5T and improves the safety margin compared to 0.50 mmol. A dose of 0.10 mmol was considered insufficient at 1.5T MRI because of too low enrichment in CSF at a vertex and too low glymphatic enhancement in the cerebral cortex and subcortical white matter. Utility of 0.10 mmol at 3T remains to be determined. Strong reflux of tracer to ventricles (grades 3–4) characterizes patients with iNPH, with redirection of CSF flow toward ventricles accompanied with ventricular tracer enrichment. Tracer enrichment at the vertex is slow, with a

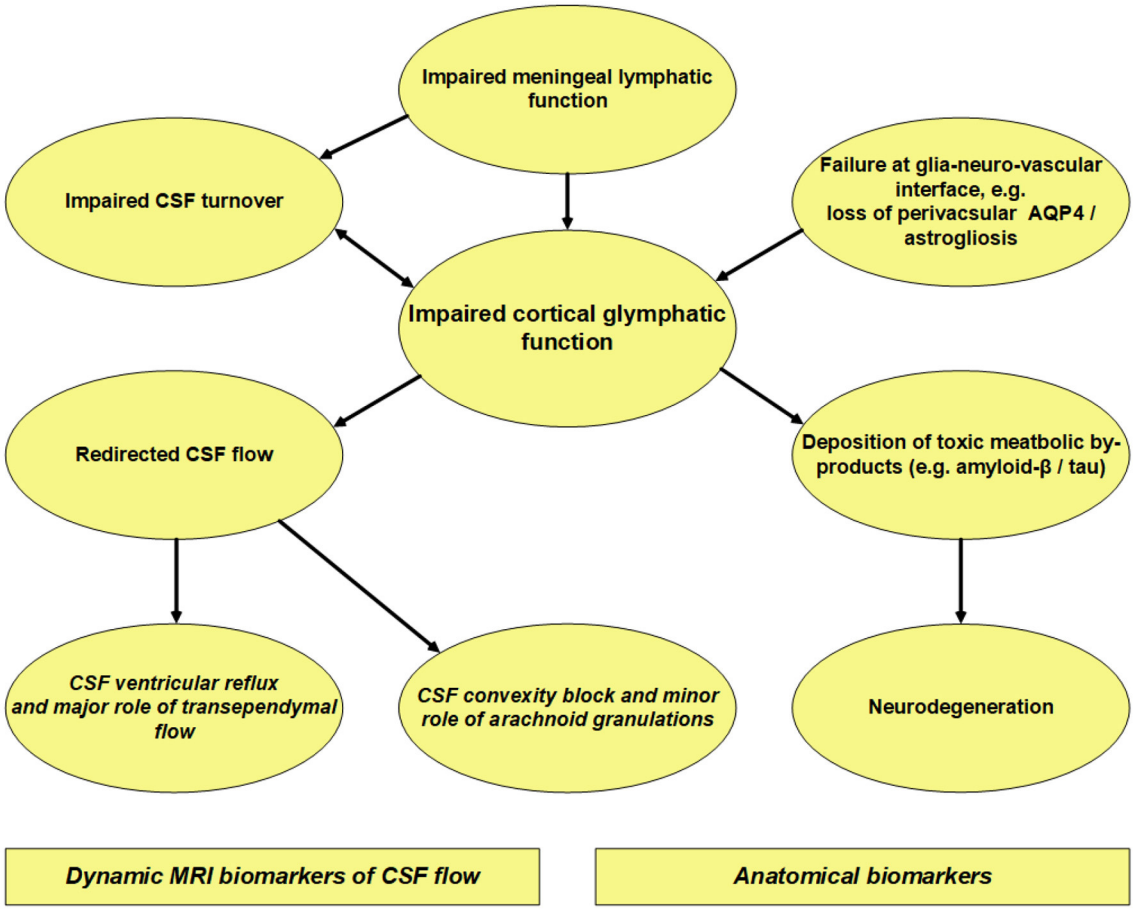

FIGURE 10 | Overview of our current thinking about iNPH pathophysiology based on MRI and histopathological observations in iNPH patients. Concerning intrathecal contrast-enhanced MRI, the contrast agent serves as a tracer within the extra-vascular compartment. This MRI modality showed delayed clearance of tracer from the cerebral cortex (24, 26, 27), which may indicate impaired glymphatic function. Moreover, iNPH demonstrated delayed clearance of tracer from CSF (24, 26) indicative of impaired CSF turnover. Enrichment of tracer in the cerebral cortex was strongly correlated with enrichment in nearby subarachnoid CSF space (24, 26), suggesting that glymphatic clearance heavily depends on molecular clearance from CSF. Histopathological studies in iNPH at cortex show astrogliosis, loss of perivascular AQP4, blood-brain barrier dysfunction, and mitochondrial abnormality (77–81), all of which may affect perivascular solute transport and thereby impair glymphatic function. A typical finding in iNPH is limited and protracted tracer enrichment at cerebral convexity with a peak at 24 h (24), much later than peak concentration in blood (59). This indicates that clearance of tracer from arachnoid granulations to the superior sagittal sinus plays a minor role, though this has traditionally been considered the major efflux route (60). On the other hand, iNPH is characterized by marked tracer reflux to ventricles (grades 3–4) (17, 18), indicative of redistribution of CSF flow to ventricles. Possibly, reversed aqueductal flow with trans-ependymal transport of CSF and further resorption of water through capillary walls may be important in iNPH. We suggest that the meningeal lymphatic vessels serve as the major efflux route for larger molecules within the CSF compartments. Impaired clearance of toxic by-products of brain metabolism due to glymphatic and meningeal lymphatic clearance failure may underlie the deposition of amyloid-β and tau in iNPH (19), and signs of neurodegeneration shown as entorhinal cortex thinning and higher grades of Schelten's MTA and Fazekas scores (18, 26).

peak at 48 h, indicating CSF clearance to occur mainly along other pathways than arachnoid granulations. The degree of glymphatic tracer enrichment within the cerebral cortex and subcortical white matter correlates strongly with enrichment within nearby CSF. In particular, we show that this is the case for the entorhinal cortex, which degenerates early in dementia, and where reduced tracer clearance is previously shown to be associated with reduced thickness.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Committee for Medical and Health Research Ethics (REK) of Health Region South-East, Norway (2015/96). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PE and GR: conceptualization and design. AL, ØG, BN, and RS: intrathecal injection procedure. ÅH-K, GL, and SV:

data management. PE, AP, LV, and GR: data analysis. PE: writing—original draft, supervision and administration, and correspondence and material requests. PE, AL, ÅH-K, ØG, BN, RS, GL, SV, AP, LV, and GR: review and editing and approval of the final manuscript. All authors contributed to the article and approved the submitted version.

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Idiopathic Aqueductal Stenosis: Late Neurocognitive Outcome in ETV Operated Adult Patients

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Objective: The aim of the present study is to evaluate a neurocognitive outcome in patients affected by late-onset idiopathic aqueductal stenosis (LIAS) who underwent endoscopic third ventriculostomy (ETV).

Materials and Methods: A prospective study was conducted between January 2015 and December 2017 in a series of 10 consecutive adult patients referred to the Neurosurgery Department of IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy. All the adult patients admitted with absence of CSF flow through the aqueduct in phase-contrast (PC)—MRI sequences or a turbulence void signal in T2—weighted images in midsagittal thin-slice MR sequences underwent a specific neuroradiological, neurological, and neurocognitive assessment pre- and postoperatively.

Results: All patients affected by gait and sphincter disturbances improved after ETV. Attentive and executive functions as well as visuo-spatial memory and verbal executive functions improved in several patients. Similarly, the affective and behavioral scales improved in almost 50% of the patients. No major complications have been recorded, and no patients required a second surgery for shunt placement.

Conclusion: Endoscopic third ventriculostomy represents a safe and effective surgical procedure for the treatment of LIAS. In addition to neurological improvement, we demonstrated also postoperative neurocognitive improvement mainly in attentive and executive functions, visuo-spatial memory, verbal executive functions, and behavioral and affective domains.

Keywords: aqueductal stenosis, hydrocephalus, endoscopic third ventriculostomy, LIAS, chronic adult hydrocephalus, late onset hydrocephalus

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INTRODUCTION

Aqueductal stenosis (AS) is a cause of obstructive hydrocephalus whose clinical presentation occurs mainly during childhood and adolescence. In the adult population, it represents about 10% of all types of hydrocephalus (1–6). AS may have several etiologies: extrinsic compression from tumoral lesions, genetic disorders, post infectious, post hemorrhagic (1, 7–11). Idiopathic

AS (IAS) consists of intrinsic congenital or acquired obstruction of the CSF pathway in the Sylvian aqueduct (12, 13). Late-onset idiopathic aqueductal stenosis (LIAS) is a clinical entity radiologically defined as a non-communicating triventricular hydrocephalus with idiopathic obstruction at the level of the cerebral aqueduct manifesting in adult age (6, 14). LIAS usually mimics normal pressure hydrocephalus symptoms (cognitive impairment, gait disturbances, and urinary incontinence), sometimes coexisting with obstructive hydrocephalus manifestations related to an increase of intracranial pressure (ICP) (e.g., endocrinological/visual/ocular disturbances, extrapyramidal signs, headache, etc.) (6).

Endoscopic third ventriculostomy (ETV) currently represents the gold standard treatment of LIAS (4, 6, 12). To date, validated scales are available to predict the surgical success and failure of ETV (7, 15–17) in AS, such as the ETV success score, that, although firstly developed for pediatric population, found its validations also among adults' cases (15). Anyway, there is still sparse literature on neurocognitive results (4, 6, 18, 19).

The aim of the present study is to evaluate the neurocognitive outcome in patients with LIAS who underwent ETV.

MATERIALS AND METHODS

A prospective study was conducted between January 2015 and December 2017 at the Neurosurgery Department of IRCCS. Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy. The study protocol was approved by the Local Ethics Committee of the local health service of Bologna, Italy (Cod. CE: 14131, 23/02/2015).

Inclusion criteria were as follows: patients aged 18 years or over; triventricular hydrocephalus with absence of CSF flow through the aqueduct in phase contrast (PC)—MRI sequences or a turbulence void signal in T2—weighted images in midsagittal thin-slice MR sequences; patients having undergone an ETV procedure. Exclusion criteria were: intracerebral tumors, history of intracranial bleeding or infection, previous cerebral surgeries, psychiatric diseases, major neurological diseases/therapies (e.g., epileptic patients with or without antiepileptic drugs).

All the recruited patients received neurocognitive evaluation pre- and postoperatively.

All the data have been prospectively recorded since the admission.

Neuroradiological Protocol

MRI was performed on a 3 Tesla whole-body scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany) using a 32-channel phased-array head coil. A sagittal and axial T1 WI sequence, a sagittal and axial T2 WI sequence, an axial FLAIR sequence, a 3D sagittal T1WI (1 mm) sequence, a turbo spin-echo T2 flow (3 mm) sequence, and a PC-MRI sequence were performed. The following neuroradiological features for every patient were evaluated: Evans' index ($<0.25/0.25 <$ EI $<0.3/>0.3$); narrow sulci (normal, parafalcine, vertex); Sylvian fissure enlargement; focally enlarged sulci; widened temporal horns ($<0.4/0.4 <$ TH $<0.6/>0.6$); a callosal angle ($>90°/60° <$ CA $< 90°/<60°$); Fazekas scale for white matter lesions; Fazekas scale; age-related white matter changes (ARWMC) (20); height of an interpeduncular cistern (and related third ventricle's bulging).

In order to assess dilation occurred in posterior segments of the lateral ventricle, the fronto-occipital horn ratio (FOHR) was indicated, when needed, to overcome such limitation of Evan's index.

All MRI exams were evaluated pre- and postoperatively by the same neuroradiologist (L.A.R.) who was blind to the neurological and neurocognitive assessment.

Neurological Protocol

The following neurological features were evaluated according to the iNPH grading score according to Kubo et al. (21), evaluating gait, sphincter, and cognitive function. The score of each domain ranges from 0 to 4, with higher scores indicating worse symptoms. The presence of a preoperative headache was recorded (Yes/No). Time of onset/duration of clinical signs and symptoms before being admitted and operated on was recorded according to Fukuhara's classification (6): Class I (symptom duration under 1 month), Class II (symptom duration from 1 to 6 months), Class III (symptom duration over 6 months).

Neurocognitive Protocol

A tailored neurocognitive evaluation was assessed before and after ETV by a dedicated neuropsychologist and with a universally recognized questionnaire. The following neurocognitive functions were evaluated with the associated tests: general screening (mini mental state examination); attentional and executive functions (attentional matrices, Trail Making A, Trail Making B, Trail Making A-B, Stroop test—error, Stroop test—time); logical-abstract reasoning (Raven's colored progressive matrices in mental deterioration battery); visuo-perceptive and visuo-constructive abilities (Montreal cognitive Rey-Osterrieth complex figure test-−10' recall); visuo-spatial memory (Corsi test, Supra-Span Corsi test, Montreal cognitive Rey-Osterrieth complex figure test-−10' recall); verbal memory (a digit span—forward, a Rey 15-word immediate recall, a Rey 15-word late recall, a Babcock story recall test); language and verbal executive functions (phonemic word fluency test in mental deterioration battery, semantic fluency); functional scales (activities of daily living, instrumental activities of daily living); affective and behavioral scales (Beck depression inventory—affective and somatic, Beck depression inventory—cognitive, Beck depression inventory—total, state-trait anxiety inventory Y1—state, state-trait anxiety inventory Y2—trait).

Individual scores of the different tests were calculated using the equivalent scores (ES) in order to correct the subject's raw score, eliminating the influence of age and education. For each test, the adjusted scores are then transferred to a 5-level scale (0–4). The ES represent a method of correcting neuropsychological tests. This method of non-parametric correction of the ES was devised by Capitani (22) and colleagues in the context of an Italian multicentric study on the calibration of neuropsychological tests (23) still today a cornerstone for neuropsychological evaluation. The Italian neuropsychological tests were constructed according to the methodology-described use—after the correction of the raw score for sex, age, and

education—a system of scores on an ordinal scale, called equivalent scores, ranging from 0 to 4, corresponding to as many segments of the distribution [0 = deficient, 1 = border line, 2 and 3 = middle inferior (between 20 and 50 percentiles), and 4, middle superior (over 50 percentile)]

Time between the first neuropsychological evaluation and intervention ranged from 1 to 65 days (mean, 17.4). Time between surgery and the second neuropsychological assessment was from 120 to 425 days (mean, 258.5).

We considered a test as improved when the postoperative score showed an increase of at least two units or only one if the initial score was 0 (pathological condition). A worse result was defined by a decrease of two units or only one if it reaches the pathological condition (0). In the same way, for BDI and STAI Y tests, the cut-off was, respectively, the 85th and 40th percentiles, and a patient was considered improved if the postoperative score was lower than or equal to these percentiles as compared to preoperatively higher values (24). The comparison was made according to Ghisi et al.

All neuropsychological examinations were conducted by the same neuropsychologist (F.S.).

Surgical Procedure

The procedure is performed under general anesthesia. Through a burr hole drilled 0.5 cm in front of the coronal suture and 2.5 cm lateral from the midline on the right side, the right lateral ventricle is cannulated using a 14F peel-away catheter with a blunt-tipped obturator. A rigid rod lens endoscope (Karl Storz LOTTA System®, 6° angle) is then inserted. The anatomical landmarks of the lateral ventricle (choroid plexus, thalamostriate, and septal veins, foramen of Monro) are identified. Through the foramen of Monro, the third ventricle is accessed with the endoscope recognizing the mammillary bodies and the infundibular recess. The standard target lies in the tuber cinereum, (e.g., the region of the third ventricle floor between the infundibular recess and the mammillary bodies, that is usually perforated with blunt-closed Decq forceps. The stoma is dilated by inflating a Fogarty catheter. Thereafter, the underlying subarachnoid space is explored with the endoscope. The clear vision of the structures of the interpeduncular cistern (the basilar artery and/or its branches, brainstem, third cranial nerve, and dura of the clivus) is the goal of surgery. The pulsation of the third ventricular floor, and mainly of the edges of the stoma, is an indirect marker of the CSF flowing through the performed stoma. All ETV procedures were performed by the same group of neuroendoscopy surgeons (G.P. and M.M).

Statistical Analysis

In the descriptive analysis, results were presented as median and interquartile range (IQR). The comparison of neuropsychological status before and after surgery was evaluated with the non-parametric Wilcoxon signed-rank test. Statistical analysis was performed using statistical package Stata SE, 14.2.

TABLE 1 | Pre- and post-operative clinical evaluation—iNPH grading score (21) and Fukuhara (6) classification.

PT	Gait		Sphincter		Cognitive		iNPH total		Headache		Fukuhara
Patients	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	2	0	1	0	1	0	4	0	N	N	III
2	1	0	0	0	0	0	1	0	Y	N	III
3	2	0	1	0	NA	0	3	0	N	N	III
4	0	0	0	0	0	0	0	0	N	N	NA
5	2	0	0	0	2	1	4	1	N	N	III
6	0	0	0	0	0	0	0	0	Y	N	=
7	2	0	2	0	2	0	6	0	N	N	III
8	2	0	1	0	1	1	4	1	N	N	III
9	2	1	2	0	2	1	6	2	N	N	III
10	2	0	2	0	2	2	6	2	N	N	III

PT, Patient; iNPH, idiopathic Normal Pressure Hydrocephalus score.

TABLE 2 | Pre- and postoperative neuroradiological evaluation.

Pt	Evan's Index		Narrowed Sulci		Sylvian fissure		Focally enlarged sulci		Temporal Horns		Callosal Angle		Fazekas DWM		Fazekas		ARWMC		Total		Interped.Cystern	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	2	2	2	0	0	0	1	1	2	1	1	1	2	2	5	4	7	6	22	17	8.4	9.1
2	2	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	3	1	9.6	10.5
3	2	2	2	0	0	0	0	0	2	2	2	1	1	0	2	0	0	0	11	5	3.7	7.7
4	2	2	1	0	0	0	0	0	2	1	1	0	0	0	0	0	0	0	6	3	7.4	9.7
5	2	2	1	0	0	0	0	0	2	0	1	0	0	0	0	0	0	0	6	2	7.4	9.9
6	2	1	2	1	0	0	0	0	2	1	1	0	1	1	3	3	4	4	15	11	5.9	7.7
7	2	2	2	0	0	0	0	0	2	2	2	2	0	0	0	0	0	0	8	6	5.02	7.24
8	2	2	0	0	0	0	0	0	2	2	1	0	2	2	4	4	10	10	21	20	3.9	6.2
9	2	2	2	0	0	0	0	0	2	1	1	1	2	2	5	4	8	8	22	19	5.6	6.9
10	2	2	0	0	0	0	0	0	2	2	1	1	1	1	1	1	0	0	7	7	4.5	5.2

PT, Patient; Fazekas DWM, Fazekas score for white matter lesions; ARWMC, age-related white matter changes.

RESULTS

Fifteen patients initially met the inclusion criteria: three were excluded because of secondary aqueductal stenosis, one for a previous surgery, and one since affected by epilepsy (on anti-epileptic drug treatment). Finally, 10 consecutive patients (5 males and 5 females) with a mean age of 50.5 years (23–73 years) were included in the study. Patients' follow-up ranged from 14 to 36 months (mean follow-up, 24.9).

No surgical and clinical intra- or postoperative complications were reported. No patients required further surgery (ETV or shunt placement).

Clinical Status

According to Fukuhara's classification, eight patients were referred with chronic symptomatology (over 6 months), one with subacute symptomatology (between 1 and 6 months), while one patient was not able to recall detailed data on onset/duration of his clinical conditions. Two patients complained of headache preoperatively, while no one was still affected once operated on. According to the iNPH grading scale, preoperatively, eight patients had gait impairment, six patients had sphincter impairment, and six patients had cognitive impairment. During the postoperative period, all the patients affected by gait and sphincter disturbances improved. Four out of the six patients with preoperative cognitive impairment improved; two had no changes. No clinical worsening was reported (All clinical data are reported in **Table 1**).

Neuroradiological Findings

All patients had a preoperative Evans' index >0.3. Preoperatively, all patients' MRI showed third ventricle's bulging. After ETV, two patients reported a reduction of Evans' index between 0.25 and 0.3; the others were stable. One patient had a preoperative callosal angle >90°, seven patients had a callosal angle between 60° and 90°, and two patients had a callosal angle <60°. After ETV, the callosal angle widened in five patients, while it was unchanged in the other five. Four patients had a preoperative Fazekas score of 0, one patient of 1, one patient of 2, one patient of 3, one patient of 4, and two patients of 5. After ETV, three patients improved, while seven were stable. The preoperative median value of interpeduncular cistern height was 5.75 mm (average, 6.14 mm; range, 3.7–9.6 mm), while, after ETV, the median value of interpeduncular cistern height was 7.7 mm (average, 8.01 mm; range, 5.2–10.5 mm). No neuroradiological worsening was observed. Postoperative T2WI in midsagittal thin slice confirmed the flow void through the stoma in all patients (All neuroradiological data were reported in **Table 2**; **Figures 1**, **2**).

Neuropsychological Status

Neurocognitive domains were carefully evaluated pre and post ETV as follows:

- MMSE: rather surprisingly, it appears normal in all patients. This finding is not typical for late-onset hydrocephalus.
- Attentive and executive function tests: two out of 10 patients improved in the attentional matrices test ($p = 0.087$); three

had best results in the trail making type A test, one patient worsened; two patients showed higher scores at the final follow-up in the trail making type B test ($p = 0.010$), and three patients in the trail making B-A test ($p = 0.010$); one patient improved in Stroop test error once operated on, while one worsened; three patients recovered post ETV in Stroop test time, only two worsened.

- Logical abstract reasoning pointed out worsened results after ETV in two patients (Raven's colored progressive matrices

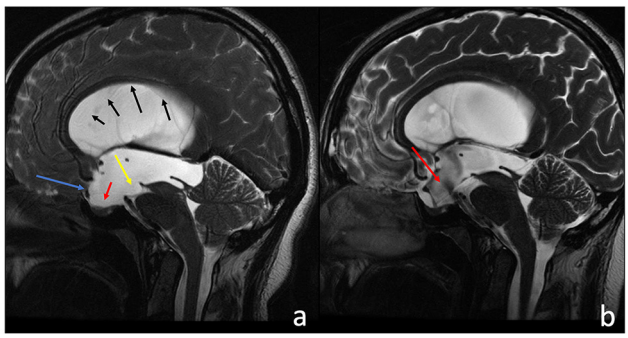

FIGURE 1 | Sagittal T2-w 3D-FIESTA acquisition of a 38-year-old male before **(a)** and after **(b)** third ventriculostomy. **(a)** The third ventricle and the lamina terminalis are concave (**a**, blue arrow), the sella turcica is empty (**a**, red arrow), and there is an evident compressive effect exerted on the brain stem and the ambiens cistern (**a**, yellow arrow). The corpus callosum appears thinned (black sequential arrows), and subarachnoid spaces have a low representation. After the third ventriculostomy **(b)**, there are evident flow artifacts at the floor of the III ventricle (**a**, red arrow). All previous neuroradiological findings clearly improved.

TABLE 3 | neuropsychological status of patients after ETV, herein in green are signaled the neuropsychological domains improved with statistical significance.

	Neuropsychological status post ETV	
Domains	**Patients improved**	**Patients worsened**
Attentional and executive functions	6	3
Logical-abstract reasoning	1	2
Visuo-perceptive and visuo-constructive abilities	1	1
Visuo-spatial memory	7	2
Verbal memory	5	4
Language and verbal executive functions	5	1
Functional scales	3	2
Affective and behavioral scales	6	1

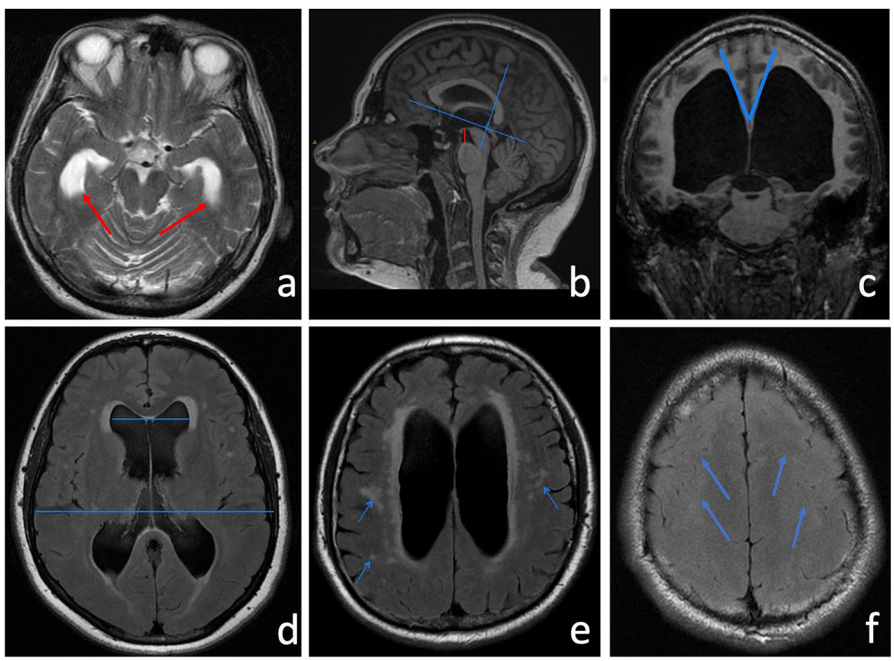

FIGURE 2 | (a) Axial T2-w showing a clear enlargement of the temporal horns (red arrows). **(b)** Sagittal 3D MPRAGE T1-w was used to measure the height of the interpeduncular cistern, which represents the shortest distance between the floor of the third ventricle and the midbrain (a red line). After identifying the AC-PC plane, the callosal angle **(c)** is measured in the coronal plane through the posterior commissure perpendicular to the anterior commissure-posterior commissure (AC-PC) plane. Neuroradiological features of LIAS mimic iNPH also for CA amplitude that usually measures <90°. **(d)** Evan's index (EI) is a direct linear measurement of the ventricular size. It is calculated from the ratio between the maximum transverse diameter of the frontal horns and the maximum internal diameter of the skull. **(e)** The FLAIR sequence shows an elevated periventricular signal ascribable to interstitial edema or reactive gliosis. Hyperintense white matter lesions attributed to chronic ischemia of the small vessels are indicated by the arrows. **(f)** Narrowed sulci at the high cerebral convexities (blue arrows).

in the mental deterioration battery test); a better result was collected in one case.
- Visual-perceptive and visual-constructive skills: one patient improved, while one worsened in the Rey–Osterrieth complex figure test.
- Visuo-spatial memory domain: five patients improved in the Corsi test, while one patient worsened at the final follow-up; four patients improved in the Corsi Supra span test; three patients of the series results were better in Rey's recall test, while one patient showed a new deficiency after surgery.
- Verbal memory field: four patients lowered their performances postoperatively in the digit span test; two patients improved, while two worsened their results in the 15-word Rey immediate test, only one patient successfully improved his preoperative results in the delayed type of the latter test; three patients finally improved in Babcock story recall test in the postoperative period.
- Language and verbal executive functions: three patients improved on phonemic word fluency ($p = 0.047$); one patient showed lower scores after ETV; a test exploring semantic fluency showed improvement after the surgical procedure in four patients.

The functional scale used to assess activities of daily living (ADL) highlighted positive changes for one patient; the instrumental activities of daily living (IADL) scale showed better scores for three and worse for two patients at the last follow-up.

Affective and behavioral domains were examined: two patients improved the results in somato-affective BDI ($p = 0.011$) compared to the preoperative period and three in the cognitive BDI, only one patient worsened his results in cognitive BDI after ETV. The total BDI score improved in three patients (</=85th percentile) compared to preoperative levels, while it was over the cut-off in one patient.

Three patients improved their results in the state-trait inventory Y1 test (state) ($p = 0.006$) and three in the state-trait inventory Y2 test (trait) (below the 40th percentile) ($p = 0.041$) (Neuropsychological domains improved after ETV are shown in **Table 3**; neuropsychological comparison before and after surgery with statistical analysis is presented in **Table 4**; all neuropsychological data are reported in even more detail in **Table 5**).

TABLE 4 | Comparison of neuropsychological status before and after ETV.

	Before Median (IQR)	After Median (IQR)	Differences Before -After	*p*-value Wilcoxon
MMSE	27.8 (27.5–28.9)	28.2 (26.8–28.8)	5 +, 5 =, 0 -	0.644
Matrices test	3.5 (2–4)	4 (4–4)	5 +, 4 =, 1 -	0.087
Trail making A	4 (2–4)	4 (4–4)	3 +, 6 =, 1 -	0.292
Trail making B	3 (1–4)	4 (4–4)	7 +, 3 =, 0 -	0.010*
Trail making B-A	3 (1–4)	4 (4–4)	7 +, 3 =, 0 -	0.010*
Stroop test error	4 (4–4)	4 (4–4)	2 +, 7 =, 1 -	0.565
Stroop test time	4 (2–4)	4 (3–4)	4 +, 4 =, 2 -	0.423
Raven's matrices	4 (4–4)	4 (4–4)	2 +, 6 =, 2 -	0.861
Rey–Osterrieth	4 (3–4)	4 (3–4)	2 +, 6 =, 2 -	0.954
Corsi test	1.5 (0–4)	3 (1–4)	5 +, 4 =, 1 -	0.123
Corsi Supraspan	2 (1–4)	4 (3–4)	5 +, 3 =, 2 -	0.131
Delayed Recall	1.5 (0–3)	2.5 (1–4)	4 +, 3 =, 3 -	0.403
Digit Span test	3.5 (2–4)	2.5 (1–4)	2 +, 3 =, 5 -	0.129
Words Rey Imm	2 (0–4)	2 (1–3)	5 +, 2 =, 3 -	0.679
Words Rey Diff	1 (0–3)	2 (0–4)	2 +, 6 =, 2 -	0.907
Babcock story recall test	2 (2–2)	2.5 (2–3)	5 +, 2 =, 3 -	0.252
Semantic fluency	0 (0–3)	3 (0–4)	4 +, 5 =, 1 -	0.151
Phonemic fluency	2.5 (0–4)	3.5 (2–4)	4 +, 6 =, 0 -	0.047*
ADL	6 (6–6)	6 (6–6)	1 +, 9 =, 0 -	0.317
IADL	5 (5–8)	5 (5–8)	3 +, 5 =, 2 -	0.659
BDI SA	70 (50–99)	55 (20–80)	7 +, 3 =, 0 -	0.011*
BDI C	75 (60–85)	65 (50–70)	5 +, 3 =, 2 -	0.232
BDI total	65 (50–96)	55 (20–80)	5 +, 3 =, 2 -	0.132
STAI Y State	43.5 (38–46)	32.5 (29–41)	9 +, 1 =, 0 -	0.006*
STAI Y Trait	44.5 (39–52)	33 (32–42)	7 +, 0 =, 3 -	0.041*

$p < 0.05$: statistical evidence; + improvement, = no differences, - worsening; MMSE, mini-mental state examination; ADL, Activities of Daily Living; IADL, Instrumental activities of daily living; BDI SA, Beck Depression Inventory affective and somatic; BDI C, Beck Depression Inventory cognitive; STAI State/Trait, State-Trait Anxiety Inventory State/State-Trait Anxiety Inventory Trait.

Matching Results

We finally matched our results to understand if there would be some predictive features for a better neurocognitive outcome. Patients with a lower Fazekas score (0–1) improved in at least 3 neurocognitive domains (above all in affective and behavioral scales and visuospatial memory), whereas the patients with preoperative higher Fazekas (2–3–4–5) had a little improvement in visuo-spatial and verbal memory and in affective and behavioral scales. One patient worsened both in affective and behavioral scales and in logical-abstract reasoning. Also, patients without preoperative compression of the sulci at the vertex seemed to do better in terms of postoperative neurocognitive outcomes in at least two domains: affective and behavioral (2 patients) and visuospatial memory (1 patient). On the other hand, patients with preoperative compression of the sulci had lower neurocognitive improvement after ETV, and, in one case, we observed impairment in three domains. Furthermore, we did not observe better postsurgical neurocognitive outcomes between the patients over or under 40 years old, as well as no difference seems to exist between the neurological and neurocognitive outcomes in the patients with chronic symptoms and the subacute onset. However, statistical analysis in a small series like this must be interpreted cautiously and has a limited value.

DISCUSSION

Excellent surgical results after ETV in adults affected by IAS have been reported (4, 7, 12, 25), but there are still controversies and lack of data on their neurocognitive outcomes (4, 18, 26, 27), as well as data clearly describing neuroradiological pre- and post-operative features. The aim of this study is to describe late neurocognitive outcomes in a highly homogenous series of patients.

TABLE 5 | Detailed description of neuropsychological pre- and postoperative evaluation tests used.

Test	PT1		PT2		PT3		PT4		PT5		PT6		PT7		PT8		PT9		PT10	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
General screening																				
Mini-Mental state examination	27,49	26,49	30	28,59	25,59	27,59	27,75	28,75	27,49	28,49	28,89	27,89	27,79	30	25,85	25,44	28,88	30	28,73	26,8
Attentional and executive functions																				
Attentional matrices	4	3	3	4	4	4	4	4	4	4	2	3	3	4	1	4	4	4	2	4
Trail Making A	4	4	4	4	2	4	4	4	2	4	3	1	4	4	4	4	4	4	1	4
Trail Making B	1	2	3	4	3	4	4	4	1	4	1	2	4	4	3	4	4	4	2	4
Trail Making B-A	0	1	3	4	3	4	4	4	1	4	1	2	4	4	3	4	4	4	2	4
Stroop test—error	4	4	4	4	4	4	4	4	4	4	2	3	4	4	1	4	4	4	4	2
Stroop test—time	2	4	2	4	4	4	4	4	0	4	2	3	4	4	4	2	4	4	4	2
Logical-abstract reasoning																				
Raven's Colored Progressive Matrices in Mental Deterioration Battery	4	4	4	4	4	4	4	4	3	4	4	2	4	4	4	4	4	0	2	4
Visuo-perceptive and visuo-constructive abilities																				
Rey–Osterrieth complex figure test—copy	2	4	4	4	4	4	4	3	4	4	4	1	3	4	4	4	4	4	0	0
Visuo-spatial memory																				
Corsi test	0	1	3	3	0	3	4	1	0	4	4	4	0	3	1	1	2	4	4	4
Supra-Span Corsi test	3	4	4	4	1	3	4	3	0	4	4	3	0	0	1	4	4	4	1	4
Montreal cognitive Rey-Osterrieth complex figure test-—10' recall	1	3	4	4	1	0	3	4	0	4	3	2	2	1	0	2	4	4	0	0
Verbal memory																				
Digit span—forward	3	4	4	4	4	3	4	2	1	1	2	0	2	3	2	0	4	2	4	4
Rey 15-word—immediate recall (IR) ability	1	2	4	3	3	1	3	4	0	3	4	0	0	0	1	2	4	4	0	2
Rey 15-word—delayed recall (DR) ability	2	1	3	3	0	0	3	4	0	4	4	3	0	0	0	0	4	4	0	0
Babcock story recall test	2	2	4	3	2	3	2	4	0	3	3	2	2	1	1	2	2	4	2	2
Language and verbal executive functions																				
Phonemic word fluency test in Mental Deterioration Battery	0	3	3	1	4	4	4	4	0	3	0	0	0	0	0	0	3	4	0	3
Semantic fluency	3	3	4	4	3	3	4	4	0	4	0	1	2	4	2	2	4	4	0	2
Functional scales																				
Activities of daily living	6	6	6	6	6	6	6	6	4	6	6	6	6	6	6	6	5	5	6	6
Instrumental activities of daily living	5	5	5	5	8	5	8	8	4	8	8	5	5	8	5	5	6	8	5	5
Affective and behavioral scales																				
Beck Depression Inventory—affective and somatic (cut- off > 85°)	85	85	99	80	70	60	20	20	99	20	50	20	50	20	50	50	70	60	99	90
Beck Depression Inventory—cognitive (cut- off > 85°)	70	70	99	70	70	60	40	40	99	40	60	60	80	50	50	70	80	99	85	70
Beck Depression Inventory—total (cut- off > 85°)	80	80	99	70	60	60	20	20	99	20	50	20	60	20	40	50	70	90	96	85
State-Trait Anxiety Inventory Y1—state (cut-off >40)	37	36	46	33	36	29	38	31	44	41	39	21	44	27	43	32	48	45	52	52
State-Trait Anxiety Inventory Y2—trait (cut-off >40)	46	42	57	32	39	33	38	31	61	41	42	32	43	33	27	32	52	56	49	51

We considered a test as improved when the postoperative score showed an increase of at least two units or only one if the initial score was 0 (pathological condition). A worse result was defined by a decrease of two units or only one if it reaches the pathological condition (0). In the same way for BDI and STAI Y tests the cut-off was, respectively, the 85th and 40th percentile and a patient was considered improved if the score was lower than or equal to these percentiles. To make easier the interpretation of this table, the authors put in green the patients that improved their preoperative scores and in red those that did worse.

IAS is a common cause of non-communicating hydrocephalus in childhood (6–66%), less frequent in adulthood, accounting for about 10% of all types of hydrocephalus (1, 2, 12). Other authors analyzed and discussed neuropsychological outcomes in longstanding overt ventriculomegaly in adult (LOVA) and outlined the role of ETV in the effective management of neurological and neuropsychological deficiency (28). We decided to take into consideration only patients affected by chronic adult hydrocephalus and confirmed MRI aqueductal stenosis, while, in other papers, there is a case mix. The authors consider interestingly this discussion since it is not yet clear if etiopathogeneses and symptoms of LOVA and LIAS are ascribable to a unique clinical entity (28–31). Neurological clinical classification of LIAS was firstly proposed by Fukuhara and Luciano (6). They distinguished patients with intracranial hypertension syndrome and patients experiencing NPH-like syndrome (Hakim's symptom triad) (32). Furthermore, they classified patients in relation to disease duration (chronic, subacute, and acute form). However, in their series, also patients with an incomplete or suspected stenosis of the aqueduct were included. In our series, all the patients had complete absence of CSF flow through the aqueduct in phase contrast (PC)—MRI sequences or a turbulence void signal in T2—weighted images in midsagittal thin-slice MR sequences. Eight out of 10 patients reported an iNPH-like chronic form, whereas one a subacute form. The coexistence of a headache together with NPH-like symptoms has been reported quite frequently (3, 4), but, in our series, only two patients complained of that. In our series, nearly all patients improved their clinical condition after surgical treatment; both patients with a preoperative headache became headache free as well as all the patients with gait and sphincter impairment (**Table 1**). These results appear to be in line with literature data (4, 12, 19, 33–39), confirming the appropriateness of the diagnostic criteria and surgical procedure, namely ETV.

While at the beginning of the twentieth century "…the difficulties encountered in treating lesions of the aqueduct of Sylvius would appear almost insuperable..." (40). Nowadays, ETV becomes the gold standard for the treatment of non-communicating hydrocephalus both in children and in adults. Many studies highlighted its safety, feasibility, low rates of intra- and postoperative complications and stable control of clinical symptoms. The rate of failure and the subsequent need for shunting are low (7, 25, 41) with a higher incidence in the pediatric population, which seems to be mostly related to age at intervention (under 6 months) (17, 42, 43).

We observed that patients' age (the symptom onset under or over 40 years old) and initial symptomatology (chronic vs. subacute form) were not related to better neurocognitive outcomes, confirming the results published by Santamarta et al. (44). After matching neuroradiological with neuropsychological pre- and post-operative results, we observed that the patients with lower Fazekas scores (lower cortical, subcortical, and periventricular hyperintensity), as well as the patients without preoperative compression of the sulci at the vertex, seemed to achieve improvement in their preoperative neurocognitive impairments even if data are not supported by statistical analysis, probably due to the small population size.

Controversies also regarding postoperative reduction in ventricular size and a favorable neurological and cognitive outcome exist. While some studies support this hypothesis (33, 45, 46), in particular, the reduction of the third ventricle size (33, 44, 47), other studies have failed to confirm this correlation, concluding that the ventricles' size is not a valid predictor of clinical and intellectual outcomes, and reliance on imaging should be avoided (38, 48, 49). In our series, Evan's ratio decreased only in two cases, while temporal horns reduction was found in six out of 10 patients. This reduction was not related to the clinical outcome (all the patients improved regardless of the ventricular size) nor to the neurological outcome. Similar findings were reported by Rodis et al. (50) in a retrospective outcome analysis where they found that only 5% of patients with LIAS reduced Evan's ratio after ETV.

Analyzing the compression of cranial subarachnoid convexity spaces (namely, vertex sulci and parafalcine sulci) (51, 52), we recorded their normalization in all cases with a good concordance of neurological improvement. These findings could reflect the fact that, as suggested by Tisell et al. (53), connections of two CSF compartments (intraventricular and subarachnoid spaces—SAS) decrease the resistance to the outflow of CSF (Rout), increasing the area of CSF absorption in both the SAS and the ventricles.

In our opinion, interpeduncular height could represent an indirect sign of normalization of the difference of pressure among intraventricular areas and SAS at the level of the cranial base (**Figure 2**). It seems to be a reliable finding since all the patients that improved neurologically had an increase of postoperative interpeduncular height. This indirect sign of third ventricle/hypothalamus relaxation corroborates Larsson's suggestion of an increased regional cerebral blood flow in the upper brain stem, hippocampi, and frontal region after shunting the procedure in iNPH (54). However, increasing interpeduncular height is related to neurological improvement but does not appear to be directly related to a neurocognitive outcome.

We found a significant improvement of attentive and executive functions as well as visuo-spatial memory and verbal executive functions after ETV, and, similarly, we observed improvements in the affective and behavioral scales (specifically assessing the rate of depression and anxiety) in almost 50% of the patients ($p < 0.05$, **Table 4**).

Our extensive neuropsychological analysis (see **Table 5**) in a highly homogeneous cohort of patients supports the hypothesis suggested by Burtscher and Hader (18, 19) that ETV may improve neurological symptoms and intellectual functions in patients with LIAS. In our experience, neurocognitive evaluation has proved to be a useful tool to define preexisting impairments due to hydrocephalus and to discriminate them from any postoperative findings (55).

Interestingly, we observed that all the patients had a normal MMSE, indeed a not typical finding in chronic late-onset hydrocephalus, suggesting that a deep neurocognitive evaluation is mandatory in these patients.

Furthermore, we recommend neurocognitive analysis in patients with LIAS to better elucidate the natural history

of this syndrome. Indeed, many of the up-to-now so-called "asymptomatic" patients affected by aqueductal stenosis did not undergo extensive neuropsychological evaluation, preventing us from knowing if "neglected" intellectual deficits may be present or may even represent the first onset. This knowledge could better define a correct follow-up (neuroradiological, clinical, and neurocognitive) and a well-timed surgical treatment also in these cases.

LIMITATIONS

This is a small case series of prospectively collected data. Only limited statistical analysis was performed due to the sample size. Our preliminary results thus need further confirmation in wider series and case-control studies. In addition, the postoperative neurocognitive evaluations were performed during a wide time span after surgery, and this represents a significant limitation of their value.

CONCLUSION

Endoscopic third ventriculostomy in patients with LIAS seems to be an effective treatment, improving both neurological and neurocognitive outcomes. Further studies are warranted to better clarify the complex neurocognitive analysis as well as LIAS natural history.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Ethics Committee of the Local Health Service of Bologna, Italy. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM and GP participated to ideate, write, and revise the manuscript. GM took part to write the draft. LR, FS, GB, CZ, DM, AC, and LC took part to the revision process. All authors contributed to the article and approved the submitted version.

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Impact of Early Intervention for Idiopathic Normal Pressure Hydrocephalus on Long-Term Prognosis in Prodromal Phase

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Objectives: Because the progression of idiopathic normal pressure hydrocephalus (iNPH) is partially irreversible, we hypothesized that early intervention would markedly improve its prognosis. To test this hypothesis, we retrospectively investigated the long-term prognosis of patients with early intervention in the prodromal phase of iNPH.

Methods: We defined the prodromal phase of iNPH as a 3m Timed Up and Go (TUG) of 13.5 s or less and a Mini-Mental State Examination (MMSE) of 24 or more. Of the 83 iNPH patients who underwent shunt surgery at Osaka Medical and Pharmaceutical University Hospital over 3 years from January 2015, 12 prodromal phase cases (73.3 ± 6.2 years, 10 males and 2 females) were included in the study. The iNPH grading scale (INPHGS), MMSE, Frontal Assessment Battery (FAB), intermittent gait disturbance (IGD), social participation status, and development of comorbidities were evaluated over 4 years.

Results: Preoperative MMSE was 27.2 ± 1.5, FAB was 14.1 ± 1.8, TUG was 10.7 ± 1.4 s, and total iNPHGS was 2.8 ± 1.4. At 1, 2, 3, and 4 years postoperatively, total INPHGS improved to 0.8, 0.9, 1.5, and 1.7, respectively, and remained significantly better than preoperatively except at 4 years postoperatively. The MMSE improved slightly to 27.5 after 1 year and then declined by 0.35 per year. After 4 years, the mean MMSE was 26.1, and only one patient had an MMSE below 23. FAB improved to 15.2 after 1 year and then declined slowly at 0.85/year. Ten patients (83%) maintained a high capacity for social participation postoperatively. The preoperative tendency to fall and IGD in 9 (75%) and 8 (67%) patients, respectively, completely disappeared postoperatively, resulting in improved mobility. Shunt malfunction associated with four weight fluctuations and one catheter rupture caused temporary worsening of symptoms, which were recovered by valve re-setting and catheter revision, respectively.

Conclusion: Early intervention in the prodromal phase of iNPH patients maintained good cognitive and mobility function and social participation ability in the long term. The maintenance of long-term cognitive function suggests its preventive effect on dementia. To realize early intervention for iNPH, it is desirable to establish an early diagnosis system for iNPH.

Keywords: idiopathic normal pressure hydrocephalus (iNPH), early intervention, CSF shunt, long-term outcome, hydrocephalus surgery, prodromal phase

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH), which is a progressive neurological disease resulting in dementia and gait and balance disorders, as well as urinary incontinence, is treatable by cerebrospinal fluid (CSF) shunting (1, 2) demonstrated that the progression of iNPH is partially irreversible manner (3). The reversible part of the progression suggests the efficacy of CSF shunting, while the irreversible part suggests that the earlier the intervention, the better the prognosis. Mild cases have been reported to have a better short-term prognosis (4, 5) and long-term prognosis of cognitive function (6). However, the prognosis of early intervention in patients with iNPH in milder cases, which may be termed the prodromal phase, is unknown.

Many neurodegenerative diseases progress irreversibly, making it difficult to improve their prognosis. In Alzheimer's disease (AD), recent large-scale clinical trials have failed (7–9). Therefore, interventions to control the progression of AD are shifting to earlier stages, i.e., mild cognitive impairment (MCI) (10) and preclinical AD (11, 12). Also in Parkinson's disease (PD), it has been suggested that intervention in the prodromal phase may improve symptom progression (13). However, even though iNPH is also an irreversible neurological disease, there is still no concept of early diagnosis and early intervention.

iNPH develops after a preclinical phase named asymptomatic ventriculomegaly with features of iNPH on MRI (AVIM) (14). Although iNPH should have a prodromal phase as in AD and PD, it has not been defined. Therefore, we defined the prodromal phase of cognitive symptoms in iNPH as an MMSE of 24 or higher, referring to the MMSE cutoff values for AD and MCI (15, 16). It has also been suggested that patients with suspected prodromal symptoms of PD have minimal motor features (MMF) (17). MMF is defined as two or more Parkinsonian signs with a Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (18) score of 1, but without sufficient clinical features for a diagnosis of PD (13). The description of a score of 1 for gait in the MDS-UPDRS is "slight: independent walking with minor gait impairment" (18). Since this definition is not quantitative, we defined a 3m-timed up and go test (TUG) of 13.5 s or less as the prodromal phase of gait balance function in iNPH, with a low risk of falling (19). On the other hand, urinary incontinence is not included in the definition of prodromal iNPH because there are many age-related urinary problems such as benign prostatic hyperplasia, overactive bladder, and abdominal stress urinary incontinence.

In this study, we hypothesized that early intervention in patients with a prodromal phase of iNPH (MMSE $\geq$ 24 and TUG $\leq$ 13.5 s) would have a very good long-term prognosis, and we tested this hypothesis retrospectively.

MATERIALS AND METHODS

Eligible Patients

The study protocol was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (No. 2844). We defined the prodromal stage of Idiopathic normal pressure hydrocephalus (iNPH) as a 3m Timed Up and Go (TUG) of 13.5 s or less and a Mini-Mental State Examination (MMSE) of 24 or more. Of the 83 iNPH patients who underwent shunt surgery at Osaka Medical and Pharmaceutical University Hospital over 3 year from January 2015, 14 (17%) were in the prodromal phase. Of these, 12 patients (72.9 $\pm$ 5.8 years old, 11 males and 2 females) who could be followed up for more than 4 years were included in the study. The two excluded patients both had symptomatic improvement after shunting but suffered sudden cardiovascular death and terminal cancer around 2 years after surgery. The indications for cerebrospinal fluid (CSF) shunt surgery were following the "Guidelines for management of iNPH (Third edition)" (20). However, we modified the definition of ventricular enlargement to an Evans' index of 0.27 or greater and emphasized the tightness of the higher subarachnoid space rather than ventricular enlargement. In the CSF tap test, the TUG and MMSE and frontal assessment battery (FAB) were assessed. Four patients were treated with ventriculoperitoneal shunting and eight with lumboperitoneal shunting. In all cases, a programmable valve was used and the initial pressure was set by referring to a quick reference table (21, 22). The initial pressure was then reset in five patients (42%).

Measurement Parameters

Measured parameters including iNPH grading scale (INPHGS) (23, 24), and cognitive function were retrospectively obtained from electronic medical records. Gait and cognitive functions were assessed by physical and speech therapists, respectively. Due to Covid-19, FAB follow-up was discontinued after 3 years. INPHGS was assessed by a neurosurgeon. High-performance activities such as sports, hobbies, and work as indicators of high social participation, development of comorbidities such as dementia and stroke, tendency to fall, and intermittent gait disturbance (IGD) (25) were also recorded for 4 years.

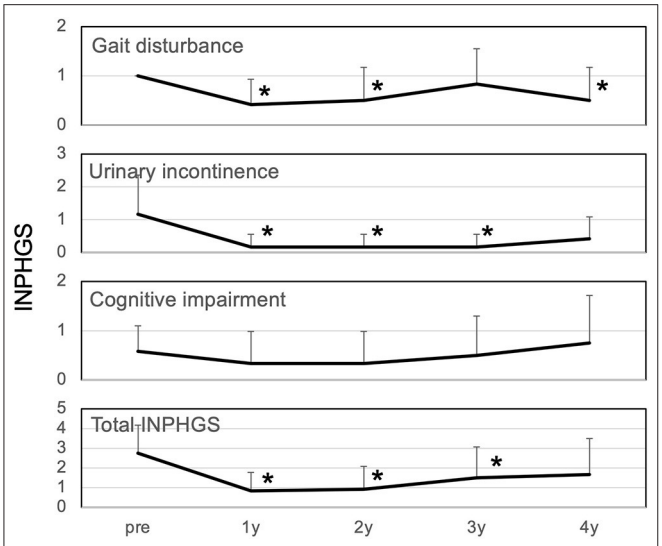

FIGURE 1 | Changes in iNPH grading scale over 4 years. All symptoms improved at 1 year postoperatively. Gait disturbance and urinary incontinence improved significantly at 1, 2, and 4 years postoperatively and at 1, 2, and 3 years postoperatively, respectively. The improvement in cognitive impairment lasted for 1-2 years but returned to the original level at 4 years. Changes in the INPHGS were assessed using Wilcoxon's signed-rank test. INPHGS, idiopathic normal pressure hydrocephalus grading scale. Asterisks indicate significant differences compared to preoperative values ($p < 0.05$).

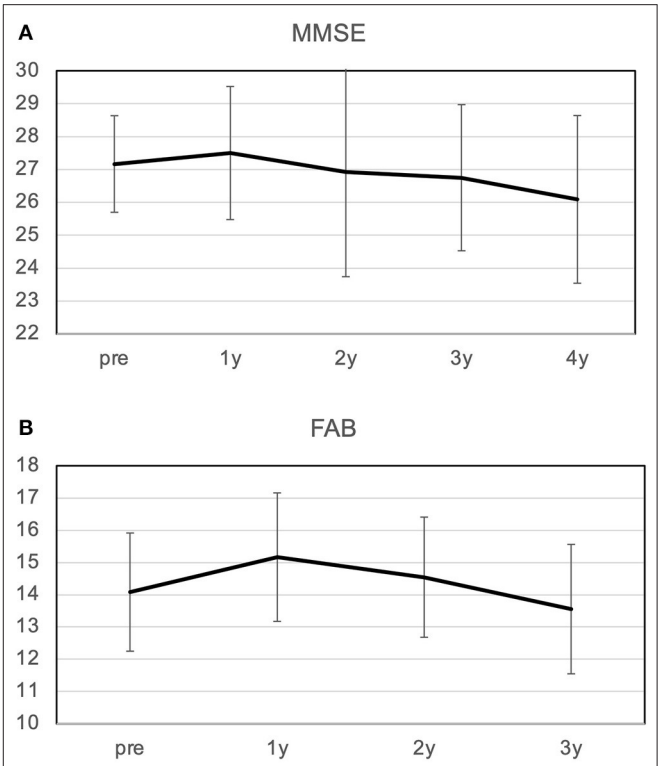

FIGURE 2 | Changes in MMSE **(A)** and FAB **(B)** over 4 years. **(A)** The MMSE improved from 27.2 to 27.5 at 1 year postoperatively and then declined slowly; the average rate of decline over 4 years was 0.26/year. **(B)** FAB improved from 14.1 to 15.2 at 1 year, and then declined slowly at a rate of 0.85/year. MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery.

Furthermore, we analyzed the process that led to the early diagnosis from the medical history.

Statistical Analysis

Data are presented as mean values (± standard deviation). Changes in INPHGS, MMSE, and FAB were analyzed using Wilcoxon's signed rank test. A p-value < 0.05 was considered statistically significant. Data analysis was performed using JMP Pro 15.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Change in INPH Grading Scale

The total iNPHGS, which was 2.8 preoperatively, continued to improve to 0.8, 0.9, 1.5, and 1.7 at 1, 2, 3, and 4 years postoperatively, respectively (**Figure 1**). The results were statistically significant up to 3 years after surgery. Among the INPHGS, improvement in gait disturbance was significant at 1, 2, and 4 years postoperatively. The improvement in urinary incontinence was significant at 1, 2, and 3 years postoperatively.

Changes in Mini-Mental State Examination and Frontal Assessment Battery

The MMSE improved slightly from 27.2 preoperatively to 27.5 at 1 year postoperatively, and decreased slightly to 26.1 at 4 years postoperatively (**Figure 2**). The mean MMSE decreased by 1.1 from 27.2 to 26.1 over the 4 years, indicating that the annual rate of decline in MMSE was 0.27/year. Patients with a preoperative MMSE of 24-27 showed a significant improvement in MMSE at 1 year and a gradual decline thereafter. On the other hand, patients with an MMSE of 28-30 also showed cognitive decline over time, and there was no difference between the two groups 4 years after surgery (**Figure 3**). The mean MMSE at 4 years was 26.1, and only one patient had an MMSE below 23 (**Figure 4**). This patient had fluctuating symptoms, and 123I-IMP SPECT showed relative cerebral hypoperfusion in the temporoparietal and occipital lobes, suggesting the development of dementia with Lewy bodies. One patient (8%) progressed to dementia defined by an MMSE of 23 or less over 4 years, suggesting an annual conversion rate of 2%/year.

The FAB improved from 14.1 to 15.2 after 1 year and then declined slowly at 0.8/year. Ten patients who originally had hobbies or jobs resumed high-performance social participation after surgery, including running a company, golf, gym, Japanese harp master, pilgrimage, blogging, and travel, and were able to maintain these activities for a long time (**Table 1**; **Figure 4**). As a result, their FAB at 3 years postoperatively was maintained at 14.3. On the other hand, two patients originally had no hobbies and continued to live inactive after surgery. They improved their FAB from 13 to 16 after 1 year, and the average annual rate of decline over the next 2 years was 2.5/year. As a result, the FAB rapidly decreased to 11 at 3 years after surgery (**Figure 4B**). In the case of the patient whose MMSE suddenly dropped to 18 2 years after surgery, the cause was functional underdrainage, as described below (**Figure 4A**).

Antidementia drugs and antidepressants may affect the MMSE. Six of the 12 patients in this study did not take any of these drugs during the study. Three patients had taken antidepressants preoperatively, and one had taken donepezil, but these were discontinued within the first year postoperatively due to improvement in symptoms. Antidementia drugs were used postoperatively in only two patients with progressive memory impairment after shunt surgery.

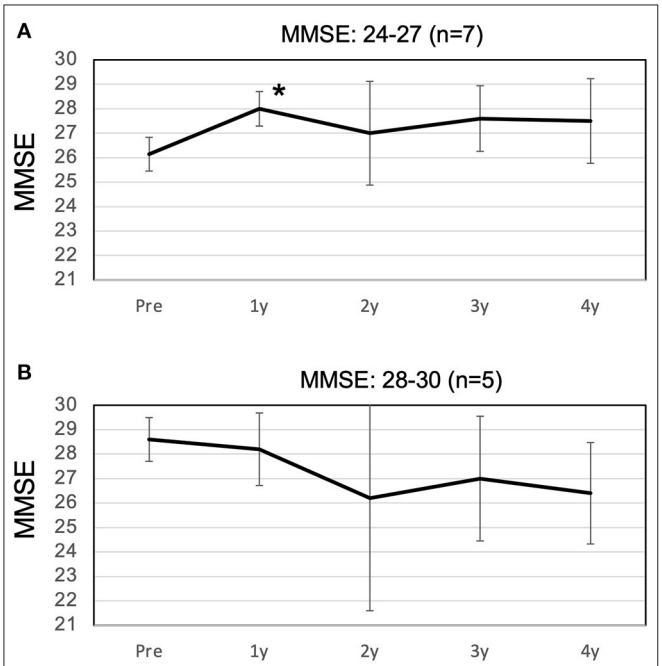

FIGURE 3 | Changes in the high and low MMSE groups over 4 years. **(A)** In the low MMSE group, with a preoperative MMSE of 24-27, the MMSE improved significantly to 28.0 at 1 year postoperatively, with only a slight decline thereafter. **(B)** In the high MMSE group, with a preoperative MMSE of 28-30, the MMSE decreased slowly until 4 years postoperatively. There was no difference between the two groups at 4 years postoperatively. MMSE, Mini-Mental State Examination. Asterisks indicate significant differences compared to preoperative values ($p < 0.05$).

Shunt Malfunction

Mechanical shunt malfunction developed in one patient. Three years postoperatively, the symptoms worsened with delayed rupture of the spinal catheter, but fully recovered with shunt revision. On the other hand, non-mechanical shunt malfunction occurred four times in three patients. There were three cases of underdrainage associated with weight gain, which we named underdrainage type weight and abdominal pressure induced shunt trouble (WAIST). In all cases, valve resetting to increase shunt flow improved symptoms immediately. However, in patients with advanced dementia due to delayed detection of shunt malfunction, recovery of MMSE was limited (**Figure 4A**). One patient had asymptomatic chronic subdural hematoma with 10 kg weight loss. We have named this phenomenon overdrainage type WAIST. Valve resetting to lower the shunt flow rate made the hematoma disappear after 1 month.

Improvement in a Tendency to Fall and Intermittent Gait Disturbance

Before surgery, 9 (75%) and 8 (67%) patients tended to fall and intermittent gait disturbance (IGD), respectively (**Table 1**). However, these completely disappeared after the surgery, resulting in the elimination of fall anxiety and a marked improvement in the patients' mobility.

Processes Leading to Early Diagnosis

Three patterns in the diagnostic process that led to early diagnosis (**Table 1**). The first is detection during the differential diagnosis of dementia or Parkinson's disease which was found in six

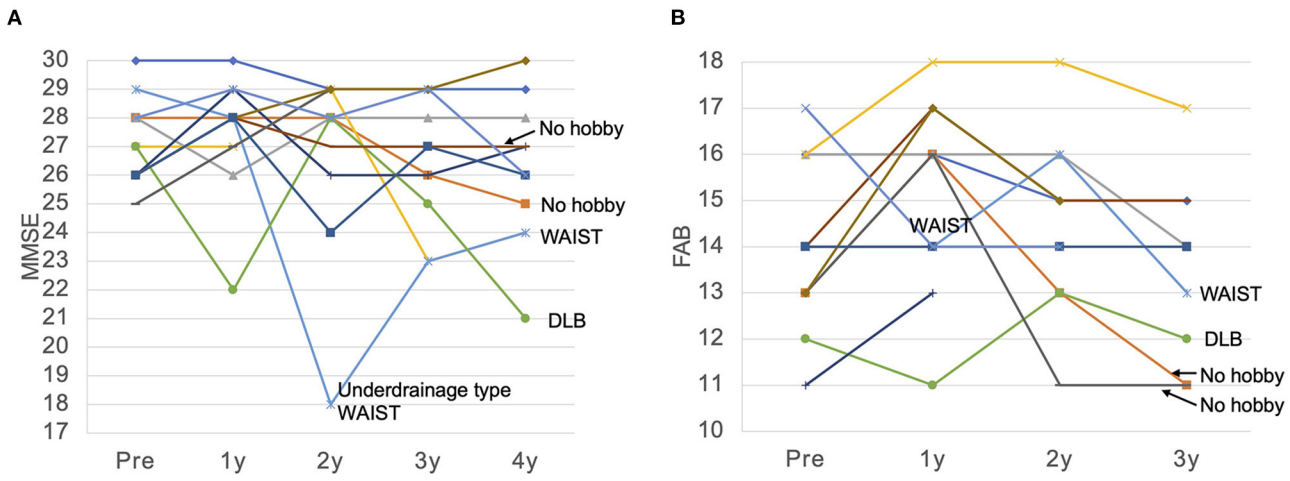

FIGURE 4 | MMSE **(A)** and FAB **(B)** for each patient over 4 years. **(A)** The MMSE remained almost unchanged for 4 years in many patients. MMSE showed a significant decrease in cases of dementia with Lewy bodies (DLB) and functional underdrainage associated with weight gain, which we named weight and abdominal pressure induced shunt trouble (WAIST). **(B)** FAB was also maintained at a high score for 4 years in many patients, but declined significantly in one patient who developed DLB, in two patients with no hobbies and a persistent inactive lifestyle, and in one patient with an underdrainage type of WAIST. MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; WAIST, weight and abdominal pressure induced shunt trouble.

TABLE 1 | Clinical characteristics and postoperative course of 12 patients with prodromal phase iNPH.

No.	Age	Sex	OP	Fall count	IGD	TUG (s)	Diagnostic trigger	High performance activity (duration)	MMSE/FAB preOP	MMSE/FAB after 1 year	MMSE/FAB after 4/3 years	Antidepressant preOP/postOP	Antidementia drug preOP/postOP
1	65	M	VP	0	–	10.8	AVIM Following	Bamboo flute (4y-)	30/16	30/16	29/15	Aripiprazole/none	None/none
2	63	M	LP	0	–	11.3	MRI for dementia Dx	none	28/13	28/16	25/11	Aripiprazole/none	None/none
3	74	M	VP	4	+	8.0	CT at fall	President(4y-), Golf(2y)	28/16	26/16	28/14	None/none	None/none
4	72	M	VP	1	+	9.9	AVIM Following	President(2y), Golf(4y-)	27/16	27/18	24/17	None/none	None/Rivastigmine
5	86	M	VP	2	+	11.6	MRI for dementia Dx	Karaoke(4y-)	29/14	28/14	24/13	None/none	None/none
6	77	M	LP	1	–	11.2	MRI for dementia Dx	Pilgrimage(1y)	27/12	22/11	21/12	None/none	None/donepezil
7	71	M	LP	1	+	8.4	MRI for dementia Dx	Gym(4y-)	26/11	29/13	27/NA	Maprotiline/none	None/none
8	77	M	LP	1	+	10.7	MRI for PD Dx	Flower Photography Blog(4y-)	26/14	28/17	27/15	None/none	None/none
9	68	M	LP	1	+	13.2	CT at fall	none	25/13	27/16	29/11	None/none	None/none
10	75	M	LP	2	+	11.5	CT at fall	Golf(4y-), Travel(4y-)	26/13	28/17	30/NA	None/none	None/none
11	74	F	LP	1	+	10.4	AVIM Following	Japanese Harp Master(4y-)	26/14	28/14	26/14	None/none	Donepezil/none
12	78	F	LP	0	–	11.9	MRI for dementia Dx	Chorus(3y), Gym(3y)	28/17	29/14	26/NA	None/none	none/none

Fall count and IGD represent the number of falls and the presence of intermittent gait disturbance (IGD) before surgery. The 4y- in duration means more than 4 years.
INPHGS, iNPH grading scale; IGD, intermittent gait disturbance; MMSE, mini-mental state examination; FAB, frontal assessment battery; LP, lumbo-peritoneal; VP, ventriculo-peritoneal; AVIM, asymptomatic ventriculomegaly with features of iNPH on MRI; PD, Parkinson's disease; Dx, diagnosis.

cases (50%). The second is when it is detected by head CT at the time of a fall, which was found in three cases (25%). The third pattern was that the patient had previously been diagnosed with asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on MRI (AVIM) and iNPH developed during follow-up, which occurred in three cases (25%).

DISCUSSION

Long-Term Outcomes of Interventions in the Prodromal Phase

This study demonstrates that early intervention in patients with idiopathic normal pressure hydrocephalus (iNPH) in the prodromal phase improves the long-term functional outcome of gait, cognition, and urination. Symptoms of gait and urinary dysfunction were significantly improved. On the other hand, early intervention maintained good cognitive function over the long term, but there was no significant difference. The reason for this non-significant difference is thought to be the ceiling effect.

The rate of decline in the Mini-Mental State Examination (MMSE) was as low as 0.27/year, and the conversion rate to dementia was as low as 2%/year. Peterson et al. reported that the rate of decline of MMSE in mild cognitive impairment (MCI) was 1.0/year (10). The rate of decline in MMSE in this study is only one quarter of that reported by them. Therefore, early intervention in prodromal phase iNPH has the potential to reduce the decline in cognitive function over time. It is also known that the annual conversion rate of MCI to dementia is 10-20% (26, 27). The conversion rate to dementia of 2%/year in this study is considerably lower than this.

The study also included five patients with MMSE scores in the normal range of 28 or higher, which may have been associated with a lower rate of cognitive decline. However, there was no difference in MMSE scores at 4 years between the high MMSE group with an MMSE of 28 or higher and the low MMSE group with an MMSE of 24 to 27 (**Figure 3**). Therefore, it can be concluded that the inclusion of patients with MMSE scores in the normal range of 28 or higher has no effect on the prognosis of cognitive function. Despite the disadvantage of the small number of cases, it suggests that early shunt surgery has a preventive effect on conversion to dementia.

Antidepressants and antidementia drugs may affect the MMSE. In this study, only 2 out of 12 patients took antidementia drugs postoperatively. This fact indicates that the influence of antidementia drugs on this study is limited. On the other hand, three patients had taken antidepressants preoperatively but discontinued them postoperatively. This fact may have contributed to the improvement of frontal lobe function.

The prognosis for cognitive function in shunted iNPH patients has been thought to be poor (28, 29). Koivisto et al. (29) reported that even among patients who responded to shunting, 46% developed dementia during a mean postoperative follow-up of 4.8 years. In the present study, only one patient (8%) converted to dementia over the 4-year period, indicating that

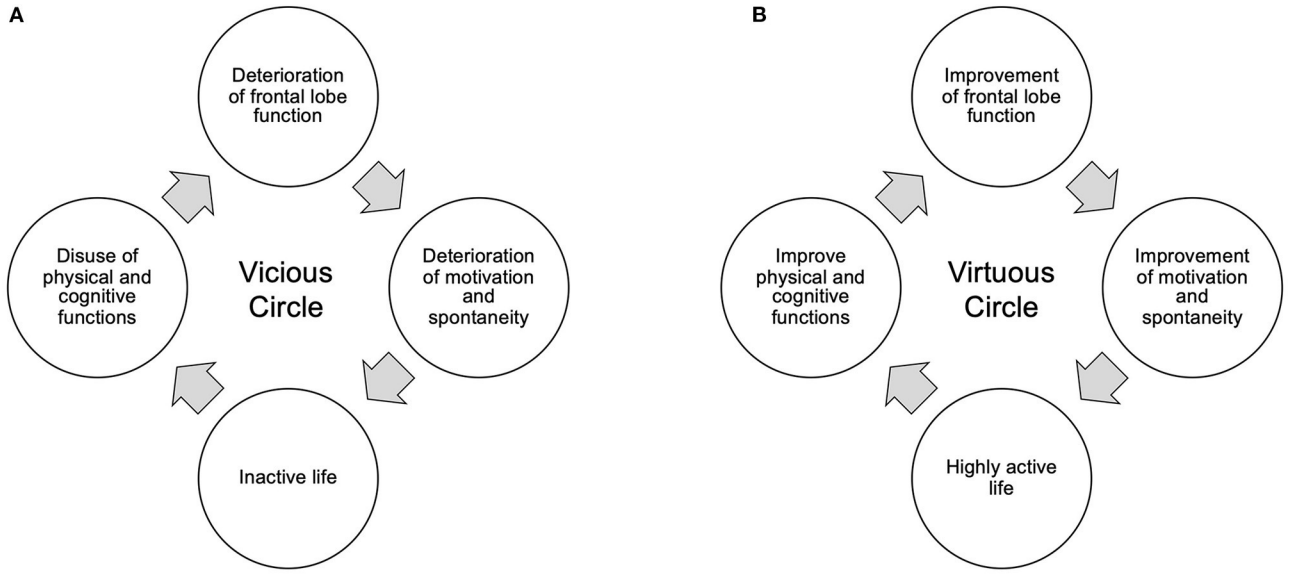

FIGURE 5 | Vicious **(A)** and virtuous **(B)** circles between frontal lobe function and activity of life. **(A)** Deterioration of the patient's frontal lobe function reduces motivation, such as spontaneity, and leads the patient to a more inactive life. As a result, cognitive and physical functions decline due to disuse, leading to a vicious cycle of further decline in frontal lobe function. **(B)** Maintaining and improving frontal lobe function maintains and improves motivation, including spontaneity, and restores an active lifestyle. As a result, cognitive and physical functions enter a virtuous cycle of improvement.

early intervention not only has the effect of slowing the rate of cognitive decline but also of preventing conversion to dementia.

Criticism and Limitation of This Study

It may be criticized that this study treated iNPH in the preclinical phase rather than the prodromal phase because of the favorable long-term prognosis. However, we believe that the patients in this study had minor symptoms of iNPH for the following three reasons. First, there was a significant improvement in gait and urinary dysfunction in iNPH grading scale (INPHGS). Second, there was a reversible progression of symptoms with shunt malfunction. Third, the preoperative tendency to fall and intermittent gait disturbance (IGD) (25), which we also call hydrocephalic intermittent claudication (HIC), is caused by balance disturbance seen in long-distance walking, disappeared after CSF shunting. The present study is a retrospective study with few cases, which limits the evidence. Therefore, prospective cohort studies and randomized controlled studies are desirable to prove the effectiveness of early intervention for iNPH at a high level of evidence.

Definition of Prodromal Phase of iNPH

The prodromal phase of iNPH in this study is defined as the prodromal phase of MCI in Alzheimer's disease (AD) (15, 16), minimal motor features (MMF) in Parkinson's disease (PD) (13, 17, 18), and the cutoff value of the 3m-timed up and go test (TUG) in fall risk determination (19) were used as a reference for definition. Therefore, we believe that the definition of the prodromal phase of iNPH is valid currently. However, further discussion on its validity, cut-off values, and the choice of assessment methods for cognition, gait, and balance is necessary.

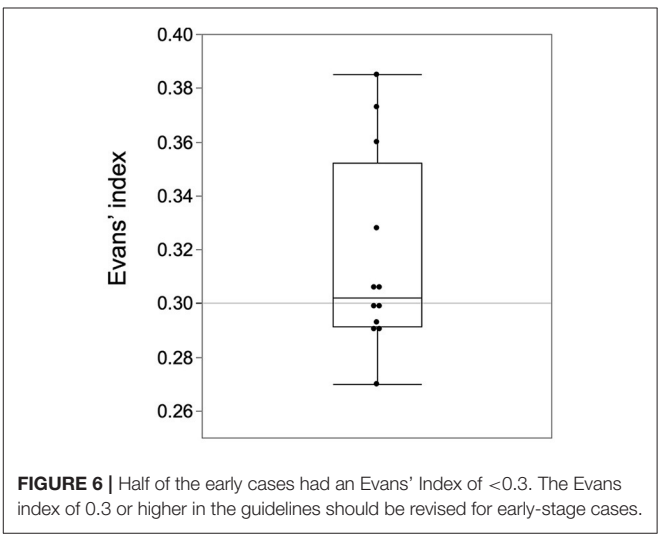

FIGURE 6 | Half of the early cases had an Evans' Index of <0.3. The Evans index of 0.3 or higher in the guidelines should be revised for early-stage cases.

Shunt Malfunction

In the present study, functional and non-mechanical shunt malfunctions caused by weight gain or loss occurred four times more frequently than mechanical shunt malfunctions. The cause of non-mechanical shunt Malfunctions is mainly due to the increase in intra-abdominal pressure with weight gain, which results in an increase in intracranial pressure outside the appropriate therapeutic window (in print). Similar shunt malfunctions have been reported rarely in pregnant women (30). However, its high frequency in iNPH patients may be due to the narrow therapeutic window for valve setting pressure

in iNPH patients. When a shunt Malfunction is found in a patient with iNPH, weight gain should be checked. If there is weight gain, lowering the valve setting is likely to improve the worsening symptoms.

Frontal Lobe Function and Social Participation

Patients with moderate iNPH are prone to a vicious cycle in which, even if gait function improves, motivation and spontaneity continue to decline, resulting in an inactive lifestyle, disuse of cognitive and motor functions, and more inactive living (**Figure 5A**). On the other hand, in the present study, many patients were able to resume or maintain a high level of social participation through work or hobbies. This suggests a virtuous cycle of activation of physical and mental activities through a high level of social participation (**Figure 5B**; **Table 1**). Even though MMSE did not significantly improve postoperatively due to ceiling effect, gait significantly improved and frontal lobe function was maintained. This is thought to have enabled the resumption and maintenance of social participation, which in turn prevented the decline in cognitive function.

It is thought that the frontal lobe functions, particularly the prefrontal cortex, are responsible for this motivation to participate in society (31, 32). A variety of executive functions such as planning, decision making, and short-term memory are essential for maintaining a high level of social participation. Its frontal lobe function can be measured by the Frontal Assessment Battery (FAB). In the present study, the FAB was maintained in the normal range in patients who were able to participate in society, while it decreased in patients who were unable to maintain social participation. In the two patients who had originally had no hobbies and poor social participation, the FAB improved to 16 1 year after surgery, and then rapidly declined to 11. These facts suggest not only that high frontal lobe function is important for social participation, but also that social participation through hobbies and work is essential for maintaining that frontal lobe function.

Medical System Leading to the Early Diagnosis of iNPH

The three diagnostic routes that led to early diagnosis had the following problems. One problem common to all the routes is the cutoff value of the Evans' Index. Evans' Index of 0.3 or higher is commonly used as a diagnostic criterion for iNPH (20). However, in the early cases of our study, half of the patients would be excluded if this criterion were used (**Figure 6**). The distribution in the histogram of the Evans' index of iNPH patients reported in the SINPHONI study has the third highest frequency of 0.30-0.32 (1). In this Evans' index distribution, there is an incongruous absence of frequencies below 0.30. This suggests that there may be iNPH patients with Evans' index below 0.30. There are two ways to avoid this problem. First, the cutoff value of 0.3 for the Evans' Index should be reviewed. Second, the tightness of the higher subarachnoid space should be the first focus of attention rather than ventricular enlargement.

The problem with detection at the time of fall is that minor gait disturbances in early-stage patients can easily be missed. TUG of $<$13.5 s in this study should have a low risk of falling, but many patients did fall. This discrepancy can be explained by gait disturbance, which we have named intermittent gait disturbance (IGD) (25). Patients with IGD can walk almost normally in the office. However, they often become propulsed by postural instability after long-distance walking (25). To avoid this oversight, patients who have fallen should be asked if long-distance walking causes gait instability.

The problem with early diagnosis from AVIM is that this method has not been generalized. When CT and MRI scans of elderly patients are performed and DESH findings are found incidentally, the patient should be provided with the following information. First, there is a 17% annual risk of conversion to iNPH (33). Second, since the symptoms of iNPH are partly irreversible and progressive, a physician familiar with iNPH care should be consulted if the disease develops.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Osaka Medical and Pharmaceutical University (No. 2844). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YK, MK, and MW made substantial contributions to the conception and design of the study. KK, YK, ST, YN, and RS collected data regarding the participants and task performance. YK and MK analyzed the data. YK wrote the manuscript. All authors read and approved the submitted version.

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The Clinical Utility of the MOCA in iNPH Assessment

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Objectives: We sought to estimate reliable change thresholds for the Montreal Cognitive Assessment (MoCA) for older adults with suspected Idiopathic Normal Pressure Hydrocephalus (iNPH). Furthermore, we aimed to determine the likelihood that shunted patients will demonstrate significant improvement on the MoCA, and to identify possible predictors of this improvement.

Methods: Patients ($N = 224$) presenting with symptoms of iNPH were given a MoCA assessment at their first clinic visit, and also before and after tap test (TT) or extended lumbar drainage (ELD). Patients who were determined to be good candidates for shunts ($N = 71$, 31.7%) took another MoCA assessment following shunt insertion. Reliable change thresholds for MoCA were derived using baseline visit to pre-TT/ELD assessment using nine different methodologies. Baseline characteristics of patients whose post-shunt MoCA did and did not exceed the reliable change threshold were compared.

Results: All nine of reliable change methods indicated that a 5-point increase in MoCA would be reliable for patients with a baseline MoCA from 16 to 22 (38.4% of patients). Furthermore, a majority of reliable change methods indicated that a 5-point increase in MoCA would be reliable for patients with a baseline MoCA from 14 to 25. Reliable change thresholds varied across methods from 4 to 7 points for patients outside of this range. 10.1% had at least a 5-point increase from baseline to post-TT/ELD. Compared to patients who did not receive a shunt, patients who received a shunt did not have lower average MoCA at baseline ($p = 0.88$) or have better improvement in MoCA scores after the tap test ($p = 0.17$). Among shunted patients, 23.4% improved by at least 5 points on the MoCA from baseline to post-shunt. Time since onset of memory problems and post-TT/ELD gait function were the only clinical factors significantly associated with having a reliable change in MoCA after shunt insertion ($p = 0.019$; $p = 0.03$, respectively).

Conclusions: In patients with iNPH, clinicians could consider using a threshold of 5 points for determining whether iNPH-symptomatic patients have experienced cognitive benefits from cerebrospinal fluid drainage at an individual level. However, a reliable change cannot be detected for patients with a baseline MoCA of 26 or greater, necessitating a different cognitive assessment tool for these patients.

Keywords: cognition, normal pressure hydrocephalus, cognitive examination, Montreal Cognitive Assessment (MoCA), reliable change index (RCI)

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INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a potentially reversible neurological condition due to altered cerebrospinal fluid dynamics, manifesting primarily in impaired gait and balance, as well as cognitive decline and urinary incontinence. iNPH is most common among older adults, however, incidence rates vary widely between studies based on the methods and operational definitions used (1). Recently, the largest study to evaluate the incidence rates of iNPH reported it to be 14.65 in 100,000 adults age 70 or older (2).

This wide range of incidence rates reflect the challenges in diagnosing iNPH. The symptomatology of iNPH has considerable overlap with more common age-related disorders, such as Alzheimer's Disease (AD). Hence, iNPH diagnosis guidelines recommend that clinicians conduct a Tap Test (TT) or extended lumbar drainage (ELD) and consider changes in their patients gait primarily when determining the likelihood of iNPH.

In addition to changes in the patient's gait, clinicians also consider improvements in their cognition when diagnosing iNPH (3, 4). Research has shown that, for some patients, cognition does significantly improve following CSF drainage either from a TT or ELD and following shunt surgery (5–9). However, these studies have focused on comparing mean differences across groups, such as gait-responders vs. non-responders (6) or shunted vs. non-shunted iNPH patients (7). Thus, clinicians still lack a validated metric for determining what is considered a "significant" cognitive improvement for individual patients. Due to the high variability of cognitive measures in impaired patients, clinicians can be misled by mild cognitive improvements (10).

TABLE 1 | Patient characteristics by diagnosis of normal pressure hydrocephalus ($n = 224$).

	All patients		No shunt ($n = 153$)		Shunt ($n = 71$)		
	N or Median	(%)(IQR)	N or Median	(%)(IQR)	N Or Median	(%)(IQR)	p^1
Age (years)	75	(70, 80)	75	(70, 80)	74	(71, 79)	0.59
Gender							
Female, *n* (%)	94	(42%)	62	(40.5%)	32	(45.1%)	0.62
Male, *n* (%)	130	(58%)	91	(59.5%)	39	(54.9%)	0.62
Education							
High school, *n* (%)	72	(32.1%)	49	(32%)	23	(32.4%)	1
College, *n* (%)	82	(36.6%)	54	(35.3%)	28	(39.4%)	0.65
Graduate, *n* (%)	70	(31.2%)	50	(32.7%)	20	(28.2%)	0.6
Race							
White, *n* (%)	202	(90.2%)	139	(90.8%)	63	(88.7%)	0.8
Black, *n* (%)	19	(8.5%)	11	(7.2%)	8	(11.3%)	0.45
Other race, *n* (%)	3	(1.3%)	3	(2%)	0	(0%)	0.55
BMI (kg/m^2)[a]	27.1	(24.5, 30.7)	26.6	(24.3, 30.7)	27.7	(25.3, 30.7)	0.49
Evan's index (x100)	36	(33.8, 40)	36	(33, 39)	37	(35, 40)	0.06
Number of falls in past six months (count)[b]	2	(0, 4)	2	(0, 4)	3	(1, 5)	0.026*
Time since onset of							
Gait problems (months)[c]	18	(9, 36)	18	(9.5, 36)	18.5	(9.8, 36)	0.85
Memory problems (months)[d]	12	(4, 24)	12	(4, 25)	12	(6, 24)	0.57
MoCA							
Baseline	22	(18, 25)	22	(18, 25)	22	(19, 24)	0.88
Pre-TT/ELD	22	(18, 24)	21	(17, 24)	22	(18, 24)	1
Post-TT/ELD	22	(18, 25)	22	(18, 25)	22	(18, 26)	0.41
MoCA improvement							
Baseline to pre-TT/ELD	0	(-3, 2)	0	(-3, 2)	0	(-3, 2)	0.59
Baseline to post-TT/ELD	1	(-2, 3)	0	(-2, 2)	1	(-1, 3)	0.17
Pre to post-TT/ELD	1	(-1, 3)	1	(-1, 3)	1	(0, 3)	0.31
Timed Up/Go,[a]							
Pre-TT/ELD (s)	16	(11.7, 24.8)	15.1	(11.4, 22.3)	18.4	(12.9, 37.9)	0.005*
Post-TT/ELD (s)	13.1	(10.3, 21.3)	12.7	(10.2, 20.1)	14.9	(10.6, 26.2)	0.24
Improvement (s)	−1.8	(-4.6,−0.4)	−1.2	(-2.7,−0.1)	−4.6	(-10.8,−1.8)	<0.001*

[1]*P-Values were generated using a Wilcoxon test for continuous variables and a Fisher's exact test or chi-square test for categorical variables. a. Missing value in 1 patient; b. Missing values in 16 patients; c. Missing values in 3 patients; d. Missing values in 7 patients.*

**P-Value < 0.05.*

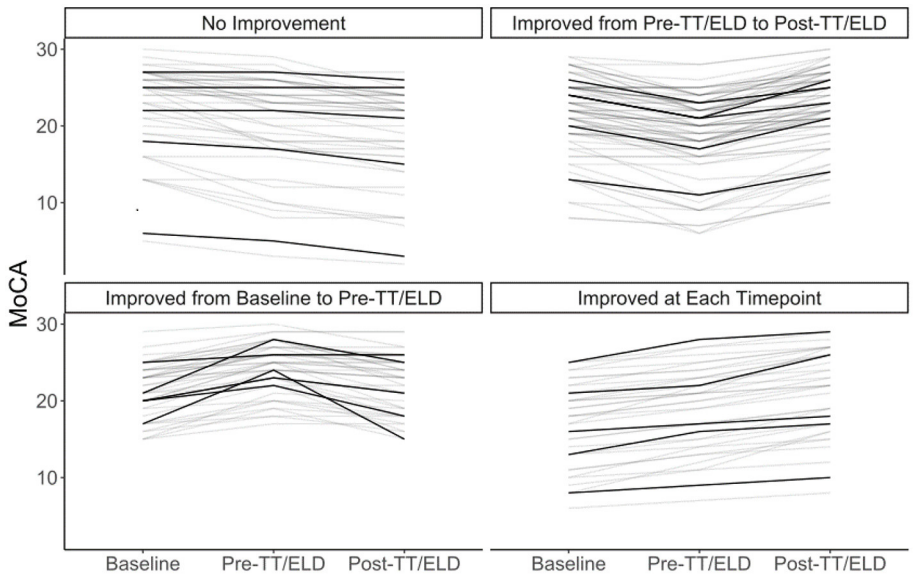

FIGURE 1 | Individual trajectories of MoCA at baseline, pre-TT/ELD, post-TT/ELD. 5 representative patients in each group identified in darker lines. No improvement ($n = 49$). Improvement from pre to post-TT/ELD ($n = 90$). Improvement from baseline to pre-TT/ELD ($n = 47$). Improvement from baseline to pre-TT/ELD and pre to post-TT/ELD ($n = 38$).

Therefore, we sought to address this gap in the literature by providing an empirically-based index for determining if an iNPH patient shows significant cognitive improvement following a TT in a commonly used cognitive test, the Montreal Cognitive Assessment (MoCA). To accomplish this aim, we compared various methods for estimating reliable change indices (RCIs) for MoCA in suspected iNPH patients undergoing a TT or ELD. RCIs express change relative to their associated error which make them particularly usual for repeated cognitive measures. Thus, RCIs have emerged as a strong empirically-based approach to improving clinical decision making and have been applied to cognitive change in patients suffering from Parkinson's disease (11), strokes (12), and concussions (13).

For this study, we calculated RCIs for Montreal Cognitive Assessment (MoCA), a brief measure of cognitive ability designed to detect mild cognitive dysfunction (14). The MoCA is well validated in older adult populations (15–17), as well as populations suffering from various types of dementia (10, 18). Furthermore, the MoCA is commonly used in iNPH populations, with studies demonstrating its sensitivity to cognitive changes at several different time points following a TT (5, 6) and even surgery (19). Importantly, RCI methods have been applied to MoCA to calculate reliable change in the cognition of healthy older adults (20) and those with mild cognitive impairment (21) but not iNPH specific populations to date.

The primary aim of this study is to extend the extant literature on RCIs for the MoCA to an iNPH-symptomatic population; thereby providing clinicians with an empirically-based index for interpreting significant cognitive improvement post-TT or post-ELD. Additionally, we sought to determine whether patients with possible iNPH selected for shunt surgery based on improvements in tests of gait and balance were more likely to exhibit a reliable change in MoCA score than those who were not selected for shunt surgery. Lastly, we aimed to determine the likelihood that shunted patients will demonstrate significant improvement on the MoCA, and to identify possible predictors of this improvement so that we may better inform clinician's and patient's expectation for a significant improvement in cognition following shunt surgery at an individual level.

METHODS

Participants

Two hundred twenty-four patients (Age: Mean = 74.4 yrs, SD = 7.8, 58% male) presenting with suspected iNPH were evaluated in the Center for CSF Disorders between October 2013 to September 2021. Patients were considered to have suspected iNPH if they presented with ventriculomegaly (Evan's Index > 0.3) and gait dysfunction with or without cognitive and urinary dysfunction, without antecedent causes. This study was approved by the Johns Hopkins IRB (Cerebrospinal Fluid Disorders Biorepository & Adult Hydrocephalus Clinical Research Network NA_00029413). All study protocols followed the guidelines set forth by the Johns Hopkins IRB. The study being a retrospective study involving only data extraction and analysis, informed consent was waived by the IRB. Data once extracted was anonymized for analysis.

Measurements and Procedures

During the initial baseline visit, patients had their cognition assessed via the MoCA by a trained psychometrician using the standard form. Alternate forms of the MoCA were not used.

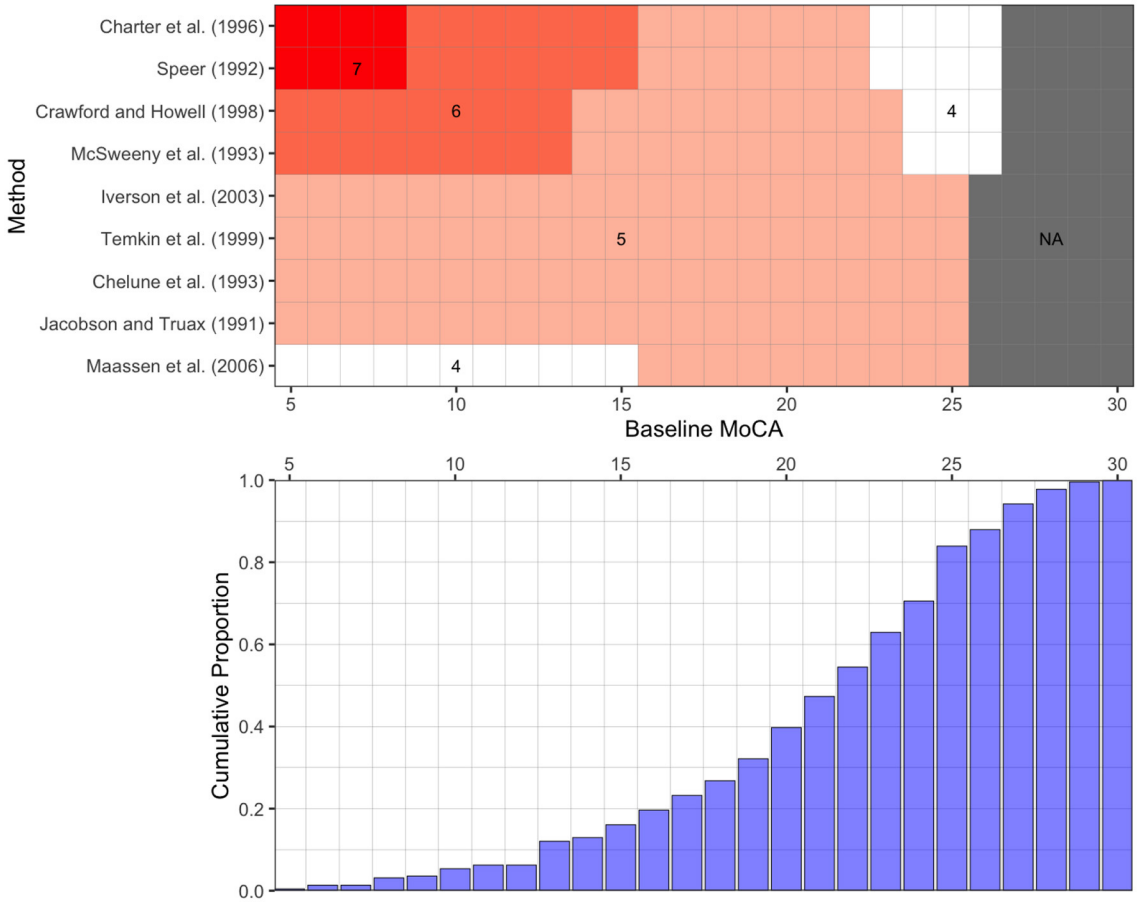

FIGURE 2 | Thresholds for Reliable Increases for the Montreal Cognitive Assessment among Patients with Suspected Normal Pressure Hydrocephalus using nine Methods. Top Panel: Given an initial MoCA score, the minimum reliable increase for a change in MoCA for nine methods. Reliable increases were generated using the 95th percentile of the prediction distribution ($z = 1.64$). Across all methods considered, a minimum increase of 5 points could be deemed reliable for a patient who initially presented with a score of 20. No reliable change could be determined for patients presenting with a score above 25, as the maximum possible MoCA score is 30. Bottom Panel: The proportion of patients presenting at or below a given MoCA score at baseline. For example, 20% of patients had a score of 16 or less at baseline.

Additionally, patients were administered mobility tests assessing their gait velocity [e.g., Ten Meter Walk Test (10MWT), Timed Up & Go (TUG)], balance [Mini-Balance Evaluation Systems test (Mini-BESTest)], and endurance [6-Min Walk Test (6MWT)]. Patients also completed several questionnaires, including the Neurology Quality of Life short forms on depression and executive function (NQL-D, NQL-ED), the Functional Activities Questionnaire (FAQ), and the International Consultation on Incontinence Questionnaire (ICIQ).

Furthermore, patients were asked to report the number of falls they experienced in the previous 6 months, the time since onset of their memory problems, and the time since onset of their gait problems. They also underwent an MRI or CT scan, and Evan's Index was calculated from their brain scans.

A few months after their baseline visit patients returned for one of two types of CSF drainage trial. They either received a tap test (TT) or an external lumbar drainage (ELD). During these visits, patients once again completed the MoCA and the mobility testing, both immediately before and after the procedure.

Physicians considered a number of factors to determine a diagnosis for iNPH, and patients who demonstrated a significant improvement in their gait parameters following TT/ELD were recommended shunt surgery. Patients who received a brain shunt later returned for a follow-up MoCA and gait testing. During our retrospective data extraction, we also gathered information on patients age, sex, race, level of education, and body mass index (BMI) from their medical charts.

Statistical Analysis

Reliable changes for the MoCA were first calculated according to the nine methods outlined by Hinton-Bayre (22–31). The changes in MoCA measurements from our patients from baseline visit to pre-TT/ELD assessment constituted the data for our "normative" population. We then implemented the nine reliable change models using the changes in MoCA measurements from our patients from baseline to post-TT/ELD (22–31). We calculated the relative probabilities of exhibiting a reliable change for patients who improved following

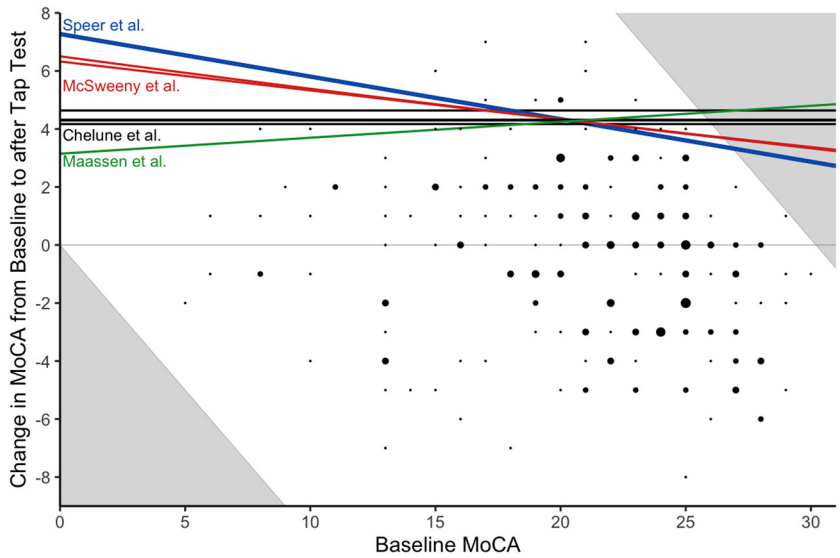

FIGURE 3 | Comparison of Changes in the Montreal Cognitive Assessment to Multiple Reliable Increase Thresholds. Thresholds for all nine reliable change methods are overlaid on the data. The choice of slope formula for the reliable change threshold was more consequential than the choice of intercept formula. Hence, each reliable change threshold is given the color corresponding to the slope formula used (i.e., Speer, McSweeny, Chelune, or Maassen et al.). Since MoCA is a discrete measurement and overlapping points were common in the scatterplot, the size of the point indicates the number of participants with that particular (x, y) combination.

TABLE 2 | Percent patients labeled as having a reliable change in MoCA from baseline to tap test, shunt insertion.

	No shunt, Post-TT/ELD (n = 129)[a]	Shunt, Post-TT/ELD (n = 59)[a]	Shunt, Post-shunt (n = 47)[a]
Jacobson and Truax (23)	10.1	10.2	23.4
Speer (24)	10.1	11.9	27.7
Chelune et al. (25)	10.1	10.2	23.4
McSweeny et al. (26)	10.9	10.2	25.5
Charter et al. (27)	10.1	11.9	27.7
Crawford and Howell (28)	10.9	10.2	25.5
Temkin et al. (32)	10.1	10.2	23.4
Iverson et al. (30)	10.1	10.2	23.4
Maassen et al. (31)	13.2	13.6	25.5

[a]*Patients with baseline MoCA of 25 or lower.*

TABLE 3 | Univariate regressions of post-shunt MoCA on prior MoCA measurements.

Measurement	Intercept[a]	(SE)	Slope	(SE)	Adjusted R-Squared
Baseline MoCA	22.46	(0.44)	0.70	(0.08)	0.56
Pre-TT/ELD MoCA	22.24	(0.43)	0.74	(0.09)	0.57
Post-TT/ELD MoCA	21.99	(0.43)	0.76	(0.09)	0.58
Average pre-shunt MoCA	22.23	(0.39)	0.84	(0.08)	0.65

[a]*MoCA measurement were centered at their respective mean values given in* ***Table 1****.*

TT/ELD and were recommended shunt surgery vs. those who did not.

For all nine methods, the initial reliable change models indicated that patients with an initial MoCA score above 25 would have needed a score above 30 (the highest possible MoCA score) for an increase to be deemed reliable. Hence, in a secondary analysis, we removed participants with an initial MoCA above 25 and re-calculated the reliable change thresholds. This secondary analysis used only the four methods which did not rely on the assumption of the first and second measurements having equal variance (26–29).

To predict MoCA after insertion of a shunt for diagnosed NPH patients, we fit a series of linear regression models. First, we regressed post-shunt MoCA on each baseline, pre-TT, and post-TT MoCA separately, as well as the average of these three MoCA measurements. We selected the MoCA measurement that predicted post-shunt MoCA with the lowest adjusted R-squared for further models. We performed best subset model selection to determine which demographic characteristics (race, sex, age, education), other baseline clinical measurements (BMI, ICIQ, FAQ, NQL-D, NQL-ED, Evan's Index), and other reported information (number of recent falls, time since onset of memory and gait problems) could be used to predict MoCA after shunt insertion. We also regressed MoCA improvement on years between shunt insertion and final MoCA score measurement to understand if and how MoCA improvement may also be a function of when the score is measured after shunt insertion. All analyses were carried out using the statistical software R, version 4.0.5.

RESULTS

Table 1 describes the patient and clinical characteristics of the 224 patients included in our analysis. There were no significant

TABLE 4 | Patient characteristics by change in MoCA from baseline to post-shunt ($n = 56$)[a].

	MoCA Improvement				*p*-value[b]
	<5 (*n* = 36)		≥5+ (*n* = 11)		
Age (years)	75.5	(71, 79.2)	74	(72.5, 78.5)	0.92
Sex					
Female, *n* (%)	14	(38.9%)	4	(36.4%)	1
Male, *n* (%)	22	(61.1%)	7	(63.6%)	1
Education					
High school, *n* (%)	15	(41.7%)	5	(45.5%)	1
College, *n* (%)	14	(38.9%)	4	(36.4%)	1
Graduate, *n* (%)	7	(19.4%)	2	(18.2%)	1
Race					
White, *n* (%)	31	(86.1%)	9	(81.8%)	0.66
Non-white, *n* (%)	5	(13.9%)	2	(18.2%)	0.66
BMI (kg/m^2)	27.2	(25.7, 30.5)	29.6	(27.8, 31.7)	0.2
Evan's INDEX (x100)	37	(36, 40)	38	(33, 39.5)	0.5
Falls in past 6 months (count)	3	(1, 6)	2	(0.2, 5.5)	0.74
Time since onset of gait problems (months)	19	(12, 36)	18	(11.5, 30)	0.85
Memory problems (months)	12	(6.5, 36)	8	(0, 12)	0.019*
Timed up/GoPre-TT/ELD (s)	18.3	(14.6, 39.2)	30.7	(21.5, 55.9)	0.06
Post-TT/ELD (s)	14.8	(10.9, 25.3)	26.8	(16, 40.3)	0.03*
Change (s)	−4.8	(−11, −2.6)	−9.6	(−15.6, −5.7)	0.16

[a]*Excludes patients with baseline MoCA > 25.* [b]*P-Values were generated using a Wilcoxon test for continuous variables and median (IQR) were presented for continuous variables and a Fisher's exact test for binary variables.*
**P-Value < 0.05.*

differences in demographic characteristics (age, sex, education, race) between patients who did and did not receive a shunt. Compared to patients who did not receive a shunt, patients who received a shunt reported more falls in the 6 months preceding their first clinic visit ($p = 0.026$), took longer during the pre-TT/ELD TUG test ($p = 0.005$), and had a greater decrease in the TUG test from pre-TT/ELD to post-TT/ELD. The remaining clinical factors were not significantly different between patients who did and did not receive a shunt.

In terms of change of MoCA scores between baseline and before and after LP/ELD's, four distinct groups could be observed (**Figure 1**). Forty Nine patients showed no improvement, 90 showed an improvement from pre to post-TT/ELD, 47 showed an improvement from baseline to pre-TT/ELD and finally 38 showed an improvement from baseline to pre-TT/ELD & pre to post-TT/ELD. Across the whole group, there was no significance between the MoCA score at pre-TT/ELD [median (IQR): 22 (18, 24)] and the MoCA score at baseline [median (IQR): 22 (18, 25)] for patients.

Figure 2 depicts the calculated reliable change thresholds using nine methods. All methods agreed that a 5-point increase in MoCA would be reliable for patients with a baseline MoCA from 16 to 22 (38.4% of patients). Reliable change thresholds varied from 4 to 7 points for patients outside of this range. The threshold varied based on the method used as well as the baseline MOCA score. **Figure 3** illustrates the nine thresholds against a scatter plot of baseline MoCA scores by changes in MoCA from baseline to post-TT/ELD.

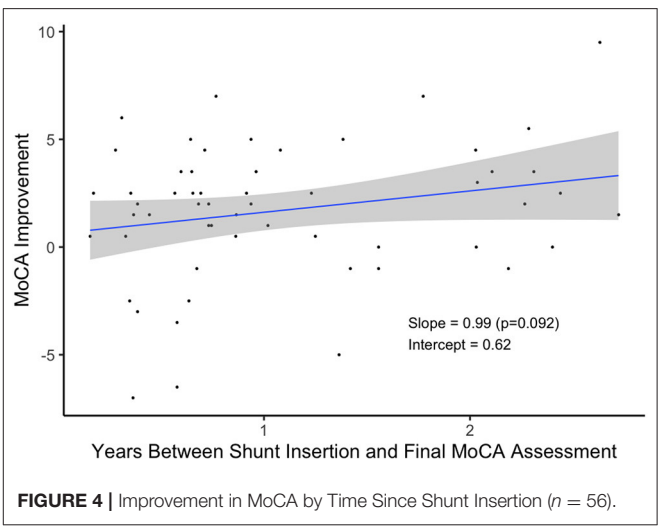

FIGURE 4 | Improvement in MoCA by Time Since Shunt Insertion ($n = 56$).

Table 2 shows percent of patients considered having a reliable change after the TT/ELD for patients who did and did not receive a shunt. The values were roughly similar across those groups. The percent of patients with a reliable change of 5 or more points for those who got a shunt ranged from 23 to 28% depending on the method used.

The best predictor of MoCA after shunt insertion was the average MoCA score prior to shunt insertion (adjusted R-Squared = 0.65, **Table 3**). Further model selection efforts revealed that after accounting for the average prior MoCA measurement, no further demographic or clinical factors helped to predict post-shunt MoCA. **Table 3** also shows, that while average of pre-shunt MoCA's is the best predictor, the other MoCA scores (baseline MoCA, pre-TT/ELD MoCA, and post-TT/ELD MoCA) are still good predictors of post-shunt MoCA (Adjusted R-Squared = 0.56, 0.57, 0.58, respectively).

Table 4 compares the characteristics of patients with vs. without reliable MoCA change (≥5) from baseline to post-shunt. There are no significant differences in most of these characteristics except for time since memory problems, which is shorter for patients who displayed a reliable change, and post-TT/ELD TUG, which is worse for patients who display a reliable change after shunt surgery. This is mainly a function of the different pre-TT/ELD TUG times. Subjects that improved on the MoCA by 5 or more had worse pre-TT/ELD TUG times (30.7 vs. 18.3 s) which was nearly significant ($p = 0.06$). The subjects with improvement in MoCA 5 or more did demonstrate a trend in greater improvement in TUG [-9.6 (95%CI:−15.6,-5.7) vs.−4.8 (95%CI:−11,-2.6), $p = 0.16$] following TT/ELD.

Patients who received a shunt and waited longer to take their final MoCA assessment tended to exhibit greater improvement in their scores (**Figure 4**). On average, patients scored nearly one point higher for each additional year they waited, but more data is needed to verify this relationship ($p = 0.092$).

Supplementary Table 1 provides more detailed information on the equations used to calculate reliable changes. **Supplementary Figures 1, 2** detail the reliable change models fit only using patients with baseline MoCA of 25 or lower.

DISCUSSION

The MoCA has recently become a widely used and standard screening tool for cognitive function, including in patients with iNPH. However, the thresholds used to define improvement in an iNPH population are not well defined and only group comparisons have been described. The present study used multiple methods to estimate reliable change thresholds for the MoCA in a population of older adults with suspected iNPH who underwent a CSF drainage procedure (TT/ELD) and a subset of them underwent shunt surgeryIf validated, this reliable change threshold could serve as a guide to patients and clinicians in management of iNPH patients.

While the Mini Mental Status Examination [MMSE; (33)] is one of the most widely used cognitive screening tests, the MoCA is now considered to be a more suitable and sensitive test for the evaluation of cognition in patients with Mild Cognitive Impairment or early dementia (34, 35). Such cognitive screening instruments are also used repeatedly to assess the progression of cognitive disorders or the response to a specific intervention. To be able to distinguish between true or reliable changes vs. changes occurring as a result of measurement error or chance, reliable change indices have been developed both for the MMSE (36) and MoCA in different populations (20). In the latter population-based study of 197 cognitively normal healthy older adults (age: 60–94 yrs) followed longitudinally for 4 years, the reliable change index for the MoCA was 4. In another population-based study of 128 cognitively normal and mildly impaired participants in whom the MoCA was administered twice with an interval of 2–4 months, the 95% minimal detectable change for the MoCA was 4 (16). This study closely mimics our patient population both in terms of age and the time interval between MoCA administrations, including the lack of use of alternate versions of the MoCA.

Prior research on the MoCA demonstrates that this brief measure is not only valid in iNPH populations, but sensitive to changes in cognition following TT (5, 6). As a result, the MoCA was selected as a tool to measure and monitor cognition in the Adult Hydrocephalus Clinical Research Network as well as in a prospective trial of shunt surgery for iNPH (19, 37, 38). In contrast to such studies evaluating group-level differences, our findings provide clinicians with an index for determining if CSF drainage has resulted in a reliable change in MoCA scores at a patient specific level with respect to their baseline MoCA.

Our analyses show that clinicians should look for a 5-point increase in MoCA as an indication that an iNPH-symptomatic patient has benefited cognitively from CSF drainage, 1 point higher than what has been reported for cognitively normal individuals. For patients that scored lower than 14 points on the MoCA, the methods give more mixed results, although most still calculated RCIs of 5–6 points. Finally, while several methods provided RCIs of 4 points for patients scoring a 26 on the MoCA, most of the methods indicated that a reliable change could not be detected for patients who presented with a MoCA score of 26 or greater, as the maximum possible MoCA score is 30. Therefore, a different and more comprehensive cognitive assessment may be needed to assess changes in cognition for suspected iNPH patients with higher baseline cognitive function.

Among the various clinical factors that we examined (e.g., Evan's Index, number of falls, etc.), the only ones that demonstrated a significant association with post-shunt cognitive improvement was the time since onset of memory problems and whether their gait improves. The shorter the duration of memory symptoms, the higher the likelihood of a reliable improvement in the MoCA score. Not surprisingly, a reliable improvement in MoCA was also more likely in those whose gait improved significantly. This association with respect to gait improvement replicates the findings of Matsuoka et al. (6), however, their study had a relatively small ($N = 32$) and homogenous (100% Japanese) sample. Hence, we have bolstered the generalizability of these findings by replicating them in a significantly larger and more racially/ethnically diverse sample.

There are, however, several caveats and limitations to these findings that one should consider. First, the majority of suspected iNPH patients undergoing a TT/ELD do not exhibit significant improvements in cognition as measured by the MoCA as opposed to delayed improvement after shunt surgery. This is also to be expected as TT/ELD are part of the selection process for shunt surgery and thus a significant percentage of patients undergoing a TT/ELD are typically not selected for shunt surgery

at our institution. Among patients who received a shunt, a higher percentage (25%) did demonstrate an improvement in MoCA after shunt insertion compared to their performance at baseline vs. the improvement immediately after a TT/ELD (**Table 2**). However, there was marginally significant evidence ($p = 0.092$) that patients who waited longer to perform the final MoCA assessment improved a greater amount. Hence, improvement in cognition following insertion of a shunt may be delayed as compared to improvement in gait, balance, and urinary continence for iNPH patients. In this study patients after shunt surgery were followed for a mean of 1.10 yrs (SD: 0.72). Longer follow-up assessments are needed to determine if these improvements are sustained.

Another caveat of applying methods for calculating reliable change criteria, is that there remains a debate in the field as to which method is best. Currently, there is no clear best method for calculating reliable change criteria (31), so we chose to compare nine of the leading methods in our study. While all of the methods agreed that an improvement of 5 points was a reliable change for patients who scored 16–22 prior to CSF drainage, the methods were conflicted on RCIs for patients who scored outside of this range. A majority of the methods still calculated an RCI of 5 for scores as low as 14 and as high as 25 and this would apply to a majority of patients with iNPH presenting at specialist centers. Lastly, we did not use alternate forms of the MoCA at baseline and pre-TT/ELD that could have accounted for practice effects (39) since that is not our routine practice in clinic. However, our analysis did not demonstrate such practice effects in this large sample as has been reported in another study in which MoCA was administered in a community sample of cognitively normal and MCI participants (21).

In conclusion, this study is the first to provide practical, empirical standards which clinicians can use when assessing potential cognitive improvement following CSF drainage. These findings can be used to improve the clinical decision making of clinicians assessing iNPH at a patient level in contrast to group differences assessed in reported research studies. As a rule of thumb, a 5-point increase in MoCA scores is indicative of a reliable cognitive improvement for iNPH-symptomatic patients following CSF drainage. Furthermore, clinicians should factor in the time since onset of patient's memory problems and whether their gait improves, when advising patients about the likelihood of a significant and reliable cognitive improvement following shunt surgery. Additional studies are needed to increase the generalizability of these findings. Particularly, future research should seek to replicate and extend these findings in populations with more diverse racial and educational backgrounds. Finally, researchers should use longer follow-up intervals to determine if symptom improvements are maintained.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Johns Hopkins IRB (Cerebrospinal Fluid Disorders Biorepository & Adult Hydrocephalus Clinical Research Network NA_00029413). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EW: conducted literature review, extracted data from medical records, and drafting/revision of the manuscript. LE: drafting/revision of the manuscript for content and including medical writing for content. SB and JC: data analysis and interpretation of results. AD, AR, and ML: major role in the acquisition of data. SY: major role in the acquisition of data and drafting/revision of the manuscript for content. JW: revised the manuscript for content and data analysis and interpretation of results. AM: study design, revision of the manuscript, major role in the acquisition of data, and interpretation of results. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Weight and Abdominal Pressure-Induced Shunt Trouble in Patients With Shunted Normal Pressure Hydrocephalus: A Comprehensive Study on Pressure Environment of Shunt System

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Objectives: We identified a new type of shunt malfunction (SM) in patients with normal pressure hydrocephalus (NPH). It is induced by weight change and can be treated with valve readjustment. There were two types of SM as follows: Underdrainage induced by the weight gain and overdrainage induced by the weight loss. This study aims to elucidate this mechanism by assessing the shunt pressure environment.

Methods: The total pressure environment of the shunt system was prospectively studied in patients with shunted NPH at Osaka Medical College Hospital from 1999 to 2005. We measured the pressure environment during the initial pressure setting of the valve by the intracranial pressure (ICP) guide, after setting the valve, and when SM was suspected. We evaluated ICP, intra-abdominal pressure (IAP), and hydrostatic and perfusion pressures of the shunt system in the sitting and supine positions. The target ICP for valve setting was empirically set at the range from −8 to −13 mm Hg in the sitting position, referring to the external auditory meatus. During the study period, we identified five cases of SM induced by weight change and assessed the changes in the pressure environment across pre-SM, SM, and post-SM.

Results: In four cases of underdrainage, gait disturbance worsened with an average weight gain of 6.8 ± 1.2 kg. With weight gain, IAP and ICP increased by 8.8 ± 1.6 and 4.8 ± 1.0 mm Hg, respectively. Consequently, ICP increased to −6.5 ± 1.9 mm Hg. One overdrainage patient developed an asymptomatic chronic subdural hematoma (CSDH) with a weight loss of 10 kg. With the weight loss, both IAP and ICP decreased by 5 mm Hg, and concomitantly, ICP decreased to −18 mm Hg. In all patients, the valve readjustment restored their ICP to the target pressure. After the valve readjustment, the gait disturbance improved immediately, and the CSDH disappeared after 1 month.

Conclusion: In patients with shunts, the weight change was linked to ICP *via* IAP. Due to the weight change, the underdrainage occurred when ICP was above the target pressure, and the overdrainage occurred when ICP was below it. We named this SM as the weight and abdominal pressure-induced shunt trouble. The patients with SM along with weight changes should be the first to be tried for the valve readjustment.

Keywords: normal pressure hydrocephalus (NPH), shunt malfunction, intra-abdominal pressure (IAP), intracranial pressure (ICP), hydrocephalus–surgery

INTRODUCTION

The patients with shunt malfunction (SM) along with hydrocephalus is the primarily associated with mechanical obstruction of the valves and catheters (1). In the present study, we have identified a new type of functional SM that is caused by weight change and can be treated by readjusting valve pressure. This study presents that the weight change affected the intra-abdominal pressure (IAP) and caused SM by altering the intracranial pressure (ICP) linked to the IAP.

We have previously reported that the IAP is crucial to the function of the shunt because it offsets 1/3 of the siphoning effect in the ventriculoperitoneal shunt in the upright position (2). Furthermore, we found that the body mass index (BMI) in the sitting position correlated with the IAP (3). These facts indicate that the BMI has a significant impact on shunt function. Sahuquillo et al. also reported that BMI influences VP shunt function *via* IAP (4). The influence of physique on shunt function suggests that the optimal shunt valve pressure can be estimated from physique (3). We clarified the correlation between height and weight on shunt HP and IAP, obtained a formula for estimating the optimal valve pressure from the regression line, and incorporated it into a practical Quick Reference Table (QRT) by the physique (**Figure 1**) (5). We have proved that the efficacy of this QRT method by the SINPHONI study showed a low resetting rate (6). Currently, the QRT method is the standard for the initial pressure setting after shunt surgery in Japan. These findings provide evidence that the physique is closely related to the shunt function. On the other hand, these facts allow us to raise the hypothesis that the weight gain or weight loss may induce shunt malfunction. We can easily explain this hypothesis from QRT, which shows that a 5 kg change in the body weight can change the optimal valve pressure (**Figure 1**). However, such shunt malfunctions associated with weight gain and weight loss have not been detected so far, except for those associated with pregnancy (7).

This study is a part of a prospective study on investigating the total pressure environment of a shunt system. We measured the shunt-related pressure, including ICP, when valve setting was required, such as during initial pressure setting or when SM was suspected, then set the valve pressure so that ICP would be within the target pressure range. During the study period, we found five patients with functional SM associated with weight gain or weight loss.

The pressure parameters of the shunt system pressure environment consist of ICP, IAP, hydrostatic pressure (HP), and valve perfusion pressure (PP) in the shunt system (2). The following equation is established between each pressure:

$$PP = (ICP - IAP) + HP$$

In this study, we measured ICP and IAP by puncturing a reservoir implanted in the patient (2). We also estimated the HP of the shunt system from the HP in the extracorporeal tubing passed between the ICP and IAP reference points. Stevin's law states that the pressure at any point in a fluid depends only on the depth of that point. Therefore, the HP on a shunt system can be simplified as the difference in height between two reference points. To measure the height difference between the two reference points, we connected a pressure transducer to a tube filled with water outside the body that passes between the two reference points. The HP can be measured as the water pressure of this height difference. Since the specific gravity of CSF is 1.005 $\sim$ 1.009, the measurement error due to filling the measured tube with water of specific gravity 1.0 is $<$1%. Thus, we can measure the shunt HP directly as the water pressure from the height difference between the two reference points. The PP of that shunt system, which determines the shunt flow, was defined and calculated by the above equation. These analyses provide deep insights into the mechanism of this new type of shunt malfunction, as well as into normal shunt function. We will also discuss the narrow therapeutic window of valve pressure in patients with NPH and ICP-based shunt management.

MATERIALS AND METHODS

The research protocol was approved by the Ethics Committee of Osaka Medical College (No. 27,27-1,2788), and informed consent was obtained in writing from all patients. The 72 patients with shunted normal pressure hydrocephalus (NPH) were prospectively studied at Osaka Medical College Hospital from January 1999 to March 2005 for shunt system pressure environment. During the study period, we found five cases of SM associated with weight change and apparent improvement after valve adjustment. The symptoms of four patients worsened slowly in about 3 months with weight gain. We readjusted the valves, and the gait symptoms improved immediately afterward. We quantitatively confirmed the improvement of the gait symptoms by the 10-m walk test (10MWT). In one patient who lost about 10 kg of weight, the CT revealed an asymptomatic chronic subdural hematoma (CSDH). We readjusted the valve and confirmed that the CSDH had disappeared 1 month later.

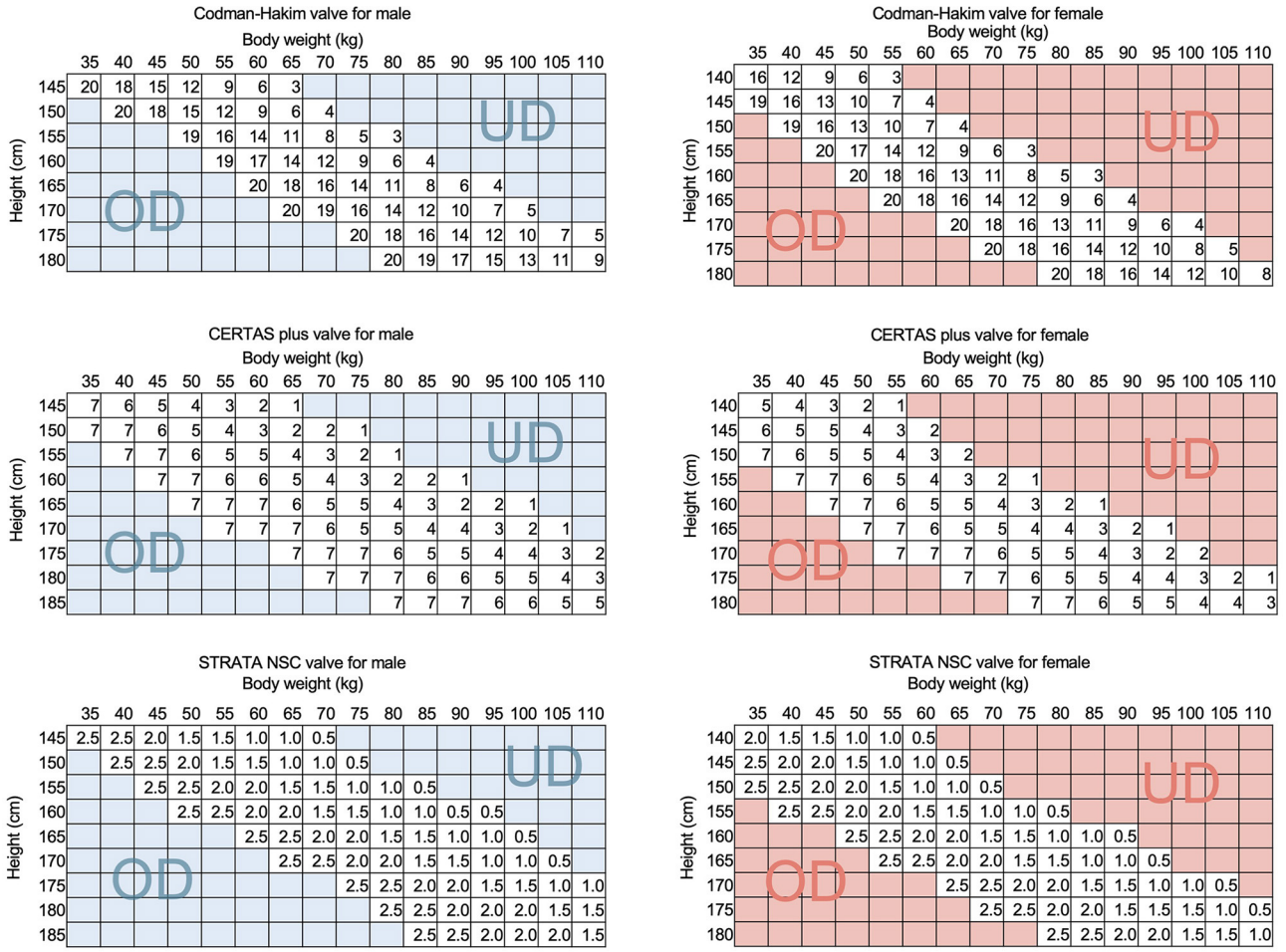

FIGURE 1 | The QRTs of representative programmable valves. The QRTs for CH valve, CERTAS plus valve, and STRATA NSC valve are shown for men and women. The SINPHONI study proved the validity of the initial pressure setting method by QRT by showing a low valve readjustment rate of 44%. This QRT simulates that if a patient's weight increases by 5 kg, the optimal settings of the CH and CERTAS plus valves will be reduced by about 30 mm H_2O and 1, respectively. This simulation suggests that a weight change of 5 kg is a risk for shunt malfunction. The UD and OD in the figure indicate that patients in this region are at higher risk for underdrainage and overdrainage, respectively. UD, underdrainage; OD, overdrainage.

Evaluation of the Total Shunt Pressure Environment

In a study of the shunt system pressure environment, we evaluated the shunt pressure environment of patients during initial pressure setting, after setting, and during shunt malfunction. The patients underwent shunting with a ventricular catheter placed by anterior horn puncture and an Ommaya reservoir (Medtronic Inc, Minneapolis, USA) implanted in the burr hole. In addition, an on-off valve (Integra LifeSciences, Plainsboro, NJ, USA), a Codman–Hakim (CH) programmable valve (Integra LifeSciences, Plainsboro, NJ, USA), and a Foltz reservoir (Integra LifeSciences, Plainsboro, New Jersey, USA) implanted in the right anterior chest wall (**Figure 2**).

We used the following procedure to assess the total shunt pressure environment. We thoroughly disinfected the skin at the puncture site with povidone–iodine. Then, we punctured the Ommaya and Foltz reservoirs with 22-gauge winged needles and measured ICP and IAP in the supine and sitting positions, respectively, using the pressure transducers connected to these needles. We set the ICP reference point at the external auditory meatus and the IAP reference point at the level of the anterior superior iliac spine at the height of the mid-axillary line. The HP of the shunt system, which is the difference in height between the ICP and IAP reference points, was measured with a pressure transducer. We calculated the PP of the shunt system by the following formula

$$PP = (ICP - IAP) + HP \quad (1)$$

The pressure transducer was connected to the lower end of a semi-open tubing filled with water so that the water surface was at the level of the external auditory meatus and the pressure transducer was at the anterior superior iliac spine. This setup

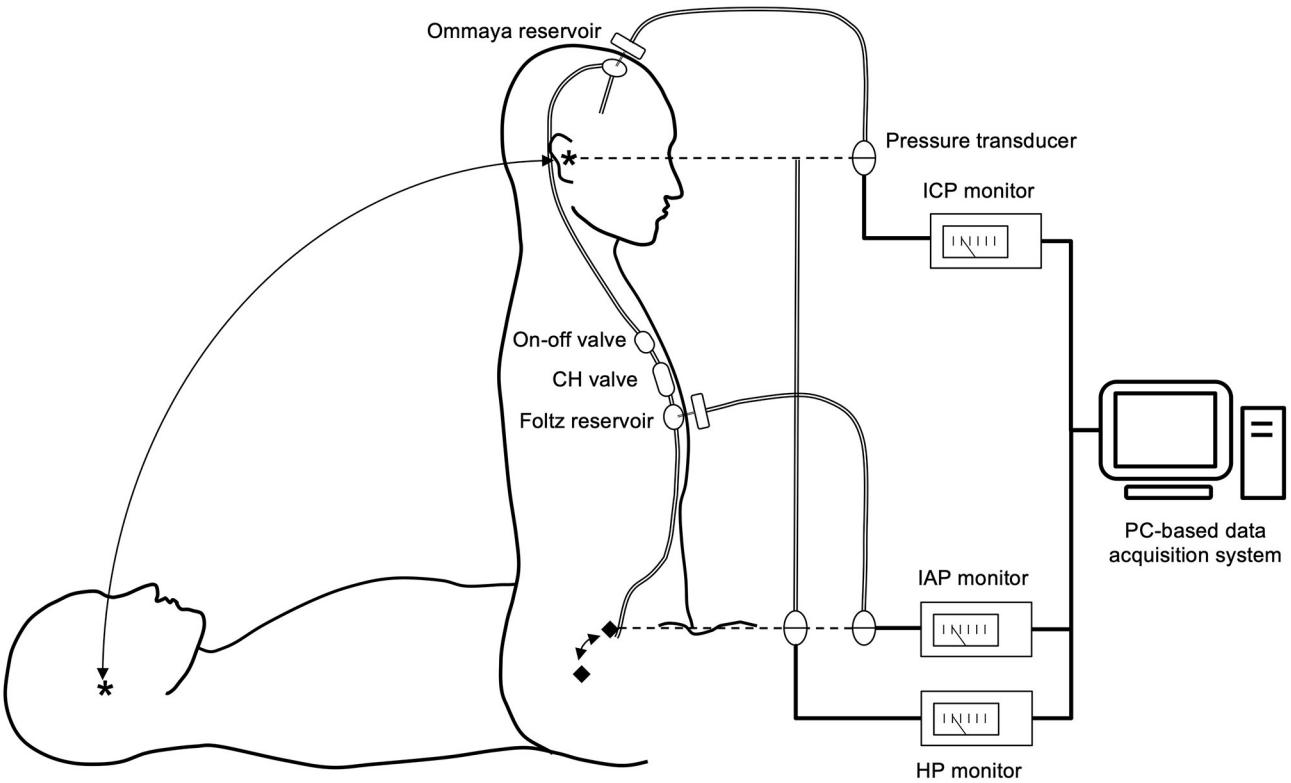

FIGURE 2 | Shunt system and shunt-related pressure measurement system. The patients were implanted with an Ommaya reservoir in the head and an on-off valve, a CH valve, and a Foltz reservoir in the chest. By puncturing both reservoirs with a 22G needle, ICP and IAP can be measured. We defined the reference points for ICP and IAP as the external auditory meatus (*) and the mid-axillary line at the level of the superior anterior iliac crest (♦), respectively. The pressure environment was measured in the supine and sitting positions. We measured the HP of the shunt system as the difference in height between the two reference points. We calculated the shunt PP based on these pressures using the following formula. PP = (ICP–IAP) + HP. Thus, this measurement system provides insight into the comprehensive shunt-related pressure environment. All measurement data were digitized and recorded in a PC-based data acquisition system.

allowed us to directly measure the HP corresponding to the height difference between the ICP and IAP reference points.

The measurement data from all pressure transducers were digitized at 200 samples/second and recorded using a computer-based measurement system. The software for the digital acquisition of data was programmed using the LabVIEW G language (National Instruments Inc., Texas, USA).

Pressure Evaluation During Initial Pressure Setting and Pressure Setting Based on ICP

In this study of the total pressure environment of the shunt system, we evaluated the shunt system pressure environment after ventriculoperitoneal shunting. With the on–off valve off for 12 h before the measurement, we first evaluated the pressure environment in the preoperative state in the sitting and supine positions. Then, we opened the on-off valve in the sitting position and sequentially lowered the CH valve setting from 200 to 140, 80, and 30 mm H_2O until the ICP was within the target pressure range. We set this target ICP range from −8 to −13 mm Hg using the external auditory meatus as a reference point and −15 to 20 mm Hg range using the Ommaya reservoir as a reference point. We determined this target pressure range empirically according to preliminary clinical data (2, 3, 8). For each valve pressure change, we recorded for at least 15 min in a sitting position to allow the pressure to stabilize.

Pressure Evaluation and Management During Shunt Malfunction

When SM was suspected, we measured the pressure environment. We can diagnose mechanical shunt malfunction, i.e., obstruction of the ventricular and peritoneal catheters, from the measured pressure waveforms (8). If the ICP was out of the target pressure range, we readjusted the programmable valve so that the ICP was at the target pressure. If the SM is improved after pressure adjustment, then the shunt pressure environment before pressure adjustment is underdrainage or overdrainage. The pressure environment after pressure adjustment is normal drainage status.

Statistical Analysis

The data are presented as mean values (± standard deviation). Assessment of ICP levels in patients with normal drainage, underdrainage, and overdrainage was compared in both the

TABLE 1 | Changes in body weight and shunt-related pressures at the time of shunt malfunction.

			Sitting		Supine	
Type	**Case no.**	**ΔBw (kg)**	**ΔICP (mmHg)**	**ΔIAP (mmHg)**	**ΔICP (mmHg)**	**ΔIAP (mmHg)**
UD	1	6	3	11	4.5	4
UD	2	6	5	7	3.5	6
UD	3	6.5	8	10	6	5
UD	4	8.5	4	10.5	0	2.5
	mean ± SD	6.8 ± 1.2	4.8 ± 1.0	8.8 ± 1.6	3.5 ± 2.5	4.4 ± 1.5
OD	5	−10	−5	−5	−4	−2

This table shows the changes in body weight, ICP, and IAP during the changes from normal drainage to underdrainage with weight gain and overdrainage with weight loss. With an average weight gain of 6.8 kg, the IAP and ICP increased by 4.8 and 8.8 mm Hg, respectively; with a weight loss of 10 kg, the IAP and ICP decreased by 5 kg. The pressure changes were greater in the sitting position than in the supine position.

UD, underdrainage; OD, overdrainage; ΔBw, change of body weight; ΔICP, change of intracranial pressure; ΔIAP, change of intra-abdominal pressure; ICP, The units of these pressures are mmHg. These numbers represent mean ± SD.

TABLE 2 | Changes in clinical parameters of WAIST patients.

						Weight (kg)		10MWT (sec)		Evans' index	
Case No.	**Type of NPH**	**Age at SM**	**Sex**	**Duration from surgery to SM**	**Types of SM**	**Post OP**	**SM**	**SM**	**After valve readjustment**	**post OP**	**SM**
1	sNPH	78	F	48 M	UD	53	57	29	14	0.296	0.309
2	iNPH	75	M	9 M	UD	50	56	23	15	0.317	0.316
3	iNPH	74	M	28 M	UD	62	68.5	17	10	0.338	0.346
4	iNPH	86	M	8 M	UD	54	60.5	NA	NA	NA	NA
5	iNPH	71	M	21 M	OD	71	61	–	–	0.282	0.216

WAIST, weight and abdominal pressure-induced shunt trouble; sNPH, secondary normal pressure hydrocephalus; iNPH, idiopathic normal pressure hydrocephalus; SM, shunt malfunction; UD, underdrainage; OD, overdrainage; 10MWT, 10-m walk test; OP, operation.

supine and sitting positions; differences in ICP between normal drainage and underdrainage were verified by Wilcoxon's signed-rank test. To evaluate the effect of BMI on IAP, a single regression analysis was performed with BMI as the independent variable. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP pro15 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Developmental Course of SM Patients With Weight Change

Four patients had a gradual worsening of gait disturbance over 3 months and an average weight gain of 6.8 kg (**Table 1**). The head CT scan showed no change in the size of the ventricles as assessed by Evans' index (**Table 2**). Smooth pumping of the Ommaya and Foltz reservoirs ruled out the possibility of mechanical shunt obstruction. We also confirmed that it was not a mechanical shunt obstruction based on the pulse wave during the shunt pressure environment measurement (8). In one patient with a 10 kg weight loss, a CT scan revealed a thin CSDH without a low-pressure headache.

Pressure Changes in Underdrainage Cases Due to Weight Gain

In the four cases of underdrainage, IAP and ICP in the sitting position increased by 8.8 ± 1.6 and 4.8 ± 1.0 mm Hg, respectively, compared with those during normal drainage (**Table 1**). **Table 3** shows the detailed pressures for each case. The body weight increased by 6.8 ± 1.2 kg compared to the postoperative period. As a result, the ICP in the sitting position increased to −6.5 ± 1.9 mm Hg, which was outside the target ICP. In the supine position, the increase in IAP and ICP was limited compared to the sitting position, with 4.4 ± 1.5 and 3.5 ± 2.5 mm Hg, respectively (**Table 1**).

By lowering the CH valve pressure by 4.4 ± 3.0 mm Hg (equivalent to 60 mm H_2O) to resolve the underdrainage, ICP decreased by 4.8 ± 2.2 mm Hg in the sitting position and by 2.1 ± 1.7 mm Hg in the supine position (**Table 1**). As a result, ICP in the sitting position decreased to −11.3 ± 3.0, recovering to within the target ICP range. On the other hand, IAP was not affected by the readjustment of the CH valve (**Figure 3**, **Table 1**). Within 1 h of CH valve readjustment, gait disturbance improved rapidly. In the three cases evaluated in the 10MWT, the average time improved from 23 s before valve resetting to 13 s after resetting.

TABLE 3 | Changes in all shunt-related pressures pre-, during, and post-shunt malfunction.

Case no.	Timing of measurement	Shunt staus	Bw (kg)	Ht (m)	BMI	CH valve (mmH_2O)	Sitting					Supine			
							VP	IAP	PP	ICP	HP	IAP	PP	ICP	HP
1	Post OP	ND	53	1.5	23.6	50	3.7	18	7	−13	38	11	−10.5	−1.5	2
	UD	UD	59	1.5	26.2	50	3.7	26	4	−8	38	15	−10	3	2
	After re-setting	ND	59	1.5	26.2	30	2.2	25	1	−12	38	16	−13	1	2
2	Post OP	ND	50	1.5	22.2	120	8.8	14	9	−8	31	6	0	1	5
	UD	UD	56	1.5	24.9	120	8.8	21	6	−4	31	12	−2.5	4.5	5
	After readjustment	ND	56	1.5	24.9	30	2.2	20	4	−7	31	14	−7	2	5
3	Post OP	ND	62	1.65	22.8	160	11.8	8.5	18.5	−12	39	2	1	−1	4
	UD	UD	68.5	1.65	25.2	160	11.8	18	15	−6	39	7	2	5	4
	After readjustment	ND	68.5	1.65	25.2	60	4.4	19	6	−14	39	9	−4	1	4
4	Post OP	ND	52	1.55	21.6	180	13.2	9.5	13.5	−12	35	5	−1.5	1.5	2
	UD	UD	60.5	1.55	25.2	180	13.2	20	7	−8	35	7.5	−4	1.5	2
	After readjustment	ND	60.5	1.55	25.2	150	11.0	20	3	−12	35	7.5	−4	1.5	2
5	Post OP	ND	71	1.71	24.3	60	4.4	18	10	−13	41	5	−4	0	1
	OD	OD	61	1.71	20.9	60	4.4	13	10	−18	41	3	−6.2	−4	1
	After readjustment	ND	65	1.71	22.2	130	9.6	14	16	−11	41	4	−4	−1	1
														(mmHg)	

The time point of normal drainage status immediately after surgery is denoted by Pre-SM, the time point of shunt malfunction by SM, and the time point of normal drainage after valve readjustment by Post-SM. All pressures are in mm Hg.

ND, normal drainage; UD, underdrainage; OD, overdrainage; Bw, body weight; Ht, height; CH valve, Codman Hakim valve; VP, valve pressure; IAP, intra-abdominal pressure; PP, perfusion pressure; ICP, intracranial pressure; HP, hydrostatic pressure.

Pressure Changes in an Overdrainage Case Due to Weight Loss

In one patient, symptoms improved and ventricular size was normal after surgery (**Figure 4A**). However, at 12 months postoperatively, the patient had lost 10.0 kg of weight, and a CT scan revealed bilateral thin chronic subdural hematomas (CSDH) (**Figure 4B**). However, the patient did not complain of a low-pressure headache. A weight loss of 10 kg resulted in a −5 mm Hg decrease in IAP and ICP. As a result, ICP decreased to −18 mm Hg, which was below the target pressure. Readjustment of the CH valve increased the ICP to −11 mm Hg, which was in the target pressure range. At 3 weeks after the readjustment, the CSDH spontaneously disappeared (**Figure 4C**, **Table 1**).

Therapeutic Window for ICP in Patients With NPH

In the sitting position, the ICP of normal drainage, underdrainage, and overdrainage were −11.4 ± 2.0, −6.5 ± 1.7, and −18 mm Hg, respectively (**Figure 5A**). In the supine position, the ICP of normal drainage, underdrainage, and overdrainage were 0.7 ± 1.2, 3.5 ± 1.4, and −4 mm Hg, respectively (**Figure 5B**). There was no significant difference in ICP between normal drainage and underdrainage both in the sitting and supine positions. The threshold pressure between underdrainage and overdrainage in the sitting position was −8 mm Hg, and that in the supine position was 2 mm Hg.

Correlation and Change Vector Between BMI and IAP

In the sitting and supine positions, BMI was positively correlated with IAP (**Figure 6**). Pearson's correlation coefficients for the sitting and supine positions were $r^2 = 0.47$ and 0.49, respectively. The corresponding p-values for the sitting and supine positions were $p < 0.0198$ and 0.0077, respectively. The slope of the vector of IAP change in BMI change was almost the same as that of the regression line of BMI and IAP (**Figure 6**).

DISCUSSION

The SM Induced by Changes in Body Weight and Abdominal Pressure

This is the first report to show that weight change can affect shunt function and induce SM in patients with NPH. The IAP, which changed in proportion to the weight change, affected the ICP and consequently induced shunt malfunction. Therefore, we named it weight and abdominal pressure-induced shunt trouble (WAIST). This WAIST consists of the following two types of shunt malfunction: Underdrainage induced by weight gain and overdrainage induced by weight loss.

The BMI and IAP

This study presented longitudinal data showing that IAP changes proportionally with increasing or decreasing the BMI. The longitudinal data proportional relationship was almost the same as the cross-sectional data. Previously, we reported having a positive correlation between IAP and BMI in the sitting position (2, 3). Many researchers have reported a similar proportional relationship between BMI and IAP (4, 5, 9, 10). However, the limitations of these studies are that they are cross-sectional, with only IAP for the supine position and no data for the sitting position. This study provides a longitudinal demonstration that BMI change in the sitting position affects IAP.

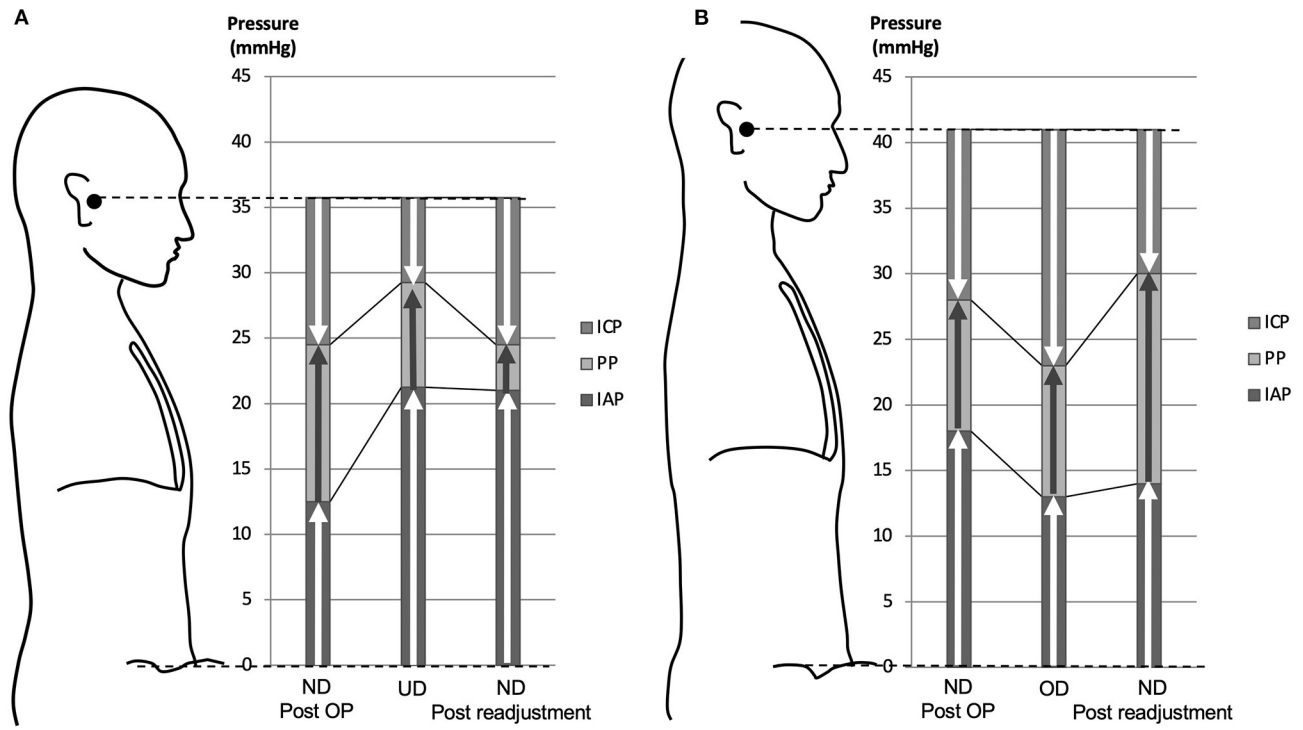

FIGURE 3 | Pressure diagram of underdrainage type WAIST **(A)** and overdrainage type WAIST **(B)**. **(A)** With an average weight gain of 6.8 kg, the IAP increased by 8.8 mm Hg and the ICP increased by 4.8 mm Hg by linking to the IAP. As a result, the ICP is −6.5 mm Hg to the external auditory meatus. This ICP value is greater than the target range of −8 to −13 mm Hg for ICP, which is the underdrainage range. Lowering the valve pressure by 4.4 mm Hg, equivalent to 60 mm H_2O, reduced the shunt PP, resulting in an immediate recovery of ICP to −11.3 mm Hg, within the target range. **(B)** A 10-kg weight loss reduced IAP by 5.0 mm Hg and ICP by 5.0 mm Hg by linking to IAP. As a result, ICP is −18 mm Hg with reference to the external auditory meatus. This ICP value is lower than the ICP target range of −8 to −13 mm Hg, which is in the overdrainage range. The shunt PP was increased by lowering the valve pressure to 5.1 mm Hg, equivalent to 70 mm H_2O, and as a result, the ICP was restored to −11.0 mm Hg, within the target range. ND, normal drainage; UD, underdrainage; OD, overdrainage.

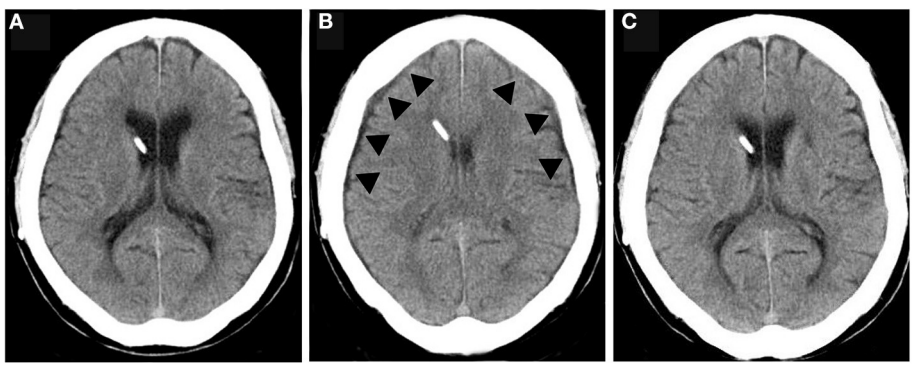

FIGURE 4 | The CSDH caused by overdrainage and disappearance after valve readjustment. **(A)** CT of normal drainage state after shunting; **(B)** CT during overdrainage reveal slit ventricle and thin CSDH (arrowhead); **(C)** CT At 1 month after the valve readjustment shows disappearance of CSDH and slit ventricle.

Linkage Between IAP and ICP in Patients With Shunted Hydrocephalus

We have shown that changes in ICP and IAP are closely related in patients with shunted NPH (**Figure 3**). Furthermore, we can theoretically prove that these changes are causally related and linked as follows. In the physiological cerebrospinal fluid (CSF) circulation, the passive absorption of CSF into the dural venous system, such as the superior sagittal sinus, depends on the pressure gradient between ICP and venous sinus pressure and CSF outflow resistance. From this relationship, ICP depends

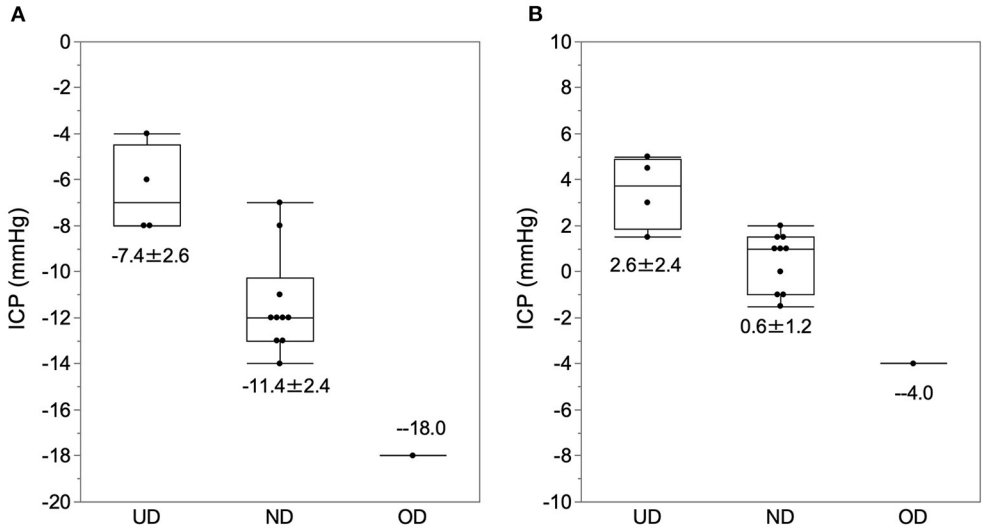

FIGURE 5 | The ICP at the time of normal drainage, underdrainage, and overdrainage. The ICP data at the time of normal drainage, underdrainage, and overdrainage and their boxplots are plotted in the sitting **(A)** and supine **(B)** positions. **(A)** In the sitting position, the ICP for underdrainage, normal drainage, and overdrainage were −7.4 ± 2.6, −11.4 ± 2.4, and −18.0 mm Hg, respectively. (B) In the supine position, ICP levels for underdrainage, normal drainage, and overdrainage are 2.6 ± 2.4, 0.6 ± 1.2, and −4 mm Hg, respectively. The cutoff values of ICP for underdrainage and normaldrainage in the sitting and supine positions were −8.0 and 2.0 mm Hg, respectively. ND, normal drainage; UD, underdrainage; OD, overdrainage.

on venous sinus pressure and CSF outflow resistance and can be described by the following equation known as Davson's equation (11, 12).

$$ICP = Ro \times If + Pss$$

Where Ro is the CSF outflow resistance, "If" is the CSF production rate, and Pss is the sagittal sinus pressure.

A recent study reported that dural lymphatic vessels absorb CSF similar to arachnoid granules (13). Thus, we can describe ICP as follows:

$$ICP = Ro \times If + Pd$$

Where Ro is the CSF outflow resistance, "If" is the CSF production rate, and Pd is the dural lymphatic and venous pressure.

On the other hand, in patients with shunted hydrocephalus, most of the CSF outflow is transferred from the physiological CSF absorption system to the shunt system.

When the ICP becomes lower than the venous pressure of the dura mater due to CSF shunting, physiological CSF absorption ceases. The shunt system drains the CSF predominantly.

We can describe the ICP of a patient with shunts in this condition by shunt resistance (Rs) and IAP with the following equation.

$$ICP = Rs \times If + IAP$$

Where Rs is the flow resistance of shunt system, "If" is the CSF production rate, and IAP is the intra-abdominal pressure.

In this equation, the ICP of a patient with shunts is a function of the IAP. This equation theoretically explains that the ICP of a patient with shunts links to the IAP.

We have previously proposed that this concept of linkage between IAP and ICP is crucial to the theory of shunt management (3).

Mechanism of WAIST

Based on these findings, we can propose the following mechanism for underdrainage type and overdrainage type WAIST (**Figure 7**). The starting point of underdrainage type WAIST is an increased IAP due to a weight gain of several kilograms (**Figure 7A**). Then, linked to the increase in IAP, ICP also increases. When the ICP exceeds the upper limit of the therapeutic window, cerebral circulatory disturbances result from compression of the capillaries and small veins of the brain (14), which leads to worsening of the symptoms of NPH. The immediate improvement in symptoms after valve readjustment suggests the involvement of cerebral circulatory disturbances.

In the overdrainage type WAIST, the starting point is a decrease in IAP linked to a weight loss of several kilograms (**Figure 7B**). ICP also decreases, linked to the decrease in IAP. As ICP falls below the lower limit of the therapeutic range, the convexity level ICP drops to about −25 mm Hg. This negative ICP exposes the medial side of the dura to significant negative pressure. The pressure in the dural venous sinus in the upright position is at the foramen magnum level, approximately the same as in the external auditory meatus, and at atmospheric pressure. Thus, a significant pressure gradient of −18 mm Hg occurs in the thin region between the intradural veins and lymphatic vessels and the subdural space. Since there are few valves in the dural

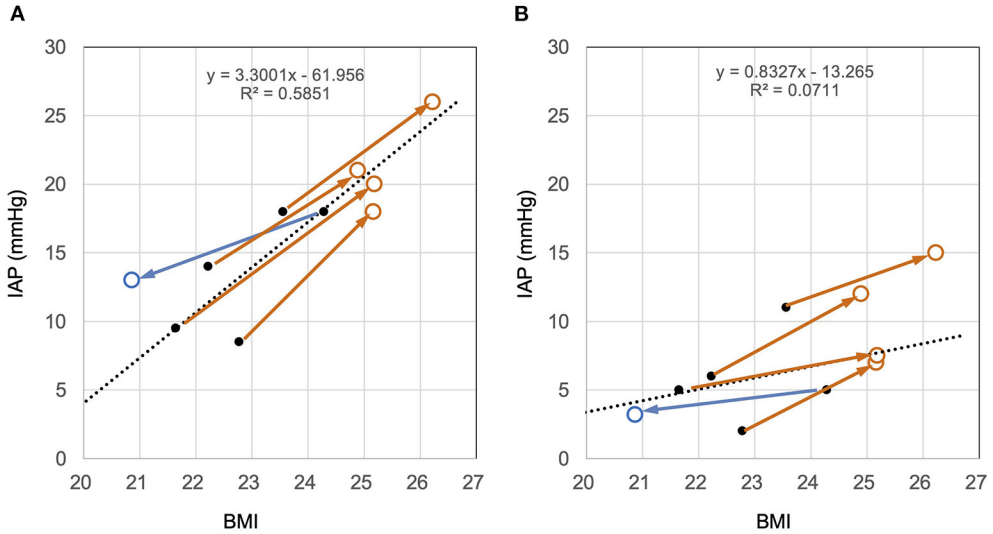

FIGURE 6 | Cross-sectional and longitudinal relationship between BMI and IAP in the sitting **(A)** and supine **(B)** positions. The black dots and dotted lines represent the relationship between the BMI and IAP immediately after surgery and their regression lines, respectively. Brown open circles represent the time point at which the patient gained weight. Blue open circles represent the time of weight loss. **(A)** In the sitting position, IAP immediately after surgery was positively correlated with BMI (dots). The change with weight change is shown as a vector. The slope of the vector and the regression line is similar. This finding indicates that the IAP change with weight change follows the correlation between BMI and IAP. **(B)** The same trend was observed in the supine position as in the sitting position. Judging from the slope of the vectors, the effect of BMI on IAP in the supine position was about half that in the sitting position.

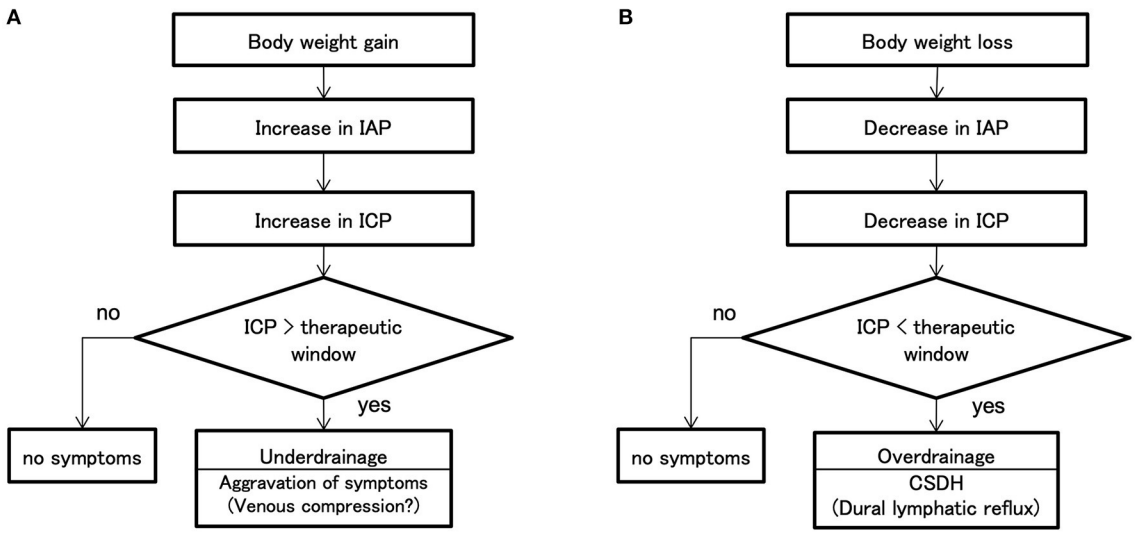

FIGURE 7 | Mechanisms of shunt malfunction associated with weight change. **(A)** Weight gain increases the IAP. In the patients with shunted hydrocephalus, ICP is linked to IAP, so weight gain also increases ICP. Symptoms worsen when the patient's ICP exceeds the therapeutic window. Neurological symptoms with underdrainage are more likely to be cerebral circulatory disturbances due to venous compression because of the immediate improvement. **(B)** Weight loss decreases IAP; ICP linked to IAP decreases simultaneously; if ICP falls below the therapeutic window, a CSDH occurs. If the patient's ICP falls below the therapeutic window, CSDH develops. In this study, we showed that at the time of overdrainage, the subdural space has a significant negative pressure of −18 mm Hg against intradural veins and lymphatic vessels. Since there are few valves in the lymphatic vessels of convexity dura, the backflow of lymphatic fluid in the lymphatic vessels may lead to lymphatic effusion in the subdural space. ICP, intracranial pressure; IAP, intra-abdominal pressure; CSDH, chronic subdural hematoma.

lymphatics in the upper skull (13), lymphatic fluid from the dural lymphatics can easily flow backward, and this becomes the subdural fluid collection. We call this the dural lymphatic reflux hypothesis.

Similarities and Differences With SM in Pregnant Women

There have been several reports of shunt failure associated with underdrainage in pregnant women. However, researchers have

believed that the cause of underdrainage is the elevated position of the peritoneal catheter (15, 16). In the hydraulic model of the abdomen, the abdominal cavity is a single fluid compartment whose density is approximately equal to that of water (2). Therefore, the position of the shunt tube does not affect the PP of the shunt system.

On the other hand, as the abdominal volume of a pregnant woman increases, the IAP increases (1). Therefore, the true cause of underdrainage in pregnancy is not the position of the peritoneal catheter, but the elevated IAP (7). Thus, the mechanism for underdrainage due to weight gain and underdrainage in pregnant women is almost the same. However, the increase in abdominal pressure in pregnant women reaches 40 mm Hg in the sitting position, while the IAP in patients with underdrainage type WAIST is only half of that (17, 18). The reason why underdrainage type WAIST is more sensitive to a slight increase in IAP than underdrainage during pregnancy may be related to the narrow therapeutic window of NPH, which will be discussed next.

The Therapeutic Window of ICP in Patients With Shunted NPH

The optimal therapeutic window for ICP in patients with shunts with NPH is still unknown. Based on our preliminary studies, we assume that the therapeutic window for ICP is in the range of −8 to −13 mm Hg, with the external auditory meatus as the reference point (2, 3, 8). Although the number of WAIST cases in our study was small, the ICP of normal drainage in the sitting position was almost the same as the target ICP range, with an upper limit of the therapeutic range of −6.5 mm Hg and a lower limit of about −16 mm Hg (**Figure 5**). However, we can verify the validity of this therapeutic window by analyzing more cases in the comprehensive study on pressure environment of shunt system.

Despite the slight ICP difference between underdrainage and normal drainage in the sitting position, it resulted in a critical difference in clinical symptoms. The reason for this is unclear, but minor compression of the cerebral venous system may affect cerebral circulation (14), and we have found evidence to support this in another study (unpublished).

Prevention and Treatment of WAIST

The following two things are essential to prevent this WAIST: First, neurosurgeons need to tell patients and their families to maintain their weight at the initial pressure setting. Second, the physician should monitor the patient's weight at follow-up. The patients should maintain their weight or let their physician know if they are planning on losing or gaining weight. If the patient's weight has increased by several kilograms, the physician should evaluate for exacerbation of symptoms such as gait disturbance. If there is an exacerbation of obvious NPH symptoms with weight gain, then the underdrainage type WAIST should be considered first. The physician should lower the valve pressure by 30–60 mm H_2O and quantitatively compare the gait function before and after valve resetting by a gait function test such as the 3-m Timed Up and Go Test. If the symptoms improve with valve readjustment, the physician should fix the pressure setting. The physician should also check the subdural fluid collection by CT scan after 1 month. On the other hand, if a patient with shunted NPH loses a few kilograms of weight, the physician should check for the development of CSDH on a CT scan. If CSDH appears, the physician should increase the valve pressure in the range of about 30–60 mm H_2O. At 1 month after the valve readjustment, the physician should check the size of the subdural hematoma with a CT scan.

Incidence of WAIST and the Reasons for Missing It

Even though mechanical SM did not occur during this study, WAIST occurred in five patients. This fact suggests that WAIST is not rare. Recently, Gutowski et al. (19) reported that 20% of patients with NPH had secondary deterioration during a mean follow-up of 2.7 years, of which 26% improved after valve reconfiguration. Although their report does not describe weight change, WAIST is likely to be the primary cause of that secondary deterioration.

There are two possible reasons for the lack of recognition of WAIST as discussed in the following: The first reason is that CT and shuntography cannot identify WAIST. CT scan and shuntography can easily show mechanical SM as a change in ventricle size or obstruction of the shunt system (1). However, in the case of underdrainage type WAIST, the shunt system is not mechanically obstructed and the size of the ventricles does not change. The second reason is that the symptoms progress slowly and over several months. Physicians tend to attribute the slow progression of symptoms in patients with shunted NPH to aging or other comorbidities.

Diagnostic Processes for Symptom Aggravation

In the case of acute aggravation, the decision process is simple because there are only a few differentiating diseases, such as mechanical shunt dysfunction and stroke (**Figure 8A**). However, in the case of gradual aggravation, there are many differentiating pathologies: mechanical shunt malfunction, WAIST, secondary deterioration (19), musculoskeletal disease, disuse dysfunction, and aging (**Figure 8B**). As a result, the diagnostic process is complicated (**Figure 8B**).

The physician must also determine whether the patient's complaints of aggravation are truthful. Therefore, the physician must prove the aggravation of symptoms by objective evaluation. Popular assessment methods are 3-m timed up and go and 10MWT for gait, and MMSE for cognition. The physician should perform these objective assessments routinely and regularly during outpatient follow-up. Weight should also be routinely measured for WAIST evaluation. Performing these assessments requires multidisciplinary collaboration among physical therapists, speech therapists, and nurses.

If the symptoms aggravate gradually over a period of about 3 months, the first step is to perform the reservoir flushing test. This test is a simple and highly accurate detection of proximal catheters, i.e., ventricular and lumbar catheters, and valve obstruction (20). If the reservoir flushing test is normal and the patient's weight has changed

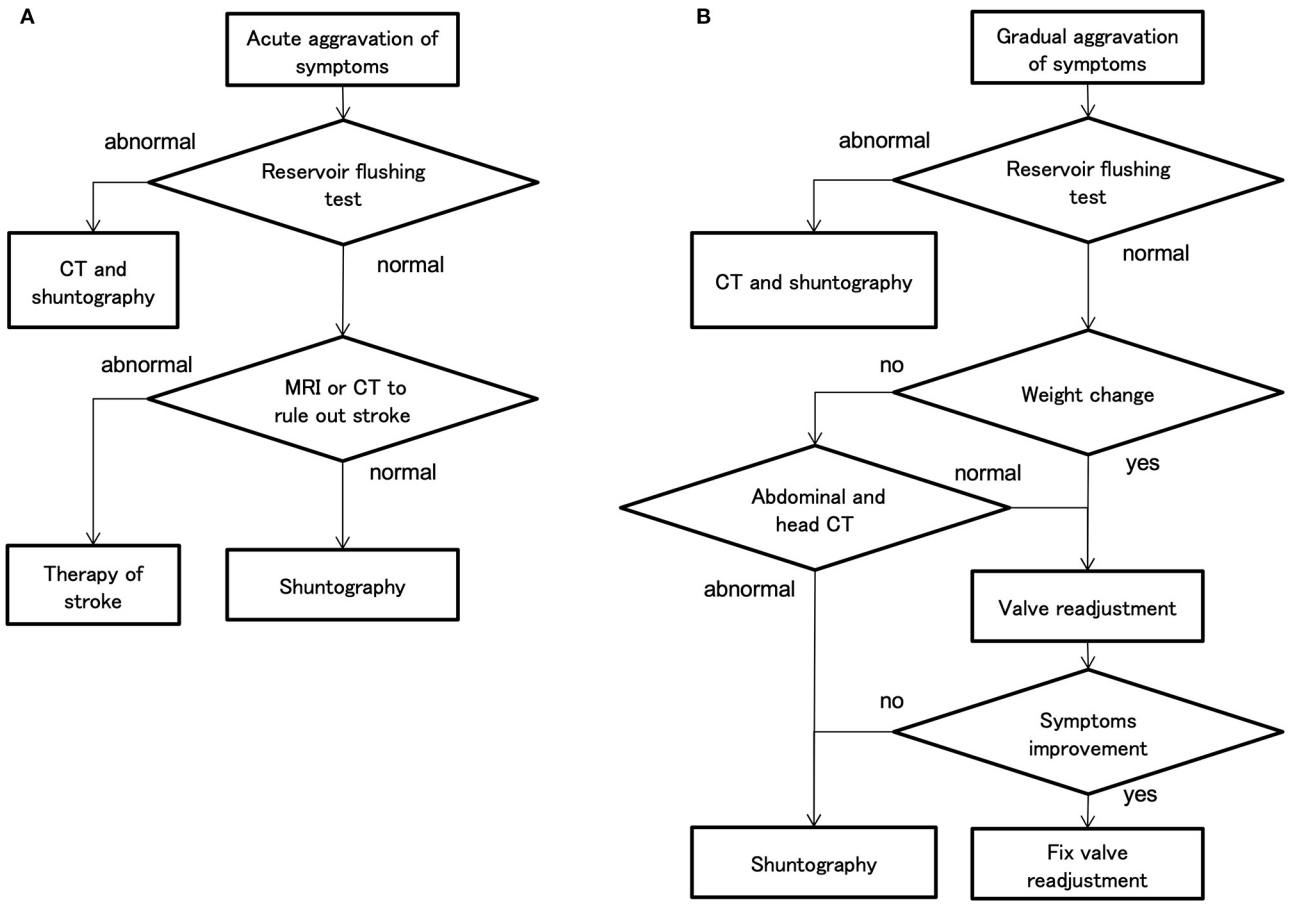

FIGURE 8 | The decision flow chart at symptom aggravation. **(A)** In cases of acute aggravation, the first step is to perform a reservoir flushing test, which can be easily performed in the examination room. If the reservoir flushing test is normal, the physician should differentiate a stroke by magnetic resonance imaging (MRI). **(B)** In cases of gradual aggravation in about 3 months, first perform a reservoir flushing test. If the reservoir flushing test is normal and the weight has changed by several kilograms, the physician should readjust the valve. In the case of weight gain, lower the setting by 30–60 mm H_2O for the CH valve and by one level for the CERTAS plus and STRATA NSC valves. If there is no improvement after 1 month of valve readjustment, the physician should consider performing shuntography.

by a few kilograms, the physician should first attempt to readjust the valve. In the case of aggravation of gait disturbance by WAIST, improvement of symptoms can be observed by objective gait assessment within 1 h after valve readjustment. However, if symptoms have not improved after 1 month, the physician should consider performing shuntography. If shuntography reveals abnormalities, i.e., occlusions, ruptures, disconnections, perform appropriate shunt revisions (21). However, such multidisciplinary cognitive and gait assessment, and diagnosis by CT and shuntography, are very tedious and consume a lot of medical resources.

Recently, the implantable ICP sensors have become commercially available, and the measured ICP can qualify the drainage status of the patients with hydrocephalus (8, 22). This study also provides evidence that ICP acutely reflects drainage status. Thus, an ICP-based patient management system using an implantable ICP sensor would simplify patient management. It would also be possible to reduce most of the management costs of the patients with shunted hydrocephalus.

CONCLUSIONS

We report a SM induced by changes in body weight and IAP in the patients with shunted NPH and named it WAIST. In underdrainage type WAIST, weight gain exacerbated the symptoms, while in overdrainage type WAIST, weight loss induced CSDH. Both are reversible by the readjustment of the valve. This study presents that weight change affected the IAP and caused shunt malfunction by altering the ICP linked to the IAP. This study recommends that physicians should monitor for changes in weight and symptoms in patients with shunted NPH.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The research protocol was approved by the Ethics Committee of Osaka Medical College (No. 27,27-1,2788) and informed consent was obtained in writing from all patients.

AUTHOR CONTRIBUTIONS

YK and HM made substantial contributions to the conception and design of the study. YK and MKamo collected data regarding the participants and task performance. MKamo, YK, and TO analyzed the data. MKamo, YK, MW, MKame, and AT wrote the manuscript. All authors read and approved the submitted version.

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Evaluation of Patients With Cognitive Impairment Due to Suspected Idiopathic Normal-Pressure Hydrocephalus at Medical Centers for Dementia: A Nationwide Hospital-Based Survey in Japan

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Objective: Treatment of idiopathic normal-pressure hydrocephalus (iNPH) requires collaboration between dementia specialists and neurosurgeons. The role of dementia specialists is to differentiate patients with iNPH from patients with other dementia diseases and to determine if other dementia diseases are comorbid with iNPH. We conducted a nationwide hospital-based questionnaire survey on iNPH in medical centers for dementia (MCDs).

Methods: We developed a questionnaire to assess how physicians in MCDs evaluate and treat patients with cognitive impairment due to suspected iNPH and the difficulties these physicians experience in the evaluation and treatment of patients. The questionnaire was sent to all 456 MCDs in Japan.

Results: Questionnaires from 279 MCDs were returned to us (response rate: 61.2%). Patients underwent cognitive tests, evaluation of the triad symptoms of iNPH, and morphological neuroimaging examinations in 96.8, 77.8, and 98.2% of the MCDs, respectively. Patients with suspected iNPH were referred to other hospitals (e.g., hospitals with neurosurgery departments) from 78.9% of MCDs, and cerebrospinal fluid (CSF) tap test was performed in 44 MCDs (15.8%). iNPH guidelines (iNPHGLs) and disproportionately enlarged subarachnoid space hydrocephalus (DESH), a specific morphological finding, were used and known in 39.4% and 38% of MCDs, respectively. Logistic regression analysis with "Refer the patient to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH is suspected." as the response variable and (a) using the iNPHGLs, (b) knowledge of DESH, (c) confidence regarding DESH, (d) difficulty with performing brain magnetic resonance imaging, (e) knowledge of the methods of CSF tap test, (f) absence of physician who can perform lumbar puncture, and (g) experience of being told by neurosurgeons that referred patients are not indicated for shunt surgery

as explanatory variables revealed that the last two factors were significant predictors of patient referral from MCDs to other hospitals.

Conclusion: Sufficient differential or comorbid diagnosis using CSF tap test was performed in a few MCDs. Medical care for patients with iNPH in MCDs may be improved by having dementia specialists perform CSF tap tests and share the eligibility criteria for shunt surgery with neurosurgeons.

Keywords: idiopathic normal-pressure hydrocephalus, medical centers for dementia, dementia specialists, evaluation, neurosurgeons, clinical guidelines, cerebrospinal fluid tap test, questionnaire survey

INTRODUCTION

Normal-pressure hydrocephalus (NPH) is a syndrome that presents as cognitive impairment, gait disturbance, and urinary incontinence, known as the triad symptoms of NPH, in patients with enlarged ventricles under normal cerebrospinal fluid (CSF) pressure (1). NPH is now regarded as a syndrome that presents with balance disorders (2), motor abnormalities involving the upper limbs (3), and disturbances of the eye (4), in addition to its triad symptoms. Generally, NPH is classified as idiopathic NPH (iNPH), which has no identifiable causative antecedent disease, or secondary NPH, which develops after antecedent disease such as meningitis or subarachnoid hemorrhage. The estimated prevalence of iNPH in elderly Japanese and Swedish populations is 1.1 and 2.1%, respectively (5, 6). These figures indicate the worldwide prevalence of iNPH. In several studies, remarkable improvement in activities of daily living was reported in 69% (7), 69% (8), and 63% (9) of patients 1 year after undergoing shunt surgery for iNPH.

Secondary NPH occurs several months after the onset of the preceding disease; hence, it is not always necessary to differentiate it from other diseases. In contrast, iNPH is a slowly progressive disorder that requires differential diagnosis from other dementia diseases such as Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and vascular dementia (VaD). In recent studies, it was reported that AD, DLB, and VaD are often comorbid with iNPH (10–12), and these comorbidities reduce the efficacy of shunt surgery (10, 11). In addition, iNPH is sometimes comorbid with schizophrenia (13), and patients with iNPH and prominent psychiatric symptoms are more likely to be admitted to psychiatric hospitals than to neurosurgical facilities (14). The prevalence of iNPH in patients with dementia as documented in memory disorder clinics is 15% (15), highlighting that many patients with iNPH visit dementia facilities. Thus, dementia specialists, including psychiatrists, should be involved in the differentiation of iNPH from other dementia/psychiatric diseases and in the diagnosis of the comorbidities of iNPH.

The elderly population is growing rapidly in Japan. It is estimated that the number of people with dementia will exceed 7 million by 2025, and that one out of every five people aged 65 years or older in Japan will experience dementia. In 2008, medical centers for dementia (MCDs) were established as part of a new national health program against dementia to ensure that Japanese citizens receive appropriate medical care for dementia regardless of where they live. The MCDs were established at medical institutions designated by the governors of the 47 prefectures in Japan or the mayors of 20 designated cities. The aim was to have at least one MCD in each secondary medical care area in Japan for a total of 500 centers nationwide. MCDs contribute to the provision of the following (16): (1) special medical consultation; (2) differential diagnosis and early intervention; (3) medical treatment for the acute stage of behavioral and psychological symptoms of dementia and concurrent medical conditions; (4) education for general practitioners and other community professionals; (5) network meetings for the establishment of cooperation among medical facilities and collaboration between medical facilities and nursing care facilities; and (6) information regarding dementia to the public. There are three types of MCDs: core-type, regional-type, and collaborative-type MCDs. Regional-type MCDs are the most common type, and psychiatric hospitals are often designated as regional-type MCDs. Core-type MCDs include university hospitals and general hospitals, and the special role of core-type MCDs is to provide training of human resources for the evaluation and treatment of patients with dementia. Collaborative-type MCDs refer to clinics, and the special role of these MCDs is community-based collaboration with relevant institutions. The number of MCDs has been increasing, reaching 456 in 2019; consequently, all patients with dementia in Japan can now receive the treatment and care they need.

In the treatment of iNPH, collaboration between dementia specialists and neurosurgeons is necessary. However, a small-scale survey we conducted in 2013 revealed that physicians in many MCDs do not perform CSF tap test and that physicians in more than half the MCDs find that "patients are referred to neurosurgeons, but the neurosurgeons said the patients are not indicated for shunt surgery" (17). These findings indicate that there may be room for improvement regarding the clinical practice of physicians in MCDs for patients with iNPH and regarding collaboration between physicians and neurosurgeons. However, there have been no large-scale studies evaluating the actual status of examinations and treatment of patients with iNPH in specialized facilities for patients with dementia. Therefore, we conducted a nationwide hospital-based questionnaire survey to evaluate how patients with cognitive impairment due to suspected iNPH are examined and treated in MCDs 6 years after our previous preliminary survey.

MATERIALS AND METHODS

Contents of the Questionnaire and Background

The contents of the questionnaire used in this study are based on the diagnostic criteria for iNPH in the second edition of the Japanese iNPH guidelines (iNPHGLs) (5). In the Japanese iNPHGLs, iNPH is categorized into three diagnostic levels: preoperatively "possible," preoperatively "probable," and postoperatively "definite." A diagnosis of a possible iNPH is made if all the following five criteria are met: (1) development of symptoms in the 60's or when older; (2) the presence of more than one of the clinical triad symptoms, namely cognitive impairment, gait disturbance, and urinary incontinence; (3) ventricular enlargement (Evans index > 0.3) on brain computed tomography (CT) or magnetic resonance imaging (MRI); (4) the abovementioned clinical symptoms cannot be completely explained by other neurological or non-neurological diseases; and (5) the absence of prior diseases that may cause ventricular dilation. A diagnosis of probable iNPH is made if all the following three criteria are met: (1) the requirements for possible iNPH are met; (2) CSF pressure of $\leq$200 mmH_2O and normal CSF content; and (3) one of the following three investigational features: (a) improvement in one or more of the triad symptoms following lumbar puncture performed to temporarily decrease the volume of CSF (CSF tap test); (b) improvement in one or more of the triad symptoms following CSF drainage test; or (c) the neuroimaging feature termed "disproportionately enlarged subarachnoid space hydrocephalus (DESH)," i.e., narrowing of the sulci and subarachnoid spaces over the high convexity/midline surface with ventricular enlargement (7), under the presence of gait disturbance. In clinical settings in Japan, a diagnosis of probable iNPH is made when one or more of the triad symptoms improve after the CSF tap test in patients with DESH. A probable iNPH patient is indicated for shunt surgery and is therefore referred to a hospital where neurosurgery is performed. Definite iNPH is defined as a patient for whom the symptoms improve after shunt surgery. The most important difference between the diagnostic criteria of the Japanese and American-European iNPHGLs (18) is the emphasis on DESH findings in the Japanese iNPHGLs.

We administered our questionnaire to assess how physicians in MCDs evaluate and treat patients with cognitive impairment due to suspected iNPH. We inquired about iNPHGLs used in MCDs and about difficulties encountered in the treatment of iNPH. We also included a question to assess the knowledge of physicians in MCDs regarding DESH (7). DESH is an important finding as it is useful for differentiating iNPH from AD and VaD (19), and it has a high positive predictive value in identifying shunt-responsive patients with iNPH (20). The questionnaire is shown in the **Supplementary Material**.

Survey Procedure

The study period was from June 7, 2019 to March 31, 2020. On October 25, 2019, the questionnaire was sent to all 456 MCDs in Japan, which include 16 core-type, 367 regional-type, and 73 collaborative-type MCDs. The questionnaire was to be completed by the head of each MCD or by a physician currently working at the MCD. The deadline for returning the questionnaire was November 11, 2019. Both the participants in this study and the patients that they treated were believed to mostly be Japanese.

The study was conducted in accordance with the Declaration of Helsinki (2013) of the World Medical Association and the guidelines of the ethics committee of the Japan Psychiatric Hospitals Association.

Analyses

We calculated the percentages of MCDs that answered "Yes" to each of the items in the questionnaire. Using Fisher's exact test, we compared the ratio of "Yes" answers between the three types of MCDs. In addition, logistic regression analysis was performed to determine factors that influence referral from MCDs to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH is suspected. The response variable was "Refer the patient to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH is suspected." The explanatory variables were (a) I use iNPHGLs; (b) I am familiar with DESH; (c) "I am not confident in my assessment of DESH on brain MRI;" (d) "Brain MRI cannot be performed;" (e) "No physician who can perform lumbar puncture is available;" (f) "I have no knowledge of the methods or criteria for evaluating clinical symptoms in CSF tap test;" and (g) "Patients are referred to neurosurgeons, but the neurosurgeons said that the patients are not indicated for shunt surgery." Odds ratios were calculated for all explanatory variables. Statistical analyses were performed using SPSS version 27, and significance level was set at $p < 0.05$.

RESULTS

Characteristics of Participating MCDs

Of the 456 questionnaires sent, 279 were returned to us (response rate: 61.2%). Of the 279 responders, 13 (4.7%) were core-type MCDs, 219 (78.5%) were regional-type MCDs, and 47 (16.8%) were collaborative-type MCDs. The response rates by MCD type were 81.3% (13/16) for core-type MCDs, 59.7% (219/367) for regional-type MCDs, and 64.4% (47/73) for collaborative-type MCDs. Regarding departments in the 279 MCDs, 246 (88.2%) had a psychiatry department, 187 (67.0%) had an internal medicine department, 123 (44.1%) had a neurology department, and 66 (23.7%) had a neurosurgery department. The combination of psychiatry and neurology/neurosurgery and the psychiatry without neurology/neurosurgery were similar in percentage in all MCDs (**Figure 1**). Given that most core-type MCDs are university hospitals or general hospitals, the percentage of core-type MCDs with the psychiatry and neurology/neurosurgery departments was found to be 69.2%. Collaborative-type MCDs have a higher percentage of centers with a neurology/neurosurgery department but without a psychiatry department than core-type or regional-type MCDs.

Regarding neuroimaging examinations, brain CT was performed in 269 MCDs (96.4%), either at the facility or at collaborating facilities. Brain MRI scans were performed in 161 MCDs (57.7%), including 11 core-type MCDs (84.6%),

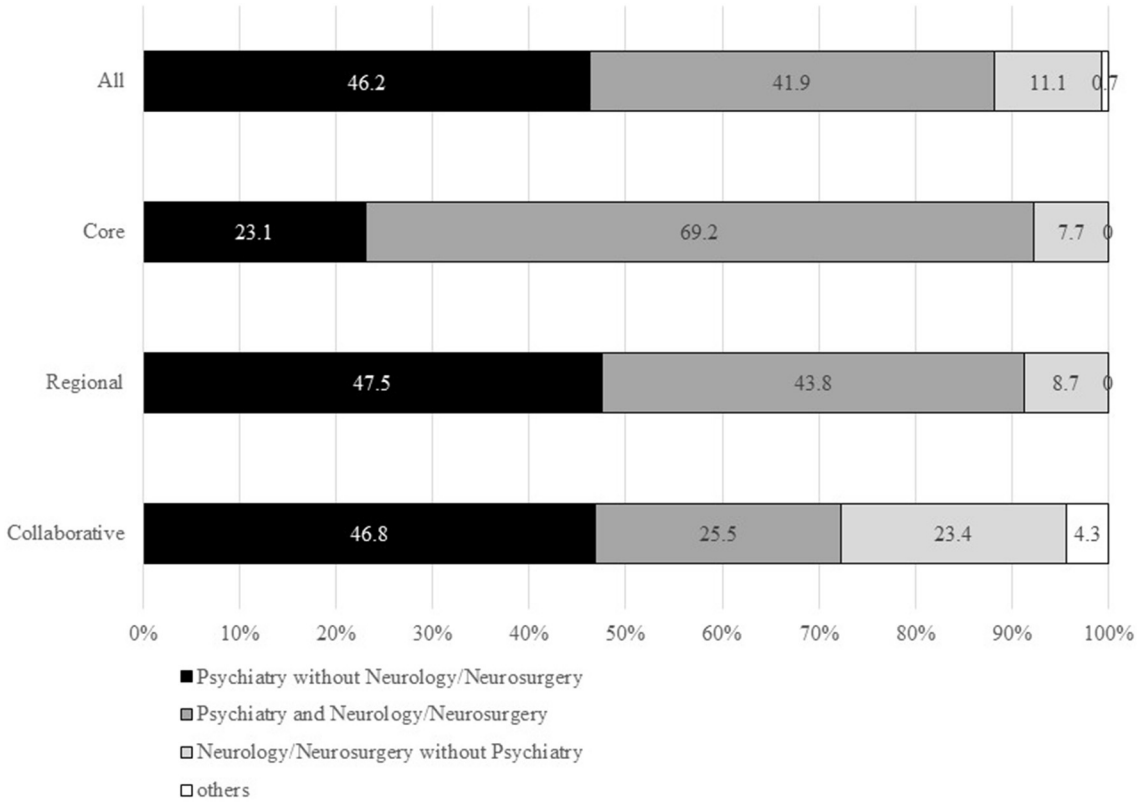

FIGURE 1 | Percentages of departments in MCDs. Department of internal medicine was not included in this figure. MCD, medical center for dementia.

119 regional-type MCDs (54.3%), and 31 collaborative-type MCDs (66.0%). CSF examination was performed in 94 MCDs (33.7%), including 10 core-type MCDs (76.9%), 72 regional-type MCDs (33.0%), and 12 collaborative-type MCDs (25.5%).

Results of Questionnaire Survey

Evaluation and Treatment of Patients With Suspected iNPH

Ten (3.6%) of the 279 MCDs had no patients with suspected iNPH (**Figure 2**). Patients with suspected iNPH were referred to other hospitals (e.g., hospitals with neurosurgery departments) from 220 MCDs (78.9%), CSF tap test was performed in 44 MCDs (15.8%), and shunt surgery was performed in 23 MCDs (8.2%). Follow-up care for patients with suspected iNPH who underwent shunt surgery and for patients with suspected iNPH who did not undergo shunt surgery was performed in 56 MCDs (20.1%) and 86 MCDs (30.8%), respectively.

Significant differences in the items "Refer the patient to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH is suspected" and "Perform CSF tap test" were observed between the three types of MCDs ($p = 0.044$ and $p = 0.033$, respectively). The rate of the former item was lower and the rate of the latter item was higher in core-type MCDs than in regional-type or collaborative-type MCDs.

Examinations of Patients With Suspected iNPH

Ten MCDs (3.6%) did not perform any examinations for patients with suspected iNPH (**Figure 3**). Cognitive screening tests, such as assessment using the Hasegawa Dementia Scale-Revised and Mini Mental State Examination, were performed in 270 of the 279 MCDs (96.8%). Other cognitive tests, including Frontal Assessment Battery, Alzheimer's Disease Assessment Scale, and Rivermead Behavioral Memory Test, were performed in 62 MCDs (22.2%). Evaluation of the triad symptoms of iNPH was performed in 217 MCDs (77.8%), and brain CT or MRI was performed in 274 MCDs (98.2%). Other neuroimaging examinations, most commonly cerebral perfusion single-photon emission CT, were performed in 35 MCDs (12.5%). CSF examination or CSF tap test was performed in 60 MCDs (21.5%).

There were significant differences in other cognitive tests, brain CT, brain MRI, other neuroimaging examinations, and CSF examination/CSF tap test between the three types of MCDs. The percentages of all items, except "Perform brain CT," were higher in core-type MCDs than in regional-type or collaborative-type MCDs.

Use of iNPHGLs

In 35 MCDs (12.5%), iNPHGLs were not known, and in 118 MCDs (42.3%), iNPHGLs were known but were not used (**Figure 4**). The first edition of the Japanese iNPHGLs (21) was used in 13 MCDs (4.7%), while the second edition of the Japanese

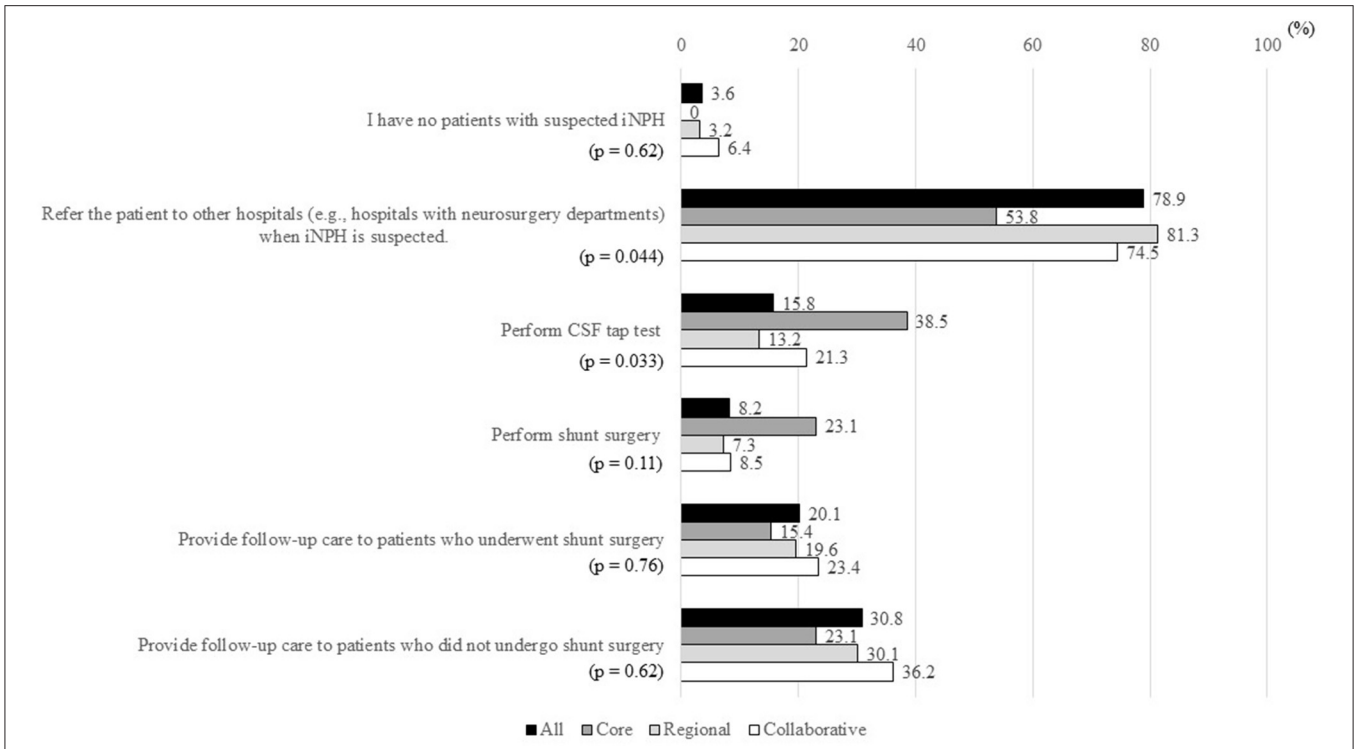

FIGURE 2 | Percentages of MCDs that answered "Yes" to items in response to the question "How do you evaluate and treat patients with suspected iNPH?". MCD, medical center for dementia; iNPH, idiopathic normal-pressure hydrocephalus; CSF, cerebrospinal fluid. *The ratio of "Yes" answers were compared between the three types of MCDs using Fisher's exact test.

iNPHGLs (5) was used in 104 MCDs (37.3%). With both editions of the Japanese iNPHGLs used in 7 MCDs, the total number (and percentage) of MCDs that use the iNPHGLs was 110 (39.4%). No MCDs reported using iNPHGLs other than the Japanese iNPHGLs. There was familiarity with DESH in 106 MCDs (38%), and no statistically significant differences in the use of iNPHGLs were observed between the three types of MCDs.

Difficulties in Evaluation and Treatment of Patients With Suspected iNPH

The item "Patients are referred to neurosurgeons, but the neurosurgeons said the patients are not indicated for shunt surgery" was the most common difficulty in MCDs, affecting 86 MCDs (30.8%; **Figure 5**). The second most common difficulty was the item "No physician who can perform lumbar puncture is available," affecting 71 MCDs (25.4%). About 12% of MCDs answered "Yes" to the items "I am not confident in my assessment of DESH on brain MRI," "I have no experience or confidence to diagnose iNPH," and "I have no knowledge of the methods or criteria for evaluating clinical symptoms in CSF tap test."

Except for the item "Brain CT cannot be performed," significant differences were not observed in any item regarding difficulties in the evaluation and treatment of patients with iNPH between the three types of MCDs. The item "Brain CT cannot be performed" was a problem only in 4.3% of collaborative-type MCDs.

Intentions for Examination and Treatment for Patients With Cognitive Impairment Due to Suspected iNPH at MCDs

Overall, 183 MCDs (65.6%) responded "Yes" to "Refer the patient to specialized institutions when iNPH is suspected," 66 MCDs (23.7%) responded "Yes" to "Perform detailed examination and diagnosis," and 24 MCDs (8.6%) replied "Yes" to "Provide treatment" (**Figure 6**). The percentages of the last two items were slightly higher in core-type MCDs than in regional-type or collaborative-type MCDs.

Predictors of Referral From MCDs to Other Hospitals When iNPH Is Suspected

Logistic regression analysis revealed that "No physician who can perform lumbar puncture is available" and "Patients are referred to neurosurgeons, but the neurosurgeons said the patients are not indicated for shunt surgery" were significant predictors of patient referral from MCDs to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH is suspected (**Table 1**).

DISCUSSION

We conducted a nationwide hospital-based questionnaire survey to determine how patients with cognitive impairment due to suspected iNPH, a treatable dementia, were evaluated and treated in MCDs in Japan. This is the first study to investigate the

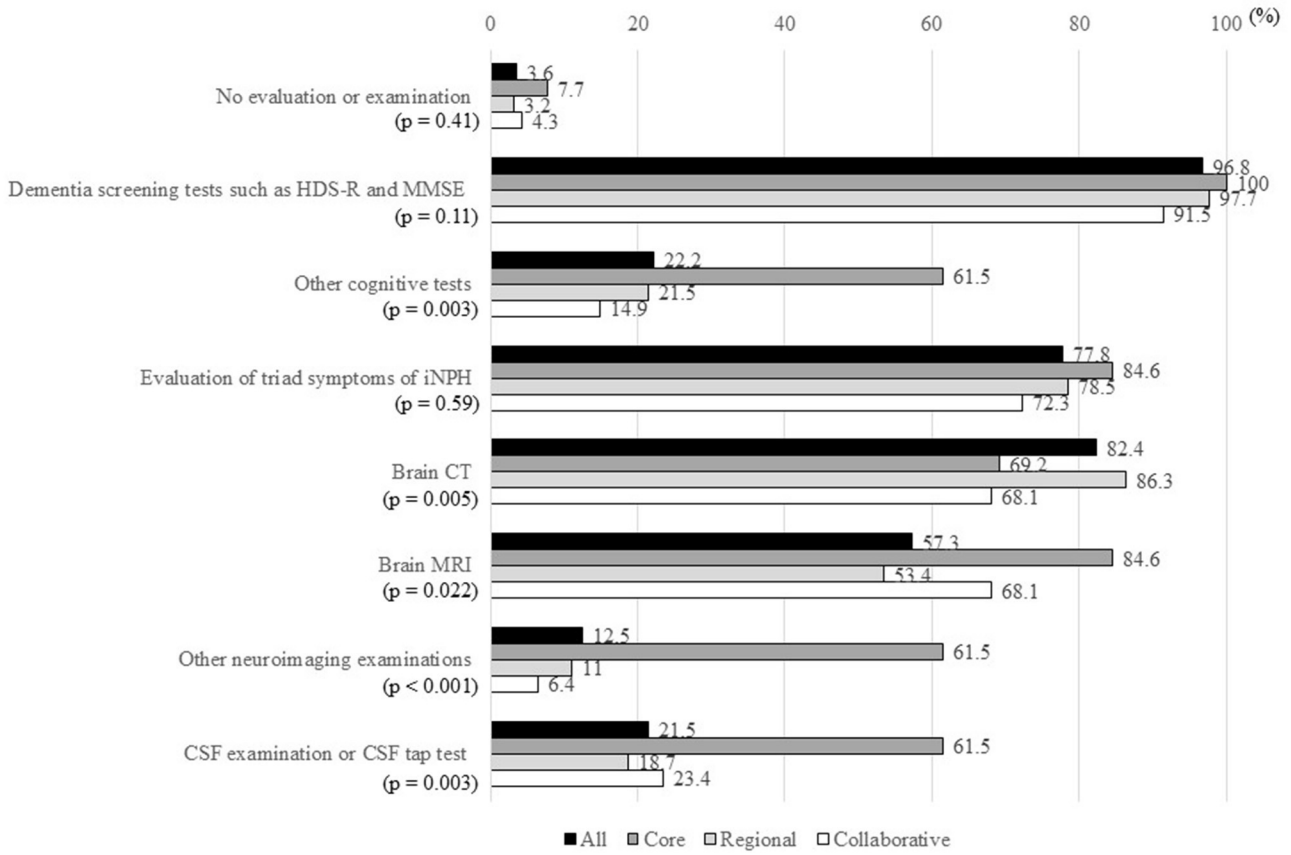

FIGURE 3 | Percentages of MCDs that answered "Yes" to items in response to the question "How do you examine patients with suspected iNPH?". MCD, medical center for dementia; HDS-R, Hasegawa Dementia Scale-Revised; MMSE, Mini Mental State Examination; iNPH, idiopathic normal-pressure hydrocephalus; CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid. *The ratio of "Yes" answers were compared between the three types of MCDs using Fisher's exact test.

actual status of examination and treatment of patients with iNPH in specialized facilities for patients with dementia. This survey revealed that most MCDs cater to patients with cognitive impairment due to suspected iNPH and that sufficient differential or comorbid diagnosis using the CSF tap test was performed at a few MCDs. Most MCDs referred patients to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH was suspected. Two hundred and seventy-nine MCDs in Japan responded to the questionnaire (response rate: 61.2%). The response rates of the three types of MCDs were around 60% or more, and the results of this study can be considered reflective of the current situation in MCDs in Japan. As regional-type MCDs are originally the most common type of MCDs, the overall results of this study are most reflective of the situation in regional-type MCDs. In terms of departments, most MCDs have a psychiatry department and a department of internal medicine. About 40% of MCDs have a neurology department, and about 20% of MCDs have a neurosurgery department.

This survey revealed that a small percentage (3.6%) of MCDs do not attend to patients with suspected iNPH, meaning that most MCDs cater to these patients. Patients with suspected iNPH underwent cognitive screening tests, evaluation of the triad symptoms of iNPH, and morphological neuroimaging examinations in most MCDs. Thus, they were diagnosed with possible iNPH in MCDs based on the presence of the triad symptoms and ventricular enlargement. However, patients with AD, DLB, or VaD may also meet the diagnostic criteria for possible iNPH. Therefore, patients with possible iNPH should be differentiated between those with probable iNPH or those with other dementia diseases. In this survey, CSF tap test was performed in only 15.8% of MCDs, and 78.9% of MCDs referred patients to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH was suspected, indicating that probable iNPH was not diagnosed in most MCDs. Since all neurosurgeons are not skilled in the differential diagnosis of dementia, all patients with possible iNPH do not receive appropriate differential diagnosis in neurosurgical facilities after referral from MCDs. Before considering shunting, it is important that patients with iNPH who also have AD or DLB and the families of these patients understand that another disease is comorbid with iNPH. Hence, it is appropriate that physicians in

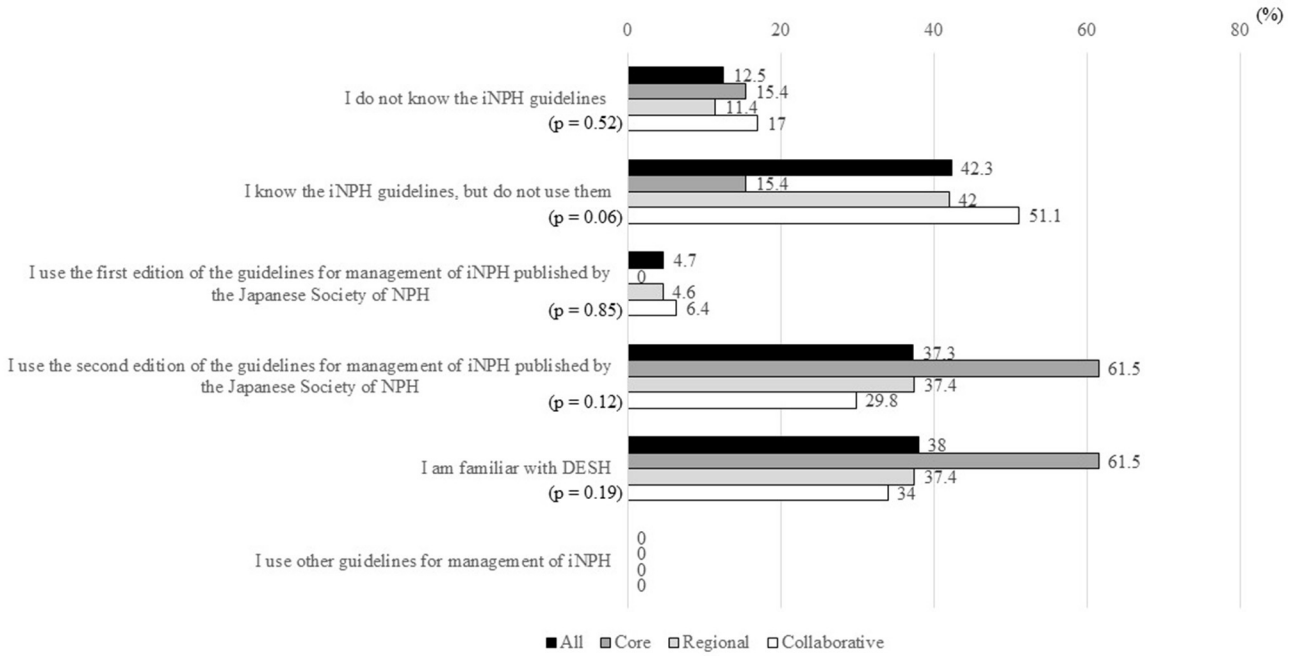

FIGURE 4 | Percentages of MCDs that answered "Yes" to items in response to the question "Do you know and use the guidelines for the management of iNPH?". MCD, medical center for dementia; iNPH, idiopathic normal-pressure hydrocephalus; NPH, normal-pressure hydrocephalus; DESH, disproportionately enlarged subarachnoid space hydrocephalus. *The ratio of "Yes" answers were compared between the three types of MCDs using Fisher's exact test.

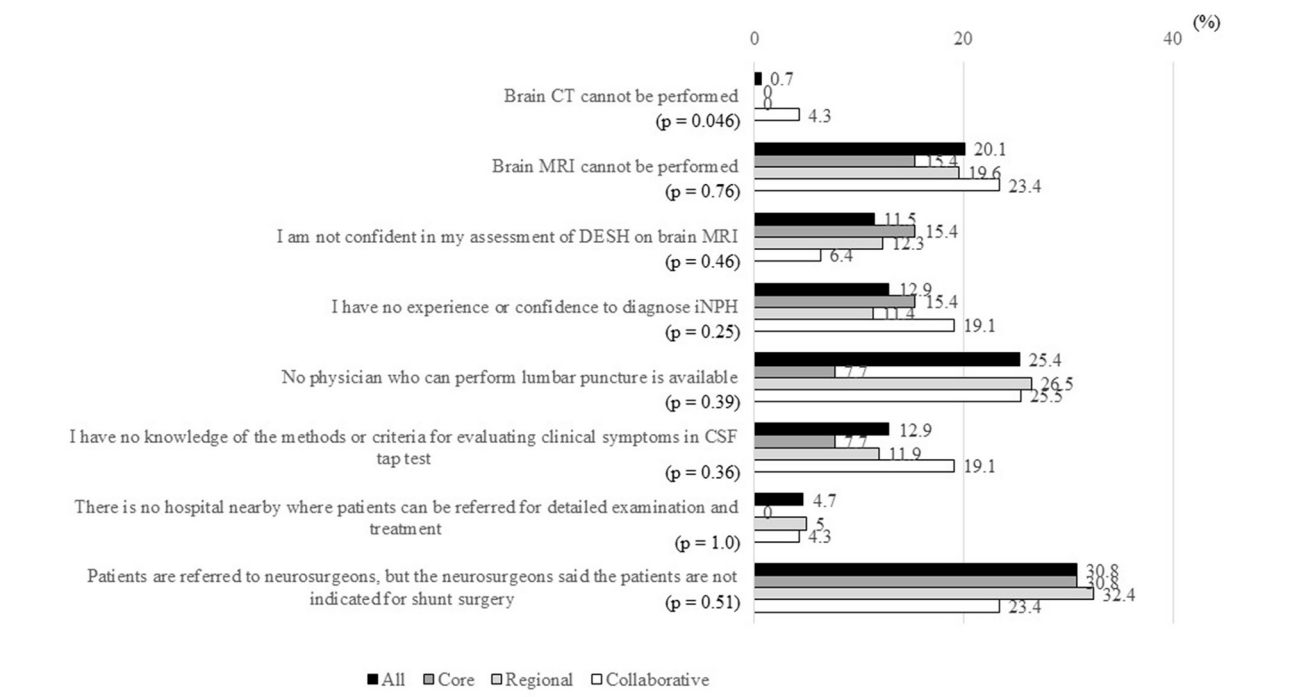

FIGURE 5 | Percentages of MCDs that answered "Yes" to items in response to the question "What are the difficulties in the evaluation and treatment of patients with suspected iNPH?". MCD, medical center for dementia; CT, computed tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; DESH, disproportionately enlarged subarachnoid space hydrocephalus; iNPH, idiopathic normal-pressure hydrocephalus; CSF, cerebrospinal fluid. *The ratio of "Yes" answers were compared between the three types of MCDs using Fisher's exact test.

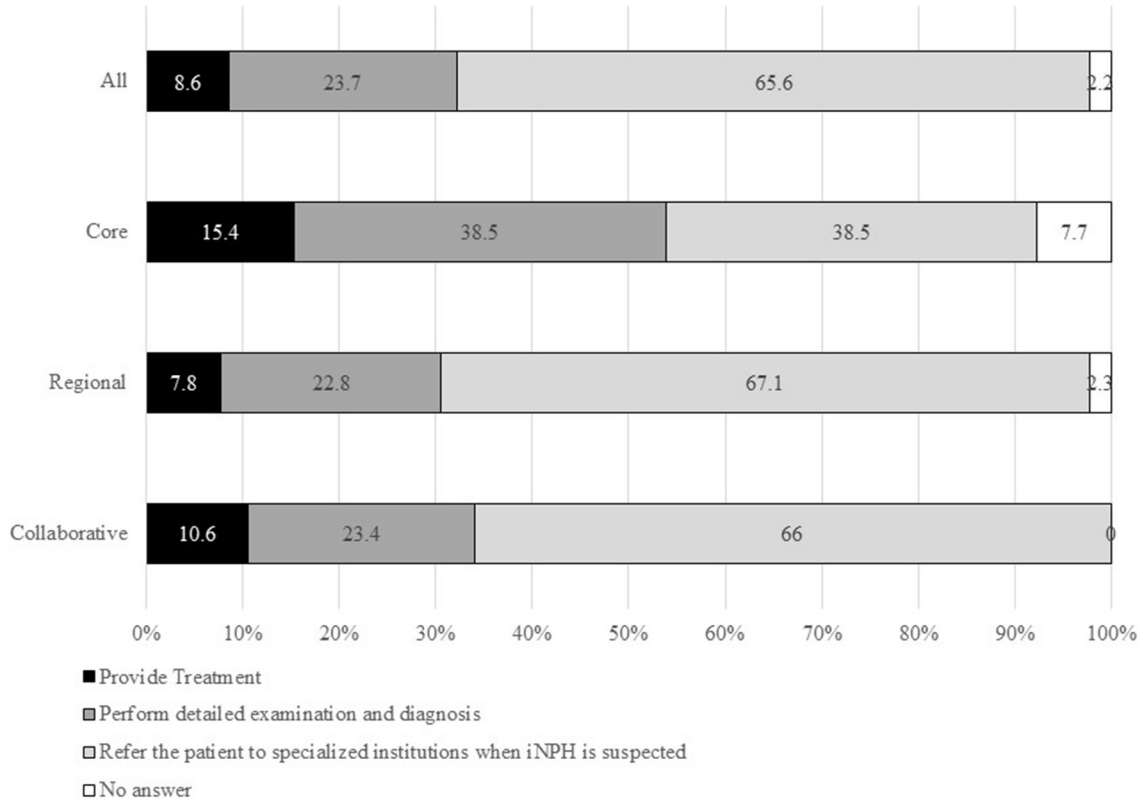

FIGURE 6 | Percentages of "Yes" in answer to "To what extent do you think MCDs should evaluate and treat patients with cognitive impairment due to suspected iNPH?".

MCDs refer patients to neurosurgery for shunting after detailed differential and comorbid diagnoses, including CSF tap test.

In this study, we determined the predictors of patient referral from MCDs to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH is suspected. Our results show that "No physician who can perform lumbar puncture is available" is a significant predictor of patient referral. This finding is logical given that CSF tap test cannot be performed without lumbar puncture, which requires training. Lumbar puncture is an important procedure for physicians in MCDs because it is often used to differentiate meningitis from dementia (22, 23). In addition, amyloid-β, phosphorylated tau, and total tau levels in CSF are useful for differentiating AD from other dementia diseases (24). CSF biomarkers also contribute to differentiating iNPH from other diseases (25–28), making a differential diagnosis of mixed cases (29), and predicting the improvement of clinical symptoms after shunt surgery in patients with iNPH (30, 31). In this survey, it was found that 23.7% of MCDs responded with "Perform detailed examination and diagnosis" to the question "To what extent do you think MCDs should evaluate and treat patients with cognitive impairment due to suspected iNPH?". Furthermore, in this survey, CSF examination was conducted in 33.7% of MCDs, which is higher than the percentage of MCDs where CSF tap test was performed (15.8%). Thus, in the near future, the number of MCDs where CSF tap test is performed is expected to increase.

The item "Patients are referred to neurosurgeons, but the neurosurgeons said the patients are not indicated for shunt surgery" was found to be another predictive factor of referral of patients with suspected iNPH to other hospitals. Physicians in MCDs who referred patients with iNPH to the neurosurgery department after performing detailed evaluations, such as CSF tap test, may feel that it is useless to examine patients, causing the physicians to immediately refer patients to the neurosurgery department. On the other hand, physicians in MCDs who referred patients with iNPH without performing detailed examinations may decide against referral to the neurosurgery department but decide to refer these patients to specialized hospitals, such as university hospitals, where detailed examinations, including CSF tap test, are performed. We were unable to verify these assumptions because the exact departments/hospitals patients were referred to are not known.

Regarding the difference in understanding between neurosurgeons and physicians pertaining to the eligibility of patients with suspected iNPH for shunt surgery, neurosurgeons may exercise caution because shunt surgery improves cognitive impairment to a lesser degree than gait disturbance (32), because patients with severe preoperative cognitive impairment

are likely to have residual cognitive impairment after shunt surgery (33), and because patients who visit dementia centers and psychiatric institutions are known to have more severe cognitive impairment than patients who visit neurosurgery departments (14). In addition, remarkable cognitive impairment in patients with iNPH may be due to other comorbid dementia diseases that can reduce cognitive improvement following shunt surgery (10, 11). Furthermore, the low proportion of MCDs where physicians are familiar with DESH in this study indicates that many physicians who are unfamiliar with DESH referred patients with suspected iNPH to neurosurgeons. Use of the iNPHGLs may help reduce the difference in understanding pertaining to the eligibility of patients with suspected iNPH for shunt surgery between neurosurgeons and physicians in MCDs. This is attributable to the fact that the results of the logistic regression analysis in this study showed that MCDs using the iNPHGLs had a lower rate of referral of patients to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH was suspected ($p = 0.085$). The iNPHGLs may help physicians in MCDs understand that the main roles of the MCDs include the differential and comorbid diagnoses for patients with suspected iNPH. The number of MCDs where CSF tap test is performed is expected to increase, as we mentioned above. If the physicians in MCDs refer the iNPH patients with DESH and whose symptoms improve on the CSF tap test to neurosurgeons, neurosurgeons will be likely to report that there is an indication for shunt surgery for patients with cognitive impairment at MCDs. Moreover, a consensus on the eligibility of patients with iNPH who have remarkable cognitive impairment and/or comorbidity for shunt surgery can be reached via direct communication between physicians in MCDs and neurosurgeons.

It is important that the contents of the questionnaire used in this study are based on the diagnostic criteria for iNPH in the second edition of the Japanese iNPHGLs (5), which differ from the diagnostic criteria for iNPH in the American-European iNPHGLs (18). The Japanese iNPHGLs include an age of onset older than 60 years and any one of the triad symptoms, whereas the American-European iNPHGLs include an age of onset over 40 years and mandatory gait or balance disturbance, in addition to one of the other two symptoms of the triad. Thus, an increasing number of patients without gait disturbance are likely diagnosed with iNPH in Japan compared with European and North American countries. Regarding neuroimaging findings, the Japanese iNPHGLs emphasize the DESH features; in contrast, in the American-European iNPHGLs, ventriculomegaly, a narrow callosal angle, enlargement of the temporal horns, and periventricular signal changes not attributable to ischemic changes or demyelination are considered important (18, 34, 35). Obtaining a diagnosis of "probable iNPH" is three times more likely as per the American-European iNPHGLs compared with the Japanese iNPHGLs (35). The number of iNPH patients with DESH may be as low as one third of all iNPH patients, and it is thus possible that fewer patients are being actively treated in Japan than in European and North American countries. Patients with iNPH who have DESH may be the focus of treatment for MCD physicians who are not experts in iNPH because patients with DESH are easier to detect and more likely to benefit from shunt surgery (20).

The results of this study may be affected by the current status of treatment for iNPH in Japan, which differs from that in European and North American countries. First, Japan has many neurosurgery hospitals, which tend to be smaller and thus have smaller referral areas than hospitals in European and North American countries. In two studies conducted in Japan, 87 patients with iNPH underwent shunt surgery in 20 centers (approximately four patients per center) (9) and 1,608 patients with iNPH underwent shunt surgery in 289 facilities (approximately six patients per center) (36). In contrast, in a European multicenter study, 140 patients with iNPH underwent shunt surgery in 13 centers in 1 year (approximately 11 patients per center) (8), and in a study conducted in North America, 151 patients were examined for 11 years in one center (∼14 patients per year per center) (37). These findings suggest that neurosurgeons in Japan have less experience in treating iNPH patients compared with those in Europe and North America. Thus, some neurosurgeons in Japan may be unfamiliar with the diagnostic criteria of the Japanese iNPHGLs. Second, although ventriculoperitoneal (VP) shunt surgery is the most common worldwide, lumboperitoneal (LP) shunt surgery is the most common shunt surgery for iNPH in Japan (36). An advantage of LP shunt surgery is that patients and their caregivers are less likely to oppose to this procedure than VP shunt surgery because the LP approach can help circumventing cranial surgery. Thus, there may be more patients with iNPH requesting shunt surgery in Japan than in other countries. Third, there may be a considerable number of iNPH patients with comorbid dementia diseases other than iNPH, such as Alzheimer's disease, because of the aging population of Japan.

In 2013, we conducted a small-scale questionnaire survey similar to this survey to evaluate how patients with iNPH are examined in MCDs (17). Ninety-eight of 205 MCDs responded to our previous questionnaire survey (response rate: 48%). We compared the results of this 2019 survey to those of our 2013 survey. The second edition of the Japanese iNPHGLs was published in 2011 (5). Thus, our two surveys were conducted 2 and 8 years after the publication of the revised iNPHGLs, respectively. The response rate and amount of data in this study were greater than those in the previous study. Compared to the 2013 survey, fewer physicians in this study responded in the affirmative to the items "I have no patients with suspected iNPH" (3.6% in 2019 vs. 8% in 2013) and "Patients are referred to neurosurgeons, but the neurosurgeons said the patients are not indicated for shunt surgery" (30.8% in 2019 vs. 56% in 2013). Further, in this survey, more physicians in MCDs answered "Yes" to the item "Provide follow-up care to patients who did not undergo shunt surgery" (30.8% in 2019 vs. 2% in 2013). These results suggest increased frequency of examinations and follow-up care of patients with iNPH in MCDs and less difference in understanding between neurosurgeons and physicians pertaining to the eligibility of patients with suspected iNPH for shunt surgery over the past 6 years. However, there was a reduction in the use of the iNPHGLs (39.4% in 2019 vs. 45.0% in 2013) and in the knowledge of DESH (38.0% in 2019 vs. 54.0% in

TABLE 1 | Predictors of patient referral from MCDs to other hospitals when iNPH is suspected.

Explanatory variables	B	SE	Waldχ2	*p*-Value*	OR	95%CI
I used guidelines for management of iNPH.	−0.636	0.369	2.959	0.085	0.530	0.257–1.093
I am familiar with DESH.	−0.082	0.378	0.047	0.828	0.921	0.440–1.932
I am not confident in my assessment of DESH on brain MRI.	0.735	0.817	0.809	0.368	2.085	0.421–10.333
Brain MRI cannot be performed.	0.731	0.535	1.869	0.172	2.077	0.728–5.921
No physician who can perform lumbar puncture is available.	1.370	0.562	5.931	0.015	3.934	1.307–11.848
I have no knowledge of the methods or criteria for evaluating clinical symptoms in CSF tap test.	0.651	0.794	0.672	0.412	1.917	0.404–9.094
Patients are referred to neurosurgeons, but the neurosurgeons said the patients are not indicated for shunt surgery.	1.358	0.426	10.170	0.001	3.888	1.688–8.958

**Logistic regression analysis.*

B, partial regression coefficient; SE, standard error; Wald χ2, Wald χ2 statistic; OR, odds ratio; 95%CI, 95% confidence interval.

2013). The 2013 survey was conducted by the organizers of the 15th annual meeting of Japanese Society for NPH. Thus, more MCDs where diagnosis and treatment of iNPH are performed may have participated in the previous survey than in this survey. These results suggest that it is necessary to further educate physicians in MCDs on the iNPHGLs and on DESH to ensure accurate diagnosis of iNPH and to improve collaboration with neurosurgeons.

Comparison of results between the three types of MCDs revealed little difference between regional-type and collaborative-type MCDs. The percentages of administration of cognitive tests other than screening tests, brain MRI and other neuroimaging examinations, and CSF examination/CSF tap test were higher in core-type MCDs than in regional-type or collaborative-type MCDs. Further, patient referral to other hospitals (e.g., hospitals with neurosurgery departments) when iNPH was suspected was less likely in core-type MCDs than in regional-type or collaborative-type MCDs. These results are considered logical since university hospitals and general hospitals constitute core-type MCDs. However, there were no significant differences in the use of the iNPHGLs and knowledge of DESH between the three types of MCDs. Since the special role of core-type MCDs is to train human resources to treat dementia, including iNPH, it is important that the percentages of administration of CSF tap test, use of the iNPHGLs, and knowledge of DESH in core-type MCDs increase.

This study has a few limitations. First, the results were not confirmed with actual figures. Second, there may be a type 2 error in the results of the comparison between the three types of MCDs due to the small number of core-type MCDs. Third, the departments of the physicians who completed the questionnaire were not determined. Fourth, serial CSF removal in older adults with iNPH may be an alternative treatment option for those patients who refuse or have a contraindication to shunt surgery (38). However, we did not include this treatment option in our questionnaire because serial CSF removal is rarely performed in Japan. Fifth, our questionnaire might not be structured to cover all the multidisciplinary aspects of the diagnostic and therapeutic work out of iNPH. Finally, the response rate to the questionnaire survey was not high.

The outcome of shunt surgery may be improved if differential and comorbid diagnoses of iNPH are performed in more MCDs before patient referral to the neurosurgery department. Creating a collaborative relationship between physicians in MCDs and neurosurgeons will be crucial to the provision of necessary multidisciplinary care to effectively evaluate, diagnose, and treat patients with iNPH.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Japan Psychiatric Hospitals Association. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HK, MH, ST, YC, TG, and KF designed the study and supervised the data collection. HK was responsible for the statistical design of the study and for performing the statistical analysis and wrote the first manuscript draft. All authors were involved in the interpretation or presentation of the data, reviewed and revised the initial draft and subsequent versions of the report, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.810116/full#supplementary-material

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Diffusion Tensor Imaging Profiles Can Distinguish Diffusivity and Neural Properties of White Matter Injury in Hydrocephalus vs. Non-hydrocephalus Using a Strategy of a Periodic Table of DTI Elements

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Background: The aim of this study was to create a simplistic taxonomy to improve transparency and consistency in, and reduce complexity of, interpreting diffusion tensor imaging (DTI) profiles in white matter disruption. Using a novel strategy of a periodic table of DTI elements, we examined if DTI profiles could demonstrate neural properties of disruption sufficient to characterize white matter changes specific for hydrocephalus vs. non-hydrocephalus, and to distinguish between cohorts of neural injury by their differing potential for reversibility.

Methods: DTI datasets from three clinical cohorts representing pathological milestones from reversible to irreversible brain injury were compared to those of healthy controls at baseline, over time and with interventions. The final dataset comprised patients vs. controls in the following groupings: mild traumatic brain injury (mTBI), $n = 24$ vs. 27, normal pressure hydrocephalus (NPH), $n = 16$ vs. 9 and Alzheimer's disease (AD), $n = 27$ vs. 47. We generated DTI profiles from fractional anisotropy (FA) and mean, axial and radial diffusivity measures (MD, L1 and L2 and 3 respectively), and constructed an algorithm to map changes consistently to a periodic table of elements, which fully described their diffusivity and neural properties.

Results: Mapping tissue signatures to a periodic table of DTI elements rapidly characterized cohorts by their differing patterns of injury. At baseline, patients with mTBI displayed the most preserved tracts. In NPH, the magnitude of changes was dependent on "familial" DTI neuroanatomy, i.e., potential for neural distortion from risk of ventriculomegaly. With time, patients with Alzheimer's disease were significantly different to controls across multiple measures. By contrast, patients with mTBI showed both loss of integrity and pathophysiological processes of neural repair. In NPH, some patterns of injury, such as "stretch/compression" and "compression" were more reversible following intervention than others; these neural profile properties suggested "microstructural resilience" to injury.

Conclusion: Using the novel strategy of a periodic table of DTI elements, our study has demonstrated it is possible to distinguish between different cohorts along the spectrum of brain injury by describing neural profile properties of white matter disruption. Further work to contribute datasets of disease toward this proposed taxonomic framework would enhance the translatability of DTI profiles to the clinical-research interface.

Keywords: normal pressure hydrocephalus (NPH), diffusion tensor imaging (DTI), white matter, traumatic brain injury (TBI), Alzheimer's disease, injury properties

INTRODUCTION

Restoration of brain functions following injury requires an understanding of the resilience of neural tissue against pathological insults. Currently, we assess white matter tracts for microstructural damage but do not describe them in terms of their potential reversibility. Participants in longitudinal cohort studies and clinical trials undergo baseline imaging to document their structural integrity and functional connectivity. However, they may have white matter injury patterns with differing capacity for neural repair or recovery. Such patients may not exhibit equivalent responses to interventions, including drug therapies or application of novel neuroprostheses. Yet, there is no standard framework to describe cohorts by their differing white matter injuries. This gap in knowledge and such differential potential of patient cohorts are likely to have been major contributors to the failures of promising drug interventions in large-scale clinical trials across acute brain injury and neurodegenerative disease.

There is an urgent need to develop more precise imaging biomarkers for correlation with assessments of intervention. In addition, our lack of understanding of how to describe the potential responsiveness of white matter injury has implications for assessing the risks vs. benefits for specific interventions in high-risk groups, such as the elderly population. The emerging field of aging neurosurgery represents such an evolving challenge. Despite the growth of the cohort of patients above 65 years presenting for surgical intervention, a cohesive approach toward a strategy for geriatric surgical needs is lacking. Elderly patients are considered high risk and yet, demonstrate potential for recovery. Specific conditions, such as chronic subdural haematoma, spinal degenerative myeloradiculopathy and hydrocephalus, have excellent results with surgical intervention (1–3). Good outcomes may be further supported with the use of risk stratification, such as frailty and comorbidity scoring. However, continuing neurological improvement may be dependent on the capacity of white matter injury for microstructural resilience. A key gap in our approach is the paucity of tools to describe the potential for neural injury to recover from pathological insults, with or without intervention. In this regard, it may be helpful to study Normal pressure hydrocephalus (NPH) as a model of reversible brain injury.

Classically described by Adams et al. (4) as a triad of gait disturbance, cognitive decline and urinary incontinence, NPH attracts up to 96% chance subjective improvement and 83% chance improvement on timed walk test at 6 months (3). Although increasing age is not a prognostic factor, various factors limit consistently good outcomes across patient groups. Challenges include developing more reliable non-invasive imaging methods for higher diagnostic certainty, with a greater capacity for predicting shunt-responsiveness (5). Symptoms attributed to the NPH triad also appear in other hydrocephalic conditions, in a spectrum from compensated to subacute obstructive forms, for which differing surgical strategies may be optimal (6). Whilst NPH is characterized by its distinctive gross ventriculomegaly, degree of ventricular dilatation is neither predictive of clinical nor functional improvement. In some cases, but not all, NPH is associated with defective cerebrospinal fluid (CSF) circulation and pressure-volume compensation. In such Classic NPH subtypes, interrogation of cerebral hydrodynamics via a CSF infusion test can be helpful in predicting improvement after shunting (7, 8). However, a further complication exists in the form of overlay with comorbid diseases. Distinctive radiological features in NPH, such as ventriculomegaly, may be common to hydrocephalus, brain atrophy as well as neurodegeneration. Neurodegenerative disorders, including Alzheimer's disease (AD), frequently co-present in the cohort with NPH symptoms. In our previous work, we have described a subtype we term "Complex NPH." This challenging cohort presents with overlay from multiple co-morbidities co-existing, particularly vascular risk burden and neurodegenerative diseases; patients still show capacity for CSF responsiveness, but testing is difficult (9). Such subtypes of Complex NPH, or patients with frailty, may benefit from screening *in vivo* to characterize the reversibility potential of their neural injury prior to invasive CSF testing.

The study of NPH is confounded by multiple theories of pathogenesis, yet unresolved. However, many major hypotheses streams, such as tissue distortion and vascular ischaemia, converge in white matter dysfunction (5). Shunt-responsive NPH patients may be demonstrating a form of 'microstructural resilience'; their white matter exhibits potential to recover from injury. Diffusion tensor imaging (DTI), has been established as a robust and reliable way of interrogating tissue microstructure, with both the capacity to document patterns of white matter injury in NPH, as well as reversibility post-shunting (10). Whilst this technique is well-accepted in conditions such as stroke, tumors and traumatic brain injury (11–15), and readily available in academic clinical centers, there are technical challenges to overcome. DTI metrics are "semi-quantitative"; dependent on (i) machine factors–site/scanner-specific, b values, number of diffusion directions, (ii) biological confounders–multiple pathophysiological processes co-existing, crossing

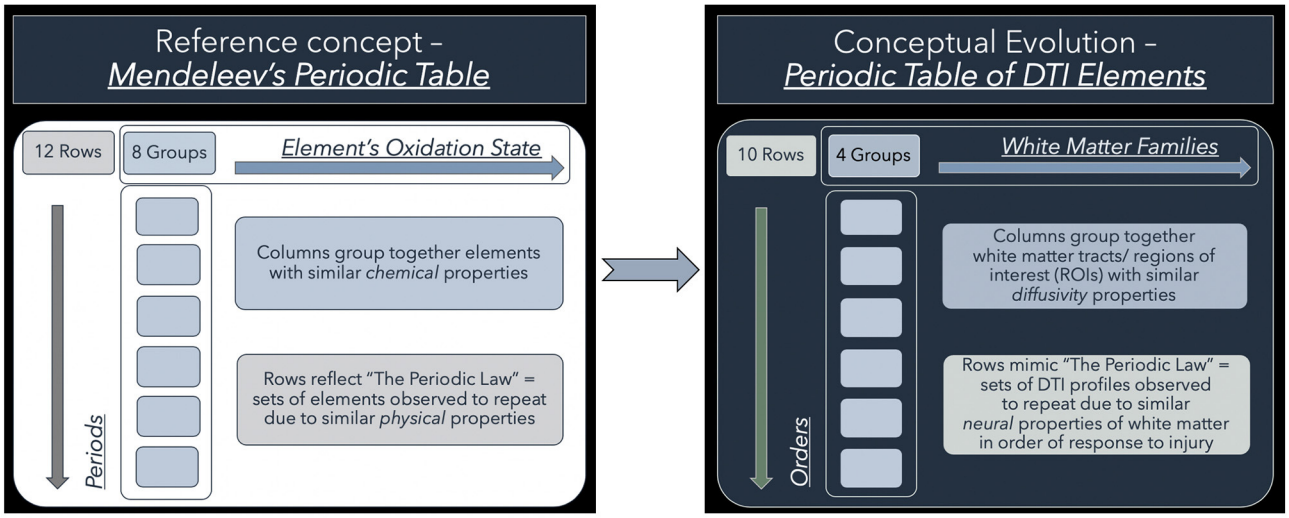

FIGURE 1 | Conceptual evolution from Mendeleev's Periodic Table to the current work. The modern periodic table in chemistry is based on atomic number. This differs from Mendeleev's original concept, which arranged the elements according to their similar chemical and physical properties. Mendeleev sorted the elements largely by atomic mass but where there were tensions in the order, he prioritized groups by their shared properties. Similarly, we have used shared *"diffusivity"* properties to group white matter tracts/ regions of interest (ROIs) into columns. This grouping into *"White matter families"* reflects their DTI neuroanatomy, changes in diffusivity profiles due to their differential risk from progressive ventriculomegaly. Mimicking the concept of periods, we have arranged sets of DTI profiles observed to repeat due to similar *"neural"* properties. These rows, which we have termed "*Orders*," reflect commonly occurring DTI profiles seen in white matter in response to injury. Note that the Order from I to X here reflects a predicted trend from reversible to irreversible injury. This is arbitrarily defined and could equally work in reverse order as long as the sequence is maintained.

TABLE 1 | Demographics for cohorts.

	Mild traumatic brain injury cohort		Normal pressure hydrocephalus cohort		Alzheimer's disease cohort	
	Healthy controls	mTBI	Healthy controls*	NPH	Healthy controls	AD
n	27	24	9	16	47	27
Age (Mean ± SD)	29.0 ± 6.76	28.6 ± 9.34	70.0	74.7 ± 5.88	72.9 ± 6.04	75.6 ± 8.52
Age (Range)	18–49	18–50	N.A.	60–84	59.9–89.1	61.8–90.4
Sex (% male)	77.8	83.3	44.4	62.5	46.8	74.1

**Demographics reported are from published data (10). N.A., data not available.*

fibers, ongoing insults/ recovery across timepoints and (iii) interpretations–post-processing algorithms and assumptions, handling of DTI conflicts. In response, there has been increasing development of higher scanning specifications and advanced imaging processing methodologies. However, such strategies reduce its attractiveness as a rapid, first-line screening tool at the clinical-research interface.

To address this conundrum, we have previously shown the utility of simplistic ROI-based DTI profiles in an at-risk model of white matter injury in NPH (10). DTI profiles are a methodology of distilling the complexity of changes, occurring across multiple DTI measures concurrently, into their most simplistic, graphical forms (9). DTI profiles display both the magnitude and direction of predominant changes to describe patterns of white matter injury in terms of their diffusion morphology. Here, we present a further contribution toward this concept. We found that, despite conflicts in DTI measures, we could observe recurring properties in DTI profiles of common patterns of white matter injury seen across cohorts. Inspired by the discussions surrounding the recent 150th anniversary of Mendeleev's periodic table in chemistry, we examined whether our observations would benefit from being organized into such an array. Mendeleev arranged his table by atomic weight, according to recurring chemical and physical properties of elements and confirmed the validity of the Periodic Law (16, 17). We believed it was possible to evolve from this concept to the notion of arranging recurring DTI profiles in a similar way (**Figure 1**). We therefore proposed a novel arrangement of white matter injury by their familial DTI neuroanatomy, rather than by functional considerations. As we based our table on the periodicity of "diffusivity" and "neural" properties of white matter in response to injury, we termed this a "*periodic table of DTI elements*." The aims of this study were to (1) examine if DTI profiles could distinguish white matter injury in hydrocephalus vs. non-hydrocephalus and if so, (ii) create a simplified taxonomy of DTI interpretation by using the strategy of a "*periodic table of DTI elements*."

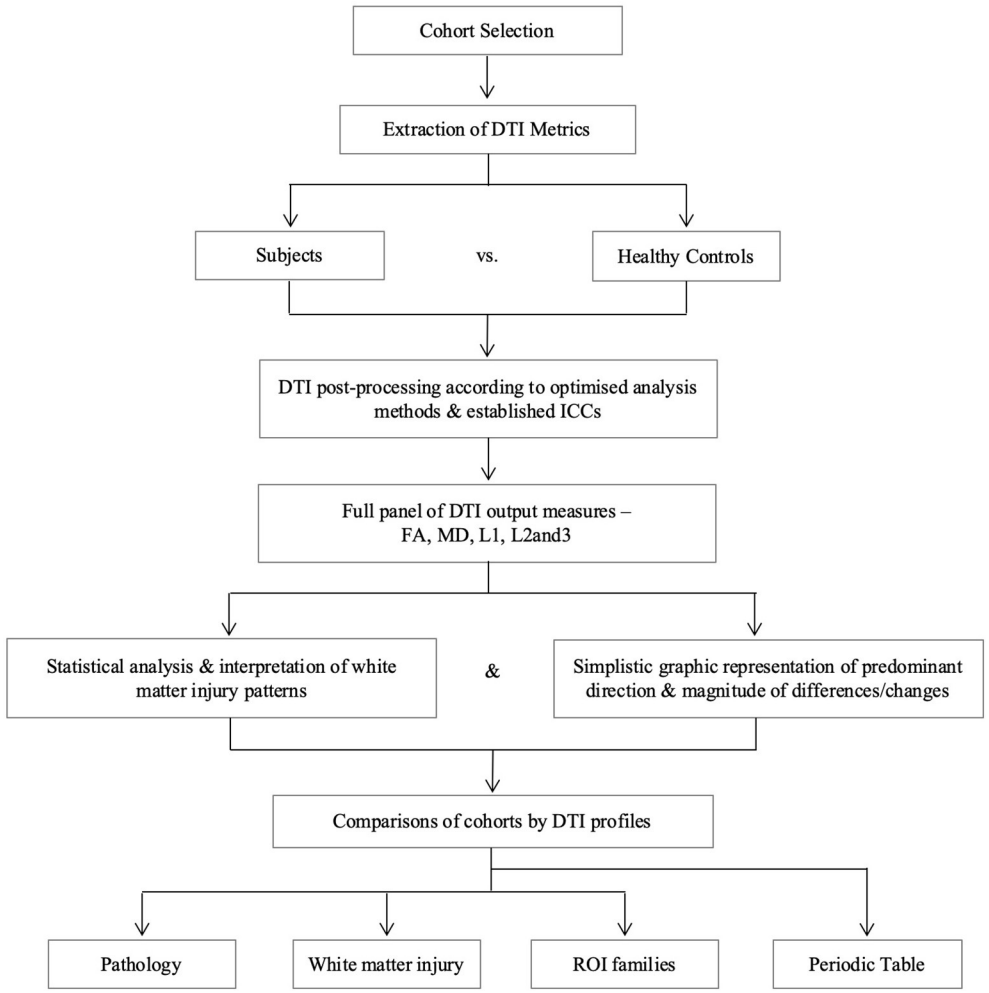

FIGURE 2 | Overview of study methodology. We refer to axial and radial diffusivities by their eigenvalues for clarity (L1 and L2 and 3, respectively), to distinguish these measures from terms we use for pathological cohorts. DTI, diffusion tensor imaging; FA, fractional anisotropy; ICC, intraclass correlation coefficient; L1, axial diffusivity, L2 and 3, radial diffusivity; MD, mean diffusivity; ROI, region of interest.

METHODS

We examined DTI profiles from a cohort of Classic NPH (ClNPH) patients, the purer form of shunt-responsive NPH, and compared them to patients with mild traumatic brain injury (mTBI; who exhibit both trajectories of recovery and persisting neurological deficits) and patients with Alzheimer's disease (AD; an exemplar cohort of irreversible brain injury due to progressive neurodegeneration). The utility of DTI examination has been shown in all three conditions; interpretations of white matter injury patterns are known (10–12, 18–23).

DTI metrics for the various clinical cohorts mTBI, ClNPH and AD–were obtained from international datasets for which methodology is well-established. Cohort demographics are described in **Table 1**. The mTBI cohort from the University of Malaya comprised 62 patients who presented with mTBI and 27 age-matched healthy controls (21 males and 6 females; mean age 29.0 years). In this analysis, we included only the 24 mTBI patients (20 males and 3 females; mean age 28.6 years) who had baseline DTI measures and 6-month follow-up data available. This dataset has been expanded from the previously published series (61 patients and 19 controls) (24), in which DTI profiles were not examined. Pre- and post-operative DTI measures for the ClNPH group, which included 16 patients with NPH (10 males and 6 females; mean age 74.7 years) and 9 healthy controls (4 males and 5 females; mean age 70.0 years), were derived from a cohort we have previously published from the University of Cambridge (10). We have previously demonstrated the use of DTI profiles in the ClNPH group (9, 10); we have expanded on the published data by including 6-month post-operative data in our analysis. Data for the AD cohort were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) and included 27 patients with AD baseline and 12-month follow-up DTI measures available (20 males and 7 females; mean age 75.6 years) and 47 healthy controls (22 males and 25 females; mean age 72.9 years). Using data expanded from

FIGURE 3 | (A) Midline (BCC) and **(B)** lateral (ILF or PTR) ROI families at baseline. At baseline, percentage differences in DTI measures of clinical cohorts are compared against corresponding healthy controls, presented as Pareto graphs and bar charts. In Pareto graphs, positive values are automatically arranged sequentially, in order of highest to lowest magnitude of differences/changes. *Indicates a significant Difference between the clinical cohort and healthy controls at $p < 0.05$.

FIGURE 4 | (A) Fronto-temporal (IFO/UNC) and **(B)** remote functional (PLIC) ROI families at baseline. At baseline, percentage differences in DTI measures of clinical cohorts are compared against corresponding healthy controls, presented as Pareto graphs and bar charts. In Pareto graphs, positive values are automatically arranged sequentially, in order of highest to lowest magnitude of differences/changes. * indicates a significant difference between the clinical cohort and healthy controls at $p < 0.05$.

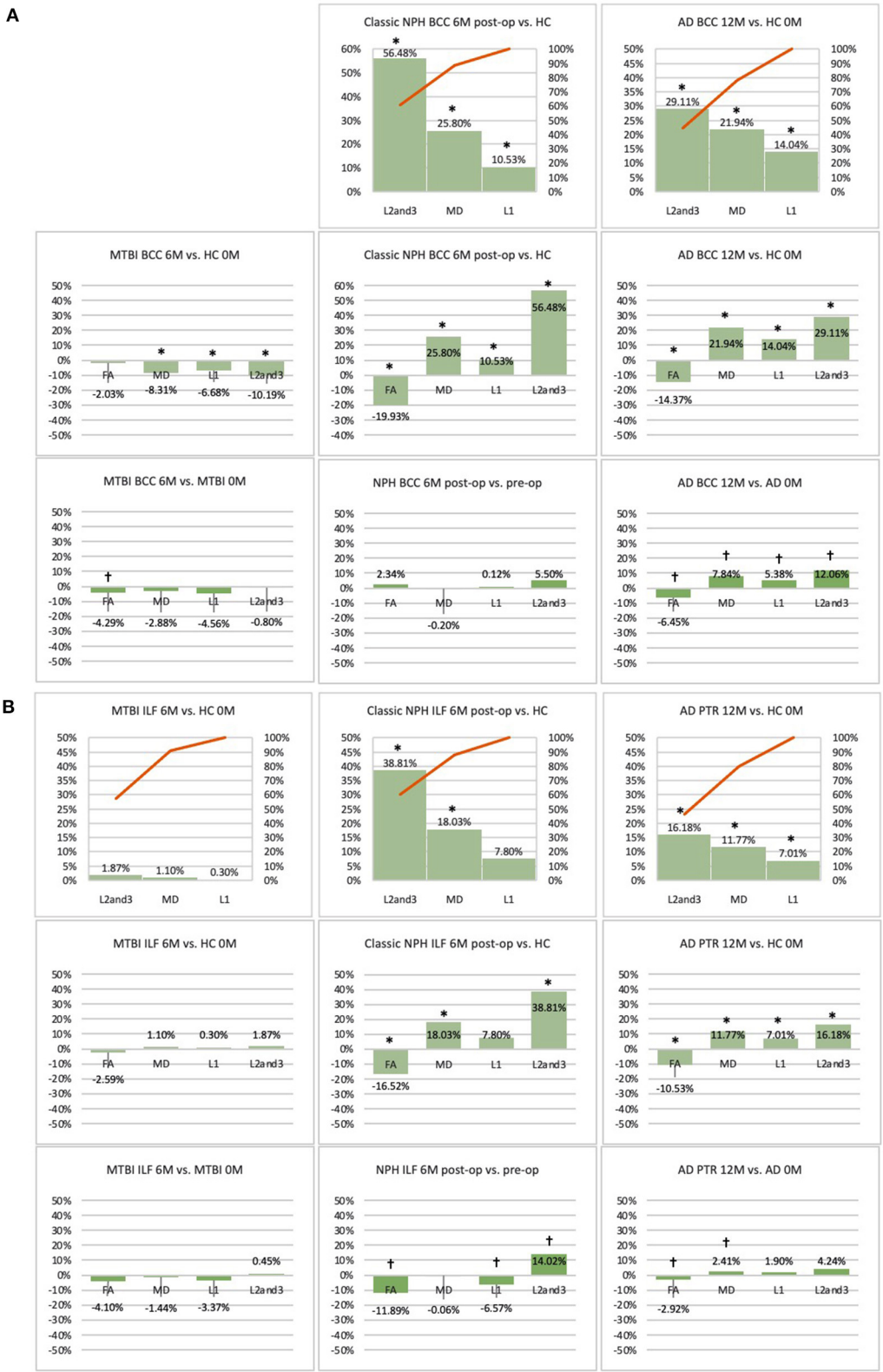

FIGURE 5 | (A) Midline (BCC) and **(B)** lateral (ILF or PTR) ROI families at follow-up. At 6 or 12-month follow-up, percentage changes in DTI measures of clinical cohorts are compared against corresponding healthy controls at baseline, presented as Pareto graphs and bar charts. At this time point, patients are also compared to themselves at baseline, presented as bar charts. We observed that, in MTBI, the BCC ROI at 6-month follow-up demonstrated an unique profile (significant decreases in mean, axial and radial diffusivity measures in the context of a non-significant decrease in FA). We suggest this is possibly indicative of processes seen in the

(Continued)

FIGURE 5 | spectrum of neural repair. At this timepoint in NPH, we found changes driven by a disproportionate increase in radial diffusivity, a DTI profile reported in other subtypes of post-operative hydrocephalus. In AD at 12-month follow-up, we found global significant deterioration across mean, axial and radial diffusivity measures, consistent loss of integrity/atrophy. By contrast, we observed that, for the ILF or PTR ROI, there was preservation of white matter tracts in MTBI at 6-month follow-up. At this timepoint in NPH, we found changes indicative of improvement in compression (a significant increase in radial diffusivity but in the context of a decrease in axial diffusivity). In AD at 12-month follow-up, we observed significant worsening of white matter due to increase in loss of integrity/atrophy. *Indicates a significant Difference between the clinical cohort and healthy controls at $p < 0.05$. †Indicates a significant Change in the clinical cohort across timepoints at $p < 0.05$.

published series was critical to testing the novel strategy of the periodic table of DTI elements as interpretation of injury patterns had already been established.

Approval for individual studies was obtained from local or institutional ethics committees. Written informed consent was obtained from all subjects or legal representatives, if appropriate, as required by local ethics committees.

DTI Acquisition

The mTBI cohort from the University of Malaya was imaged on a 3T MRI scanner (Signa HDx; General Electric, Harvey, IL) using an eight-channel head coil (24). The DTI sequence was obtained using these parameters: TR = 13,000 ms; TE = 81.2 ms; FOV = 24 mm; matrix = 128 x 128; slice thickness = 3.0 mm; 32 directions; diffusion weighted factor, b = 700 s/mm^2; and image scan time of 7 min 22 s.

MRI for the NPH cohort was performed on a 3T Siemens Tim Trio using a 12 channel head matrix radio frequency receive coil (10). The DTI sequence was acquired by using a spin echo diffusion weighted echo planar imaging sequence with the following parameters: TR/TE, 8,300 ms/98 ms, matrix dimensions 96 x 96, FOV 192 x 192, slice thickness 2 mm giving a voxel size of 2 x 2 x 2 mm. Diffusion weighted images were acquired in 12 non-collinear directions each at 5 b-values of 350, 650, 1,000, 1,300 and 1,600 s/mm^2, along with 4 b-0 images.

The AD cohort from the ADNI were scanned on 3T GE Medical Systems scanners at 14 acquisition sites in North America (25). Diffusion weighted images were acquired with the following parameters: 256 × 256 matrix; voxel size: 2.7 × 2.7 × 2.7 mm^3; TR = 9,000 ms; scan time = 9 min. Forty-six separate images were acquired for each DTI scan: 5 T2-weighted images with no diffusion sensitization (b0 images) and 41 diffusion-weighted images (b = 1,000 s/mm^2).

Pre-processing and ROI Analysis

Pre-processing, image registration, and analysis for the mTBI dataset was carried out with FSL and AFNI software packages. Initial preprocessing involved corrections for head movement and eddy currents, brain tissue extraction, and fitting of the diffusion tensor model. The FSL tool fnirt was used for non-linear special registration of each subject to the FMRIB58_FA standard-space image. Predefined ROIs for each individual subject were mapped with the AFNI 3dROIstats tool and median FA, MD, L1, and L2 and 3 values obtained for each tract (24).

In the NPH dataset, the FDT diffusion toolbox in FSL analysis tools was used for eddy current correction and DTI pre- and post-processing. Co-registration of the structural 3D volumetric image and DTI images was performed using SPM5. MPRAGE images were re-sliced to match the DTI image space using the s0 volume (the b = 0 volume with optimal signal-to-noise ratio). A DTI-based white matter tract atlas was used for anatomical identification of key fiber bundles and ROIs were placed on the structural images and applied to co-registered DTI files (10).

ADNI DTI metrics used in this paper were the UCLA DTI ROI summary measures for ADNIGO and ADNI2. Pre-processing steps for head motion and eddy current correction and removal of non-brain tissue were done using FSL. T1-weighted anatomical images were aligned to a standard brain template; skull-stripped b0 images were aligned and then registered to their respective T1-weighted scans. A study-specific template was created, each individual subject's initial FA map elastically registered to the template, and resulting deformation fields applied to diffusivity maps to align them to the same coordinate space. The mean of all voxels from each of the regions of interest from the atlas were obtained (25).

Generation of DTI Profiles

DTI region of interest (ROI) values for fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (L1), and radial diffusivity (L2 and 3) obtained using established methodology were used in this analysis (10, 24, 25). Axial and radial diffusivities are referred to by their eigenvalues (L1 and L2 and 3, respectively) to avoid confusion with acronyms for pathology, e.g., AD for Alzheimer's Disease. Previous work in the NPH study confirmed no significant differences in right- and left-sided ROIs, therefore right-sided tracts were used for this study to avoid over-averaging across multiple ROIs and within groups. However, as midline tracts were acquired as single ROIs for the NPH and mTBI groups, the averaged value of right and left body and genu of the corpus callosum in the AD group was used for comparison. We generated DTI profiles as per the workflow in **Figure 2**. Here, we preferred Pareto graphs; this graphical format automatically displays positive DTI measures in order of decreasing magnitude of changes, thereby allowing concurrent examination of both predominant direction and magnitude of differences. To reflect smaller, and usually negative changes in FA, we also correlated findings seen on the Pareto graphs with bar charts and standard statistical analyses (**Figures 3–6**, **Tables 2**, **3**).

Arrangement of White Matter Injury by DTI Neuroanatomy and Profile Properties

We observed recurring common properties in DTI profiles across the spectrum of brain injury and developed a novel arrangement of white matter injury as a "periodic table of DTI elements" (**Figure 1**, **Table 4**). We grouped ROIs into columns of "white matter families" according to the distortion potential to their DTI neuroanatomy from risk of ventriculomegaly (**Figure 7**). We then determined the "Order" of DTI profiles according to

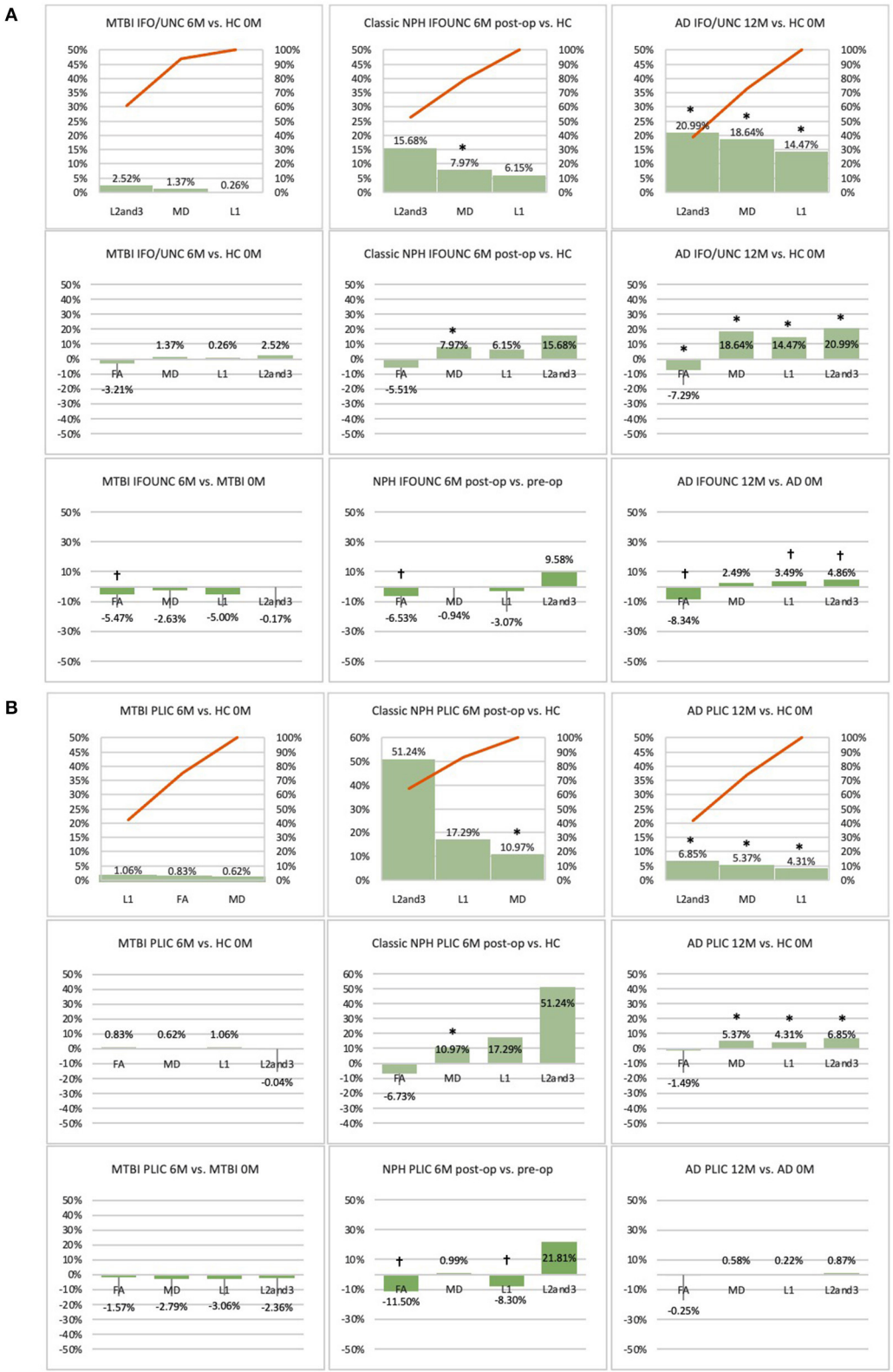

FIGURE 6 | (A) Fronto-temporal (IFO/UNC) and **(B)** remote functional (PLIC) ROI families at follow-up. At 6 or 12-month follow-up, percentage changes in DTI measures of clinical cohorts are compared against corresponding healthy controls at baseline, presented as Pareto graphs and bar charts. At this time point, patients are also compared to themselves at baseline, presented as bar charts. We observed that, in MTBI, the IFO/UNC combination ROI at 6-month follow-up demonstrated a pattern of distortion/oedema (predominant increase in radial diffusivity with a significant decrease in FA), whereas in NPH, we found changes consistent with

(Continued)

FIGURE 6 | non-significant improvement in distortion of the tract (increase in radial diffusivity but in the context of decreases in axial and mean diffusivities). In AD at 12-month follow-up, we found global deterioration across all diffusivity measures (with a significant decrease in FA) consistent with progressive neurodegeneration. By contrast, we observed that, for the PLIC ROI, there was preservation of white matter tracts in MTBI at 6-month follow-up and in NPH, improvement in compression (increase in radial diffusivity but in the context of a significant decrease in axial diffusivity). In AD at 12-month follow-up, we observed non-significant worsening of white matter due to likely neurodegeneration. *Indicates a significant Difference between the clinical cohort and healthy controls at $p < 0.05$. †Indicates a significant Change in the clinical cohort across timepoints at $p < 0.05$.

predicted reversibility of white matter injury. We reviewed the literature and considered references across multiple neurological conditions of interest that listed the full panel of DTI measures (FA, MD, L1, and L2 and 3), and where pathophysiological findings of disease correlated with DTI interpretation. Following multiple iterations of the initial prototype to accommodate findings from the literature across pathologies, we determined the final hierarchical algorithm for mapping results to the periodic table (**Table 5**, **Figure 8**).

Statistical Analysis

Statistical analyses were conducted using SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, USA). Data is reported as mean ± standard deviation, unless otherwise stated. Independent samples *t*-tests were used to test for differences between clinical cohorts and healthy controls, and paired samples *t*-tests for changes in clinical cohorts over time. All statistical tests were two-tailed, and significance level was set at $p < 0.05$.

RESULTS

DTI Profiles Derived at Baseline Across the Spectrum of Brain Injury

At baseline, it was possible to distinguish patient cohorts vs. healthy controls in NPH and AD using DTI profiles alone. When comparing differences in AD patients vs. controls, white matter families in the midline, lateral to the ventricles and remote functional tracts showed evidence of oedema (**Figures 3**, **4**, **Tables 2**, **4**; Order VII). The magnitude of differences was greatest for fronto-temporal tracts, described by Order VIII (white matter at risk) confirming its relevance toward AD pathology.

By contrast, the reverse was true for NPH, where magnitude of changes were worst for white matter tracts in the midline and lateral to the ventricles. The most preserved white matter families were remote functional, followed by fronto-temporal tracts (**Figures 3**, **4**, **Tables 2**, **4**). It was possible to reproduce at least three distinct patterns of white matter injury. The body of the corpus callosum was characterized by Order VI; the inferior longitudinal fasciculus showed worse changes at Order VII; stretch/oedema. By contrast, fronto-temporal and remote functional tracts displayed differences consistent with stretch/compression and compression (Orders V and IV, respectively).

Patients with mTBI displayed white matter tracts that were entirely preserved at baseline compared to healthy controls across all white matter families tested (**Figures 3**, **4**, **Tables 2**, **4**; Order I). By comparison, we further generated DTI profiles from a published dataset of severe TBI (sTBI) patients undergoing normobaric hyperoxia (Veenith et al. (77), an independent study coincidentally performed at the same site as the NPH cohort). We have represented this as Order X due to the life-threatening nature of acute brain injury (**Table 4**); this does not preclude a change to a more reversible Order with time or following intervention, using the strategy of the *periodic table of DTI elements*. There were no follow-up results presented in this published dataset.

The Effect of Time and Intervention on DTI Profiles After Brain Injury

Using the cohort with AD from ADNI, we found that it was possible to demonstrate the effect of progression of neurodegeneration. At 12 months' follow-up, the white matter changes progressed in all midline, lateral and fronto-temporal tracts tested (**Figures 5**, **6**, **Tables 2–4**). When patients were compared to themselves, changes in the midline and fronto-temporal tracts confirmed neuronal degeneration (AD^{12C}, Order IX; **Figures 5**, **6**). For tracts lateral to the ventricles, the posterior thalamic radiation showed evidence of loss of integrity/ atrophy (AD^{12C}, Order VIII. Only remote functional tracts showed no significant deterioration between cohorts (AD^{12C}, Order I), although the cohort at 12 months remained severely disrupted compared to controls at baseline.

In NPH, at 6 months, differences driven by radial diffusivity that were highly disproportionate to other measures remained despite intervention (Order VI). This DTI profile was common to all post-operative white matter families, suggesting that it may be a DTI tissue signature of shunted hydrocephalus. In tracts midline to the ventricles, the pattern of distortion/ oedema (Order VI) was not amenable to improvement. However, white matter families with DTI profiles of stretch/oedema, stretch/compression and compression showed improvement in compression ($ClNPH^{6C}$, Order III).

Interestingly, patients with mTBI, who had uniformly displayed preserved white matter tracts compared to controls at baseline, demonstrated two contrasting new patterns. Changes in fronto-temporal tracts in patients at 6 months' follow-up vs. themselves at baseline were consistent with Order IX, suggesting neuronal degeneration (**Figure 6**, **Tables 3**, **4**). In the midline tracts, changes evolved at 6 months consistent with hypothesized mechanisms of neural repair (**Figure 5**, **Tables 3**, **4**; Order II). **Figure 8** demonstrates DTI profiles mapped onto the Periodic Table.

DISCUSSION

In this paper, we examined the utility of creating a simplified taxonomy, to promote transparency and consistency in, and reduce complexity of, interpreting DTI profiles across a spectrum

TABLE 2 | Comparison of example DTI region of interest values between clinical cohorts and healthy controls.

DTI Regions of Interest	Example ROI	Cohort	Time-point	*n*	FA	% difference*	*p*-value*	MD (10^{-4} mm^2/s)	% difference*	*p*-value*	L1 (10^{-4} mm^2/s)	% difference*	*p*-value*	L2 and3 (10^{-4} mm^2/s)	% difference*	*p*-value*
Midline	BCC	HC	0 M	27	0.508 ± 0.032			9.704 ± 0.76			15.626 ± 0.98			6.742 ± 0.75		
right-left tracts		mTBI	0 M	24	0.520 ± 0.065	+2.4	0.418	9.162 ± 1.07	−2.6	**0.040**	15.280 ± 2.21	−1.1	0.465	6.104 ± 0.70	−4.2	**0.003**
adjacent to		mTBI	6 M	24	0.498 ± 0.057	−2.0	0.440	8.898 ± 0.32	−8.3	**<0.001**	14.583 ± 0.87	−6.7	**<0.001**	6.055 ± 0.45	−10.2	**<0.001**
ventricles		HC	0 M	9	0.612 ± 0.090			7.416 ± 1.08			13.072 ± 1.19			4.589 ± 1.29		
e.g., BCC,		NPH Pre-op	0 M	16	0.478 ± 0.097	−21.8	**0.003**	9.348 ± 1.45	+26.0	**0.002**	14.430 ± 1.50	+10.4	**0.029**	6.807 ± 1.67	+48.3	**0.002**
GCC		NPH Post-op	6 M	16	0.490 ± 0.104	−19.9	**0.007**	9.329 ± 1.26	+25.8	**0.001**	14.448 ± 1.22	+10.5	**0.012**	7.181 ± 2.30	+56.5	**0.005**
		HC	0 M	47	0.387 ± 0.048			12.560 ± 1.18			17.958 ± 1.14			9.862 ± 1.26		
		AD	0 M	27	0.355 ± 0.053	−7.7	**0.008**	14.202 ± 1.58	+11.3	**<0.001**	19.434 ± 1.38	+6.6	**<0.001**	11.363 ± 1.83	+12.1	**0.001**
		AD	12 M	27	0.332 ± 0.075	−14.4	**<0.001**	15.315 ± 3.30	+21.9	**<0.001**	20.480 ± 2.65	+14.0	**<0.001**	12.733 ± 3.65	+29.1	**<0.001**
Lateral to	ILF/PTR	HC	0 M	27	0.416 ± 0.052			8.728 ± 0.41			12.842 ± 0.76			6.671 ± 0.51		
ventricles (long		mTBI	0 M	24	0.423 ± 0.077	+1.0	0.721	8.953 ± 1.08	+2.6	0.320	13.329 ± 2.77	+3.3	0.385	6.765 ± 0.45	+2.0	0.490
or short)		mTBI	6 M	24	0.405 ± 0.051	−2.6	0.457	8.824 ± 0.32	+1.1	0.361	12.880 ± 0.81	+0.3	0.863	6.796 ± 0.41	+1.9	0.344
anterior-posterior		HC	0 M	9	0.575 ± 0.070			6.610 ± 1.14			11.302 ± 1.69			4.264 ± 0.95		
		NPH Pre-op	0 M	16	0.545 ± 0.051	−5.2	0.233	7.807 ± 0.69	+18.1	**0.003**	13.040 ± 1.38	+15.4	**0.010**	5.191 ± 0.55	+21.7	**0.005**
e.g. ILF, ATR		NPH Post-op	6 M	16	0.480 ± 0.074	−16.5	**0.005**	7.802 ± 0.62	+18.0	**0.002**	12.184 ± 1.20	+7.8	0.141	5.919 ± 1.24	+38.8	**0.002**
tracts, PTR,		HC	0 M	47	0.385 ± 0.033			9.212 ± 0.87			13.172 ± 0.92			7.228 ± 0.88		
CGC		AD	0 M	27	0.355 ± 0.028	−5.1	**<0.001**	10.054 ± 0.86	+6.8	**<0.001**	13.832 ± 0.97	+3.7	**0.005**	8.055 ± 0.98	+7.8	**<0.001**
		AD	12 M	27	0.345 ± 0.031	−10.5	**<0.001**	10.296 ± 1.08	+11.8	**<0.001**	14.095 ± 1.10	+7.1	**<0.001**	8.397 ± 1.09	+16.2	**<0.001**
Fronto-	IFO/ UNC	HC	0 M	27	0.434 ± 0.035			9.116 ± 0.32			13.714 ± 0.49			6.816 ± 0.40		
temporal,		mTBI	0 M	24	0.444 ± 0.056	+1.4	0.428	9.491 ± 1.09	+2.3	0.095	14.473 ± 2.41	+3.0	0.116	7.000 ± 0.56	+1.5	0.181
multi-		mTBI	6 M	24	0.420 ± 0.034	−3.2	0.160	9.241 ± 0.34	+1.4	0.180	13.749 ± 0.53	+0.3	0.804	6.988 ± 0.41	+2.5	0.139
directional		HC	0 M	9	0.399 ± 0.048			6.550 ± 0.38			9.499 ± 0.57			5.075 ± 0.43		
tracts		NPH Pre-op	0 M	16	0.403 ± 0.059	+1.1	0.852	7.140 ± 0.42	+9.0	**0.002**	10.402 ± 0.75	+9.5	**0.005**	5.358 ± 0.74	+5.6	0.306
e.g. IFO, UNC		NPH Post-op	6 M	16	0.377 ± 0.054	−5.5	0.319	7.072 ± 0.47	+8.0	**0.009**	10.083 ± 0.73	+6.1	0.051	5.871 ± 1.10	+15.7	0.050
		HC	0 M	47	0.271 ± 0.030			8.988 ± 1.02			11.581 ± 1.08			7.742 ± 1.01		
		AD	0 M	27	0.274 ± 0.038	+0.2	0.697	10.404 ± 1.33	+14.8	**<0.001**	12.810 ± 1.40	+9.5	**<0.001**	8.933 ± 1.39	+13.4	**<0.001**
		AD	12 M	27	0.251 ± 0.031	−7.3	**0.009**	10.664 ± 1.41	+18.6	**<0.001**	13.257 ± 1.39	+14.5	**<0.001**	9.367 ± 1.44	+21.0	**<0.001**
Remote	PLIC	HC	0 M	27	0.604 ± 0.039			8.350 ± 0.24			14.928 ± 0.67			5.063 ± 0.35		
functional tracts		mTBI	0 M	24	0.618 ± 0.046	+1.7	0.223	8.644 ± 1.12	+1.6	0.190	15.563 ± 1.99	+2.3	0.125	5.183 ± 0.76	+0.5	0.463
distorted by		mTBI	6 M	24	0.609 ± 0.032	+0.8	0.625	8.403 ± 0.24	+0.6	0.444	15.087 ± 0.45	+1.1	0.332	5.061 ± 0.34	0.0	0.983
ventricles,		HC	0 M	9	0.713 ± 0.064			5.350 ± 0.30			9.677 ± 3.40			2.621 ± 0.39		
superior-		NPH Pre-op	0 M	16	0.751 ± 0.034	+5.3	0.063	5.879 ± 0.44	+9.9	**0.004**	12.377 ± 1.01	+27.9	**0.006**	3.255 ± 2.01	+24.2	0.392
inferior		NPH Post-op	6 M	16	0.665 ± 0.077	−6.7	0.122	5.937 ± 0.54	+11.0	**0.007**	11.350 ± 0.99	+17.3	0.075	3.964 ± 2.13	+51.2	0.094
e.g., PLIC,		HC	0 M	47	0.525 ± 0.033			7.182 ± 0.47			11.950 ± 0.62			4.791 ± 0.46		
CST		AD	0 M	27	0.518 ± 0.032	−0.4	0.415	7.524 ± 0.45	+3.3	**0.003**	12.437 ± 0.73	+3.1	**0.003**	5.075 ± 0.49	+3.6	**0.014**
		AD	12 M	27	0.517 ± 0.035	−1.5	0.346	7.568 ± 0.45	+5.4	**0.001**	12.464 ± 0.56	+4.3	**0.001**	5.120 ± 0.49	+6.9	**0.005**

ATR, anterior thalamic radiation; BCC, body of the corpus callosum; CGC, cingulum; CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; GCC, genu of the corpus callosum; HC, healthy controls; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; L1, axial diffusivity, L2 and 3, radial diffusivity; MD, mean diffusivity; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; UNC, uncinate fasciculus.

** Percentage differences and p-values given are for Differences between clinical cohorts compared against healthy controls. The bold values represent significant p values at $\alpha < 0.05$.*

TABLE 3 | Comparison of example DTI region of interest values within clinical cohorts at baseline and at 6 or 12-month follow-up.

DTI Regions of Interest	Example ROI	Cohort	Time-point	n	FA	% change	*p*-value	MD (10^{-4} mm^2/s)	% change	*p*-value	L1 (10^{-4} mm^2/s)	% change	*p*-value	L 2and 3 (10^{-4} mm^2/s)	% change	*p*-value
Midline right-left tracts adjacent to ventricles e.g., BCC, GCC	BCC	mTBI	0 M	24	0.520 ± 0.065	−4.3	**0.022**	9.162 ± 1.07	−2.9	0.246	15.280 ± 2.21	−4.6	0.137	6.104 ± 0.70	−0.8	0.681
			6 M	24	0.498 ± 0.057			8.898 ± 0.32			14.583 ± 0.87			6.055 ± 0.45		
		NPH Pre-op	0 M	16	0.478 ± 0.097	+2.3	0.601	9.348 ± 1.45	−0.2	0.954	14.430 ± 1.50	+0.1	0.959	6.807 ± 1.67	+5.5	0.486
		NPH Post-op	6 M	16	0.490 ± 0.104			9.329 ± 1.26			14.448 ± 1.22			7.181 ± 2.30		
		AD	0 M	27	0.355 ± 0.053	−6.5	**0.006**	14.202 ± 1.58	+7.8	**0.014**	19.434 ± 1.38	+5.4	**0.010**	11.363 ± 1.83	+12.1	**0.013**
			12 M	27	0.332 ± 0.075			15.315 ± 3.30			20.480 ± 2.65			12.733 ± 3.65		
Lateral to ventricles (long or short) anterior-posterior e.g., ILF, ATR tracts, PTR, CGC	ILF/PTR	mTBI	0 M	24	0.423 ± 0.077	−4.1	0.133	8.953 ± 1.08	−1.4	0.604	13.329 ± 2.77	−3.4	0.438	6.765 ± 0.45	+0.5	0.743
			6 M	24	0.405 ± 0.051			8.824 ± 0.32			12.880 ± 0.81			6.796 ± 0.41		
		NPH Pre-op	0 M	16	0.545 ± 0.051	−11.9	**0.002**	7.807 ± 0.69	−0.1	0.981	13.040 ± 1.38	−6.6	**0.037**	5.191 ± 0.55	+14.0	**0.030**
		NPH Post-op	6 M	16	0.480 ± 0.074			7.802 ± 0.62			12.184 ± 1.20			5.919 ± 1.24		
		AD	0 M	27	0.355 ± 0.028	−2.9	**<0.001**	10.054 ± 0.86	+2.4	**0.009**	13.832 ± 0.97	+1.9	0.127	8.055 ± 0.98	+4.2	0.054
			12 M	27	0.345 ± 0.031			10.300 ± 1.08			14.095 ± 1.10			8.400 ± 1.09		
Fronto-temporal, multi-directional tractse.g., IFO, UNC	IFO/ UNC	mTBI	0 M	24	0.444 ± 0.056	−5.5	**0.032**	9.491 ± 1.09	−2.6	0.306	14.473 ± 2.41	−5.0	0.180	7.000 ± 0.56	−0.2	0.914
			6 M	24	0.420 ± 0.034			9.241 ± 0.34			13.749 ± 0.53			6.988 ± 0.41		
		NPH Pre-op	0 M	16	0.403 ± 0.059	−6.5	**0.032**	7.140 ± 0.42	−0.9	0.567	10.402 ± 0.75	−3.1	0.073	5.358 ± 0.74	+9.6	0.148
		NPH Post-op	6 M	16	0.377 ± 0.054			7.072 ± 0.47			10.083 ± 0.73			5.871 ± 1.10		
		AD	0 M	27	0.274 ± 0.038	−8.3	**0.013**	10.404 ± 1.33	+2.5	0.118	12.810 ± 1.40	+3.5	**0.010**	8.933 ± 1.39	+4.9	**0.018**
			12 M	27	0.251 ± 0.031			10.664 ± 1.41			13.257 ± 1.39			9.367 ± 1.44		
Remote functional tracts distorted by ventricles, superior-inferior e.g., PLIC, CST	PLIC	mTBI	0 M	24	0.618 ± 0.046	−1.6	0.234	8.644 ± 1.12	−2.8	0.314	15.563 ± 1.99	−3.1	0.266	5.183 ± 0.76	−2.4	0.424
			6 M	24	0.609 ± 0.032			8.403 ± 0.24			15.087 ± 0.45			5.061 ± 0.34		
		NPH Pre-op	0 M	16	0.751 ± 0.034	−11.5	**<0.001**	5.879 ± 0.44	+1.0	0.559	12.377 ± 1.01	−8.3	**<0.001**	3.255 ± 2.01	+21.8	0.390
		NPH Post-op	6 M	16	0.665 ± 0.077			5.937 ± 0.54			11.350 ± 0.99			3.964 ± 2.13		
		AD	0 M	27	0.518 ± 0.032	−0.3	0.752	7.524 ± 0.45	+0.6	0.469	12.437 ± 0.73	+0.2	0.800	5.075 ± 0.49	+0.9	0.542
			12 M	27	0.517 ± 0.035			7.568 ± 0.45			12.464 ± 0.56			5.120 ± 0.49		

ATR, anterior thalamic radiation; BCC, body of the corpus callosum; CGC, cingulum; CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; GCC, genu of the corpus callosum; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; L1, axial diffusivity, L2 and 3, radial diffusivity; MD, mean diffusivity; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; UNC, uncinate fasciculus. The bold values represent significant p values at $\alpha < 0.05$.

TABLE 4 | Recurring common properties of DTI profiles, arranged by expected order of white matter reversibility.

Order	Occurrence	DTI profile properties	White matter injury patterns	Key references supporting interpretation of injury
I.	Difference/ change	No significant difference/ change in cohorts vs. controls or themselves.	Preserved integrity	For diffusion patterns affected by aging, (26, 27).
II.	*Difference/ change*	Small **change** in FA, concurrent and **significant decreases** in MD, L1 and L2 and 3. With further recovery, **increase** in FA due to **significant increase** in L1, **decrease** in L2 and 3.	*Consistent with a range of processes implied by the mechanisms of Neural Repair*	Dynamic changes in DTI profiles in subacute injury appear as DTI conflicts (see Order VIII; at-risk). Recovery is seen with FA increase, significant L1 increase and L2 and 3 decrease (20, 28). In chronic TBI, FA increase, correlated with cognitive functioning, is suggestive of neuroplasticity (29, 30).
III.	*Change only*	**Decrease** in L1 but with ½>2.5-fold (or much higher) **increase** in L2 and 3. A decrease in MD is typical. Decrease in FA due to previous increase in compression, proportional to improvement in L1/L2 and 3.	Improvement in Compression	The hallmark of compression, a predominant increase in L1, is remediable with intervention across hydrocephalic conditions, from acute to chronic (9, 31–33). For this contradictory profile in early and late post-operative stages, Keong et al. (10) and this study. For MD decrease, Ivkovic et al. (34). For a decrease in post-operative FA only in shunt responders, Kanno et al. (19).
IV.	Difference	Driven by **significant** increase in L1, **disproportionate** >2.0-fold vs. MD/L2and3 measures. Increase in FA.	Compression	Typical of acute pediatric hydrocephalus, (31, 32). For NPH, in remote functional white matter families, e.g., PLIC, Hattori et al. (21) and this study. For FA and L1 increases in pediatric hydrocephalus, (35).
V.	Difference	**Increase** in L1 **predominant** (or **predominant decrease** in L2 and 3), **significant** increase in FA/MD.	Stretch/ Compression	For **"predominant stretch/compression"** in NPH/ hydrocephalus, (9, 10, 21, 31, 36). In brain tumors, displacement causes fiber tension or high alignment, Schonberg et al. (15).
VI.	Difference/ change	Driven by L2and3, **highly disproportionate increases** >2.5-fold vs. MD/L1 measures. FA may be **decreased**, even significant	Distortion predominantly due to fluid and /or *post-operative hydrocephalus*	For "**predominant transependymal diffusion with the presence of stretch/compression"** in pre-and post-operative NPH, Keong et al. (10). Increased L2 and 3 and MD reflect axonal disruption, reversal of CSF flow through ependyma and expansion of extracellular space (interstitial oedema); increased L1 is due to stretch. For all 3 changes and decreased FA in pediatric hydrocephalus, Mangano et al. (37). For post-operative young adult hydrocephalus, small ventricles; decreased FA driven by L2 and 3, Tan et al. (38). DTI profile in common for post-operative hydrocephalus; seen across subtypes and white matter tracts.
VII.	Difference	**Disproportionate differences in L 2and 3** >1.5 to <2.5-fold vs. lowest non-FA measure. **Global DTI profile of worsening =** concurrent decrease in FA, **increases** in MD, L1, L2 and 3. If L2and3 increase predominant, follow Order VI/VII. If L2and3 increase <1.5-fold or MD/ FA predominant, follow Order VIII/IX.	Oedema and/or loss of integrity	For vasogenic oedema post-TBI, Mac Donald et al. (38) and Veeramuthu et al. (24). For significant decreases in FA due to increases in L2 and 3 in compressive pituitary tumor patients with demyelination, and DTI variability along optic tracts due to anatomy, Paul et al. (39). LI followed by MD increase, were the most sensitive markers in Mild Cognitive Impairment; in MCI and Alzheimer's disease (AD), FA was the least sensitive (25). In early prion disease, Lee et al. (40).
Order	**Occurrence**	**DTI profile properties**	**White matter injury patterns**	**Key references supporting interpretation of injury**
VIII.	Difference/ change	**Global DTI profile of worsening**; L2 and 3 increase not disproportionate (<1.5-fold) or predominant/significant individual DTI measure of global change (i.e., FA/MD). **For Differences -MD increase predominant orFA decrease predominant or FA decrease significant and Global DTI profile;** but fails to match Order VI/VII (not disproportionate increases) **or FA decrease significant and At-risk profile;** decrease in L1, increase in L2 and 3. **For changes –MD increase significant or predominant and global DTI profile; but fails to match order VI/ IX (not disproportionate or too few significant increases).** **At-risk profile; decrease in L1, increase in L2 and 3.**	*White matter at-risk of injury* disruption due to compression/ stretch/oedemaand/or loss of structure/ atrophy	DTI profile of risk of white matter injury across multiple pathologies. For an NPH model of White Matter At-Risk, Keong et al. (10). For oedema and distension in NPH, (41–45). Stretch component if L1 increase significant. For **"stretch/oedema,"** impact of proximity to ventricle disrupts both axons and periventricular vasculature, causing impaired autoregulation and increased interstitial fluid (10). For a rat model of hydrocephalus, Yuan et al. (46). For ventricular risk/ FA conflicts, (10, 18, 31, 47). For increased MD in pediatric hydrocephalus, reversing with surgery, Isaacs et al. (48). For high self-corrected ΔADC in NPH vs. controls/atrophy, Takatsuji-Nagaso et al. (49). For TBI, Castano-Leon et al. (28) and Sidaros et al. (11); L1 decrease as marker of TBI severity, Lawrence et al. (50). MD increase has been found to be consistently more sensitive than FA decrease in both MCI and AD, across early to late disease (25, 51).

(Continued)

TABLE 4 | Continued

Order	Occurrence	DTI profile properties	White matter injury patterns	Key references supporting interpretation of injury
				For Complex vs. Classic NPH; Lock et al. (9). For NPH, MCI and AD; Horinek et al. (52) and Lee et al. (53). For brain tumors, Yuan et al. (54); low anisotropy (q), high isotropy (p), Price et al. (55). For neurodegeneration, (25, 56–64). For decreased FA post-concussion, (12, 30, 65). For vegetative state in ischaemic hypoxic brain injury and TBI, Newcombe et al. (66).
IX.	Change only	FA **decrease significant** & **predominant or** 3 **significant concurrent increases** in MD, L1 and L2 and 3. Diffusion in all directions increased with significant loss of microstructural integrity.	Neuronal degeneration	For neurodegeneration, (13, 14, 67–72). For correlation to multimodal MR imaging in atypical AD; Sintini et al. (73). For significant FA reductions, increased with disease duration in prion disease, Lee et al. (40). For axonal degeneration/ demyelination in TBI, Mac Donald et al. (38), Lawrence et al. (50); increases in MD and L2and3. For increases in all 3 non-FA measures in MCI/ AD, Mayo et al. (74) and Bigham et al. (75). In comparing both MCI and AD to controls, effect sizes for MD, L2and3 and L1 were greater than FA; L1 and L2 and 3 increases were the most discriminatory in early vs. late changes respectively (25), Both associated with white matter deficits and clinical impairment; L1 and MD increases being "state-specific," remaining relatively static with advancing disease, whereas L2and3 increase with FA decrease was "stage-specific," being increasingly abnormal with disease progression. Longitudinal analysis showed progressive changes in the latter always occurred in areas that had first shown the former; thought to suggest that L1 increase represents an upstream event preceding neuronal loss (51). Despite known limitations of DTI and its variability across scanning sites, consistent findings of early L1 increase and sensitivity of MD over FA as a biomarker of disease reported across AD studies (76). Neurodegenerative changes provide support for DTI profile properties in Orders VII-IX, representing a proposed pattern of progression toward more irreversible injury in the periodic table.
X.	*Difference/ change*	Significant **decrease** in FA, driven by **significant decreases** in MD and L1. L2 and 3 may be either **decreased/ increased/**equivocal.	Swelling/hyper-acute/acute &/or *irreversible injury*	For severe TBI patients, Veenith et al. (77) and Lawrence et al. (50). For worse outcome from chronic TBI, Castano-Leon et al. (25). For reactive astrocytic gliosis without neuronal degeneration in prion disease, Caverzasi et al. (75).

*Mimicking the concept of periods, "Orders" reflect commonly recurring patterns of DTI profiles in white matter (i.e., their "neural" properties) seen in response to injury. Here, we arrange them from Order I to X in our predicted trend from reversible to irreversible brain injury (see Discussion for published literature); interpretation for white matter injury patterns in italics are the authors' proposed hypotheses. In "Occurrence," we specify whether these "neural" properties are to be found when examining a Difference between cohorts (Patient Cohorts vs. Controls), a Change between them (Cohorts vs. Themselves across different timepoints) or both. To solve the Order of mapping DTI profiles to the periodic table, we devised a hierarchical algorithm of rules (**Table 5**). The colour coding for the Periodic table signifies the following interpretation of white matter tissue signatures: Blue - Normal-appearing integrity or Healthy DTI profiles. In the Order spectrum from reversible to irreversible DTI profiles, a code akin to a "traffic light" warning system: Green - Potential for reversible brain injury; Amber - Risk of progressing towards irreversibility of injury; Red - Likelihood of irreversible brain injury.*

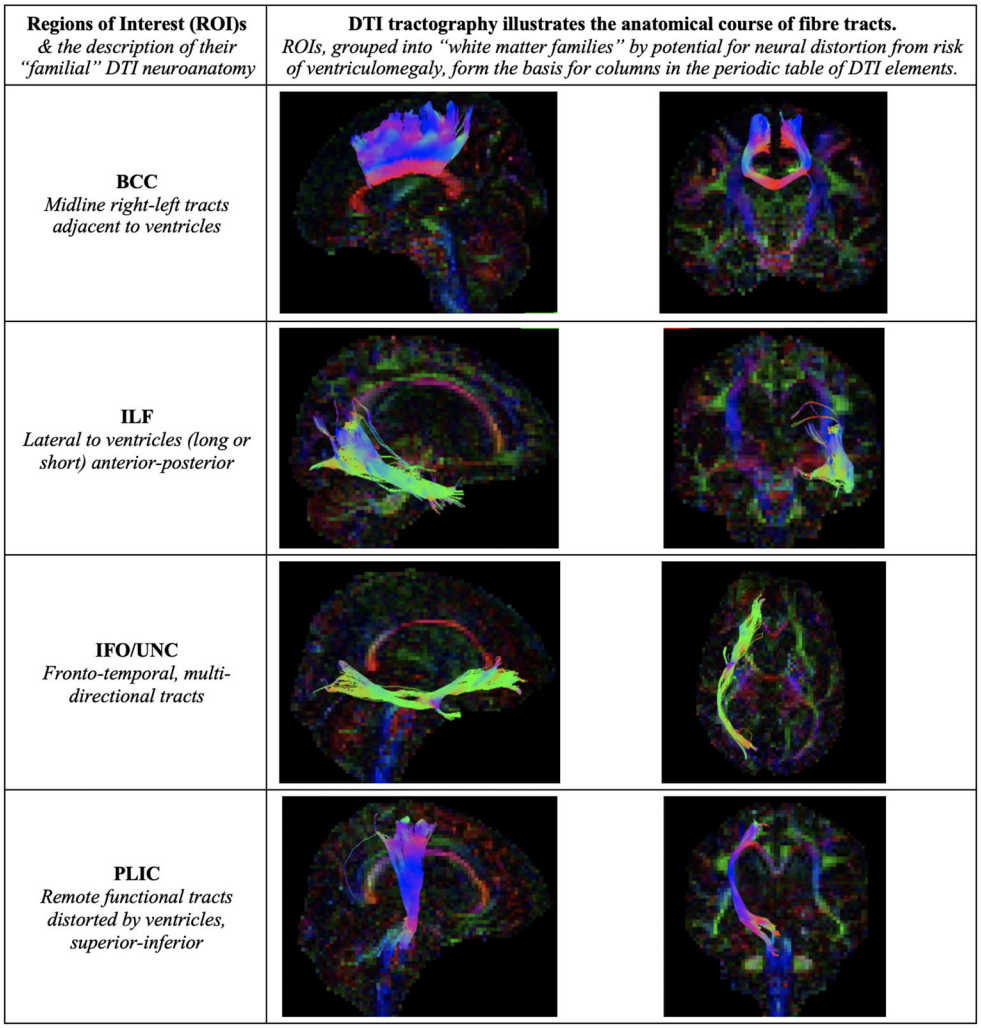

FIGURE 7 | Illustration of Regions of Interest (ROIs). We grouped ROIs into "white matter families" by their predicted potential for neural distortion due to risk of ventriculomegaly. The familial nature of these white matter tracts can be seen in the common anatomical arrangements of their fibers, e.g., right-left or superior-inferior in direction. When grouped in this way, rather than by functional considerations, we demonstrate how tractal families share diffusivity properties. This is the basis for columns in the periodic table of DTI elements. BCC, body of the corpus callosum; ILF, inferior longitudinal fasciculus; IFO/UNC, combination ROI of the inferior fronto-occipital/ uncinate fasciculi; PLIC, posterior limb of internal capsule.

of brain injury. When we grouped white matter tracts by their familial DTI neuroanatomy, rather than their functional organization, we found recurring patterns of DTI measures across cohorts. By deconstructing these morphological patterns into DTI profiles, we were able to observe their periodicity, and so arrange white matter responses according to their diffusivity and neural properties. These properties distinguished white matter injury, when comparing cohorts of mTBI, ClNPH and AD, by the order of their potential reversibility. Using this novel strategy of a *periodic table of DTI elements*, we demonstrated it was possible to characterize cohorts of hydrocephalus vs. non-hydrocephalus and their varying changes over time, and with interventions. The capacity to describe white matter distortion across brain injury cohorts by their neural properties supports a higher diagnostic certainty of neural disruption and more precise evaluation of outcomes from current and emerging therapies. Taken together, the periodic table of DTI elements, and NPH as a human model of reversible disease, show how white matter can recover from varying mechanisms of injury. We term this concept of reversible injury a form of "microstructural resilience."

At present, such a strategy is lacking; at baseline, cohorts are routinely described by their structural imaging features and less commonly, their white matter metrics, but not by the resilience of their "neural materials." This is important because reliance on single DTI metrics alone may lead to misleading reports. In literature, fractional anisotropy (FA) is associated with structural integrity, and therefore, a drop in FA is found in most neurological disorders. This reduction in FA would be consistent with microstructural damage of fibers, such as seen in demyelination and axonal degeneration. However, we have

TABLE 5 | Hierarchical algorithm for mapping DTI profiles to the Periodic Table. We mapped Differences between patient cohorts vs. healthy controls at baseline and 6- or 12-month follow-up and Changes between cohorts vs. themselves across timepoints (**Tables 2**, **3**, **Figures 3**–**6**). For consistency and reproducibility of interpretation, the Periodic Table requires a Hierarchical Algorithm.

I. For differences between patients and controls:				***Algorithm***	***Position***
A1			*No significant changes.* There is a presumption of white matter integrity to avoid *over*-interpretation.	⇒	*Order I*
A2			Contradictory differences, small *change in* FA, significant ↓ MD, L1 and L2 and 3. *In recovery, FA increase, significant ↑ L1 and ↓ L2 and 3*	⇒	*Order II*
A3			DTI profile driven by *significant* ↑ L1		
	Bi		Disproportionate ↑ L1>2.0-fold vs. MD/L2 and 3 changes	⇒	*Order IV*
	Bii		L1 ↑ predominant (or predominant ↓ L2 and 3), significant ↑ FA/MD	⇒	*Order V*
A4			DTI profile driven by *significant* ↑ L2 and 3		
	Bi		Highly disproportionate ↑ L2 and 3 >2.5-fold vs. MD/L1 changes	⇒	*Order VI*
	Bii		Disproportionate ↑ L2 and 3 >1.5 to <2.5-fold vs. MD/L1 changes	⇒	*Order VII*
A5			Global DTI profile of worsening = ↓ FA ↑ MD ↑ L1 ↑ L2 and 3 *(concurrent) But if -*	⇒	*Order VIII*
	Bi		L2 and 3 ↑ predominant, follow algorithm above, *except if FA/MD highest % value*	*A6Bi and A6Ci*	
			L2 and 3 ↑ <1.5-fold, FA ↓ not significant but MD and L1 ↑ significant ↑ L2 and 3	⇒	*Order VIII*
		Ci	If FA ↓ significant, follow algorithm below	*A4Bi and A4Bii*	
A6			Predominant/significant *individual DTI measure of Global change* (i.e., FA/MD)		
	Bi		MD ↑ predominant (highest % value)	⇒	*Order VIII*
			FA ↓ predominant (highest % value)	⇒	*Order VIII*
		Ci	FA ↓ significant &	⇒	
			a. Global DTI profile *(see A4/A5), disproportionate ↑ L2and3*	⇒	*Order VI/VII*
			b. Global DTI profile but not matching Order VI/VII	⇒	*Order VIII*
			c. At-risk profile: ↓ L1 ↑ L2and3	⇒	*Order VIII*
			d. Significant ↓ in MD and L1		*Order X*
II. For changes between cohorts and themselves:				***Algorithm***	***Position***
A1			*No distinct morphological DTI profiles (A2/A4-6) & no significant differences.* There is a presumption of white matter integrity to avoid *over*-interpretation.	⇒	*Order I*
			Exception for post-operative hydrocephalus, follow algorithm below and also ⇒	A4Bi	
A2			Contradictory changes		
	Bi		Small ↓ FA, significant ↓ MD, L1 and L2 and 3	⇒	*Order II*
			In recovery, FA increase, significant ↑ L1 and ↓ L2 and 3	⇒	*Order II*
	Bii		↓ L1 but >2.5-fold ↑ L2 and 3 vs. MD/L1 changes ↓ *FA significant due to ↑ L2 and 3 with ↓ L1*	⇒	*Order III*
		Ci	*↓ L1 significant or predominant (highest % value), ↓ FA significant due to ↓ L1*	⇒	*Order III*
A4	Bi		Highly disproportionate ↑ L2 and 3 >2.5-fold vs. MD/L1 changes Presumed default DTI profile in common for post-operative hydrocephalus	⇒	*Order VI*
A6	Bi		MD ↑ *significant or predominant (highest % value)*		
			a. Global DTI profile of worsening, but not *A4Bi or A6BiCi-iii.*	⇒	*Order VIII*
			b. At-risk profile: ↓ L1 ↑ L2 and 3	⇒	*Order VIII*
		Ci	FA ↓ significant & predominant *(highest % value)*	⇒	*Order IX*
		Cii	3 significant ↑ MD ↑ L1 ↑ L2 and 3	⇒	*Order IX*
		Ciii	Significant ↓ in FA, MD and L1	⇒	*Order X*

To solve the Order of the periods.

a. ***Table 2*** *for Differences between Patients vs. Controls and.* ***Table 3*** *for Changes between Cohorts vs. Themselves.*

b. Resolve the Algorithm in order of (A) Morphological Profiles, (B) Thresholds and (C) Significance of Changes.

*A. Firstly, describe DTI profiles by their concurrent directions and magnitude of changes (****Figures 3****–****6****).*

What morphological descriptor (A2-A6) best describes the DTI profiles seen? If none match, A1 is the default position.

B. Within the morphological descriptor (A2-A6), differentiate DTI profiles by their thresholds for proportions of changes.

Disproportion = compare non-FA changes; divide the highest % value by the lowest % value (irrespective of +/- direction).

*C. Lastly, resolve the remaining DTI profiles by the level of significance of their changes (****Tables 2****,* ***3****).*

D. For conflicts that remain unresolved after steps A-C, describe.

a. Differences between cohorts by up to two most favorable (lowest ordered) position.

b. Changes within cohorts by up to two most favorable (lowest ordered) positions of best fit.

Order	Region of Interest			
	Midline, adjacent to ventricles, R-L, e.g. GCC, BCC	Lateral to ventricles, Long or short A-P, e.g. ILF, ATR, PTR, CGC	Fronto-temporal, multi-directional, e.g. IFO, UNC	Remote functional, distorted by ventricles, S-I, e.g. PLIC, CST
I.		$MTBI^{0}$ $MTBI^{6}$ $MTBI^{6C}$	$MTBI^{0}$	$MTBI^{0}$ $MTBI^{6}$ $MTBI^{6C}$ AD^{12C}
II.	$MTBI^{0}$ $MTBI^{6}$			
III.	$MTBI^{6C}$	CNPH^{6C}	CNPH^{6C}	CNPH^{6C}
IV.				CNPH^{0}
V.			CNPH^{0}	
VI.	CNPH^{0} CNPH^{6} CNPH^{6C}	CNPH^{6} CNPH^{6C}	CNPH^{6} CNPH^{6C}	CNPH^{6} CNPH^{6C}
VII.	AD^{0} AD^{12}	AD^{0} AD^{12}		AD^{12}
VIII.		CNPH^{0} AD^{12C}	$MTBI^{6}$ AD^{0} AD^{12}	AD^{0} (AD^{12*})
IX.	AD^{12C}		$MTBI^{6C}$ AD^{12C}	
X.	$STBI^{0}$	$STBI^{0}$	$STBI^{0}$	$STBI^{0}$

FIGURE 8 | Periodic table of DTI elements. Recurring common properties of DTI profiles arranged vertically by predicted reversibility of white matter injury (see **Table 4** and Discussion). ROIs grouped in columns of 'white matter families' according to distortion potential from ventriculomegaly. Differences at baseline for clinical cohorts at 0 months vs. healthy controls at 0 months mapped onto the periodic table. In addition to baseline DTI profiles, cohorts mapped across timepoints; $MTBI^{6}$, CNPH^{6} and AD^{12} cohorts are mapped at 6 and 12 months respectively against healthy controls at 0 months; CNPH^{6C} and $MTBI^{6C}$ are mapped at 6 month follow-up against the respective clinical cohorts at 0 months. Order X has been derived from STBI data in a published cohort by Veenith et al. (77); coincidentally, this unrelated study was performed on the same scanner as the *C*NPH cohort being described in this work. $^{0/6/12}$, DTI profiles at 0 month baseline, 6/12 month follow-up, ^{C}, denotes cohorts vs. themselves across timepoints, A-P, anterior-posterior; AD, Alzheimer's Disease; BCC, body of the corpus callosum; *C*NPH, Classic NPH; DTI, diffusion tensor imaging; FA, fractional anisotropy; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; L1, axial diffusivity, L2 and 3, radial diffusivity; MD, mean diffusivity; MTBI, mild traumatic brain injury; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; R-L, right-left; ROI, region of interest; S-I, superior-inferior; STBI, severe traumatic brain injury; UNC, uncinate fasciculus.

found that in hydrocephalus, FA can be shown to both increase and decrease (10, 79). For example, Kanno et al. and our group have reported that a reduction in FA at baseline compared to healthy controls, along with an increase in mean diffusivity (MD), is compatible with cohorts of NPH shunt-responders (10, 18). However, they have also shown a decrease in post-operative FA, only in shunt-responders (19). Whilst this may appear to be an FA conflict, we were able to accommodate both findings, arranged as Order VIII pre-operatively *for "white matter at-risk"* and Order III post-operatively for *"improvement in compression,"* using the periodic table of DTI elements. Indeed, Assaf et al. originally reported both significantly increased and decreased FA in acute pediatric hydrocephalus, with significant decrease in FA (internal capsule) post-surgery (31, 32). Tan et al. also found brain-wide reductions in FA in successfully shunted young hydrocephalic patients (37). Conversely, Hattori et al. and others have also convincingly demonstrated that FA values in NPH patients were higher than in healthy controls (21). Mechanical distortion from ventriculomegaly may increase compaction of fibers along the direction of main diffusivity measures, leading to high FA values. Significant increases in FA or MD may be due to changes driven by predominant increases in L1, even if significant decreases in L2 and 3 are present (9, 10, 21, 31, 35, 36). These DTI profiles of *"compression"* and *"stretch/compression"* appear in the periodic table as neural properties differentiated by proportion; Orders IV and V, respectively.

Apparent DTI conflicts and inconsistencies reflect both the known mathematical derivation of DTI metrics (FA and MD being heavily dependent on changes occurring across other diffusivity measures), as well as specific patterns of white matter tracts and their distortions by CSF compartments described in NPH, such as ventriculomegaly and disproportionately enlarged subarachnoid space hydrocephalus (DESH) (80). Differing brain regions may respond differently to forces of pressure or deformation. The inherent "neural material properties" of white matter affected by pathological processes may determine their capacity for microstructural resilience vs. progressive neuronal degeneration. Differentiation of DTI profiles is important; it allows for multiple patterns of white matter injury to co-exist within individual cohorts. In NPH, we have shown that an *a priori* model of at-risk white matter tracts comprising only six key ROIs is sufficient to demonstrate at least three

distinct and concurrent patterns of neural distortion (10). DTI profiles differed according to their risk of proximity to the expanding ventricles. In this study, we have used the strategy of a *periodic table of DTI elements* to reproduce the three known patterns of neural distortion seen in NPH, now refined as Orders IV, V and VI, respectively. We showed that some patterns of injury were more reversible than others. Early post-intervention, we found *"predominant stretch/compression"* to be the most amenable to reversibility; this contradictory decrease in L1 with concurrent increase in L2 and 3, now described as Order III for *"improvement in compression,"* preceded changes in clinical outcome (10). Here, at six months post-shunting, we found "*compression*" and *"stretch/ compression"* to be the most reversible patterns of injury (i.e., pre-operative Orders IV and V, respectively), matching findings from our previous work. Using the periodic table, this profile of improvement is described by Order III. Interestingly, by mapping cohorts to the periodic table of elements, it became apparent that, despite differing pre-operative DTI measures, all post-operative hydrocephalus tracts had a DTI profile in common. Order VI, in which FA decrease is driven by highly disproportionate increases in L2 and 3, was also observed by Tan et al. in their young adult hydrocephalic cohort without ventriculomegaly (37). This suggests Order VI may be a shared tissue DTI signature of treated, post-operative hydrocephalus. In addition, all tracts with improvement shared the DTI profile of Order III.

In this study, we sought to compare DTI profiles in hydrocephalus compared to brain injury and neurodegeneration within the spectrum of reversible to irreversible injury. Using the strategy of a *periodic table of DTI elements*, it has been possible to demonstrate where patterns of neural injury diverge, or where they are overlap. The cohorts in Orders VII to VIII of the periodic table match ADNI studies suggesting that ventriculomegaly may be an early imaging signature of AD and/or NPH. The progression in the AD cohort at 12 months toward neuronal degeneration (Order IX; in midline and fronto-temporal tracts), is consistent with known interpretations of ADNI data; white matter damage in AD follows neurodegenerative staging and progression of disease (75). Despite the known limitations of DTI and its variability across scanning sites, consistent DTI profiles, that of early L1 increase, sensitivity of MD over FA as a biomarker of disease and L2 and 3 increase with FA decrease being increasingly abnormal with disease progression, have been reported across AD studies (25, 51, 76). This provides further support of the morphology of DTI profiles described in Orders VII-IX, representing a proposed progression from reversible to irreversible injury in the arrangement of the periodic table of DTI elements. Our findings also support the model of acute-to-chronic traumatic brain injury with differing patterns of neural response and recovery. In the inferior longitudinal/ uncinate fasciculi, changes at 6 months suggested neuronal degeneration (Order IX). Previous work from a subset of this cohort confirmed that, patients demonstrated cognitive deficits within this timeframe (24). By contrast, at 6 months, DTI profiles seen in the midline tracts (Order II) would be consistent with expected diffusion patterns if pathophysiological processes of neural repair, such as dendritic pruning, influx of inflammatory cells, deposition of biomarker proteins and disorganized neural regeneration, were occurring. Further work is required to characterize these changes, and in particular, confirm that DTI profiles represented by Order II match reports of improvement of cognitive functioning and other deficits in the literature, suggestive of neuroplasticity (29, 30). Presently, the interpretation of DTI profiles is highly dependent upon studies of unambiguous pathophysiological processes, such as stretch distortion/compression due to tumors, variable patterns of oedema (interstitial, vasogenic, cytotoxic), demyelination and Wallerian degeneration [Orders V-IX]. Therefore, in constructing the periodic table, we also sought out further interpretations in literature for comparisons of DTI measures across pediatric to adult hydrocephalus, experimental models of injury, acute-to-chronic TBI, tumors and forms of neurodegeneration (**Table 4** for key references), in order to situate DTI profiles within their appropriate context for comparisons.

Limitations

Our study has a number of limitations. Firstly, ROI methodology has known disadvantages, as compared to more advanced analysis techniques such as semi-automated tractography. However, in our work and that of others, high intraclass correlation coefficients have been reported in clinical use, confirming both its reliability as a research method and applicability to standard practice. Secondly, due to methodological considerations, inter-site DTI variability is a known concern, as diffusivity measures are highly dependent upon machine specifications and acquisition parameters. Whilst this therefore renders it challenging to directly compare DTI output across international collaborative sites, it is still possible to appreciate strong morphological features comprising specific DTI profiles of disease, such as differential diffusion metric sensitivity in early vs. late stages of AD [50, 75; see (**Table 4**)]. In this study, we have made comparisons across multiple international cohorts but have only compared patients against controls from their own individual sites, thereby avoiding such pitfalls of DTI variability. Furthermore, our findings in normal pressure hydrocephalus are consistent across the variety of techniques employed in literature for DTI post-processing and interpretation (manual to semi-automated methodologies, comprising voxel-based analysis, tract-based spatial statistics, deterministic fiber tractography and ROI-based analyses) (10, 25, 31, 79, 81, 82) confirming the robustness of DTI in its descriptions of microstructural injury.

In reviewing the literature, we included in the analysis sources that listed the full panel of DTI measures, and where pathophysiological findings of disease correlated with DTI interpretation. However, we were limited in that not all papers of interest published their full panel of DTI measures. As global DTI measures are influenced by disproportionate changes in individual metrics, we tried to include papers that took this into account. Additionally, for purposes of clarity, there may be a limit to the number of datasets that

can be presented via a periodic table. DTI profiles may be better suited to visual representation in other ways, such as being plotted as a normal distribution curve, or as milestones along a spectrum line from reversible to irreversible brain injury. Subclassifications of DTI profiles may be needed to more accurately represent cohorts with overlapping tissue signatures. Whilst we tested three cohorts vs. controls and one exemplar within a much wider spectrum of brain injury, we expect this methodology to be translatable to other conditions comprising acute-to-chronic pathology. Crucially, the order of potential reversibility of white matter injury is determined *a priori*.

The concept of the periodic table is proposed as a strategy to navigate the pitfalls of DTI interpretation, rather than trying to solve its known shortcomings. This would be the first description of a taxonomy for classifying and describing DTI profiles, and we expect that this will only be its first iteration. We shall seek to address the limitations and considerations mentioned in future work; we hope that community efforts may contribute toward this concept.

CONCLUSION

Our study has demonstrated that it is possible to distinguish between different cohorts along the spectrum of brain injury by describing the properties of their DTI white matter profiles. We proposed a simplified taxonomy to improve the reproducibility and reduce the complexity of DTI interpretation to differentiate cohorts of hydrocephalus vs. non-hydrocephalus using a novel strategy of a periodic table of DTI elements. In this way, DTI profiles provide, both at baseline and in response to interventions, a form of rapid characterization of cohorts within the context of known tissue signatures across pathologies. As potential reversibility of white matter injury is assessed *in vivo*, this methodology may contribute to the understanding of the use of biomarkers to track changes in disease cohorts.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by local or institutional Ethics Committees. Written informed consent was obtained from all subjects or legal representatives, if appropriate, as required by local Ethics Committees. The mTBI study was regulated by the University of Malaya Research Ethics Committee and Hospital Ethics Committee (UM/EC Ref: 947.15). The NPH study was approved by the local Research Ethics Committee of the Cambridge Health Authority (LREC: 06/Q0108/330). Individual ADNI sites received approval from their respective governing Institutional Review Boards. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NK conceptualized the experimental design. NK, CL, and SS analyzed the data. NK and CL wrote the manuscript, as well as provided visualizations for the data and led revisions of the work. AH contributed to data acquisition, imaging post-processing, and analysis from the UM site. ZC, MC, JP, and VN contributed to the acquisition of data used in this paper and provided comments and suggestions toward improving revisions. All authors reviewed the manuscript.

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Clinical Outcomes After Ventriculo-Peritoneal Shunting in Patients With Classic vs. Complex NPH

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Objective: Normal pressure hydrocephalus (NPH) is a neurological condition characterized by a clinical triad of gait disturbance, cognitive impairment, and urinary incontinence in conjunction with ventriculomegaly. Other neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and vascular dementia share some overlapping clinical features. However, there is evidence that patients with comorbid NPH and Alzheimer's or Parkinson's disease may still exhibit good clinical response after CSF diversion. This study aims to evaluate clinical responses after ventriculo-peritoneal shunt (VPS) in a cohort of patients with coexisting NPH and neurodegenerative disease.

Methods: The study has two components; (i) a pilot study was performed that specifically focused upon patients with Complex NPH and following the inclusion of the Complex NPH subtype into consideration for the clinical NPH programme, (ii) a retrospective snapshot study was performed to confirm and characterize differences between Classic and Complex NPH patients being seen consecutively over the course of 1 year within a working subspecialist NPH clinic. We studied the characteristics of patients with Complex NPH, utilizing clinical risk stratification and multimodal biomarkers.

Results: There was no significant difference between responders and non-responders to CSF diversion on comorbidity scales. After VPS insertion, significantly more Classic NPH patients had improved cognition compared to Complex NPH patients ($p = 0.005$). Improvement in gait and urinary symptoms did not differ between the groups. 26% of the Classic NPH group showed global improvement of the triad, and 42% improved in two domains. Although only 8% showed global improvement of the triad, all Complex NPH patients improved in gait.

Conclusions: Our study has demonstrated that the presence of neurodegenerative disorders co-existing with NPH should not be the sole barrier to the consideration of high-volume tap test or lumbar drainage *via* a specialist NPH programme. Further characterization of distinct cohorts of NPH with differing degrees of CSF responsiveness due to overlay from neurodegenerative or comorbidity risk burden may aid toward more precise prognostication and treatment strategies. We propose a simplistic conceptual framework to describe NPH by its Classic vs. Complex subtypes to promote the clinical paradigm shift toward subspecialist geriatric neurosurgery by addressing needs for rapid screening tools at the clinical-research interface.

Keywords: Alzheimer's disease, dementia, neurodegenerative disease, Normal Pressure Hydrocephalus (NPH), Parkinson's disease, ventriculo-peritoneal shunt (VPS)

INTRODUCTION

The pathophysiology of Normal Pressure Hydrocephalus (NPH) still provokes great debate. It is classically a characterized by a clinical triad of gait disturbance, cognitive impairment and urinary incontinence in conjunction with radiographic findings of ventriculomegaly (1). Other neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease or parkinsonism, and vascular dementia share some overlapping clinical features. Certain phenotypes of disease, namely NPH with comorbidities, are especially difficult to treat. Patients who present with neurodegenerative disease or vascular risk burden are considered poor candidates for intervention. Studies have postulated that such patients may have dual-pathology. Yet, their clinical characteristics are also atypical for neurodegeneration, such as Alzheimer's or Parkinson's diseases. Brain biopsy or advanced imaging such as single-photon emission computed tomography (SPECT) scans may provide for accurate diagnosis to aid the prediction of surgical outcomes but are either highly invasive or impracticable to deliver in screening programmes for NPH. This clinical conundrum results in such patients receiving neither intervention for neurodegenerative disease, nor consideration of CSF shunting.

The co-existence of NPH with neurodegenerative diseases has been reported (2–6), and several studies have described good clinical response after CSF diversion in patients with NPH, coexisting with Parkinsonism or Alzheimer's disease (7–11). It is known that such cohorts may demonstrate a degree of responsiveness to CSF drainage. Methodical supplementary testing and risk stratification are critical to understanding the potential scope for intervention. Identification of comorbidities is an important aspect of the management of idiopathic NPH (INPH). Indeed, this was the basis of a consensus statement by the International Society for Hydrocephalus and Cerebrospinal Fluid Disorders (ISHCSF) (12). However, the relative contribution of comorbidities to CSF responsiveness has not been examined even in large studies on INPH. Few studies have focused on NPH patients with significant comorbidities as a distinct cohort presenting within the spectrum of INPH. The cohort of NPH patients with comorbidities are believed to have a higher risk of non-responsiveness to CSF drainage than typical INPH patients (i.e., the classic cohort of NPH). Yet, the influence of individual comorbidities upon CSF responsiveness is uncertain.

In this study, we present the results of a progressive multi-year change in practice within a subspecialist NPH programme, to understand and adapt to the needs of this uncertainty. Firstly, we performed a pilot study focused primarily on characterizing the risk stratification of patients presenting with NPH but with overlay from significant vascular and neurodegenerative disease. As these patients demonstrate features of Classic NPH but both their level of CSF responsiveness and degree of comorbidities need to be quantified, we have proposed the term "Complex NPH" to distinguish this cohort from more typical patients within the INPH spectrum. Key features of this pilot include (i) the use of global risk scoring and multi-modal MRI for the characterization of Complex NPH (ii), correlation of semi-automated quantitative MRI changes with responsiveness to CSF drainage and (iii) genotyping for assessment of neurodegenerative risk potential. Our aim was to produce a well-characterized dataset of biomarkers that may serve as a basis for the future evaluation and consideration of such patients as a separate cohort of complex NPH as distinct from Classic NPH, in which more standard levels of responsiveness to CSF diversion would be expected. Following work in the pilot, we then performed a retrospective study on 1 year of consecutive patients with NPH being seen via a subspecialist clinic. We examined this unfiltered patient group for subtypes of NPH presentation, shunting intervention in cohorts of Classic vs. Complex NPH and confirmed their outcomes at 2 years.

MATERIALS AND METHODS

Study Setting and Rationale

The study has two components; (i) a pilot study was performed that specifically focused upon patients with Complex NPH and following the inclusion of the Complex NPH subtype into consideration for the clinical NPH programme, (ii) a retrospective snapshot study was performed to confirm and characterize differences between Classic and Complex NPH patients being seen consecutively over the course of 1 year

within a working subspecialist NPH clinic. In the pilot study, we studied the characteristics of patients with Complex NPH, utilizing clinical risk stratification and multimodal biomarkers (including imaging biomarkers and genotypic risk). We had previously published the characteristics of white matter injury in this cohort using diffusion tensor imaging (DTI) (13). We found that comorbidities did not predict CSF responsiveness in our cohort of Complex NPH. In the retrospective study, we performed clinical risk stratification according to our revised conceptual framework of Classic vs. Complex NPH instead. The two study components and cohorts are illustrated in **Figure 1**.

Study Samples

In the pilot study, 13 patients diagnosed with Complex NPH undergoing the extended CSF drainage protocol under the NPH programme at the National Neuroscience Institute, Singapore between 2016 and 2017 were selected for the study. We recruited NPH patients with known significant comorbidities, such as cardiovascular risk burden or neurodegenerative disease overlay from all patients presenting with NPH and meeting clinical criteria for further testing. Within the NPH programme, patients who were deemed to have shown significantly positive responses to high-volume tap testing were offered shunt insertion without additional supplementary testing (13). However, patients who demonstrated low or borderline positive results on tap testing or had comorbidities confounding the assessment of short-term responsiveness to CSF drainage were offered the extended CSF drainage protocol. We have previously published the DTI profiles and clinical characteristics for this pilot study cohort of patients with Complex NPH (13). In this study, we present multi-modal MR findings and biomarkers to elucidate the characteristics of Complex NPH not previously reported in our prior work.

In the retrospective study, we screened the list of outpatients under a single surgeon (NCK) in at the National Neuroscience Institute from October 2017 to October 2018. 141 patients were reviewed in out-patient clinic for probable NPH, idiopathic NPH and secondary NPH. 67 out of these 141 patients were responders who demonstrated a positive response to a lumbar tap test or lumbar drainage. Only 35 responders underwent ventriculo-peritoneal shunt (VPS) insertion. Among these 35 patients, 2 patients who had VPS insertion more than 10 years ago and 1 patient who had surgery in a private hospital were excluded.

Diagnosis of NPH

Clinical descriptions for all patients met criteria, according to published guidelines, for either probable or possible NPH (14). Patients referred to the NPH programme but deemed unlikely to have NPH were excluded from further testing. All patients met the criteria for communicating hydrocephalus. We have previously published our criteria for defining ventriculomegaly as an Evans' index (maximum width of frontal horns of the lateral ventricles divided by the transverse inner diameter of the skull) $\geq$0.30, and a Bicaudate index (minimum intercaudate distance divided by the brain width along the same line) $\geq$0.25 (13).

In our study, patients with probable NPH demonstrated two or more features of the classic clinical triad of gait disturbance, cognitive impairment and urinary incontinence. Where patients were deemed to have possible NPH, they exhibited symptoms of either (a) incontinence and/or cognitive impairment, but without significant gait disturbance or (b) gait dysfunction or cognitive impairment alone. As per guidelines, these symptoms in patients with probable or possible NPH were not thought likely to be entirely attributable to other neurological, psychiatric, or general medical disorders, even if such disorders were found to be co-existing (14). All patients referred to the NPH programme were independently evaluated by subspecialist neurology or geriatric teams and did not solely fit the diagnostic criteria for Alzheimer's and Parkinson's diseases, and/or had limited response to disease-modifying drugs such as levodopa. Patients were only offered entry into the NPH programme, including supplementary testing, if they were not of more than moderate risk of surgical intervention.

Methodologies for the Pilot vs. Retrospective Study Components

In the pilot, all participants underwent insertion of a lumbar drain to according to our previously published extended CSF drainage protocol (13). Two participants required the insertion of an Ommaya reservoir for testing due to failure to achieve lumbar drainage. One patient exhibited significant psycho-behavioral symptoms and could not cooperate with MR imaging. Whilst he did have ventriculo-peritoneal shunting, we excluded him from subsequent study analysis. 12 participants underwent the full NPH programme for CSF drainage according to our previously published protocol (13) including clinical gait and cognitive testing, pre- and post-drainage inpatient MR imaging and *APOE* genomic analysis. Patients with a lumbar drain *in-situ* underwent a three-day drainage/ seven-day global assessment protocol, achieving $\geq$300 mls total CSF withdrawal whereas the patient undergoing serial taps *via* Ommaya reservoir had a modified protocol achieving $\geq$150–200 mls total CSF withdrawal to account for the tolerance needed for more rapid drainage and increased infection risk from repeated tapping.

In the retrospective study component, a final set of 32 NPH patients was included in this study. Demographic and clinical data, including age, sex, comorbidities, presenting symptoms and clinical responses after VPS were collected retrospectively from clinical records. Tinetti gait and balance scores pre- and post-VPS insertion were collected (1 Complex NPH patient did not have pre- and post-VPS Tinetti). Mini-Mental State Examination (MMSE) scores pre-VPS are reported in this study (2 Classic NPH patients did not have pre-VPS MMSE), although post-VPS MMSE scores were excluded from analysis due to missing data.

We categorized these patients into the proposed conceptual framework; (i) Complex NPH, comprising 13 patients had underlying neurodegenerative diseases which include Alzheimer's disease, Parkinson's disease or parkinsonism, and vascular dementia, and (ii) Classic NPH, the other 19 patients who did not have such clinical risk burden. The diagnoses of neurodegenerative diseases were established by either a neurologist or geriatrician prior to referral to the NPH programme under the Department of Neurosurgery.

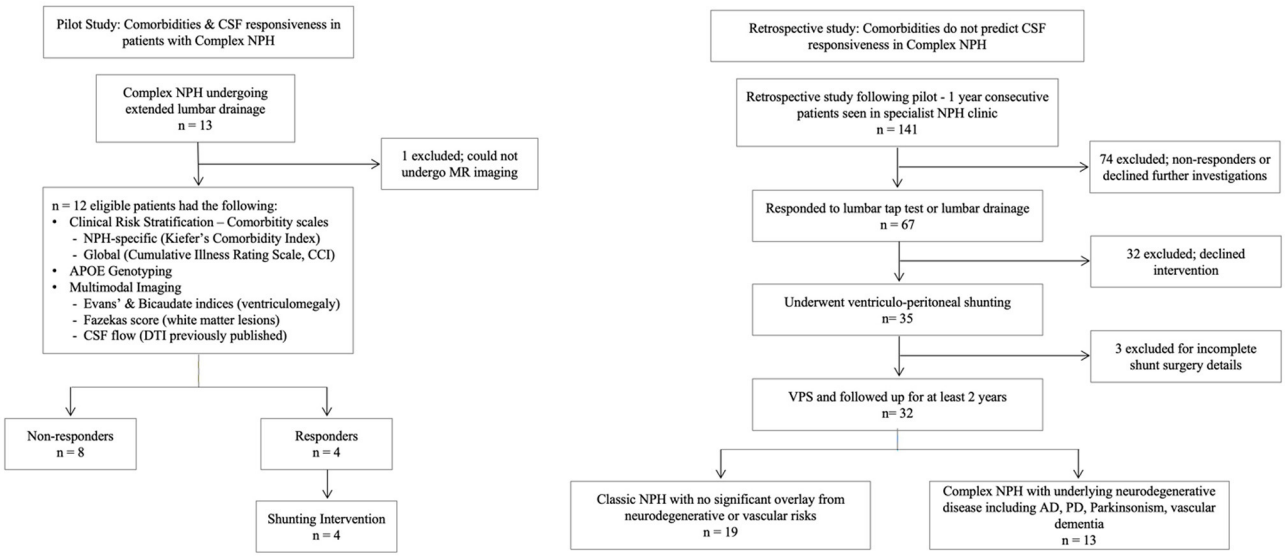

FIGURE 1 | Flow diagram describing the pilot and restrospective studies.

Comorbidity and Frailty Risk Assessments

Three comorbidity scales were used to risk stratify the pilot study cohort—Kiefer's Comorbidity Index, the Cumulative Illness Rating Scale, and the Charlson Comorbidity Index; each was scored by two independent raters. Kiefer's Comorbidity Index (CMI) is an NPH-specific scale, with patients scoring >3 points less likely to be shunt-responsive (15–17). We further refined CMI grading to clarify the cerebral infarction criterion as meaning lobar or territorial strokes, excluding lacunar infarcts and microhaemorrhages. We used the latter two scales to report global comorbidity risk burden.

In scoring the Modified Cumulative Illness Rating Scale (CIRS), we used guidelines adapted by Salvi et al. (18) for elderly patients with more complex comorbidities but modified it for use in NPH. We considered ventriculomegaly or NPH diagnosis as primary conditions; these were therefore excluded as neurological comorbidities for scoring, to demonstrate overlay from other neurological diagnoses. Similarly, we excluded age as a comorbidity on the Charlson Comorbidity Index (CCI) (19), since NPH is almost exclusively seen in the elderly population.

In the retrospective study, we explored the use of frailty indices to describe NPH cohorts. Frailty has been shown to be predictive of health outcomes and post-operative morbidity and mortality (20–22). Frailty risk was scored using the Canadian Study of Health and Aging Clinical Frailty Scale (CFS) and the 11-factor modified frailty index (mFI−11).

Imaging

MR imaging data for the pilot study were acquired with a 3.0-T MR scanner (Ingenia, Philips Medical Systems, Best, the Netherlands), including 3D T1, T2 and FLAIR sequences. A few patients were downgraded to the 1.5-T scanner due to clinical MR safety concerns.

Fazekas scoring for white matter intensities was performed for all pre- and post-lumbar drainage FLAIR MRI sequences and independently verified by a second rater. We rated the periventricular white matter and deep white matter scores based on the presence, size and confluence of white matter lesions (23). Scoring was performed according to established convention; periventricular white matter ratings of 0 = absent, 1 = pencil-thin lining, 2 = "halo", 3 = irregular periventricular signal extending into deep white matter and deep white matter ratings of 0 = absent, 1 = punctate foci, 2 = beginning of confluence, 3 = large, gathered confluence. Confluence of white matter lesions were considered present if seen across two or more imaging cuts with extensions into deep white matter.

Genomic Analysis

Genomic DNA was obtained from leukocytes using the QIAamp® DNA Blood Midi kit (Qiagen GmbH, Hilden, Germany). *APOE* genotypes were determined using Taqman® allelic discrimination assays (for SNPs rs7412 and rs429358) and genotyping was carried out on a 7,500 fast real-time PCR machine (Applied Biosystems) using standard protocols as recommended by the manufacturer.

Gait, Balance, and Cognitive Assessments

Inpatients underwent therapist-led examinations of the 10 m walking test, Tinetti gait and balance examination, and MMSE assessments, as per our protocol for the NPH programme (13). After CSF drainage, patients and/or caregivers were asked to grade their own perceived levels of improvement or deterioration at home to the nearest 10%, from—to +100% levels, with 0 being no perceivable difference. A positive response to CSF drainage was defined as an increase of ≥10% in any measure of inpatient gait, balance or cognitive testing (24) or ≥20% functional improvement on the patient's own self-report measure.

TABLE 1 | Demographic and clinical data for the pilot study.

	Total	Non-responders	Responders
N	12	8	4
Age (years)	71.3 ± 7.61	72.8 ± 8.65	68.5 ± 4.66
Sex (male)	10 (0.83)	7 (0.88)	3 (0.75)
Comorbidity			
PD or parkinsonism	5 (0.42)	4 (0.50)	1 (0.25)
AD or other dementia	3 (0.25)	2 (0.25)	1 (0.25)
Diabetes mellitus	5 (0.42)	2 (0.25)	3 (0.75)
Hypertension	10 (0.83)	7 (0.88)	3 (0.75)
Hyperlipidaemia	8 (0.67)	4 (0.50)	4 (1.0)
Cardiac disease	4 (0.33)	2 (0.25)	2 (0.50)
CVA/TIA	8 (0.67)	5 (0.63)	3 (0.75)
Comorbidity scores			
Charlson Comorbidity Index	1.42 ± 1.08	1.38 ± 1.06	1.50 ± 1.29
Modified Cumulative Illness Rating Scale	14.33 ± 4.70	14.25 ± 5.04	14.50 ± 4.65
Kiefer's Comorbidity Index	3.83 ± 2.52	3.63 ± 2.20	4.25 ± 3.40
Presenting symptoms			
Gait disturbance	12 (1.0)	8 (1.0)	4 (1.0)
ADL-Dependent	5 (0.42)	3 (0.38)	2 (0.50)
Tinetti score	15.7 ± 6.99	14.6 ± 7.63	18.3 ± 5.51
Cognitive impairment	7 (0.58)	5 (0.63)	2 (0.50)
MMSE score	20.9 ± 7.12	19.8 ± 7.34	23.3 ± 6.99
Urinary incontinence	7 (0.58)	3 (0.38)	4 (1.0)

Age and assessment scores presented as mean ± standard deviation; all other variables presented as number of patients (ratio). AD, Alzheimer's Disease; ADL, Activities of Daily Living; PD, Parkinson's Disease.

Shunt Implantation

Thirty two patients underwent programmable VPS insertion between 2014 and 2018. Programmable shunt valves (with and without antisiphon devices) were implanted. Shunt valve models were decided according to surgeon's preference; predominantly, Strata (Medtronic) and proGAV (Miethke) valves were used, following all manufacturers' recommendations. Post-operative imaging, comprising a CT brain and shunt series radiographs, was performed to confirm satisfactory placement of all shunt components (proximal to distal). Shunt valve setting adjustments were performed to optimize desired settings to match best patient functional performance. Patients underwent physiotherapy-led clinical assessments and outcomes were recorded using published NPH grading scales. All patients were followed up in outpatient clinic for at least 2 years. In addition, confirmational report was obtained from the patients or their caregivers on any improvement or deterioration in the clinical symptoms i.e., gait disturbance, cognitive impairment, and urinary incontinence.

Statistical Methods

Statistical analyses were performed using SPSS Statistics Version 23.0 (IBM Corp., Armonk, NY, United States). Continuous variables were analyzed with *t*-tests. Categorical variables were analyzed with the chi-square test. All statistical tests were two-tailed, and significance level was set at 0.05.

RESULTS

Patient Characteristics

Pilot Study

We have previously published patient characteristics from this pilot cohort elsewhere (13). Following the exclusion as described above, the pilot study cohort comprised of 12 participants (10 male, 2 female) with mean age 71.3 years. All patients presented with gait disturbance and just over half also had cognitive impairment or urinary incontinence/ bladder dysfunction (**Table 1**). All participants underwent pre-drainage MMSE testing for a baseline assessment, and MMSE scores were not significantly different between responder and non-responder groups.

10 of 12 patients completed the Tinetti assessment at baseline, with a mean score of 15.7 ± 6.99. 8 of 12 patients were able to complete a 10 m walking test at 0-, 48- , and 72-h CSF drainage. one patient missed their 48-h assessment and responsiveness was based on the assessment at 72 h only. The remaining three patients were not able to undergo either baseline or any gait assessments and their responsiveness was based on other domains tested. Median time for the participant group

TABLE 2 | Demographic and clinical data for the retrospective study.

	Total	Complex NPH	Classic NPH	*P*
N	32	13	19	
Age (years)	70.0 ± 8.41	73.1 ± 8.62	67.9 ± 7.80	0.087
Sex (male)	21 (0.66)	11 (0.85)	10 (0.53)	0.061
Comorbidity				
PD or parkinsonism	6 (0.19)	6 (0.46)	0 (0.0)	0.001
AD or other dementia	7 (0.22)	7 (0.54)	0 (0.0)	<0.001
Diabetes mellitus	13 (0.41)	5 (0.38)	8 (0.42)	0.837
Hypertension	25 (0.78)	8 (0.62)	17 (0.89)	0.060
Hyperlipidaemia	19 (0.59)	6 (0.46)	13 (0.68)	0.208
Cardiac disease	9 (0.28)	3 (0.23)	6 (0.32)	0.599
Vascular disease	3 (0.09)	1 (0.08)	2 (0.11)	0.787
CVA/TIA	8 (0.25)	4 (0.31)	4 (0.21)	0.533
Frailty				
CFS score	4.66 ± 0.75	4.92 ± 0.760	4.47 ± 0.697	0.094
mFI-11 score	2.56 ± 1.41	3.23 ± 1.54	2.11 ± 1.15	0.024
Presenting symptoms				
Gait disturbance	32 (1.0)	13 (1.0)	19 (1.0)	N.A.
Tinetti score	15.9 ± 7.99	14.2 ± 6.12	16.9 ± 8.97	0.354
Cognitive impairment	25 (0.78)	10 (0.77)	15 (0.79)	0.892
MMSE score	21.0 ± 7.57	20.2 ± 6.61	21.6 ± 8.37	0.601
Urinary incontinence	18 (0.56)	9 (0.69)	9 (0.47)	0.221
Improvement after VPS				
Gait disturbance	28 (0.88)	13 (1.0)	15 (0.79)	0.077
Post-shunt Tinetti score	20.2 ± 6.66	18.4 ± 5.76	21.4 ± 7.11	0.238
Cognitive impairment	17 (0.53)	3 (0.23)	14 (0.74)	0.005
Urinary incontinence	8 (0.25)	3 (0.23)	5 (0.26)	0.835

Age and assessment scores presented as mean ± standard deviation; all other variables presented as number of patients (ratio). AD, Alzheimer's Disease; CFS, Clinical Frailty Scale; CVA, cerebrovascular accident; mFI-11, 11-factor modified frailty index; NPH, Normal Pressure Hydrocephalus; PD, Parkinson's Disease; TIA, transient ischaemic attack.

to complete a 10 m walk was 12.9 Sec (IQR = 11.8–28.5 Sec) at 0 h and 14.8 Sec (IQR = 12.8–19.1 Sec) at 72 h post-CSF drainage.

Retrospective Study

Thirty two patients with NPH were included in this study—13 Complex NPH with overlay from neurodegenerative diseases and 19 Classic NPH without overlay from neurodegenerative or significant vascular risks. Among the 13 Complex NPH patients, 6 patients had parkinsonism or Parkinson's disease, 4 patients had Alzheimer's disease, 2 patients had vascular dementia, and 1 patient had mixed Alzheimer's and vascular dementia. There was no significant difference in the age and sex of Complex (73.1 ± 8.62 years; 85% male) and Classic NPH (67.9 ± 7.80 years; 53% male) groups.

All patients presented with gait and balance issues, with mean Tinetti score of 14.2 ± 6.12 in Complex NPH patients and 16.9 ± 8.97 in Classic NPH patients. 77% of Complex NPH and 79% of Classic NPH had cognitive impairment, with mean MMSE score of 20.2 ± 6.61 and 21.6 ± 8.37 respectively. 69% of Complex NPH and 47% of Classic NPH reported urinary symptoms. Although differences in symptom presentation between the groups were not statistically significant, 8 of 13 patients (62%) in the Complex NPH group presented with the complete triad of gait disturbance, cognitive impairment, and urinary incontinence, as compared to 7 of 19 patients (37%) in the Classic NPH group.

Comorbidities

Pilot Study

Main comorbidities present were in the domains of hypertension (83%), neurological (83%), endocrine/metabolic (75%), genitourinary (58%), musculoskeletal (42%), and cardiac (33%). 42% had a diagnosis of parkinsonism. We were unable to distinguish vascular risk characteristics unique to responders. Mean scores were 3.83 ± 2.52 using the CMI, 1.42 ± 1.08 using the CCI, and 14.3 ± 4.70 using the modified CIRS. No significant differences were observed between responders and non-responders on all comorbidity scales, although the responders tended toward higher comorbidity scores overall.

Retrospective Study

The retrospective cohort mainly had comorbidities of hypertension (78%), hyperlipidaemia (59%), and diabetes (41%). The proportion of patients with comorbid conditions was not significantly different in Complex NPH and Classic NPH patient cohorts (**Table 2**). For frailty risk, Complex NPH

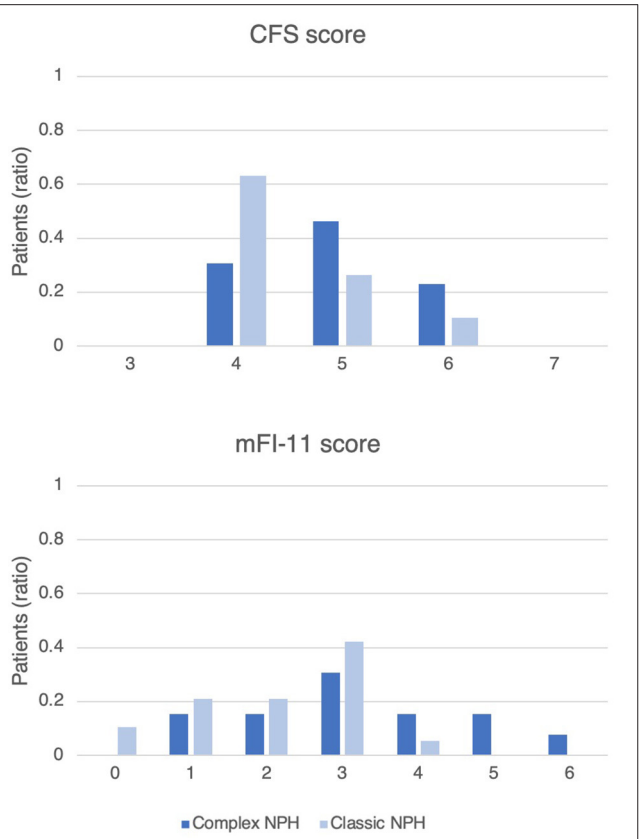

FIGURE 2 | Histogram of frailty scores on the CFS and mFI-11, demonstrating the distribution of frailty risk in Complex NPH and Classic NPH patients. The y-axis represents the ratio of patients in each group.

patients had significantly higher scores on the mFI-11, 3.23 ± 1.54 compared to 2.11 ± 1.15 for Classic NPH patients. **Figure 2** demonstrates the distribution of frailty scores in the two groups.

Correlation Between Imaging Biomarkers, *APOE* Genotyping and CSF Responsiveness

All patients exhibited ventriculomegaly with Evans' and Bicaudate indices ≥0.30 and ≥0.25 respectively. The degree of ventriculomegaly did not distinguish between responders vs. non-responders; there were no significant differences post-drainage in either group. CSF drainage did not influence CSF peak flow rates consistently in either group. One patient was excluded from CSF flow analysis for technical reasons. However, CSF peak flow values showed an interesting dichotomy between groups. Non-responders demonstrated both low and ultra-high values at baseline (3–15 and 65–90 ml/min), whereas responders only demonstrated CSF peak flow in a clustered range (13.2–35 ml/min—**Figure 3**).

White matter hyperintensities scored by the Fazekas scale did not distinguish between responder and non-responder groups.

APOE genotyping for 11 participants did not demonstrate a difference between responders and non-responders in genetic predisposition toward developing Alzheimer's disease (**Table 3**). One non-responder was excluded due to inadequate sample. As the sample size was small, no statistical analysis was performed to compare the distribution of the *APOE* genotypes between groups. As expected, the ε3ε3 genotype was the most common across both groups; this is the most common genotype universally. The ε3ε4 genotype carrying the ε4 risk allele was detected in both groups (1 in 4 responders vs. 1 in 7 non-responders), whilst the protective ε2 allele was found in a responder with the ε2/ε3 genotype (1 in 4 responders).

Patient Outcomes

Pilot Study

We have previously reported clinical outcomes for this pilot study cohort of patients with Complex NPH (13). In summary, there were four CSF responders (and one patient subsequently excluded from analysis due to lack of compliance) who were offered surgical intervention. Six ventriculo-peritoneal shunts were inserted; one procedure was a shunt reinsertion for a patient who required shunt externalization due to a non-infected pseudocyst. Two responders demonstrated higher than expected levels of improvement. Of the non-responders, one patient died from a cerebrovascular accident and another improved post-discharge but declined intervention.

Retrospective Study

Post-surgery, three patients had infections requiring shunt removal, and one patient underwent a shunt revision due to blockage of the shunt. Two patients passed away within 3 years of shunt insertion; one developed sepsis secondary to ventriculitis, and the other had a subdural haematoma after a fall (**Table 4**).

After VPS insertion, significantly more Classic NPH patients had improved cognition compared to the Complex NPH group ($p = 0.005$). Improvement in gait and urinary symptoms was not significantly different between the groups. 26% of the Classic NPH group showed global improvement of the triad, and 42% improved in two domains. Although only 8% showed global improvement of the triad, all Complex NPH patients improved in gait. Tinetti scores were significantly higher in both groups after VPS insertion ($p < 0.001$ in Complex and $p = 0.002$ in Classic NPH).

DISCUSSION

Comorbidities and frailty confound the diagnosis of NPH in older people. With the increasing trend toward a rise in the aging population, encountering patients with concurrent NPH and neurodegenerative disease burden is becoming increasingly common. Modern guidelines and best practices are predominantly focused upon idiopathic NPH, almost at the exclusion of patients who have overlay from neurodegenerative diseases and significant comorbidity burden. Highly invasive procedures such as brain biopsy or advanced imaging biomarkers including SPECT imaging or DTI profiles have shown promise in their utility toward more precise characterization and prognostication of such complicated patients (25, 26). However,

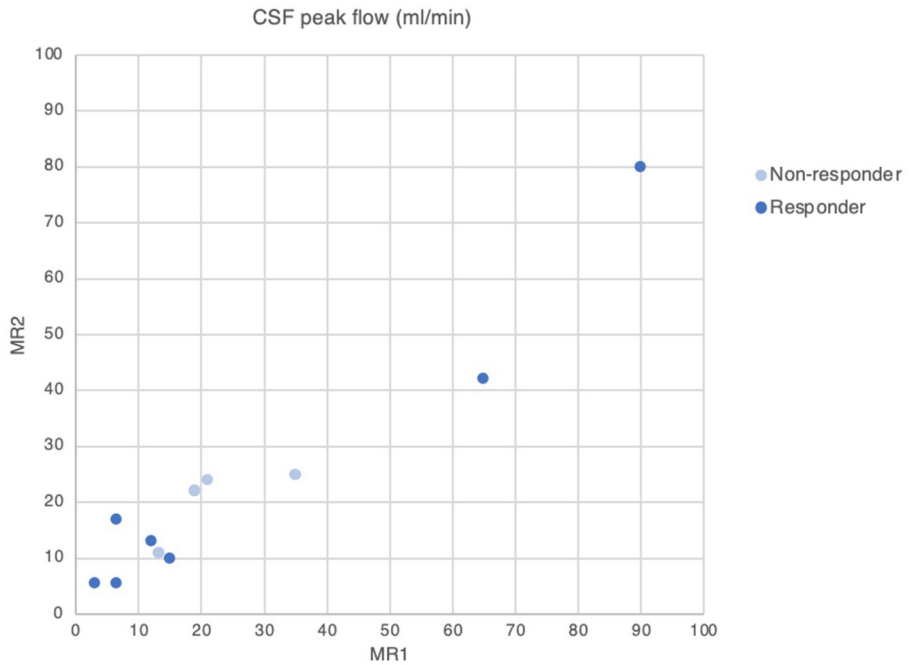

FIGURE 3 | CSF peak flow in NPH patients before (MR1) and after (MR2) CSF drainage.

the usefulness of such tools may be limited by time, expertise, and resources available at the clinical-research interface.

NPH represents a whole spectrum of disease that is greater than the sum of its parts; indeed, it may be considered a model disorder for the development of a new paradigm of clinical thinking, i.e., toward geriatric neurosurgery as a formal sub-specialization of increasing importance. Our study supports such aims. By proposing a more simplistic conceptual framework of characterizing NPH into two distinct cohorts of Classic vs. Complex forms of disease, we aim to aid in a more rapid shorthand for clinical risk stratification and expectations for treatment strategies. We believe ours to be the first study presenting a multimodal biomarker characterization specific to Complex NPH, with a further study documenting longer-term clinical outcomes.

TABLE 3 | *APOE* genotypes in the pilot study cohort.

***APOE* genotype**	**Non-responders ($n = 7$)**	**Responders ($n = 4$)**
ε2/ε2	0	0
ε2/ε3	0	1
ε2/ε4	0	0
ε3/ε3	6	2
ε3/ε4	1	1
ε4/ε4	0	0

APOE ε4 is the main genetic risk factor for Alzheimer's disease. The risk associated ε4 allele conveys an increase in risk of around 2–3x in heterozygous form, and around 15x in homozygous form, while the ε2 allele is associated with decreased risk.

Characterization of Complex NPH

Our pilot study has demonstrated that, in patients with Complex NPH, the presence of a comorbidity burden does not preclude responsiveness to CSF drainage. We found that risk assessment based on NPH-specific comorbidity indices was insufficient in patients with Complex NPH. In Classic NPH, significant differences have been demonstrated between patients with excellent and poor outcome following shunting using the CMI (2 vs. 4 points, $p = 0.001$) (15). Our data confirm that, in patients with Complex NPH, the CMI did not significantly distinguish between responders and non-responders; there was, in fact, a trend toward a higher comorbidity burden in responders. CMI was also not correlated to gait and Tinetti assessment scores.

Such findings are consistent with observations previously noted in NPH literature on comorbidities (12). The ISHCSF report recommended that global measures of risk burden be considered (such as for cardiovascular or ischaemic stroke conditions) when evaluating risk factor profiles. Our data support that need. We have demonstrated, using the modified CIRS and CCI scores, that mean global comorbidity scores of patients with Complex NPH were better than published scores of their hospitalized elderly peers, for whom a range of interventions are routinely considered. This implies that patients with Complex NPH should not be declined surgical intervention based on comorbidities alone. To our knowledge, this is the first study to use both NPH-specific and global risk stratification scores in Complex NPH.

TABLE 4 | Outcomes and complications for the retrospective study.

	Complex NPH	Classic NPH
Shunt revision	0 (0.0)	1 (0.05)
Shunt infection requiring shunt removal	1 (0.08)	2 (0.11)
Deterioration after initial improvement	2 (0.15)	1 (0.05)
Passed away within 3 years of shunt insertion	1 (0.08)	1 (0.05)

Data presented as number of patients (ratio).

Such global risk scales also distinguished between comorbidity risks and responses to CSF drainage. Our study revealed that responders and non-responders had differing profiles of comorbidity risks. A higher overall burden of comorbidities significantly correlated with cognitive impairment in the dementing range at presentation. Certain domains appeared predominant within Complex NPH patients, i.e., vascular risk burden (cardiac disease and hypertension domains) and functional symptomatology (genitourinary, psychiatric and behavioral scores). Hypertension and parkinsonism outweighed other comorbidities in predisposing to non-response following extended CSF drainage. Surprisingly, we found a heavy load of individual comorbidity risks in responders. These included dementia (other), cardiac disease and hyperlipidaemia (all twice as common in responders), cerebrovascular disease (13% higher), as well as diabetes (three times as common). We therefore concluded that there was no evidence that individual comorbidity risks directly correlated with lack of response, but some risks appeared more important than others. Overall, as expected, most of the group were non-responders. The response rate in Complex NPH was lower than that expected of Classic NPH (approximately 33% vs. 60–70% responders) (25, 27). However, responses were comparable to in-house rates for extended CSF drainage in Classic NPH patients without significant comorbidities, but borderline responses to lumbar tap testing.

The striking trends of comorbidity burden in responders may be due to the smaller sample of responders, leading to overrepresentation of risks. However, certain patterns merit further discussion. NPH patients are known to have a higher vascular risk burden than expected (12). Hypertension is more common in NPH compared to age-matched controls, even where other neurological disorders are present. This implies a possible causality in the relationship between hypertension and NPH pathophysiology. It is thought that arterial pulsations in the ICP curve may contribute to the development of progressive ventriculomegaly. However, it is currently unknown if, in established NPH, vascular risk factors actively influence the response of CSF drainage and if so, how they should be scored. Further work is required to understand if remediation of vascular risk factors would promote enhancement of either responsiveness of ventriculomegaly to intervention or host response to compensating for hydrocephalus. Despite this, our results suggest that vascular risk burden, and specifically hypertension, does not necessarily preclude a favorable response to extended CSF drainage.

We also found that vascular imaging burden, namely periventricular and deep white matter hyperintensities, did not distinguish between responders and non-responders. White matter lesions did not improve following CSF drainage in either group. Whilst it could be argued such lesions should be permanent, other groups have demonstrated changes in white matter hyperintensities following CSF drainage in NPH (26). Equally, we found no significant differences in structural measurements for ventriculomegaly, such as Evans' and Bicaudate indices, pre- and post-CSF drainage. This suggests that static uniplanar measurements for ventriculomegaly may be unhelpful in determining the degree of responsiveness in Complex NPH. CSF flow measurements are a more dynamic method of interrogating CSF disturbance but are subject to a multitude of technical considerations (28).

We found that, in Complex NPH, CSF peak flow rates were dichotomized according to group. Non-responders demonstrated CSF peak flow rates at both extremes of low and ultra-high values. By contrast, CSF peak flow rates for responders clustered near the thresholds of 18–24.5 ml/min found in classic shunt-responsive NPH (29, 30). CSF flow dynamics from our Complex NPH cohort, who present late for intervention due to investigations for comorbidities, appear to confirm findings from CSF infusion studies that resistance to CSF outflow have a strong tendency to decrease with time with the duration of symptoms beyond 2 years (31). This suggests there exists a threshold, beyond which damage from CSF disturbance becomes irreversible, leading to likely shunt failure even in the presence of radio-physiological biomarkers of shunt-responsiveness. Recent work from our group confirms the presence of such cohorts (32).

The Value of a Classic vs. Complex NPH Framework

Our retrospective study focused on comparing patients with Classic NPH vs. Complex NPH; the latter group comprise patients presenting with features of NPH, as well as a spectrum of neurodegenerative diseases including parkinsonism/Parkinson's disease, Alzheimer's disease, and vascular dementia. The patients in the group termed Complex NPH were older than the group with Classic NPH. This finding is consistent with current published literature (2, 3, 8, 9). There was no significant difference in distribution of sex in the published work whilst our data showed a predominance in males (8, 9). However, this is likely to reflect the small sample size of our study.

It is not surprising that the group without neurodegenerative disorders did better. However, it was striking that, despite older age and overlay from neurodegenerative disease, all patients with Complex NPH showed improvement in their gait. However, only 15% in this group showed improvement in cognition or urinary incontinence. The published literature regarding coexistence of Alzheimer's disease and NPH are few and their conclusions vary. Savolainen et al. postulated that the relatively high prevalence of Alzheimer's disease in patients with NPH may explain the unsuccessful recovery of many patients after

shunt placement and hence recommended cortical brain biopsy (6). Conversely, studies by Golomb et al. and Yasar et al. concluded that concomitant Alzheimer's disease pathology does not strongly influence the clinical response to shunt surgery (7, 9). A published study in 2015 by Pomeraniec et al. found that those NPH patients with AD will ultimately suffer recurrence and worsening of presenting symptoms, though majority of these patients enjoyed initial clinical improvement following ventriculo-peritoneal shunting (8).

There is a paucity of published data regarding specific outcomes from the concurrence of NPH and vascular dementia; this is likely because the relationship between small vessel diseases to the pathogenesis of NPH has been postulated (28, 33). Conversely, more work has been published concerning NPH with Parkinsonism and its correlation with dopaminergic degeneration. Some studies proposed Parkinsonism to be assessed as one of the outcome measures—these studies had reported good clinical responses after shunt surgery. A recent study done in Taiwan advised using ^{99m}Tc- TRODAT-1 SPECT scans to look for dopaminergic degeneration in order to predict the surgical outcomes because this comorbidity was thought to neutralize the degree of improvement after surgery (12).

Due to the heterogeneity of neurodegenerative disorders, their presentations from typical to atypical and differences in clinical diagnostic criteria, it may be argued that the presence of neurodegenerative diseases themselves may confound the understanding of Complex NPH *per se*. It may be that some neurodegenerative diseases are more important to the understanding of NPH compared to others.

Indeed, some authors have suggested that NPH and Alzheimer's disease are closely connected and may simply occupy different extremes of a common spectrum of disease (34). The deposition of amyloid plaques, the hallmark of Alzheimer's disease, has been proven in NPH, in both PET and cortical biopsy studies (35, 36). A heavier burden of amyloid deposition is thought to predispose to non-responsiveness to shunting. We expected to confirm the presence of risk factors for neurodegenerative disease within the complex NPH cohort. However, similar to findings in classic NPH (37), we found the majority of Complex NPH patients lacked the genotypic risk factor for late-onset Alzheimer's disease. The *APOE* ε4 allele was equally demonstrated in both responder and non-responder groups ($n = 1$ each), although the *APOE* ε2 allele phenotype, thought to be a protective factor, was only exhibited in one responder. The presence of this protective allele in NPH and its contribution to CSF responsiveness is largely unknown in literature but we note our small sample size is a limitation in our further interpretation of these results.

The myriad of neurodegenerative disease subtypes and presentations demonstrates the value of a more simplistic framework of NPH distinguishing Classic vs. Complex NPH cohorts. This is because the specific diagnostic criteria, or lack thereof, of neurodegenerative disorder is not as critical to CSF responsiveness as quantifying the "NPH component of disease" remediable to surgical intervention, regardless of such overlay. We apply the same rationale to the inclusion of significant comorbidities as criteria for Complex NPH; specifically scoring individual comorbidity and frailty burdens alone did not distinguish the two NPH cohorts, whereas regarding their clinical risk stratification as a whole was more effective in separating their differing thresholds of outcomes. In more recent work, we have suggested a further refinement of the term Complex NPH, by expanding on our definition for consistency (38), to address shortcomings in our preliminary approach to this concept.

Limitations

Our study had several limitations. Firstly, our pilot study focused upon the assessment of global comorbidity risks in patients with complex NPH undergoing extended CSF drainage, without considering the wider implications of such findings either to longer-term shunting or the pathophysiology of NPH itself. Further work is needed to characterize the contribution of specific components of vascular risk burden (for example, cardiac vs. hypertensive risks), as well as individual neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. Functional outcome is difficult to test in such patients. The group size was small and reflects both the relatively low incidence of NPH, as well as the smaller subgroup of complex NPH within the overall spectrum of disease.

Despite this, our study numbers do match previous published cohort sizes for extended lumbar drainage (26). Due to the small group size, however, comorbidities and other risks may appear to be overrepresented within the groupings, especially within the responders. This is also true of complication rates, which may appear higher due to the small sample size (16.7% in 6 shunts). Interestingly, these are similar thresholds to the 12–13% complication rates reported by recent large international series in classic NPH (15, 39) and lower than others (40). It may also be possible to pursue strategies to achieve complication rates $<10\%$ with modern shunting (27, 41). Although the response rate in Complex NPH with comorbidities is lower than in NPH without major comorbidities, the risk-benefit ratio for such patients still favors intervention if complication rates for shunting remain comparable to that of Classic NPH.

Indeed, our larger retrospective study demonstrated much lower complication rates specific to shunting interventions, although decline and mortality from overlay of other conditions were still important determinants of longer-term outcomes. In addition, as described above, our aim was to develop a more simplistic conceptual framework for rapidly screening NPH subtypes according to expectations of treatment outcomes. More precise tools for confirming and characterizing neurodegenerative disorders, such as the use of brain biopsy, CSF biomarkers and advanced imaging tools, such as SPECT and DTI, may offer more sophisticated ways of distinguishing these cohorts.

CONCLUSIONS

Our study has demonstrated that the presence of neurodegenerative disorders co-existing with NPH should not be the sole barrier to the consideration of high-volume tap test or lumbar drainage via a specialist NPH programme.

Further characterization of distinct cohorts of NPH with differing degrees of CSF responsiveness due to overlay from neurodegenerative or comorbidity risk burden may aid toward more precise prognostication and treatment strategies. We propose a simplistic conceptual framework to describe NPH by its Classic vs. Complex subtypes to promote the clinical paradigm shift toward subspecialist geriatric neurosurgery by addressing needs for rapid screening tools at the clinical-research interface.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the SingHealth Centralised Institutional Review Board. Written informed consent was obtained from participants of the pilot study. The ethics committee waived the requirement of written informed consent for participation in the retrospective study.

AUTHOR CONTRIBUTIONS

NK, CL, and ETG contributed to the conceptualization and design of the study and wrote the manuscript. ETG, CL, AT, BLT, SL, and JK contributed to data collection and analysis. SK contributed to design of the imaging protocol as well as interpretation. AA–A and VN contributed to genomic analysis. RP, YJT, AN, EKT, ZC, MC, and JP contributed to the characterization of the NPH cohorts and provided feedback on the project. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Update on the Cognitive Presentations of iNPH for Clinicians

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This mini-review focuses on cognitive impairment in iNPH. This symptom is one of the characteristic triad of symptoms in a condition long considered to be the only treatable dementia. We present an update on recent developments in clinical, neuropsychological, neuroimaging and biomarker aspects. Significant advances in our understanding have been made, notably regarding biomarkers, but iNPH remains a difficult diagnosis. Stronger evidence for permanent surgical treatment is emerging but selection for treatment remains challenging, particularly with regards to cognitive presentations. Encouragingly, there has been increasing interest in iNPH, but more research is required to better define the underlying pathology and delineate it from overlapping conditions, in order to inform best practise for the clinician managing the cognitively impaired patient. In the meantime, we strongly encourage a multidisciplinary approach and a structured service pathway to maximise patient benefit.

Keywords: Idiopathic Normal Pressure Hydrocephalus, dementia, Alzheimer's disease, Lewy body disease, progressive supranuclear palsy, corticobasal degeneration, vascular dementia, cognitive

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INTRODUCTION

Idiopathic Normal Pressure Hydrocephalus (iNPH) is a clinical syndrome (1) derived by analogy from NPH but in the absence of a preceding insult (2). iNPH is characterised by the clinical trial of progressive and prominent decline in mobility, followed by less prominent but equally progressive cognitive impairment and bladder disturbance. When supported by ventriculomegaly on brain imaging, the diagnosis should be straightforward. In clinical practise, however, patients suspected of having iNPH frequently present significant cognitive impairment, often preceding or starting at the same time as the mobility disorder. This review focusses on such patients emphasising the clinical, imaging and neuropsychological differential diagnosis, highlighting gaps in our understanding, describing recent developments and making suggestions for future research.

CLINICAL

Cognitive impairment in iNPH is not universal but is frequently present. Insidious onset and more prevalent causes of cognitive impairment, such as vascular dementia (VaD) and Alzheimer's disease (AD), make early diagnosis of iNPH challenging. Significant cognitive impairment in the absence of an early, prominent and typical decline in mobility mandates consideration of other underlying causes given their impact on prognosis and therapeutic decision making.

The typical cognitive profile of iNPH is "subcortical" with impaired attention, reduced psychomotor speed and inefficient memory (3).

VaD results in a similar profile, making these two entities difficult to separate on clinical grounds (4). Cerebrovascular disease (CVD) is frequently present on routine MRI scanning but unless severe its significance is often uncertain. Furthermore, neuroimaging findings between iNPH and CVD overlap.

The commonest cognitive profile of AD, that of progressive amnesia (5), may not be detectable early on. Assessment beyond the Mini-Mental State Examination (MMSE) is required and may include cognitive batteries such as the CANTAB (6). Imaging may identify typical patterns of brain volume loss. CSF biomarkers and amyloid positron emission tomography (PET) may demonstrate AD neuropathological change (ADNC) but do not necessarily prove a causal link to the patient's cognitive impairment. Brain biopsies may be obtained at the time of shunt insertion but are therefore only available for those patients who have already been selected for surgery. Our understanding of the role of those biomarkers in the diagnosis of AD has evolved, recognising that they are increasingly prevalent with age and the apoE4 genotype, even in asymptomatic individuals (7). There is an association between CSF biomarkers and outcome (8, 9). While this is not categorical; it seems most robust for Amyloid-β (Aβ)-42 (10). To complicate matters, clinico-pathological relationships in vascular cognitive impairment (VCI) (11) and AD (12) are variable, co-pathology is common, and their interaction on the phenotype remains poorly understood (13).

Typical presentations of Lewy body disease (LBD) (14), progressive supranuclear palsy (PSP) (15) and corticobasal degeneration (CBD) (16) should not pose differential diagnostic difficulties. However, their combination of physical and cognitive decline may be phenotypically similar to iNPH. In their early stages, hallmark clinical features may not have emerged yet and structural brain imaging can be equivocal. Therefore iNPH has to be considered in the differential diagnosis, but co-pathology and mimicry should not be excluded. In this scenario biomarker findings of neurodegenerative disease are either evidence of pathology or co-pathology. If the index of suspicion for iNPH is high, such as after positive tap test, then shunting should be considered. In the shunt responsive iNPH patient neurodegenerative co-pathology seems to modify the clinical phenotype (17). Abnormal DaT imaging is proof of impaired dopaminergic function in the basal ganglia but is aetiologically non-specific and has also been described in iNPH (18, 19). CSF tau species in PSP and CBD have yielded conflicting results (20), CSF RT-QuIC of alpha-synuclein in LBD and tau in PSP and CBD (21) may be more promising.

Little has been published on frontotemporal dementia (FTD) and iNPH. FTD should not cause differential diagnostic problems as difficulties with mobility occur late in the course of the disease. If present early, and typical for iNPH, co-pathology should be suspected. A case report of a C9orf 72 positive patient, with co-occurrence of typical features of FTD and iNPH, described post-shunt improvements in gait and executive tests, while the behavioural disorder remained unaffected (22).

The differential diagnostic assessment of patients suspected of having iNPH, who have early and/or significant cognitive impairment, requires clinical expertise in cognitive and atypical movement disorders to delineate the presenting symptoms and signs. The assessment should conclude with a probabilistic diagnostic statement attributing the findings either to a single (atypical) morbidity or postulating co-morbidity. Neuroimaging, neuropsychology and CSF biomarkers all provide important diagnostic information, emphasising that the best approach to managing patients suspected of having iNPH with significant cognitive impairment is the protocol-driven multidisciplinary team assessment (23).

The existing evidence of cognitive outcomes after shunting has recently been systematically reviewed. Improvement was found in 61% of patients (24). The authors acknowledge several limitations, including a lack of uniform and standardised cognitive outcome measures, and rated the evidence as low to medium.

Probable iNPH patients who also have clinical features or biomarker evidence of CVD (25), AD (26), or LBD (17), if carefully selected for shunt surgery in a tertiary, multidisciplinary setting, have a good chance of improvement, in their gait disorder. They may also experience partial and temporary improvement of their cognitive impairment.

Long-term outcome studies of treated iNPH patients suggest that the numbers developing dementia are significantly greater than in the general population (27, 28). A longitudinal cohort study applying disease modelling to shunted iNPH patients found an overrepresentation of AD compared to the general population after a medium follow up of 5.3 years. Significant predictive factors were cortical biopsy, medial temporal atrophy on MRI and clinical symptoms (29).

Neither aetiology nor pathogenesis of iNPH are well understood (30). The potential role of a loss-of-function variant in CFAP43 (recently described in a Japanese kindred of familial iNPH and confirmed by a knocked out mouse model) in the aetiology of "sporadic" iNPH is currently uncertain (31). Post mortem studies do not go beyond case series and "definite" iNPH, pathological findings remain non-specific (32, 33). There is controversy over whether pathological findings of AD, CVD, LBD and PSP, represent co-morbidity (17), wrong diagnosis (34–36) or even subtype (26). Impaired glymphatic function has been found in AD and iNPH [for a review see (37)] which is probably mediated by aquaporin channels and represents the putative underlying pathophysiology of hydrocephalus and its compensation mechanisms [for a summary see (38)].

Experience from AD, may serve as a model for future research (see **Table 1**): cooperation between basic science and clinical researchers studying deeply phenotyped, multi-modality assessed and post mortem verified patients has led to increased understanding of aetiology and pathogenesis. These efforts have defined pathological hallmarks and resulted in the development of disease biomarkers. Amyloid PET and CSF amyloid and tau are now available clinically. They have revolutionised clinical treatment trials (39) and are used to screen for ADNC in patients suspected of having iNPH but their role needs to be further clarified. For iNPH, a better understanding of aetiology and

TABLE 1 | The pathological basis of cognitive impairment in iNPH and the treatment response to shunting of cognitive impairment in iNPH requires further study.

Gaps	Future research
Clinico-pathological relationships of cognitive impairment in iNPH not well understood	Longitudinal cohort studies using "deep cognitive phenotyping", multimodal and novel biomarkers, post-mortem
Treatment: only few high-level studies with advanced cognitive outcome measures controlling for confounding factors (age, education, disease duration, co-morbidities, and cognitive practise effects), cognitive outcome secondary	Multicentre RCTs using composite of detailed cognitive and social outcome measures in addition to multimodal biomarkers

pathogenesis, definition of pathological hallmarks and discovery of iNPH specific biomarkers would transform the field. Yet clinical treatment trials in Alzheimer's disease illustrate the challenges of RCT designs in a cognitive disorder. Using multiple modalities and complex sets of cognitive and social outcome measures, they remain in search of the best combination for providing high sensitivity and specificity to reliably demonstrate cognitive change over short time frames (40, 41).

IMAGING

Since the delineation of iNPH as a clinical syndrome, imaging has been needed to demonstrate ventriculomegaly and help evaluate differential diagnoses, including alternative or co-existing causes for cognitive impairment (42). Here, we review the role of imaging in assessing the cognitive aspects of iNPH, focussing on the more recent developments in the evaluation of brain/CSF morphology, diffusion tensor imaging, resting state functional MRI, amyloid PET, and imaging targeting glymphatic clearance.

Morphology: DESH

In the context of iNPH a widely studied pattern of CSF space morphology is the combination of (i) hydrocephalus (Evans index $\geq$0.3), (ii) high-convexity/midline tightness and (iii) Sylvian fissure enlargement. This "disproportionately enlarged subarachnoid-space hydrocephalus" (DESH) (43, 44) is found in many but not all (45) cases of iNPH, and as a potential marker of response to shunt surgery (44, 46, 47), some centres have incorporated it into management pathways (30). The pathophysiological mechanisms underlying DESH are unclear but it is likely to be associated with disrupted CSF dynamics (48).

A number of recent studies have now investigated the presence of DESH in the wider population, where it is found in 1–7% and associated with poorer cognition (49–52). A study examining over a thousand participants with either no or only mild cognitive impairment found that DESH was a predictor of progressive cognitive decline independent of established features including age, cortical thickness, or APOE status (48). There is also evidence that in some cases DESH may be a marker of preclinical iNPH: a long term follow up study of asymptomatic individuals with DESH imaging features found that approximately 17% per year subsequently progressed to symptomatic iNPH (53).

Structural Connectivity: DTI

Diffusion tensor imaging (DTI) is an MRI technique which measures orientation-specific water diffusivity to interrogate brain micro-structure and characterise white matter tracts. White matter injury and dysfunction are proposed components of iNPH pathogenesis and DTI has demonstrated differences in white matter when compared to healthy controls, particularly the corticospinal tract (54) and corpus callosum (55). In several recent studies measures of cognitive impairment in iNPH have been correlated with abnormalities in specific neuroanatomical regions of interest: the forceps minor (56), frontal subcortical white matter (57), right cingulum-hippocampus (58), internal capsules and centrum semiovale (59); these findings are suggestive of the circuits involved in cognitive impairment although study samples are relatively small and patient populations are at risk of other causes of dementia such as AD and VaD. Interestingly, there is evidence that DTI white matter abnormalities can respond to shunt surgery (55, 60) and are potentially partially reversible. Most investigations in iNPH patients have relied on conventional DTI but a few have applied more advanced techniques to further probe tissue microstructure, including kurtosis DTI (57), q-space imaging (61) and neurite orientation dispersion and density imaging (60). There are known technical challenges with comparing DTI datasets between different scanners, however recent experience has confirmed that repeatability and cross-scanner comparability is possible across differing sites (62), allowing future multicentre longitudinal trials.

Functional Connectivity

Whilst DTI provides measures of structural brain connectivity, MRI techniques are also able to probe functional connectivity. Resting state functional MRI (rsfMRI) examines correlations in brain activity, identifying sets of brain regions that activate simultaneously in the absence of a specific cognitive task. One such set, known as the default mode network (DMN) (63), has been widely studied and changes in DMN connectivity have been associated with cognitive dysfunction across a range of different pathologies (64–66). Altered DMN connectivity has been found in iNPH patients where it is associated with executive dysfunction (67, 68) and poorer cognitive outcomes after shunt placement (68).

Moreover, further studies suggest that the dysfunction seen in iNPH may involve multiple networks in addition to the DMN (69, 70) and can partially normalise after a CSF tap test (70).

Glymphatic Imaging

There has been increasing interest in imaging targeting the "glymphatic system": the glia-lymphatic structures which allow the interchange between cerebrospinal fluid and the interstitial space (71–73); this interchange is critical in maintaining interstitial homeostasis and glymphatic dysfunction has been implicated in a range of neurological diseases (74). Multiple *in vivo* MR imaging techniques have been explored (75), particularly

those which directly follow the transport of gadolinium based contrast agents (GBCA) after intrathecal administration (76–79). A number of other pilot studies have used MR techniques which do not require an exogeneous tracer: intravoxel incoherent motion MRI (80), DTI (81), chemical exchange saturation transfer imaging (82) and visualisation of lymphatic channels (83).

When applied in iNPH patients, intrathecal GBCA studies have demonstrated differences in CSF redistribution of tracer compared to controls, with significantly more ventricular reflux (77–79)–a finding consistent with previous radionuclide cisternographic studies (84). Interestingly, there also appears to be delayed clearance of GBCA within brain parenchyma (77, 79), including the entorhinal cortex of the mesial temporal lobe (85). It must be noted, however, that the control populations for the above studies were significantly younger than the iNPH group, and increasing age is known to be associated reduced glymphatic function in animal studies (86). Moreover, in the control population the rate of clearance appears to vary widely (77). Further investigation will be required to confirm these findings. The challenges associated with these techniques are well known (75, 87) and, although none are currently suitable for clinical implementation, this is an area of active development.

Amyloid PET Imaging

Recent work has highlighted the potential of PET imaging for the *in vivo* assessment of amyloid deposition. Amyloid-β (Aβ) is the main component of the plaques found in AD, a frequent co-morbidity in iNPH patients that contributes to cognitive decline (42, 88, 89). Cortical biopsies in iNPH patients frequently detect Aβ, a finding which confers a tenfold increase in the risk of subsequent Alzheimer's disease (90). The PET radiopharmaceutical [^{11}C] Pittsburgh Compound B and newer [^{18}F]-labelled tracers (flutemetamol, florbetapir, florbetaben) now offer the ability to identify Aβ non-invasively (91–94). Multiple studies have demonstrated strong concordance between histopathology for Aβ and amyloid PET imaging in iNPH patients (91, 95–98), offering a new window on the assessment of this significant pathology.

NEUROPSYCHOLOGY

Individuals with iNPH perform significantly worse than controls on various cognitive measures (6, 99–101). Poorer baseline cognitive status is associated with older age, longer disease duration, worse motor performance (100), and increased mortality after shunt surgery (28). However, variable cognitive patterns have been reported in the literature. Many studies demonstrate early executive dysfunction and psychomotor slowing (102), followed by more widespread cognitive decline at later stages (103). Yet others report early and diffuse cognitive changes, including visuospatial dysfunction and memory impairments (99).

Some studies report post-tap test improvements using either cognitive screens (104) or more comprehensive neuropsychological testing (101). Benefits to cognition have also been reported 3, 12 months (105, 106), and 1–3 years after shunt surgery (107). One meta-analysis (108) reported robust improvements in memory and executive function after shunt surgery. However, post-treatment cognitive outcomes can be variable, and their relationship to other iNPH symptoms remains unclear. Bugalho et al. (99) found no relationship between cognition and gait. Yasar et al. (109) found no improvement in cognitive status after shunt surgery, but an improvement in balance and gait; and Grasso et al. (107) found cognition was not maintained alongside gait improvements at 10 year follow up.

Cognitive screens, such as the MMSE (110), are commonly used in assessment, but may be inadequate for differentiating iNPH from other neurodegenerative disorders (3, 6). Furthermore, practice effects are an important consideration when quantifying true change in cognitive performance across serial assessments (111). Significant practice effects are seen in healthy participants (112) and in post-surgical patients (113) within the first 3 months of serial testing, but were not evident in a sample of iNPH patients over 4 consecutive days (114). It is likely that practice effects differ based on a variety of factors, including age, disease status, test selection, and test-retest interval (111). Interestingly, Duff (111) suggests that practise effects themselves may be important predictors of future cognitive status and treatment outcomes.

Even studies that control for practice effects show variable outcomes. Kambara et al. (115) showed that MMSE scores improved at 3 and 6 months post-surgery, but declined in association with age and poorer scores on an iNPH grading scale. In a large, well-designed study, Solana et al. (116) reported improvements in all cognitive domains 6 months after shunt surgery in group analysis, but only 50% of their participants showed significant improvements on individual analysis.

Another reason for variability in cognitive outcomes may be the presence of alternative or co-morbid neurodegenerative diseases. In one study with a median follow up of 4.8 years, 80% of a shunt responsive group demonstrated cognitive decline, and 46% met the criteria for dementia, with the most common diagnoses being AD and VaD (117). The best predictor of dementia was having memory problems as the first symptom (117). Detailed neuropsychological testing comparing iNPH and Parkinson's disease (PD), in their first year of symptom onset, found more frequent (65% iNPH vs. 25.5% PD) and diffuse cognitive deficits in iNPH (118). Laidet et al. (119) reported that iNPH "mimics" – including PD, atypical PD, VaD, and FTD – failed to demonstrate cognitive improvements after CSF tap test, and that verbal fluency scores distinguished iNPH from this mixed-diagnosis group. Similarly, Liouta et al. (120) used comprehensive neuropsychological tests to show that an iNPH group demonstrated post-tap test and post-shunting cognitive improvements (86 and 97%, respectively), while none of a group including VaD, atypical PD, and FTD showed improvements.

In studies examining neurodegenerative biomarkers, the results are also mixed. A higher incidence of AD biomarkers has been reported in iNPH compared with controls, and was associated with cognitive decline at 2 years (121). While individuals with pathological levels of biomarkers on CSF analysis may show cognitive improvements after

tap test (26) and shunt surgery (122, 123), others show less improvements in cognition (122–124). Nerg (6) examined biopsy-acquired AD biomarkers alongside cognition, and found poorer verbal fluency and clock drawing in iNPH, and worse word list learning and picture naming in AD, but little relationship between AD biomarkers and cognitive results.

Specific neuropsychological markers can aid in distinguishing iNPH from other neurodegenerative disorders (6, 117, 125–127), but a discussion of their relative merits is beyond the scope of this review. Therefore, detailed cognitive analysis by a trained neuropsychologist is essential.

Summary of Neuropsychology

Cognitive impairments in iNPH typically involve executive dysfunction, but may be accompanied by more widespread deficits. Poorer cognition is associated with older age, longer disease duration, co-morbidity, variable outcomes after shunt surgery, and increased mortality.

Variable outcomes may be due to inadequate control for confounding factors, inadequate cognitive measures, or whole-group analyses which average-out individual variability (see **Table 1**). Where significant cognitive improvements are reported, effect sizes tend to be small, and hence their clinical relevance to individual patients remains uncertain.

Robust neuropsychological methods that control for practice effects in serial testing are needed (128). Detailed cognitive analysis by a trained neuropsychologist is a crucial part of a wider multidisciplinary consensus diagnosis.

DISCUSSION

We have presented evidence to inform patient management for practitioners confronted with cognitively impaired patients in whom a suspicion of iNPH has been raised. Recent developments have helped to improve differential diagnosis and patient selection for treatment. Neuropsychological differential diagnosis, advanced imaging, and CSF biomarkers are powerful tools starting to enter mainstream clinical use. We encourage active management of these patients through the optimal use of these tools within a structured clinical service. Hence the complex needs of patients with iNPH are best met within a multidisciplinary team. The nosology requires further clarification in prospective cohort studies in cooperation with basic science. An iNPH specific biomarker would revolutionise the field. However, agreement needs to be reached on standardised assessment methods and outcome measures of gait and cognition, where advanced neuropsychological batteries may serve to stratify clinical populations by cognitive features in future RCTs.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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