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Neurorehabilitation – case report collection 2022, 2nd Edition

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Table of contents

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CASE REPORT
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Effects of tDCS on Depression and Comorbid Generalized Anxiety Disorder: A Brain Function Imaging Case Report

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Background: Transcranial direct current stimulation (tDCS) is a type of non-invasive brain stimulation technique that has proven effective for neuropsychiatric disorders. Generalized anxiety disorder (GAD) and depression are common psychiatric disorders that often are comorbid, meaning they occur simultaneously. Current evidence supports the value of tDCS for GAD. The objectives of this report is to explore the effect of tDCS on clinical symptoms and cerebral function in a patient with comorbid GAD and depression.

Methods: Our subject was a semiprofessional athlete diagnosed with comorbid GAD and depression. Symptoms included palpitations, sweating, continuous tension, and anxiety. We designed a B-A-B experimental protocol and used the Beck Anxiety Index (BAI), Beck Depression Index (BDI), and Pittsburgh Sleep Quality Index (PSQI) as assessment tools. Treatment consisted of 2 series of 15 days each, separated by a 3-week washout period. We collected functional near-infrared spectroscopy (fNIRS) data before and after both series, as well as fNIRS data immediately after the first treatment in both series. In addition, we collected functional magnetic resonance imaging data before and after the second series.

Results: After the first series, the scores of the three questionnaires (BAI, BDI and PSQI) decreased significantly, which showed the trend of improvement. The functional connection of bilateral prefrontal partial channels decreased significantly immediately after tDCS treatment. The results of the fNIRS before the second-series treatment showed that prefrontal connectivity returned to the state before the first intervention after the washout period. The results of the fNIRS after the second series treatment showed that the symptoms of depression and anxiety alleviated. The results of the fNIRS showed that the prefrontal connectivity decreased again.

Conclusion: In the treatment of comorbid GAD and depression, tDCS can alleviate symptoms and improve sleep quality and social behavior. Brain imaging is widely used to observe functional changes by tDCS such as fMRI and fNIRS. The study also showed that fNIRS can be a safe, simple, and efficient method to assess brain activity.

Keywords: transcranial direct current stimulation, generalized anxiety disorder, depression, functional near-infrared spectroscopy, fMRI

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INTRODUCTION

Generalized anxiety disorder (GAD) and depression are common psychiatric disorders that often are comorbid (1). The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), published by the American Psychiatric Association, substantially revised the diagnostic criteria for GAD to distinguish it from mood and adjustment disorders, other anxiety disorders, non-pathological anxiety, and other diseases, while it is usually used as an additional diagnosis for other mental illnesses (2). The DSM-V further refined the definition of GAD to include individuals who may have difficulty inhibiting their fears and worries, and who often experience fatigue, difficulty concentrating, irritability, and other symptoms such as muscle tension and sleep disturbance (3). Many studies have shown that anxiety and depression can be lifelong comorbidities (1). For treatment of GAD, psychotherapy is first considered, and psychotropic drugs are also usually recommended to control clinical symptoms of anxiety and depression after diagnosis. However, some patients refuse to adopt psychotherapy or psychotropic drugs. Research has shown non-invasive brain stimulation to be effective and more easily accepted than drugs for psychiatric disorders (4). Transcranial direct current stimulation (tDCS) is a type of non-invasive brain stimulation that regulates the excitability of the cortex by delivering a weak direct current to the brain with two electrodes of opposite polarity (anode and cathode) placed on the scalp (5). Generally, anodic stimulation can excite neurons, whereas cathodic stimulation leads to inhibition (6).

Compared to the side effects of drugs, tDCS is a safer treatment technique. If it is used according to the standard procedures recommended by the latest clinical studies of psychiatric disorders, side effects are rare (5). Common side effects of tDCS include redness, itching, slight tingling, and mild superficial electrolytic burn (7), and these are more acceptable to patients than drug side effects.

MATERIALS AND METHODS

Materials

Our subject was a 33-year-old male semiprofessional athlete who experienced recurring panic attacks and other anxiety symptoms. During an inquiry into his medical history, the patient reported heart discomfort, and the physician ordered a 24-h dynamic electrocardiogram for him. The results showed an average heart rate of 43 beats per minute, with bradycardia as slow as 28 beats per minute at night. Thus, the patient repeatedly worried about sudden death due to bradycardia, and became afraid of his training course. He developed other symptoms such as palpitations, sweating, and tremor, with continuous tension and anxiety during the days. After meeting with a psychiatrist, the patient was diagnosed with GAD, depression, and sleep disorders. The diagnosis of comorbidity was made by psychiatrist according to international Classification of diseases-10(ICD-10). He reportedly worried a lot and had sleep problems due to life pressure and financial pressure. He complained of nightmares, pain, and discomfort during sleep, and reported being easily awakened at night even though he could fall asleep normally. The patient also had a history of alcohol intake. Our patient refused to adopt psychotherapy or psychotropic drugs. It was known that he had treatment with traditional Chinese herbs and acupuncture for his mental illness, but there was no obvious improvement. Thus, he was referred to us for further treatment, and he was willing to try tDCS treatment. The Beck Anxiety Index (BAI), Beck Depression Index (BDI) (8), and Pittsburgh Sleep Quality Index (PSQI) (9) before the first treatment were assessed as 46, 10, and 12, respectively, which classified the patient as having severe anxiety, moderate depression, and normal quality of sleep.

Methods

All treatments and data acquisitions were performed in the Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Chinese Traditional Medicine. We used a B-A-B design for the treatment protocol (**Figure 1**). In a single case research, all designs should be attributed to the logic of how to arrange baseline condition (A) and intervention condition (B) (10). The patient may have violent tendencies due to emotional problems, for ethical reasons, we did not collect baseline data in order to avoid potential risks to ourselves and others. Thus, a B-A-B design was adopted, and the experimental sequence was intervention, removal of intervention and re-intervention. The patient accepted the treatment plan after we explained the principles of tDCS. The first intervention series was 15 treatments of tDCS, 5 times a week for 3 weeks, with no intervention on weekends, and this experiment was designed according to another study published in 2014 (11). We used a Volcan model VC-8000F (Nanjing, China) for the treatments. For each 30-min treatment, the anode of the stimulator was placed on the left dorsolateral prefrontal cortex (DLPFC), while the cathode was placed on the right shoulder. During the first treatment with a 1.4 mA current, the patient suffered a mild superficial electrolytic burn, and so we decreased the dose to 1.0 mA. After 1 week, the dose was increased to 1.2 mA. To evaluate the cerebral functional connection of the patient, fNIRS was conducted before and immediately after the first treatment as well as after the last treatment. We also orderd fMRI for the patient, but he refused to complete the evaluation due to fear of the closed environment of the fMRI laboratory. Treatment was suspended for a 3-week washout period between the first and second series. The patient was treated with traditional Chinese medicine and acupuncture during both the treatment series and the washout period.

After the 3-week washout period, the therapists repeated a second series of evaluation and intervention. In this series, we suggested the patient to accept the fMRI. After negotiation with the patient, the patient still expressed fear of the closed environment of the fMRI laboratory, however, the patient told us that he was willing to have a try. This change of his attitude also indicated the improvement of his emotion. This series included functional magnetic resonance imaging (fMRI) scans before the first treatment began and after the last one ended, to explore the effects of tDCS on the subcortical nucleus. As in the first series, the tDCS dose was 1.2 mA and the duration was 30 min. After 15 treatments, we performed fNIRS, fMRI, and behavioral assessments on the patient.

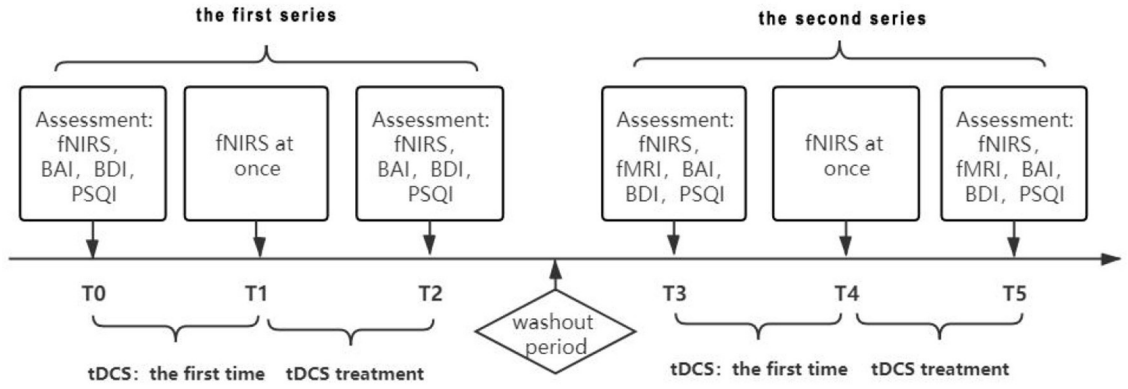

FIGURE 1 | The experimental protocol.

RESULTS

Physical Examination

The patient suffered a mild superficial electrolytic burn in the first series of tDCS treatment. There is a 1 × 1 cm-shallow red mark in the forehead of the patient. During the following treatment and follow-up, we paid close attention to the problem of skin lesion, the skin lesion healed in a week and did not appear again in the following treatment. In the follow-up, we also checked the stiuation of the skin lesion and acceptability of tDCS and the patient indicated that he was very likely to accept the tDCS treatment and the side effects. The patient also told us that the skin lesion did not affect his daily life and treatment.

BAI, BDI, PSQI Scores

After the first series, the BAI score decreased from 46 to 36 and the BDI score decreased from 10 to 9. The total PSQI score decreased from 12 to 7, while the sub-score of sleep quality and disorder declined from 3 to 2, the sub-score of persistence declined from 2 to 1, and the sub-score of daytime dysfunction declined from 3 to 1.

After the 3-week washout period, we evaluated and intervened again. The pre-intervention evaluation showed that the BAI score was 36, the BDI was 8, and the PSQI score was 4. The sub-scores of sleep quality, sleep disorder, and daytime dysfunction were all decreased by 1 point in the PSQI assessment. After 15 treatments, the results showed a BAI of 37, BDI of 7, and PSQI of 3 (**Figure 2A**). After an initial decrease, the BAI score remained flat with no significant difference, while the rest of the scores continued to decrease. Sleep problems improved significantly, and the depression level was reduced to the level categorized as "light."

fNIRS Data

We collected the fNIRS data with a 45-channel device (NirSmart, Huichuang Medical Equipment, Danyang, China). In the resting state data processing, the Pearson correlation coefficient of oxyhemoglobin on time series of each channel was defined as the resting state functional connection strength between corresponding channels. The fNIRS performed after the washout period and before the first treatment of the second series showed that the patient's prefrontal connection level had returned to the state before the first series (0.66609). The results of the fNIRS immediately after the first intervention of the second series showed that the connection level decreased again (0.56749). At the end of the second series of 15 interventions, the prefrontal connection level reached the highest state (0.71045) (**Figure 2B**). This result may have been influenced by external factors such as the patient watching a jiu-jitsu match, or from experiencing fear and anxiety in anticipation of the fMRI test.

The results showed that the functional connection strength of bilateral prefrontal partial channels decreased significantly after tDCS treatment (**Figures 3A,B**). The mean Pearson correlation coefficient of the prefrontal lobe before the first intervention of the first series was 0.61181. After the first tDCS intervention, it was significantly reduced to 0.24195. Following the complete series of 15 interventions, the mean Pearson correlation coefficient remained at a low level (0.2482). After that, treatment was suspended for a 3-week washout period.

fMRI Data

The fMRI data acquisition was performed with a 3T MRI scanner (Siemens Verio, Erlangen, Germany). We collected the resting state data of the patient, and all statistical analysis was performed with the CONN toolbox. We used a seed-to-seed analysis to assess differences in connections between brain regions before and after treatment in the second series. False discovery rate (FDR) corrections for multiple comparisons was $p < 0.05$. The seed-to-seed analysis of resting state data showed a significant hypo-connectivity between the left amygdala (AMYG.L) and left prefrontal cortex (PFC.L) ($p = 0.0391$, FDR corrected) and a significant hyper-connectivity between the left median cingulate and paracingulate gyri (DCG.L) and right supramarginal gyrus (SMG.R) ($p = 0.0262$, FDR corrected) (**Figure 3C**). However, no significant differences were found using the AMYG.L, PFC.L, DCG.L, and SMG.R as seeds in a seed-to-voxel analysis.

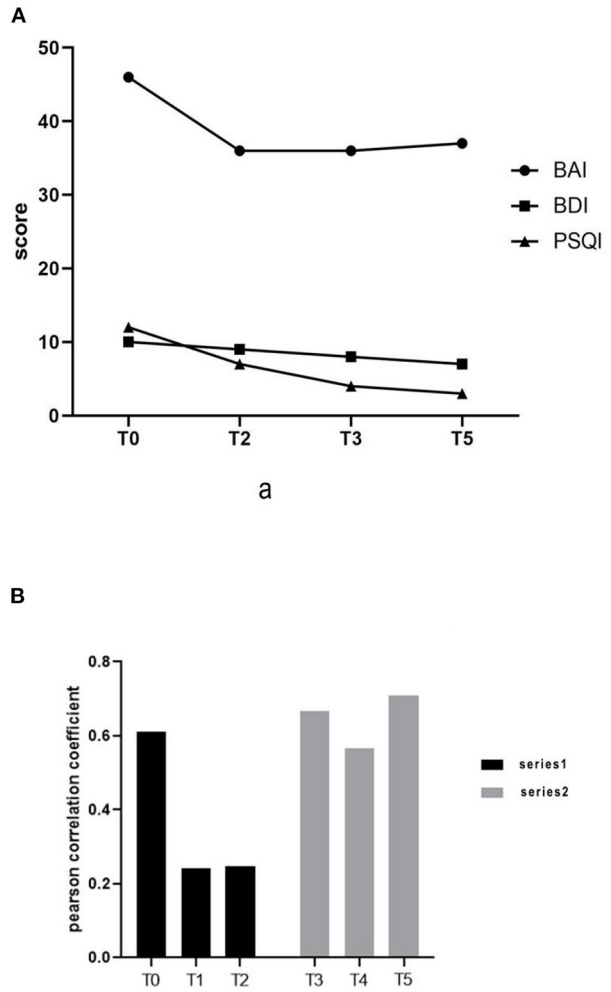

FIGURE 2 | (A) Changes in Beck Anxiety Index, Beck Depression Index, and Pittsburgh Sleep Quality Index scores. **(B)** Functional connection of prefrontal cortex.

DISCUSSION

In 2014, Shiozawa et al. (11) published a case report of the use of tDCS to treat GAD. Unlike our case, that study used the cathode to treat the right DLPFC, and only the anxiety and depression scale were used for evaluation. The results showed that tDCS did have a significant effect on GAD. A systematic review by Vicario (4) points out that most of the current studies of tDCS intervention on GAD use cathodic inhibition, but that anodic stimulation using tDCS is becoming a trend. Research published by Ana Lucia (12) took into account the comorbidity of depression and anxiety, performed anode stimulation on the left DLPFC, and used the anxiety and depression scale to evaluate the short-term effect of tDCS in the treatment of GAD. This was the first randomized controlled trial to detect the short-term effect of tDCS on GAD, but the effect was not significant due to the relatively short intervention period.

Drawing from the positive results of individual cases and randomized controlled studies, we selected anode intervention on the left DLPFC for 15 days (except weekends) to observe the long-term effects of anode tDCS intervention in our patient with comorbid anxiety and depression. In addition, we also used fNIRS and fMRI to monitor and analyze the brain function. At present, ours is the first study we have found using fNIRS and fMRI data to obtain a more detailed understanding of the effects of tDCS on the brain regulation in GAD.

In our case study, the behavioral assessment showed that tDCS did have an effect on the patient's anxiety symptoms, and the reduction in anxiety lasted for a significant period of time. However, the second series achieved only a maintenance effect and not a diminishing effect. This may have been due to increased anxiety caused by factors in the patient's environment.

Compared with the first series of the treatment, during the second series, the patient's mental symptoms were more stable, and he was motivated to participate in more social activities such as doing high-intensive sports due to improved mood. This increased social activity may have increased his anxiety. For example, before his last two treatments, the patient watched a jiu-jitsu game and left the venue due to discomfort and fear caused by the environment, and reported that it took him 4 h to calm down. The patient's anxiety symptoms might have more significantly improved if he were able to moderate and reduce his participation in situations that increased anxiety. In contrast, through the behavioral evaluation, we observed a steady decline in the patient's depression index and sleep index values. Depression and sleep conditions continued to improve even while the patient was in the washout period. The results support the use of tDCS for patients with depression or sleep disorders. However, the non-specific interventional effects by care-giving and placebo effects by patients' expectations can also contribute to the behavioral changes, which could be relevant confounding factors when the research is based on a single case.

The fNIRS data showed that in the first series, the reduction in prefrontal cortex connection was more obvious than in the second series, both after the first tDCS treatment and at the end of the series. Functional connection values in the first data collection following the washout period increased compared to the values in the first series. We speculated that the increase was due to the suspended tDCS treatment, but we did not rule out mood change caused by increased social activities and the patient's self-reported fear of the fMRI examination in the later period.

The increase in fNIRS connection values after the washout period and the relative reduction after the first intervention indicate that the patient's emotional state was volatile, but the short-term effectiveness of tDCS was evident. The increase in values at the end of the second series showed that adverse external events can have a great impact on patients, which suggests that we should expand the sample size in subsequent studies to minimize the impact of such events.

Although there are certain differences between the results revealed by fNIRS and the behavioral results, we conclude that fNIRS may be a more rapid and effective way to monitor a patient's emotional fluctuations. However, compared with fNIRS, the fMRI results showed no significant difference before and

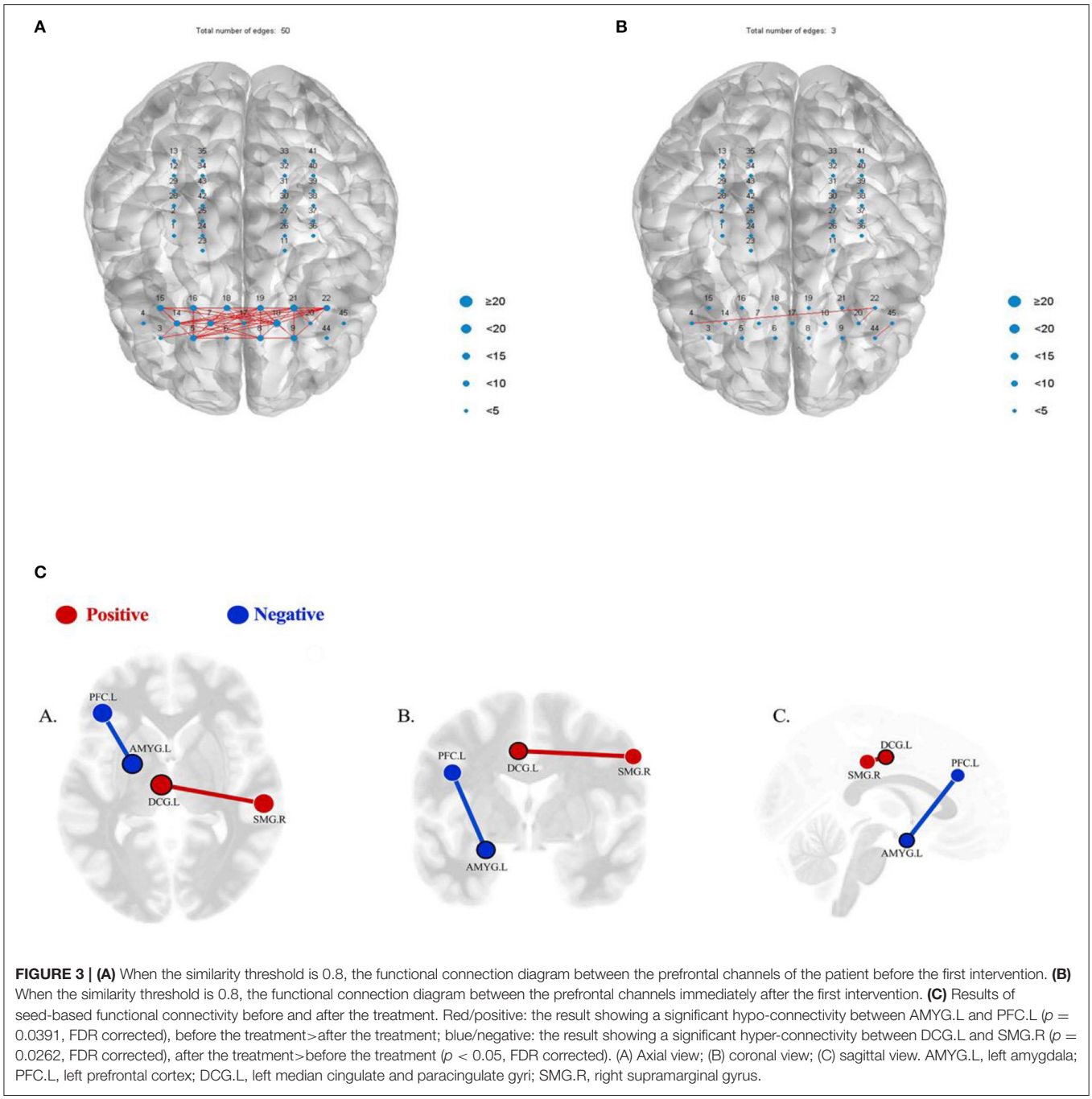

FIGURE 3 | (A) When the similarity threshold is 0.8, the functional connection diagram between the prefrontal channels of the patient before the first intervention. **(B)** When the similarity threshold is 0.8, the functional connection diagram between the prefrontal channels immediately after the first intervention. **(C)** Results of seed-based functional connectivity before and after the treatment. Red/positive: the result showing a significant hypo-connectivity between AMYG.L and PFC.L ($p = 0.0391$, FDR corrected), before the treatment>after the treatment; blue/negative: the result showing a significant hyper-connectivity between DCG.L and SMG.R ($p = 0.0262$, FDR corrected), after the treatment>before the treatment ($p < 0.05$, FDR corrected). (A) Axial view; (B) coronal view; (C) sagittal view. AMYG.L, left amygdala; PFC.L, left prefrontal cortex; DCG.L, left median cingulate and paracingulate gyri; SMG.R, right supramarginal gyrus.

after the second series of treatments. Because fMRI can increase anxiety in the patient, it may not be the best tool to evaluate the patient's emotional fluctuations, but it could still be useful to observe the influence of tDCS and environmental factors on the patient's brain connections.

Our case study showed that tDCS intervention for the patient with GAD comorbid with depression did have some effect, particularly on the patient's depression and sleep conditions. However, after initial improvement, the patient's anxiety level showed no additional progress from the end of the first series through the end of the second. This result may be related to the patient's increased participation in social activities in the later period, or it may be related to the dose. Additionally, the limitation of this case report is lack of quantitative data by means of standardized measures regarding functional outcomes. Therefore, in the future, we may focus on the effects of different doses and exercise conditions on patients. Most of the measures studied here showed major changes during the first week, but not thereafter. This may indicate that a shorter period of stimulation (or smaller number of stimulation) is sufficient to

obtain maximum effects of tDCS, which is worthy of further exploration and research in the future. In addition, literature related to GAD intervention (8) mentions that some patients continue using drugs while undergoing tDCS. It may be that in patients who use drugs combined with tDCS, anxiety symptoms can improve more quickly and effectively. In recent studies, we have learned that tDCS does have advantages for mental health, so in the future we may focus on the exploration of multimodal brain functional mechanisms.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YW and LT designed and conceptualized the study, drafted the manuscript, and created the therapeutic intervention. XS and ZZ collected the information and organized the data. YL and CS analyzed the data. All authors approved the final version of the manuscript.

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CASE REPORT
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Case Report: Functional Outcome of COVID-19 Subjects With Myasthenia Gravis and Critical Illness Polyneuropathy

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Background: The COVID-19 disease can affect subjects suffering from myasthenia gravis (MG) and worsen its clinical course, leading to intensive care unit (ICU) admission. Critically ill subjects can develop a neuromuscular complication called ICU-acquired weakness (ICUAW). This disorder has also been detected in ICU subjects with COVID-19, but the association between MG and ICUAW has never been described in critically ill patients. We describe the case and functional outcome of a COVID-19 patient suffering from MG who developed critical illness polyneuropathy (CIP).

Case Presentation: A 66-year-old man with a history of hypertension and ocular MG had COVID-19 and required ICU admission. The patient underwent mechanical ventilation and tracheotomy and was treated with remdesivir and corticosteroids. Fifteen days after admission, he complained of tetraparesis without the ocular involvement that remained unchanged despite the increase in anticholinesterase therapy. The length of stay (LOS) in ICU was 35 days. On day 2 of admission, the patient underwent a frontal muscle jitter study that confirmed the MG, and electroneurography (ENG) and electromyography (EMG) that showed overlapping ICUAW with electrophysiological signs characteristic of CIP. The cerebrospinal fluid (CSF) showed normal pressure, cell count, and protein levels (<45 mg/dl) without albumin-cytologic disassociation. The CSF/serum glucose ratio was normal. The CSF culture for possible organisms, laboratory tests for autoimmune disorders, the panel of antiganglioside antibodies, and the paraneoplastic syndrome were negative. Strength and functional outcomes were tested with the MRC scale, the DRS, Barthel scale, and the Functional Independence Measure (FIM) at admission, discharge, and follow-up. Muscular strength improved progressively, and the MRC scale sum-score was 50 at discharge. Anticholinesterase therapy with pyridostigmine at a dosage of 30 mg 3 times daily, which the patient was taking before COVID-19, was resumed. His motor abilities recovered, and functional evaluations showed full recovery at follow-up.

Conclusion: In the described subject, the coexistence of both neuromuscular disorders did not affect the clinical course and recovery, but the question remains about generalization to all patients with MG. The rehabilitation interventions might have facilitated the outcome.

Keywords: neurology, myasthenia gravis, COVID-19, ICUAW, neurorehabilitation, outcome

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INTRODUCTION

COVID-19 viruses cause characteristic interstitial pneumonia, which causes respiratory failure, but multi-organ systems are also involved, particularly the nervous system, both the central and the peripheral components. Variable conditions and neuropathies affecting the peripheral nervous system (PNS), including Guillain-Barrè syndrome and its variants (1), cranial multifocal neuropathy, dysautonomia (2), and brachial plexus lesion (3), have been described in subjects with COVID-19. Furthermore, neuromuscular disorders such as myalgia, myositis, and, in particular, myasthenia gravis (MG) have also been described (4–6). With regard to the association between MG and the COVID-19 infection, it has been observed that COVID-19 can exacerbate myasthenic crisis (7), promoting worsening of the clinical course and causing severe respiratory failure requiring intensive care unit (ICU) admission (8). It is well-known that, during and after ICU stay, critically ill subjects can develop a neuromuscular complication called ICU-acquired weakness (ICUAW) that embraces a spectrum of disorders including critical illness polyneuropathy (CIP), critical illness myopathy (CIM), and overlapping forms (CIP/CM or CIPNM) (9). The occurrence of ICUAW types in patients with COVID-19 has been reported (10), and this neuromuscular disorder resulted in a common neurological complication in this population during ICU stay. Comorbidities might complicate the course of patients with COVID-19, but concomitant neuromuscular disorders such as MG and ICUAW have not been reported. We have described the case and functional outcome of a man with COVID-19 suffering from MG who developed critical illness polyneuropathy (CIP).

CASE DESCRIPTION

After obtaining the approval of the local ethics committee (Section Giovanni Paolo II- IRCCS Casa Sollievo della Sofferenza) and written informed consent, we report the case of a 66-year-old man with a history of hypertension and ocular MG. This disorder was diagnosed 2 years before the pandemic onset by electromyography (EMG) and frontal muscle jitter study at the neurology unit of our hospital (**Figure 1**). AChR antibodies were detected, and and the thymoma ascertainment results were negative. He undertook pharmacology therapy consisting of pyridostigmine at a dosage of 30 mg three times daily, which was efficacious in treating myasthenic symptoms. The strength quantification performed by the Medical Research Council (MRC) was normal before the pandemic. At the beginning of December 2020, he developed fever, cough, myalgia, and dyspnea with progressive severe respiratory failure, which required ICU admission. He underwent chest computer tomography (CT) and nasopharyngeal swab that were positive for COVID-19 and was treated with remdesivir and corticosteroids. The patient underwent mechanical ventilation and tracheotomy. Laboratory tests did not detect an increase in the serum CK level. He also developed infections caused by multi-drug resistant germs, including *Klebsiella pneumonia*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, and underwent multiple antibiotic therapies. The Simplified Acute Physiology Score was 35. During the ICU stay, 15 days after admission, he complained of muscle weakness that evolved into the manifestation of tetraparesis without ocular involvement. Despite this development, pyridostigmine was increased to 60 mg three times daily; the strength remained unchanged. The length of stay (LOS) in ICU was 35 days. After improvement of the clinical conditions, the patient was transferred to our neuro-rehabilitation (NR) unit. At admission, the patient breathed spontaneously but needed 3 L/m oxygen by mask. Capillary oximetry was 97%; he had a central venous catheter, a tracheal tube, and a nasal-gastric tube for nutrition. The neurological picture showed severe tetraparesis that involved predominantly the lower limbs, and he had absent tendinous reflexes. No deficit in ocular or facial muscles was detected, and superficial and deep sensibilities were normal. Given the neurological feature, on day 2 of admission, the patient underwent electroneurography (ENG), electromyography (EMG), and frontal muscle jitter study that confirmed MG and showed overlapping ICUAW. In this respect, the electrophysiological exam revealed signs characteristic of CIP (**Table 1**). However, a lumbar puncture was performed, and cerebrospinal fluid (CSF) was collected and processed for standard analysis to exclude Guillain-Barrè syndrome and polyneuropathies of different etiology. Pressure, cell count, and protein levels (<45 mg/dl) of the CSF were normal without albumin-cytologic disassociation. CSF/serum glucose ratio was normal. The CSF culture results for possible organisms, such as human immunodeficiency virus, hepatitis B virus, hepatitis C virus, bacteria, Mycobacterium tuberculosis, fungi, Borrelia, enteroviruses, Herpes viruses, and CMV, were negative. Similarly, the laboratory test for autoimmune disorders, including lupus anticoagulant, anticardiolipin antibodies, a panel of antiganglioside antibodies, including anti-GM1, -GM2, -GM3, -GD1a, -GD1b, -GT1b, and -GQ1b, and a panel for paraneoplastic syndrome, were negative.

Strength and functional evaluation were quantified through the MRC scale sum-score, the Disability Rating scale (DRS), the Barthel scale (BS), and the functional independence measure (FIM) at admission, discharge, and 6 months of follow-up. During NR stay, the patient underwent a personalized and tailored rehabilitation treatment for 3 h daily, 6 days a week. Furthermore, he performed 2 h of daily electrical muscular stimulation on the lower limbs by placing surface electrodes on the quadriceps and anterior tibial muscles bilaterally. The muscular strength improved progressively, and the MRC sum score was 50 at discharge. The anticholinesterase therapy with pyridostigmine at the dosage of 30 mg three times daily, the same that the patient was taking before he had COVID-19, was resumed. His motor abilities recovered and, at discharge, he was able to walk without support but remained with left foot drop, which required the application of an ankle-foot orthosis (AFO). Furthermore, he complained of mild fatigue with reduced endurance, which improved over time. At follow-up, the MRC scale sum score and all functional scale scores resulted to be normal (**Table 2**). The LOS in neuro-rehabilitation was 42 days.

SFJ couple	N	MCD	MSD
1.1	55	180.86	151.08
2.1	69	124.86	125.38
3.1	98	284.95	456.38
Mean		178.22	244.28
Median		160.86	151.08
Numbers			

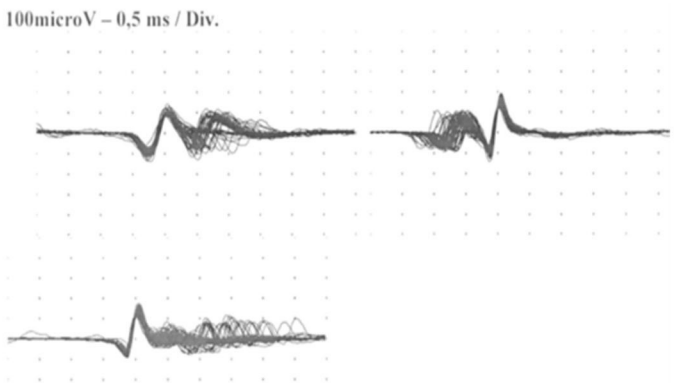

FIGURE 1 | SFEMG jitter by frontal muscle. SFEMG, single fiber electromyography; SFJ, single fiber jitter.

DISCUSSION

We reported a patient with COVID-19 suffering from MG that developed CIP during the ICU stay. To the best of our knowledge, this is the first case of a subject who had ICUAW that was associated with MG. After rehabilitation, the patient gained back his motor ability, although he required the application of AFO to the left limb and reached full recovery 6 months after discharge. COVID-19 might favor MG. AchR antibody-associated MG (5), MUSK antibody-associated MG (11, 12), and new-onset ocular MG (6) have been reported, but our patient suffered from MG before the pandemic. Viral and bacterial infections, including COVID-19, are established triggers for a myasthenic crisis in patients with preexisting MG (7). Thus, it is conceivable that, in our patient, COVID-19 itself or an exacerbation of myasthenic crisis induced by COVID-19 might have caused respiratory failure, which required ICU admission. The clinical course of patients with MG and COVID-19 can be variable, although the infection does not dramatically influence the course of MG (13). In this respect, long-term chronic corticosteroid treatment, older age, and previously unsatisfactory control of MG symptoms are risk factors for worsening of outcome and high mortality rate in these patients (8, 14). Furthermore, comorbidities are relevant, affecting the clinical course and favoring myasthenic exacerbation, particularly in elder patients with MG (15, 16). In those with MG and COVID-19, comorbidities could be responsible for poor outcomes (17–19). Although our patient developed CIP, he did not have any of the factors, and this condition might explain the favorable outcome of the myasthenic disorder. A recent study has detected a favorable outcome in people with MG vaccinated against COVID-19 and has reported 44% of mortality due to COVID-19 in unvaccinated patients (20). Our patient did not receive any dose of vaccination at the time of COVID-19 contraction because vaccines were not available; nevertheless, he reached full recovery. The impact and effects of anti-COVID vaccination on people with MG are important, but several questions are still unclear. There are no specific guidelines concerning vaccinations of patients with MG, and several doubts remain unsolved, including efficacy, timing and type of vaccine, and risk of exacerbation of MG after COVID-19 (21). Regarding the occurrence of ICUAW in this subject, several hypotheses can be made. ICUAW is a common neurological complication in ICU patients, and a median prevalence of 43% has been reported (22). Therefore, ICUAW could occur regardless of clinical conditions that require ICU admission. In this respect, ICUAW has been frequently detected in critically ill subjects with COVID-19 who experience a severe inflammatory condition (23). The same risk factors and the severity of the systemic disease itself might favor the occurrence of ICUAW in subjects with COVID-19. Therefore, unsurprisingly, our patient with MG developed ICUAW. This disorder can produce severe impairment and persistent disability with poor quality of life. Concerning that point, although several questions remain unsolved about the rehabilitative strategies to carry out on these subjects, a recent systematic review has detected that 70.3% of ICU survivors with ICUAW could achieve a good recovery (24). However, the outcome in patients with COVID-19 who developed ICUAW remains uncertain. We have recently described the clinical course and functional outcome of four patients with COVID-19 and ICUAW, and, at the same time, we performed a review of the literature on this issue. Regarding the functional outcome, the percentage of subjects with COVID-19 and ICUAW who gained good recovery was lower than that of general patients with ICUAW. On the other hand, we observed that the functional outcome in our subjects with COVID-19 and ICUAW was in line with the findings reported in the literature. Indeed, three out of four subjects (75%) reached full recovery. Several reasons may explain this contrasting finding: one could be the measurements used for the functional evaluation and another one could be that ICU specialists may have preferred to describe this neurological complication in patients with COVID-19 during the ICU stay or at discharge and overlooked to report the recovery. However, in particular, the main reason could be that the rehabilitative

TABLE 1 | Neurophysiological study of patient.

Nerve	Amplitude mV	Velocity m/s
L ulnar motor		
distal	4.6	
proximal	3.2	46.2
R ulnar motor		
distal	4.2	
proximal	3.6	45
L ulnar sensory	-	-
R ulnar sensory	2.3	44
L median motor		
distal	4.5	
proximal	3.7	46
R median motor		
distal	4.2	
proximal	3	45
R median sensory	-	-
L median sensory	1.5	43
Lower Limb		
R peroneal		
distal	<0.2	
proximal	<0.2	35.5
L peroneal		
distal	<0.2	
proximal	<0.2	40
R tibialis		
distal	<0.2	
proximal	<0.2	33
L tibialis		
distal	<0.2	
proximal	<0.2	37.8
Sural		
Right	-	-
Left	-	-

TABLE 2 | Strength and functional measures scores.

	EN/EMG	MRC	BS	DRS	FIM
Admission	CIP	26	5	10	48
Discharge		50	95	4	115
Follow-up		60	100	0	126

CIP, critical illness polyneuropathy; MRC, Medical Research Council scale; BS, Barthel scale; DRS, disability rating scale; FIM, functional independence measure.

treatment may have had a role in producing the reported benefits and in improving the outcome. The COVID pandemic has significantly influenced the outcome in patients affected by neuromuscular disease, including patients with MG with relevant consequences on the quality of life, leading to an increase in sedentary behavior and a related decrease in the practice of physical activity (25). In this respect, the patient described in this report underwent a tailored rehabilitation program, and the rehabilitative interventions might be the reason for the observed benefit during recovery.

Some limitations should be considered. This case report concerned "ocular MG" and not the generalized type that might present a different course. Indeed, previous studies have reported worse outcomes in patients with generalized MG and COVID-19. Therefore, the present finding cannot be extended to different types of MG. Furthermore, subtype (ocular versus generalized), serotype, and immunosuppression are important factors to be taken into account. The AChR-MG subtype presents a different response to immunomodulatory regimens compared to antiMuSK (26), and the differences might reflect a different behavior after the COVID-19 infection.

Another factor to take into account when considering COVID-19 is the possible direct damage caused by the virus on the nerves and muscles. Even without evidence of viral invasion of the nervous system, immune-mediated events, through either the cytokine or the chemokine pathway, may lead to tissue and organ damage (27). Therefore, it is conceivable that the same pathological conditions that affect critically ill subjects characterize COVID-19 subjects and may represent a milieu that favors ICUAW.

CONCLUSION

The association between MG and ICUAW has never been described in patients with COVID-19 so far. Although in the present subject, the coexistence of both neuromuscular disorders did not affect the clinical course and recovery, unsolved questions remain about generalization to all patients with MG. The rehabilitation intervention might have facilitated the outcome.

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 local Ethics Committee (Section Giovanni Paolo II-IRCCS Casa Sollievo della Sofferenza). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DI and FR: conceptualization. AC, MG, and LA: data extraction. DI, AC, and FR: manuscript preparation. DI, MG, and FR: review and revision. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: SMART ANTON: Anton-Babinski Syndrome in Stroke-Like Migraine Attacks (SMART) After Radiation Therapy: Two Rare Syndromes, One Case

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Introduction: We describe the case of a 57-years-old patient who presented an Anton-Babinski syndrome in the context of a stroke-like migraine attack after radiation therapy (SMART).

Case Report: The patient was brought to the emergency room following a sudden loss of vision in the context of a pre-existing left-sided hemianopia after excision of a right occipital astrocytoma followed by radio-chemotherapy 35 years prior to his admission in our services. At admittance, he also presented hyperthermia, hypertension, and a GCS of 7. The MRI showed a leptomeningeal enhancement in the left temporal, parietal, and occipital lobes. After exclusion of other differential diagnoses, we diagnosed a cortical blindness in the context of a SMART syndrome affecting the left hemisphere. While the symptoms improved under corticosteroid therapy, the patient successively presented an Anton-Babinski syndrome, a Riddoch syndrome and a visual associative agnosia before finally regaining his usual sight.

Discussion: This is, to our knowledge, the first report of an Anton-Babinski syndrome in the context of a SMART syndrome. A dual etiology is mandatory for cortical blindness in SMART syndrome since the latter affects only one hemisphere. A SMART syndrome affecting the contralateral hemisphere in respect to the radiation site seems to be uncommon, which makes this case even more exceptional.

Keywords: SMART syndrome, Anton-Babinski syndrome, dual etiology, Riddoch syndrome, visual associative agnosia, cortical blindness

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INTRODUCTION

The Anton-Babinski syndrome (ABS) is a rare phenomenon observed in few cases of cortical blindness characterized by the lack of awareness for the visual deficits (anosognosia) and vivid confabulations (1). It was first described in 63 AD by the roman politician Seneca as he depicted the strange behavior of his wife's blind maid who kept denying her blindness (2). The name was given centuries later as a tribute to the neurologists Gabriel Anton and Joseph Babinski for their research in related fields (3, 4).

The Stroke-Like Migraine Attacks after Radiation Therapy (SMART) syndrome is a rare late-onset complication of brain radiation therapy characterized by a unilateral cortical gadolinium enhancement typically associated with seizures and stroke-like episodes with prolonged reversible symptoms (5).

While the Anton-Babinski syndrome has previously been described in the context of radiation-induced leukoencephalopathy (6), this is, to our knowledge the first report of an Anton-Babinski syndrome in the context of a Stroke-like Migraine Attack after Radiation Therapy.

CASE REPORT

The 57-year-old patient's neurological history started 35 years prior to his admission to our hospital with the surgical excision of an astrocytoma in the right occipital lobe followed by a local radio-chemotherapy (Carmustine, 54 Gy) and a subsequent permanent left sided hemianopia. The patient was hospitalized 3, 12 and 21 years after this treatment following a sudden transient cortical blindness, left-sided occipital headache, meningeal signs, disorientation, sensory aphasia, and a right sided hemiparesis. Since the patient also presented fever, he was treated with antibiotics and virostatics at least once, though no evidence of viral or bacterial infection could be objectified. No evidence in favor of an autoimmune genesis, a status epilepticus or a posterior reversible encephalopathy syndrome was found. Twenty years after resection, the patient developed a focal status epilepticus and was put under antiepileptic treatment with valproate and phenobarbital. The treatment was switched to levetiracetam 1,000 g/day and lamotrigine 50 g/day following a valproate encephalopathy 9 years after treatment initiation. For the past 5 years prior to his admission, the patient had remained seizure free.

The current hospitalization occurred following a sudden loss of vision followed by a comateous state according to the patient's wife. He was initially announced by the paramedic services with a GCS of 7, hyperthermia and hypertension and had been given 1,000 mg levetiracetam and 3 mg midazolam on suspicion of a seizure considering his medical history. MRI showed signs of a pronounced left-sided temporo-parieto-occipital meningoencephalitis with cortical blood-brain barrier damage, leptomeningeal enhancement as well as a small left-sided parieto-occipital infarction (**Figure 1**). The patient regained consciousness within 2 h following admission. The neurological exam showed an anomic aphasia, disorientation as well as a discrete weakness of the right hand.

An EEG at admission showed theta-dominant background activity with recurrent mostly bifrontal generalized rhythmic delta activity, as well as a moderate focal slowing of the posterior left hemisphere and a mild slowing focus with a breach effect of the posterior left hemisphere without signs of ongoing epileptic activity or spreading of the bifrontal delta activity.

A cerebrospinal fluid analysis showed a slight pleocytosis (10 cells /mm^3) as well as elevated protein (1.43 g/L) and lactate (2.7 mmol/L) levels. Recurrent microbiology analysis of both cerebrospinal fluid and blood showed no sign of infection or autoimmune condition. A cerebral biopsy was performed in the left parietal lobe, where immunohistochemistry objectified the presence of disseminated single CD4-, CD8- and CD3-positive T-cells and CD68-positive macrophages. No signs of IgG-mediated disease (B-cells), neoplastic lesion or infection were found.

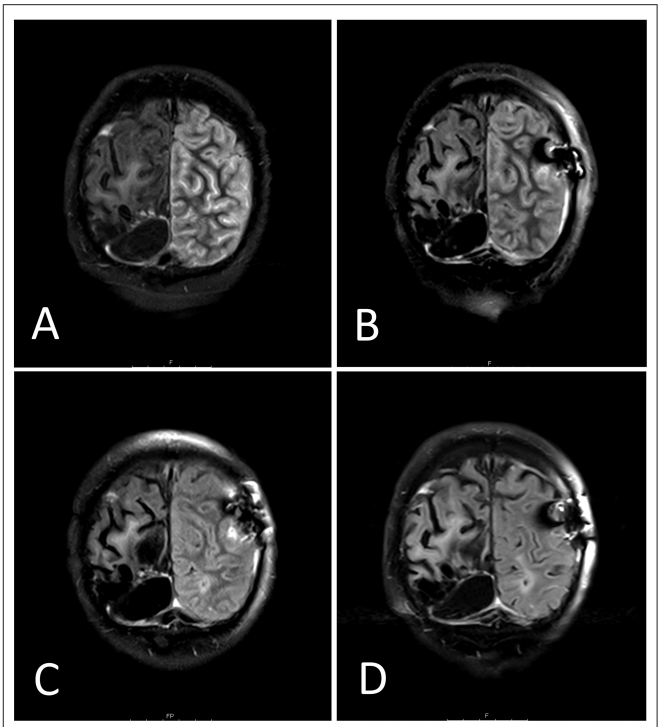

FIGURE 1 | Side to side comparison MRI flair day 1 **(A)**, day 6 **(B)**, day 14 **(C)** and day 45 **(D)**. The follow-up MRIs shows a gradual reduction of the initially displayed leptomeningeal enhancement in the left temporal, parietal and occipital lobes. The substance defect after astrocytoma excision appears as a liquid-filled black cyst in the lower part of the right hemisphere (left-sided in the pictures).

After exclusion of other potential etiologies, a stroke-like migraine attack after radiation therapy (SMART) was diagnosed. Although there was no evidence of epileptic activity on admission nor in following EEGs, we suspected, based on the initially displayed symptoms (decreased awareness, fever, hypertension), that a seizure might have occurred beforehand, either as a symptom or as a trigger of the SMART syndrome. We therefore increased the patient's previous seizure prophylaxis to 3,000 mg levetiracetam per day. We also initiated a steroid therapy starting with a steroid pulse therapy with intravenous methylprednisolone 1 g per day for 3 days followed by a switch to a body-weight adapted oral steroid therapy with prednisolone 100 mg per day. The latter was gradually reduced while the patient's symptoms steadily improved. Neuroradiology confirmed a continuous regression of the inflammation under this treatment. After 4 weeks at the acute care unit, the patient was transferred to our neurorehabilitation department. At admission, he presented an Anton-Babinski syndrome as well as a discrete residual right-sided hemiparesis and was still receiving 50 mg prednisolone per day. The neuropsychological assessment at admission revealed a severe formal thought disorder including logorrhea, tangential speech, loose association, perseverations, semantic and phonematic paraphasia and neologisms. We also

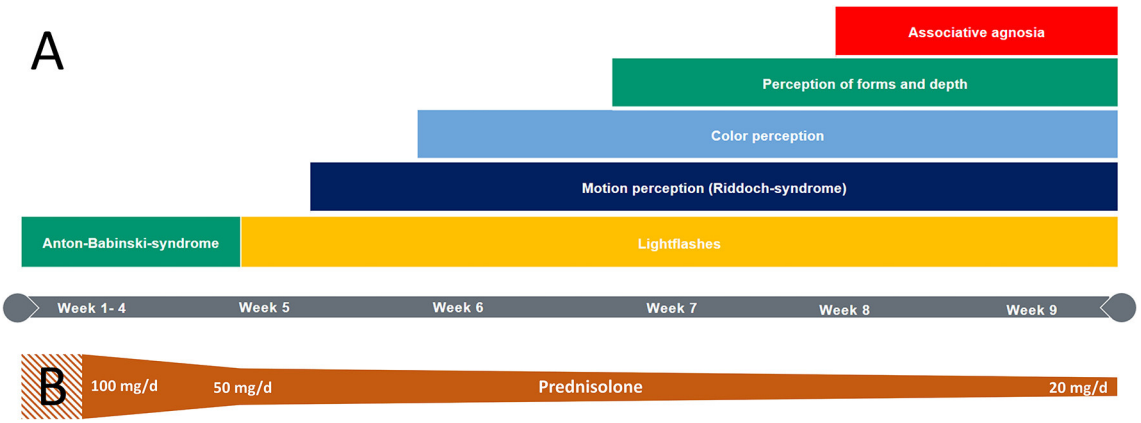

FIGURE 2 | (A) Visual perception recovery during hospitalization (right hemifield); **(B)** Visualization of the treatment with corticosteroids: Steroid pulse therapy with 1 g intravenous methylprednisolone during the first 3 days (striped pattern) followed by oral therapy with prednisolone 100mg gradually reduced over 9 weeks.

found severe mnestic deficits, a reduced alertness, and mild deficits in verbal fluency.

During the patient's 6-week stay in neurorehabilitation, the steroid therapy was gradually reduced from 50 to 20 mg prednisolone per day. His symptoms rapidly improved under this treatment (**Figure 2**). On the third day after admission to neurorehabilitation, he was able to perceive and react to flashlights. After a week, he began perceiving rapid hand movements. Interestingly, motion perception was objectified in both hemifields despite the preexisting left-sided hemianopia after partial occipital resection. Counting up to three fingers was possible when kept in motion. After another week, the patient began perceiving colors in his right hemifield and could describe shapes on the same side another week later. Eight to nine weeks after symptom onset, the patient merely showed a slightly impaired visual acuity in the right hemifield (beside the pre-existing left sided hemianopia after astrocytoma excision). Accordingly, a distinct regression of the inflammation was found in MRI (**Figure 1**).

Although the patient's eyesight had mostly recovered, we noticed that he had troubles naming objects. While he could describe them, he could name the objects only after touching them. We therefore diagnosed a visual associative agnosia, which eventually resolved 2 weeks later, after which he was transferred to another hospital.

While the patient was glad to have recovered his eyesight and hence his independence in most of the basic activities of daily life, he persisted on never having been blind and blamed his temporary vision problems on an inadequate correction of his glasses.

DISCUSSION

Diagnosis and Treatment of the SMART Syndrome

Black et al. (7) proposed revised diagnostic criteria including a typical patient profile (history of irradiation, no signs of residual or recurrent neoplasm), typical neuroimaging findings (transient unilateral cortical gadolinium enhancement) with a matching typical symptomatology (e.g., seizure, headache, unilateral motor, sensory or visual deficits) and the exclusion of other potential underlying causes. Our patient's case, with a history of a known cerebral irradiation in the context of astrocytoma in 1985, the displayed prolonged but mostly reversible neurological symptoms (anomic aphasia, motor and visual deficits) many years after irradiation, the massive unilateral band-shaped gadolinium uptake in MR diagnostics and finally the lack of evidence for another cause of the symptomatology, largely meets these criteria with one atypical feature though: the affected hemisphere was not the one that had been primarily targeted 35 years earlier. It is partly because of this untypical feature that a cerebral biopsy was performed in order to exclude other differential diagnoses, although it has been pointed out as potentially harmful and doubtfully useful for the diagnostic of a SMART syndrome (5, 8). The contralateral affection in our case may in fact be related to an incidental co-irradiation of the contralateral hemisphere due to technical targeting inaccuracy.

The precise mechanism of pathogenesis of the SMART syndrome is still unclear. It has been discussed whether it might be triggered by epileptic seizures acting as a second hit on a brain already pre-damaged by a previous radiation therapy which highlights the importance of sufficient seizure prophylaxis (5). The blood-brain barrier disruption and the subsequent brain oedema objectified via gadolinium enhancement makes the use of steroids seem sensible and may speed up symptom regression, although full recovery has also been described without the use of steroids (8).

SMART-Related Cortical Blindness and Its Dual Etiology

Cortical blindness describes a specific form of blindness involving a bilateral functional impairment of the visual cortex. The SMART syndrome, on the other hand, is a radiologically unilateral condition (7), which implies that a dual etiology

is mandatory for the occurrence of a SMART-related cortical blindness. In our case, the preexisting functional impairment consisted in a tissue defect in the right occipital lobe following an astrocytoma excision 35 years earlier.

As mentioned above, the hemisphere affected by the SMART syndrome in our patient was not the one targeted during radiation therapy. A contralateral affection has been described before (7) but seems to be rather uncommon according to larger case series (9, 10), which makes our case even more exceptional.

Cortical Blindness With Residual Motion Perception

While our patient slowly regained his eyesight, we noticed that he could perceive motions in both hemifields despite the preexisting left-sided hemianopia after partial occipital resection. Since the SMART syndrome only affected his left hemisphere, we assume that the residual motion perception in the left hemifield was unaffected by the SMART syndrome but had been overlooked at admittance due to the severe formal thought disorder and the confabulations initially displayed by the patient. Residual motion perception can indeed be found in ABS (1). In our case, the residual motion perception is likely related to the right visual area V5, which is critical for motion perception (11) and had been spared during the excision of the astrocytoma. V5 has direct connections to the posterior thalamus and superior colliculus (12) allowing visual information to bypass the primary visual cortex (PVC) and directly access V5 for further processing, eventually leading to motion perception in the blindfield of patients with an ipsilateral damaged PVC, a phenomenon called Riddoch syndrome found in many cases of hemianopia and sometimes in cortical blindness (13, 14).

Anton-Babinski Syndrome: Confabulations, Anosognosia and the Global Network Theory

The emergence of confabulations and anosognosia has been discussed for quite some time, a much-cited paper from 1989 by McGlynn and Schacter (15) offers several potential explanations. In the light of some particular features of our case, we considered Bernhard J. Baar's Global Workspace Theory on conscious perception of stimuli for some interesting alternative theoretical approaches.

According to the Global Workspace Theory (GWT) proposed by Baars et al. competing perceptual information from the cortices form coalitions based on the internal consistency of the information they convey (16). The strongest coalition induces a "winner-take-all" equilibrium by broadcasting its information to other cortical areas, hence creating an internally consistent information stream that rises into consciousness. This theoretical background gives rise to the following approaches on the emergence of confabulations and anosognosia in ABS:

V5

A damage to the PVC leads to a disruption of the feedback-loop between the PVC and the thalamus, which means that neither the lack nor the existence of visual perception is reported. A residual motion perception in cortical blindness conveyed by a still functional area V5 like in our case may, based on the principle "winner-take-all" and without opposing information from the PVC, suggest an intact visual perception to consciousness, ultimately resulting in anosognosia. The perception of a stimulus thus suggested combined with the missing ability to fully perceive this same stimulus eventually creates an internal conflict when the patient tries to produce a verbal description of what he sees. This conflict can ultimately only be solved by the unconscious fabrication of an imaginary description, in short: a confabulation.

Parietal Stream

The distinction of relevant information from irrelevant requires an considerable computational effort (17). The mammalian brain addresses this problem by using the global workspace to broadcast only relevant information into consciousness recruiting cortical resources, while irrelevant information is processed unconsciously in specialized and localized brain areas (18). These so-called "frames" in which relevant visual stimuli are interpreted are part of the parietal stream and are critical for the integration of visual perception into consciousness (16). A disruption of these frames disturbs the conscious visual perception and can lead to a neglect of visual input in the contralateral hemifield. Cases of bilateral neglect have been reported (19). Patients presenting both a neglect and a hemianopia are often unaware of their visual deficit, which is why the distinction between the two is challenging at times (15, 20). While neglect is most common in afflictions of the parietal lobe (e.g., middle cerebral artery stroke), it has also been described in posterior cerebral artery strokes in association with damage to white matter regions of the occipital lobe (21). Accordingly, a patient with a bilateral occipital damage under involvement of underlying white matter regions may be blind and at the same time neglect both hemifields, hence neglecting his blindness and simultaneously be anosognostic, a mechanism also discussed by McGlynn et Schacter, though in the context of hemianopia (15). This hypothetical approach does not entirely match our case though. While a right-sided negect could be related to the involvement of the left parietal lobe [since per definition the SMART syndrome only affects gray matter regions (7)], a left-sided neglect would have to be related to the occipital white matter damage after tumor excision and would hence be permanent, which was not the case.

LIMITATIONS

This case report has a few limitations. First, the visual field was not measured with objective methods (e.g., perimetry), the described improvements are hence solely based on clinical observation. Second, while the SMART syndrome is a probable diagnosis, it remains a diagnosis of exclusion (7), another etiology may have been overseen. Finally, the confabulations could also be interpreted in the context of the initial severe formal thought disorder, the latter would not sufficiently explain the persistent anosognosia for the cortical blindness though.

CONCLUSION

This is, to our knowledge, the first report of an Anton-Babinski syndrome with a dual etiology, but also of an Anton-Babinski syndrome in the context of a SMART syndrome. A dual etiology is required for an Anton-Babinski syndrome to occur in the context of a SMART syndrome. The Global Workspace Theory offers interesting approaches to understand the underlying mechanism of confabulations and anosognosia in Anton-Babinski syndrome.

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

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NN collected the clinical data and wrote the first draft of the paper. RM supervised the work and corrected the paper several times during the drafting process. All authors approved the final version.

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An omission to the funding section of the original article was made in error. The following sentence has been added: "Open access funding was provided by the University of Bern."

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Case report: Improved behavioral and psychiatric symptoms with repetitive transcranial magnetic stimulation at the bilateral DLPFC combined with cognitive and behavioral therapy in a patient with unilateral thalamic hemorrhage

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Behavioral and psychological symptoms are not uncommon after thalamic stroke, and are often intractable despite medication and behavioral interventions. Repetitive transcranial magnetic stimulation (rTMS) is as an adjunctive therapeutic tool for neuropsychiatric diseases, and bilateral rTMS has been recently introduced to maximize the therapeutic effect. Herein, we report the case details of a patient with unilateral left thalamic hemorrhage without cortical lesions who had treatment-resistant neuropsychiatric symptoms. We hypothesized that bilateral rTMS targeting the bilateral dorsolateral prefrontal cortices (DLPFCs) would positively affect thalamocortical neural connections and result in neuropsychiatric symptom improvement. The patient received a total of 10 sessions of bilateral rTMS over 2 weeks, applied at the DLPFCs, with high frequency in the left hemisphere and low frequency in the right hemisphere. After each rTMS treatment, computer-based cognitive-behavioral therapy was administered for 30 min. Behavioral and psychological symptoms, including hallucinations, aggressiveness, aberrant motor activity, disinhibition, and abrupt emotional changes, were significantly improved as assessed by the Neuropsychiatric Inventory Questionnaire. These effects persisted for up to 1 month. This case demonstrates the clinical potential of bilateral rTMS treatment in patients with intractable neurocognitive impairment after thalamic stroke.

KEYWORDS

thalamic stroke, repetitive transcranial magnetic stimulation, dorsolateral prefrontal cortex, intervention, cognitive-behavioral therapy

Introduction

Thalamic stroke is not a rare disease, and can occur in isolation or in combination with other structural involvements (1, 2). It presents with various symptoms, depending on its location, volume, and lateralization, and can affect memory, emotions, the sleep-wake cycle, general cortical alerting responses, sensory processing, sensorimotor control, and the relay of information to the cortex (3). Regarding lesion-based neuropsychiatric symptoms after thalamic stroke, tuberothalamic lesions deteriorate arousal, orientation, learning, memory, personality, and executive function (4). Bilateral paramedian lesions cause decreased arousal, learning, and memory (4). Although neuropsychiatric symptoms and neurocognitive deterioration are prominent in patients with bilateral thalamic stroke, symptoms can also persist in unilateral lesions (5).

Pharmacological management and behavioral interventions are still mainstream treatments for neuropsychiatric symptoms in patients with thalamic stroke. However, many patients do not improve with such treatments. Non-invasive brain stimulation (NIBS) is an effective adjunctive therapy for treatment-resistant neuropsychiatric symptoms (6). Repetitive transcranial magnetic stimulation (rTMS), a type of NIBS that has been widely used in the neurorehabilitation field (7) has emerged as a therapeutic tool to facilitate neuroplasticity, with clinical benefits in neuropsychiatric diseases. Stimulation targeted to the dorsolateral prefrontal cortex (DLPFC) has been proven as clinically effective in mild cognitive impairment, obsessive-compulsive disorder, and major depressive disorder (6, 8). Furthermore, in patients with stroke, rTMS has shown promising results in improving cognitive impairments and mood disorders (9–12). Recently, bilateral rTMS was introduced to maximize the therapeutic effectiveness (13–15). However, there is a lack of consensus regarding the intensity and frequency of the rTMS protocol, and no previous studies have applied bilateral rTMS to treat stroke-related neuropsychiatric symptoms.

Here, we report a case of unilateral thalamic stroke with treatment-resistant neuropsychiatric symptoms, improved by the application of bilateral rTMS at the bilateral DLPFCs, with high frequency in the left hemisphere and low frequency in the right hemisphere.

Case presentation

A 63-year-old man was admitted to our hospital with left thalamic hemorrhage. He was in a comatose state when he arrived to the emergency room. His initial Glasgow Coma Scale (GCS) score was 7, but his consciousness level rapidly improved to a GCS score of 14. He had subjective right-sided weakness, but no obvious motor impairment was observed on physical examination. Rehabilitative intervention was conducted focused on locomotion and activities of daily living rather than limb weakness. Computed tomography (CT) revealed a left thalamic hemorrhage with intraventricular hemorrhage (IVH). He received conservative treatment with blood pressure control. Serial follow-up brain CT revealed a newly developed, tiny IVH, but no other hemorrhage. Brain magnetic resonance imaging (MRI) revealed moderate small-vessel disease in the white matter and amyloid angiopathy with diffuse mild cortical atrophy (Figure 1). Although his alertness rapidly improved, he showed fluctuations in consciousness with delirium at night, disorganized thought, inattention, and perceptual disturbances. Antipsychotics were administered, but these symptoms did not improve.

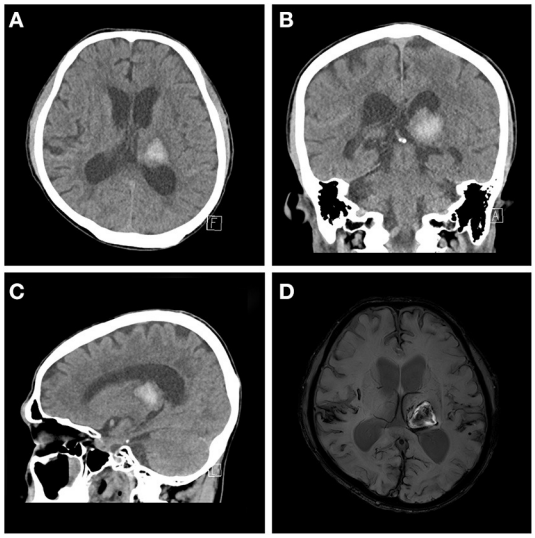

FIGURE 1
Baseline brain magnetic resonance imaging and computed tomography (CT) scan. Acute intracerebral hemorrhage at the left thalamus is observed on axial **(A)**, coronal **(B)**, and sagittal views **(C)** of the brain CT scan and the axial view of the diffusion-weighted image **(D)**.

Three weeks after stroke onset, the patient was referred to our rehabilitation department for cognitive rehabilitation. Neurocognitive assessment revealed various behavioral and psychological symptoms. Long-term memory was relatively spared, but short-term memory was markedly reduced. Orientation in space, time, and person was severely impaired. Visual hallucinations of something crawling on the curtains and abrupt changes in emotional status were also observed. The Neuropsychiatric Inventory–Questionnaire (NPI-Q) indicated moderate to severe symptoms, and moderate caregiver distress. His scores on the Korean version of the Mini-Mental Status Exam (K-MMSE); score: (12), Clinical Dementia Rating (CDR); global score: 3; sum of box score: (13), and the Korean version of the Montreal Cognitive Assessment (MOCA-K); score:

(2) indicated severe neurocognitive impairment (Table 1). We attempted to administer an overall cognitive assessment battery, but this was impossible because of the patient's inattention and perseveration.

A N-methyl-D-aspartate antagonist (NMDA) receptor antagonist (memantine, 10 mg) and anti-depressant (escitalopram 10 mg) were administered to improve his attention and emotional lability, and a small amount of atypical antipsychotics (quetiapine, 12.5 mg) was administered to alleviate his delirium. A neuro-stimulant (methylphenidate) was also administered to improve his attention, but this was stopped because his irritability was aggravated. He received computer-based cognitive-behavioral therapy (CCBT) using CoTras (Netblue Co., Ltd, Korea) software (16) for 3 weeks. However, there was no noticeable change in his cognitive function and neuropsychiatric symptoms. Thus, we decided to apply bilateral rTMS to the DLPFCs, with the consent of the patient and caregiver.

rTMS protocol

rTMS was performed with a Magstim Super Rapid Stimulator (Magstim Co., United Kingdom) with a 70-mm, figure-eight shape, air cooled coil. The handle was oriented posteriorly, with a 45° angle sagittally. Single-pulse transcranial magnetic stimulation was conducted at the bilateral primary motor cortices to identify the motor hot spot in each hemisphere. The motor-evoked potentials (MEPs) were recorded in the contralateral abductor pollicis brevis, and the motor threshold (MT) was defined as the stimulus intensity required to provoke MEPs of >50 μV in peak-to-peak amplitude, in five of 10 sequential trials. The stimulation target of the DLPFC was defined as 5 cm anterior to the motor hot spot, parallel to the sagittal midline (17). For low-frequency rTMS, 1-Hz stimulation at 80% MT was applied in three trains of 5-min duration each, with a 1-min inter-train interval, and a total of 900 pulses (a total period of 20 min). For high-frequency rTMS, 10-Hz stimulation at 80% MT was applied in 40 trains of 5-s duration each, with a 25-s inter-train interval, and a total of 2,000 pulses (a total period of 20 min). Low-frequency rTMS was applied to the right DLPFC, followed by high-frequency rTMS to the left DLPFC, with a 5-min pause. CCBT was administered within 30 min after rTMS treatment. A schematic of the treatment protocol is provided in Figure 2. During the rTMS treatment period, the existing medications (memantine, escitalopram, quetiapine) were continuously used.

Bilateral rTMS was applied 53 days after onset of thalamic hemorrhage followed by a total of 10 sessions over 2 weeks. There were no adverse events, such as headaches, seizures, and other neurologic deficits, and there was only mild scalp discomfort during the treatment sessions. Behavioral and psychological symptoms were markedly improved, as assessed by the K-NPIQ (Table 1). Both symptom severity and caregiver distress were improved in all domains, with the exception of delusions, a nocturnal and prandial aberrant activity that was not observed, even before treatment. The MOCA-K score also improved. However, amnestic symptoms were only slightly enhanced. These effects of rTMS persisted for 1 month after treatment.

Discussion

To our knowledge, this is the first case report of bilateral rTMS to the DLPFCs in a patient with behavioral and psychological symptoms after thalamic stroke. This patient showed a clear clinical response to bilateral rTMS treatment targeting the bilateral DLPFCs. Hallucinations, agitation, irritability, and anxiety were significantly improved after the treatment, and these effects remained after 1 month. We found that these behavioral and psychological symptoms were the main causes of caregiver distress. In contrast, working memory and executive function were not improved. There were no adverse events associated with bilateral rTMS.

The thalamus is recognized as one of the major cognitive centers for neural processing, and routes information across the brain in cortico-cortical, cortico-striatal, hippocampo-cortical, and cerebello-cortical pathways (18). There are numerous neuroscientific studies on contributions from different parts of the thalamus to cognitive functions in non-human primates. In memory and learning processes, the anterior thalamus is particularly driven by the hippocampus, and interacts with the cortex in memory processing and spatial navigation in rodent studies (19). Minamimoto et al. showed that the intralaminar thalamus interacts with the basal ganglia, and contributes to counteracting behavioral biases, enabling behavioral flexibility (20). The mediodorsal thalamus is a component in a neural circuit involving the prefrontal cortex that has a crucial role in spatial working memory which enables the transformation of retrospective information into prospective information (21, 22). It also shows preferential connectivity with the DLPFC, as demonstrated in a previous tractography study (23). Strong relationships between the cortex and thalamus have also been shown in human research. Behrens et al. revealed a specific connection between the human thalamus and cortex using quantitative diffusion imaging data (24). Furthermore, in a positron emission tomography study, significant ipsilateral hypometabolism was observed in the cortex of patients with neuropsychological deficits after vascular thalamic injury (25).

Among the NIBS techniques for neurocognitive disorders, deep brain stimulation can directly stimulate deep neural structures, and has proven to be effective when targeted to

TABLE 1 Change in neurocognitive assessment scores after repetitive transcranial magnetic stimulation.

K-NPIQ	Before treatment		Immediately after treatment		1 month after treatment	
	Severity	Distress	Severity	Distress	Severity	Distress
Delusions	NA		NA		NA	
Hallucinations	2	3	1	1	1	1
Agitation	3	3	2	2	NA	
Depression	2	2	1	1	2	1
Anxiety	2	2	1	1	1	1
Euphoria	1	2	1	1	1	1
Apathy	3	2	1	1	1	1
Disinhibition	3	2	1	1	1	1
Irritability	3	4	1	1	1	1
Aberrant motor activity	3	3	1	1	1	1
Nocturnal aberrant activity	NA		NA		NA	
Prandial aberrant activity	NA		NA		NA	
Total	22	23	10	10	9	8
MOCA-K	2		7		6	
CDR						
Global score	3		3		2	
Sum of box	15		15		12	
K-MMSE	12		14		14	

NA, not applicable; K-NPIQ, Korean Neuropsychiatric Inventory-Questionnaire; MoCA-K, Korean version of Montreal Cognitive Assessment; CDR, Clinical Dementia Rating; K-MMSE, Korean version of Mini-Mental State Examination.

subgenual regions in mood disorders and the thalamus in dystonia, Parkinson's disease, and essential tremor (26–29). rTMS is a NIBS technique based on producing a rapidly shifting magnetic field over the scalp, which induces an electric current in the cortex parallel to the magnetic coil. It can modulate the neuronal excitability of the cortical surface directly underneath the coil and associated other brain regions (30). Low frequency rTMS (1 Hz) reduces cortical excitability, whereas rTMS at high frequency (10 Hz) facilitates neuronal excitability. Unfortunately, rTMS is largely limited to the cortical surface and deeper neural structures, such as the thalamus, cannot be selectively and directly stimulated. Therefore, in neuropsychiatric situations, the DLPFC is the most commonly used therapeutic target for rTMS, based on its importance in neural networks.

In post-stroke rehabilitation, rTMS has been shown to be a safe and well-tolerated intervention, and has been recommended as a viable therapy to enhance clinical recovery and functional improvement (31). Evidence-based guidelines suggested the definite efficacy of LF-rTMS of contralesional M1 and probable efficacy of HF-rTMS of ipsilesional M1 in hand motor recovery (32). Moreover, they reported clinical effectiveness in post-stroke apahsia and hemispatial neglect. Several studies have shown evidence of rTMS targeting DLPFC in post-stroke depression and cognitive impairment (9, 33).

DLPFC is the most frequently used stimulation target for post-stroke non-motor symptoms, and evidence of a functional connection between the thalamus and DLPFC has been reported recently. Neurophysiologic study using short-latency afferent inhibition revealed the direct thalamocortical connectivity and highlighted its importance as a marker of cognitive and behavioral activity in the neurorehabilitation field (34, 35). Li et al. also showed the functional connectivity between DLPFC and thalamus. A single session of active rTMS at DLPFC inhibits brain activity of the thalamus in fractional amplitude of low frequency fluctuation (36). It has been hypothesized that rTMS targeting the DLPFC might affect deeper regions that share the same neural pathway (7, 8). We also hypothesized that DLPFC rTMS positively affects thalamocortical neural connections, resulting in neuropsychiatric symptom improvement in unilateral isolated thalamic stroke without cortical lesions.

Stimulation localization is the crucial component to enhance the efficacy of rTMS. The "5 cm rule" introduced by Pascual-Leone et al. was widely used in early research trials to localize the DLPFC (37). The motor hotspot for the contralateral abductor pollicis brevis muscle is first identified during motor evoked potential testing, and then a target site is defined 5 cm anteriorly to this site for DLPFC stimulation. Neuro-navigation system based on structural brain MRI to find DLPFC as the boundary

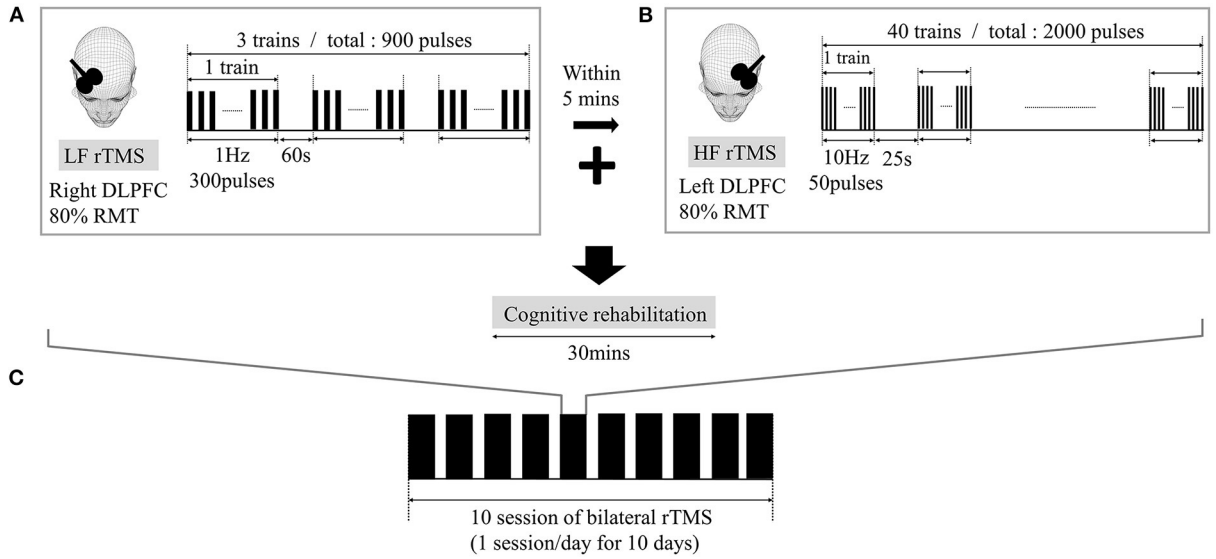

FIGURE 2
Repetitive transcranial magnetic stimulation (rTMS) montage and intervention protocol. High-frequency rTMS was applied to the left dorsolateral prefrontal cortex (DLPFC) and low-frequency rTMS was applied to the right DLPFC **(A,B)**. Low-frequency rTMS was applied first, followed by high-frequency rTMS during each session, and a total of ten sessions were performed **(C)**.

between BA 9 and 46 seems to be the most reasonable method (38). But it is challenging because of technical difficulty and cost. Other alternative methods such as F3/4 EEG location based on standard 10–20 system, Beam F3 method, and neuro-cardiac-guided TMS have been introduced recently (39). Since we localized DLPFC using the conventional 5-cm rule without using a navigation system, there were limitations in obtaining better therapeutic effects.

In neuromodulation using rTMS, besides the stimulation location, it is also very important to establish a protocol including frequency, intensity, time interval of stimulation, and total pulses with sessions. It is challenging to establish physiologic evidence for setting the value with the best therapeutic effect in each parameter. Therefore, we designed our protocol based on well-designed previous randomized controlled studies, in which rTMS was performed targeted to DLPFC in patients with post-stroke cognitive and mood disorders (11, 12).

Bilateral rTMS has been scrutinized as a novel approach in recent studies. Khedr et al. reported that a 10-day protocol of low-frequency (1 Hz) rTMS over the unaffected right Broca's area with 1,000 pulses, followed by 20-Hz high-frequency rTMS over the affected left Broca's area with 1,000 pulses resulted in language function improvement in non-fluent aphasia (13). In a study by Fitzgerald et al., 6 weeks of 1-Hz rTMS to the right DLPFC with 430 pulses, followed by 10-Hz rTMS to the left DLPFC with 750 pulses was compared with sham stimulation for 6 weeks; a marked benefit of bilateral rTMS in intractable depression was demonstrated (15). Based on these previous studies, we applied high frequency rTMS within 5 min after low frequency rTMS of 1Hz.

The patient in the present case report did not show any improvement in neuropsychiatric symptoms after 2 weeks of behavioral interventions and pharmacological treatment. Neurostimulants could not be continued because of adverse events. Therefore, to maximize the treatment effect, we applied sequential bilateral rTMS, with combined high-frequency and low-frequency rTMS. A few studies have examined the effects of rTMS on neurocognitive capacity after stroke and highlighted its positive effects on cognitive function and daily activities (9, 10, 12). After 2 weeks of rTMS treatment, hallucinations, aggressiveness, aberrant motor activity, disinhibition, and abrupt emotional changes were markedly improved, and this improvement lasted for a month. Consistent with our findings, rTMS has shown a positive effect on hallucinations in schizophrenia (40), disinhibition in obsessive-compulsive disorder (41), and nicotine dependence (42). Unfortunately, the decline in cognitive functions, including working memory, orientation, and executive function, did not improve.

There are some limitations to generalizing the effect of bilateral rTMS based on this study. Since it was an acute stage after stroke, improvement of symptoms due to spontaneous recovery could not be ruled out. In addition, although medication was unavoidably used to control the patient's symptoms, the continued use of medicines that affect brain activity during the rTMS treatment session may have affected the results.

Conclusion

This is the first report of successful bilateral rTMS treatment in a patient with neurocognitive impairment due to thalamic stroke. Thalamic stroke causes behavioral and psychological symptoms, which are often intractable despite medication or behavioral interventions. This case study supports research opportunities for the therapeutic use of rTMS for treatment-resistant neuropsychiatric symptoms after thalamic stroke. Future studies are needed to evaluate the impact of rTMS on neurocognitive impairment in large cohort groups. More evidence for the effect of rTMS on thalamocortical connections should be established.

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 Institutional Review Board (IRB) of Keimyung University Dongsan Hospital (IRB No: 2021-11-062). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant for the publication of this case report.

Author contributions

HCA designed and implemented the data analysis and wrote the manuscript. KTK participated in data interpretation, analysis, and design of the rTMS protocol. Both authors participated in editing. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Botulinum toxin injection combined with traditional swallowing rehabilitation improved cricopharyngeal dysfunction in neuromyelitis optica spectrum disorder: A case report

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Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune diseases of the central nervous system, and often influence optic nerve and medulla oblongata. Previous studies found out that brain abnormalities were not rare in these patients. Medulla oblongata (MO) was commonly involved and usually located at dorsal part. Patients who diagnosed NMOSD with MO lesions were more likely to have dysphagia. Previous reports indicated that the symptoms and signs of NMOSD patients could be controlled after immunosuppressive therapy. This patient was a 49-year-old Asian woman presented with recurrent vomiting and diagnosed NMOSD with MO involvement. However, after immunotherapy in other hospital, she still suffered from dysphagia. She then came to our department and completed videofluoroscopic swallowing study (VFSS) and high-resolution pharyngeal manometry (HRPM). Her UES was not opening with aspiration and the UES residue pressure was higher than normal range, we figured that she had cricopharyngeal (CP) dysfunction. Then the SLP gave her traditional treatment, including catheter balloon dilation. But she failed improvement after treatment for 2 weeks. Then the clinicians decided to inject botulinum toxin (BTX) into her CP muscles, which needed specific location and appropriate dosage. Her UES residue pressure decreased after three times BTX injection. During this time, her SLP adjusted the treatment strategies based on her VFSS and HRM results. Combined BTX injection with traditional treatment, she can now eat food orally without restrictions. This case report we presented can provide treatment strategies for similar patients with dysphagia.

KEYWORDS

neuromyelitis optica spectrum disorder, dysphagia, botulinum toxin, cricopharyngeal muscle, case report

Background

Neuromyelitis optica (NMOSD) is an autoimmune, demyelinating, inflammatory disease affecting the central nervous system, especially affecting the optic nerve and spinal cord (1). It often occurs in female patients, and the incidence is higher in non-white ethnicity (2). Recent studies have also reported brain abnormalities were not rare in NMOSD patients. Medulla oblongata (MO), especially dorsal part, was frequently involved, with prevalence 12.8 to 91.3% (3). NMO-IgG is a specific antibody that can bind to Aquaporin 4 (AQP4) and has high sensitivity and specificity to NMO recognition (4). High AQP4 expression is generally believed to be associated with brain stem injury (5).

Previous study indicated that dysphagia frequently occurs in NMOSD with MO involvement (6–8), which can be detected through questionnaires and instrumental examination (7, 8). Also oropharyngeal swallowing disorder might lead to the pneumonia and disability (8). Some studies reported improvement in the symptoms of NMOSD (diplopia, facial palsy, dysphagia, etc.) after immunotherapy (3, 9, 10). However, few studies have reported the safety and effectiveness of these patients' swallowing process and swallowing rehabilitation. Hence, we present a case of a patient with NMOSD with MO involvement who continued to have dysphagia despite 6 months of immunotherapy.

The patient provided informed consent for the publication of this report.

Case report

A 49-year-old Asian woman presented with recurrent vomiting in September 2020. Spinal cord magnetic resonance imaging (MRI) showed no obvious abnormality of the cervical or thoracic spinal cord. Brain MRI demonstrated abnormal lesions in the medulla oblongata, bilateral hypothalamus, and white matter of the cerebral hemispheres (Figures 1A,B). Cerebrospinal fluid (CSF) analysis revealed positive oligoclonal IgG bands (OCBs). Her tests for AQP4-IgG in CSF (1:1) and serum (1:10) were positive, confirming the diagnosis of NMOSD. Her muscle strength of left upper and lower limbs were rated 5^{-} level and her right limbs were normal. Her muscular tension were normal but tendon reflex was active. Her binocular diplopia and distal vision decreased. Also, the pharyngeal reflex was disappeared. During September 2020 to the end of February 2021, she lived at local hospital and ate mycophenolate mofetil dispersible tablets 0.75 mg bid and prednisone 20 mg qd. At the end of February 2021, the overall situation has improved. Her strength of limbs and tendon reflex return back to normal level. Her pharyngeal reflex was weakened. Her binocular diplopia was alleviated, and distal vision decreased slightly. Then she visited the neurology outpatient department of our hospital on 1 April, 2021, the attending doctor adjusted the dose of prednisone to 15 mg qd and mycophenolate mofetil dispersible tablets 0.75 mg bid. She went to the neurology clinic again in June. Given the stability of the condition, the doctor reduced the dose of prednisone to 10 mg qod and mycophenolate mofetil dispersible tablets 0.75 mg bid until now. However, the dysphagia persisted even after the immunotherapy treatment. Consequently, she presented to our department in 23 March 2021 for further intervention.

Initially, a videofluoroscopic swallowing study (VFSS) indicated that she has an aspiration and her UES was not opening on swallowing 3 ml of an extremely thick bolus (Softia-S, Nutri. Co., Ltd., Japan). The first fiberoptic endoscopic evaluation of swallowing (FEES) revealed moderate residue in the epiglottis valley and piriform sinus (11). Her functional oral intake scale (FOIS) score was 1 (12). On high-resolution pharyngeal manometry (HRPM), the upper esophageal sphincter (UES) residue pressure was 259.5 mmHg when she swallowed 3 ml of an extremely thick bolus. The normal reference value for UES residual pressure is < 12 mmHg (13–15), this patients' UES residue pressure was higher than the normal range. The VFSS and HRPM results represented that she had cricopharyngeal muscle (CPM) dysfunction. Hence, the speech-language pathologist (SLP) treated her with catheter balloon dilation. However, her swallowing function failed to improve after 2 weeks of training. Since the botulinum toxin (BTX) relieves muscle tone, the clinician decided to inject her CPM with 50 U of onabotulinum toxin A (Botox®, Irvine, CA, USA), diluted to 100 U/ml with normal saline, under the combined guidance of a catheter balloon, ultrasound, and electromyography (BECURE).

After the first injection, her UES residue pressure was still higher than normal (151.9 mmHg). Considering that the dosage was insufficient, another 50 U of BTX was injected into the CPM (16). Her swallowing dysfunction persisted despite 2 weeks of training. Fifteen days after the second injection, her UES residue pressure remained high (74.0 mmHg) and she could not eat. The clinicians deemed it safe and necessary to administer the third dose of 50 U of BTX into the CPM. Sixteen days after the third injection, the patient's UES residue pressure further decreased to 47.5 mmHg. And the VFSS results showed that her UES were opening without aspiration (Figure 1D). She was able to eat 100 ml of extremely thick food and spit out 20 ml. At the 6- and 9-month follow-ups after the last injection, she could consume an unlimited variety of foods orally.

Discussion

In a study that compare different clinical features of NMOSD with and without MO involvement indicated that: dysphagia, headache, dizziness, nystagmus, dysphonia, intractable hiccup nausea, dyskinesia, and neuropathic pain are more common in patients with MO involvement. Meanwhile, MO involvement often leads to a high recurrent rate and poor prognosis (3).

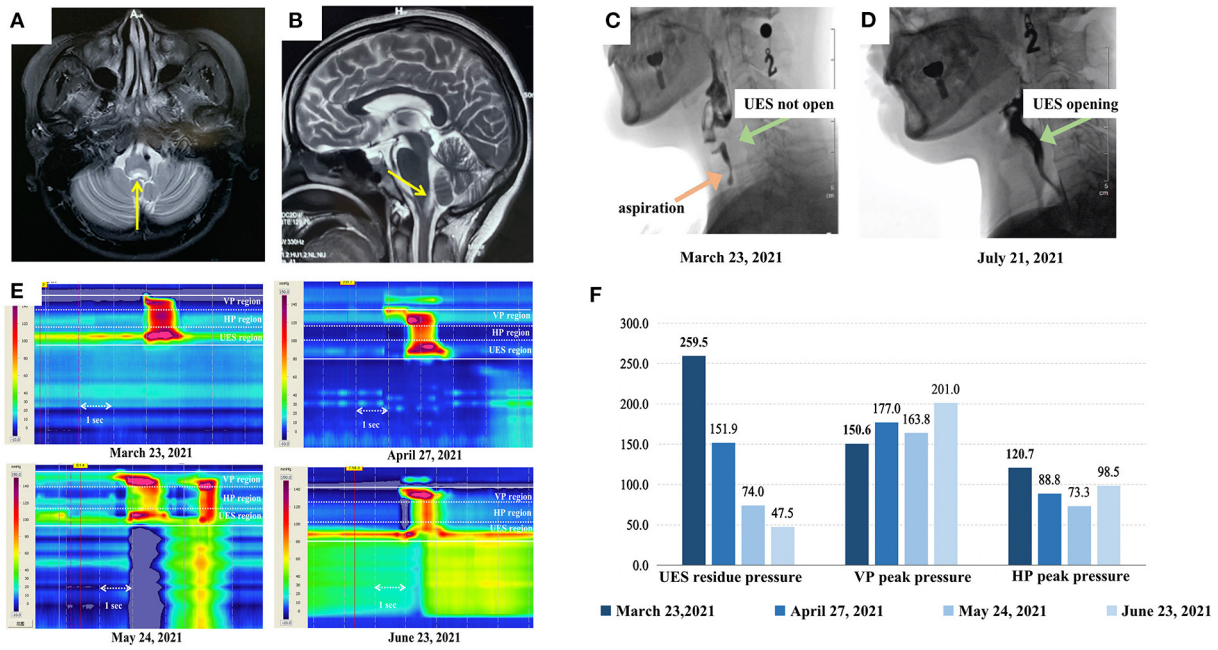

FIGURE 1
Magnetic resonance imaging (MRI) of the patient and the swallowing evaluation results **(A)** and **(B)** show the transverse and sagittal plane of the patient's brain MRI scan. The yellow arrows indicate the abnormal lesions in the medulla oblongata. **(C)** and **(D)** show the videofluoroscopic swallowing study (VFSS) imaging of this patient (captured as she ate 3 ml of extremely thick food). Her upper esophageal sphincter (UES) was completely not open with aspiration in **(C)**, while **(D)** shows that her UES was completely open with no aspiration after treatment. **(E)** is the high-resolution pharyngeal manometry (HRPM) space-time diagram of the patient (analyzed as the patient ate 3 ml of extremely thick food) and **(F)** shows the specific statistics of HRPM. The four diagrams in **(E)** and the colors from dark to light in **(F)** represent the timeline of the patients' treatment process: before the injection, and after the first, second, and third injections, respectively. In figure **(E)**, The x-axis represents time (the arrow indicates 1 s), the y-axis represents the structure from the velopharynx (VP) to the esophagus, and the color represents the pressure (mmHg) (the warmer the color, the higher the pressure). It can be observed that her UES residue pressure gradually declined. Her VP peak pressure was always in the normal range (>100 mmHg). Considering the dispersal of BTX to the hypopharynx (HP), her HP peak pressure dropped after the first and second injections. Therefore, her speech-language pathologist conducted pharyngeal balloon pressure training, then her HP peak pressure got back to normal.

Milewska et al. (7) reported that 37.5% of the 72 multiple sclerosis and Devic's syndrome patients had dysphagia, of which pharyngeal dysphagia (repeated swallowing, dysphagia, coughing, feeling of food stuck in the throat) was much more common. In our study, the patient presented with severe residue in the epiglottis valley and the piriform sinus in VFSS (Figure 1C) and high UES residue pressure in HRM (Figures 1E,F), which indicated that her problem concentrated on pharyngeal stage. The patient's symptoms were consistent with previous studies. Cousins et al. (9) and Li et al. (10) reported that the symptoms and signs of dysphagia were controlled by immunosuppressive therapy in patients with NMOSD. Also in Li's case (10), the patient's symptoms did not recur after 15 months. Though the patient of our study started using immunotherapy since September 2020, she still suffered from dysphagia. After the combination of BTX injection and traditional therapy, she could eat orally. Furthermore, the evaluation of our case was comprehensive. Previous studies using FEES and questionnaires to evaluate NMOSD patients' dysphagia (7, 8). Except from FEES and subjective evaluation, we added VFSS and HRPM. VFSS clearly shown the safety and effectiveness of swallowing, while HRPM measured the muscle pressure quantitatively. With a comprehensive evaluation, we could confirm the CP dysfunction of this patient and determine what to do next.

Catheter balloon dilation is generally used in patients with CPM dysfunction. However, some patients show no improvement in swallowing even after balloon training. For these patients, BTX injection into the CPM may be considered. The CPM is a C-type skeletal muscle with a length of 1–2 cm. Precise injection is necessary for safety and effectiveness. Our team have applied this innovative technique to more than 20 patients and achieved good outcomes (13). Beside the location, the dosage of BTX is also important. Based on previous literature, the dosage of BTX was often decided by the clinician and varied from 4U to 100U (16–18), and the average dose was 39 ± 19 units (17). It was at minimum spread degree when diluted the BTX to 50-100 U/ml with normal saline (18). According to Ahsan (19), when the patients' UES residue pressure were 30 mmHg and 40 mmHg, they

injected 60 U. Our team have injected 30–100 U to 21 patients with no adverse prognosis (13). The single dose was 50 U usually. Consider the above information comprehensively, we decided to inject 50 U diluted in 0.5 ml normal saline to this patient. The main considerations were to reduce side effects and have effects.

The lesions in the medullary swallowing center may be the cause of increased UES residue pressure in NMOSD patients with postrema syndrome. Three factors may affect the UES opening (20): (1). oncoming swallowed bolus-generated pressure (A); (2). anterior laryngeal movement and pharyngeal shortening-generated pressure (B); (3). UES relaxation and compliance (C). Patients can eat when $A + B \geq C$. This complex series of movements is considered to be controlled by medullary swallowing center, which is called swallowing central pattern generators (CPG), especially the neucleus of the solitary tract (NTS) and other medullary or supra-medullary structure (21–24). The lesions in the medullary structure can lead to the pressure of UES, which should be decreased when swallowing, increased (21). According to the literature reported, NMOSD with MO involvement was more likely to have dysphagia (6–9). Hence, with the MO involvement may influence the CPG and NTS, and then lead to the higher UES residue pressure.

Although the UES residue pressure reduced after the first and second injections, the velopharyngeal and hypopharyngeal peak pressures remained lower than the UES residue pressure (Figure 1F), and the patient was unable to eat. Three BTX injections have rarely been reported in previous literature (16). However, since our patient's UES residue pressure remained high, a third injection was necessary. Although BTX helped in lowering the UES residue pressure, the patient's hypopharynx peak pressure dropped after the first and second injections, which might have been caused by the dispersal of BTX to the hypopharynx. Therefore, apart from the basic training, the SLP also added pharyngeal pressure training with the assistance of catheter balloon dilatation in the pharyngeal region. Per the evaluation results of VFSS and HRM, her treatment plan was changed. After all the treatment, her hypopharynx peak pressure returned to normal (Figure 1F). Also, the coordination of swallowing and neuroplasticity might be affected by catheter balloon dilation and oral intake training. Hence, the swallowing function can be maintained.

Previous studies found out that NMOSD patients with MO involvement tend to have a higher recurrence rate. According to our follow-up, the patient is currently taking a small dose of immunodrug maintenance (prednisone 10 mg qod and mofetil dispersible tablets 0.75 mg bid). She still ate orally without restriction after 1 year's treatment. We will continue to follow the patient's prognosis in future.

Conclusion

BTX injection into the cricopharyngeal muscle, along with traditional treatment, could help improve the swallowing function in patients with NMOSD with MO involvement. This case report provides a novel treatment strategy for such patients.

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 authors.

Author contributions

ZH and FZ completed the swallowing evaluation and treatment for the patient in this case report, collected the data of this case report, completed the chart drawing, and completed the preliminary draft. YS helped revise the draft and completed the clinical examination of patients as a doctor. ZD and HW guided the operation of the whole project, revised the draft, and gave the fund. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Case report: Ultrasound-guided multi-site electroacupuncture stimulation for a patient with spinal cord injury

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Introduction: Spinal cord injury causes permanent neurological deficits, which have devastating physical, social, and vocational consequences for patients and their families. Traditional Chinese medicine uses acupuncture to treat neuropathic pain and improve nerve conduction velocity. This treatment can also reduce peripheral nerve injury joint contracture and muscle atrophy in affected patients. And it's got a remarkable restoration when electrical stimulation therapy on impaired peripheral nerves in animal models and clinical trials.

Case description: A 48-year-old woman was hit by a heavy object that injured her lower back. The patient had a T12-L1 vertebral flexion and stretch fracture with traumatic spinal stenosis. The patient was transferred to the rehabilitation department after posterior T12-L2-segment pedicle screw system distraction and reduction, internal fixation, decompression, and bone graft fusion. Ultrasound-guided electroacupuncture was used to stimulate the sacral nerve, the spinal nerve, and the head of the patient, accompanied by spinal joint loosening training, respiratory training, lumbar comprehensive sports training, paraplegic limbs comprehensive training, and other manipulative treatment.

Outcomes: After the intervention, the patient showed significant improvements in sensory and motor scores, resulting in functional recovery according to ASIA and FIM. The patient gradually showed reasonable functional remission.

Discussion: The sacral nerve, the spinal cord, and the head were electrically stimulated by ultrasound-guided electroacupuncture in terms of intervention, and various functions of the patient were alleviated to a certain extent. The efficacy of ultrasound-guided electroacupuncture stimulation in treating neurologic symptoms should be validated in future clinical trials.

KEYWORDS

spinal cord injury, nerve, electroacupuncture stimulation, ultrasound-guided, case report

Introduction

Spinal cord injury (SCI) is an acute injury that occurs in response to an external physical impact, such as a motor vehicle injury, sports-related injury, or violence (1). The spinal cord has poor potential for internal recovery and is, therefore, prone to permanent neurological damage. Furthermore, patients with spinal cord injury can have significant physical issues, owing to bladder dysfunction and urinary incontinence (UI). The major secondary lesions of death in patients with SCI are renal failure and urinary sepsis. Although survival rates for patients with SCI have improved over time, the mortality rate in these patients is higher than that in an age-matched control group (1). Mortality increases with the severity and severity of the injury (i.e., cervical spine trauma has a higher mortality rate than lumbar trauma), age of the patient, and presence of multi-system injuries and high-energy injury mechanisms. In addition, bladder dysfunction and urinary incontinence impose a heavy physiological burden on patients with SCI. Renal failure and uremia caused by SCI are the main causes of death in these patients even after recovery from the initial injury.

When conservative treatment fails, sacral neuromodulation (SNM) may well be used for the treatment of pelvic urinary indications and neurogenic bladder. According to data from animal and human pilot studies, the procedure is minimally invasive and carries low risk. Bladder compliance and bladder volume will be maintained through this treatment. In the same way, urinary tract infections will be reduced in acute situations following SCI (2, 3). Epidural electrical stimulation (EES) enables rodent, feline, and non-human primate models of leg paralysis to stand, walk in various directions, and run. This is because treatment can make the executive centers coordinate a wide range of motor behaviors immediately when it is applied to the lumbar spinal cord (4). In the clinic, EES is less used than other techniques. The main reason is that, in EES, an implantable electrode enclosed within a catheter is implanted into patients. Therefore, patients need a long recovery time, and the incidence of postoperative complications and treatment costs are also increased. The rate of postoperative complications is as high as 35–40% when patients receive the treatment according to related research (5). Transcranial current stimulation (TCS) is a non-invasive brain stimulation technique that involves applying a persistent, low-intensity electrical current over the scalp. Anodal TCS is an excellent treatment that can help the brain reach an optimal state of excitability, speed up motor learning, and accelerate training effects for spinal cord patients (6, 7), because anodal stimulation increases cortical excitability. However, its low focalization and high cost have limited its use as a standard and continuous treatment (8). Furthermore, the treatment-related expenses are expensive. Approximately, one-third patients will develop complications, and part of the complications will require huge treatment costs. So, we need to find a cheap and easy way to simulate SNM, EES, and TCS in patients with spinal cord injury (9).

Acupuncture, which originates from traditional Chinese medicine, can improve nerve conduction velocity and alleviate neuropathic pain (10, 11). It can improve the condition of patients who have muscle wasting and joint contracture due to peripheral nerve injuries (12). The results of electrical stimulation when used to treat injured nerves in animal and human models have been satisfactory (13, 14).

Electroacupuncture (EA) is a simple and effective treatment approach for SCI. Based on relevant research, after rat SCI, the effects of acupuncture on dorsal neuron function and neuroprotection are important. EA stimulation can promote neuronal functional recovery greatly when it acts on SDU26 and DU16 (Shuigou and Fengfu). Acupuncture's antioxidation, anti-inflammatory, and antiapoptotic effects are likely responsible for these improvements (15). But the selection of EA electrode targets usually depends on traditional Chinese medicine, and does not consider the properties of electrical transmission. Furthermore, in previous studies, 1.3% nerve injuries were caused by acupuncture, so improving the precision is crucial (16, 17).

This study examines the efficacy and outcome of ultrasound-guided EA stimulation in a patient with SCI who did not respond to general rehabilitation exercises, such as spinal joint loosening training, breathing training, lumbar-integrated movement training, and paraplegic-integrated limb training.

Case description

History

The patient was a 48-year-old woman who sustained a lower-back injury after being hit by a heavy object. She immediately experienced pain in her lower back and loss of sensation in her lower limbs and was unable to move. Upon admission, she was diagnosed with T12-L1 vertebral flexion and stretch fracture accompanied by traumatic spinal stenosis (Figures 1A,B). The final diagnosis was SCI with paraplegia (The American Spinal Injury Association impairment scale: B). Combined with physical examination and imaging, no obvious contraindications were found in various laboratory tests. The posterior thoracic T12-L2 pedicle screw system was used for distraction reduction, internal fixation, lamina decompression, and bone graft fusion (Figure 1C).

The patient was transferred to the rehabilitation department 2 weeks after the operation for manipulation therapy, including spinal joint loosening training, breathing training, lumbar-integrated exercise training, and paraplegic limb comprehensive training. However, the patient's symptoms did not significantly

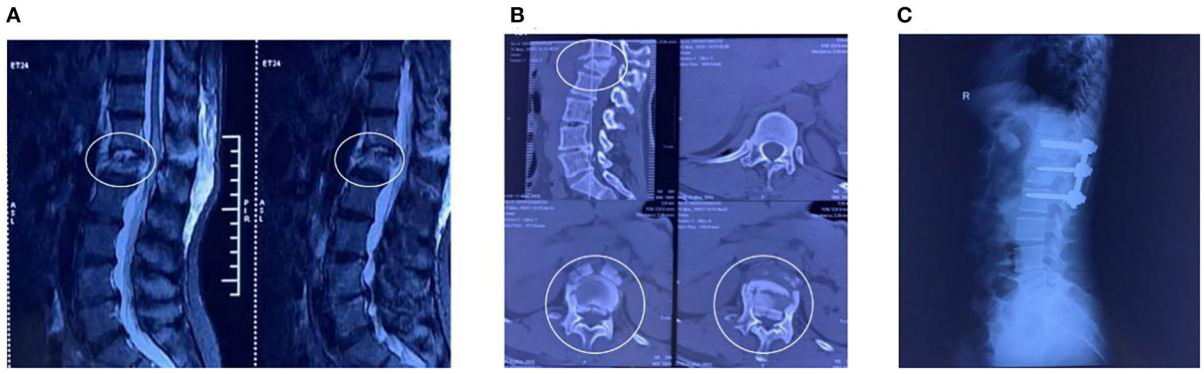

FIGURE 1
MR images and Radiographic before treatment. **(A,B)** Lumbar magnetic resonance imaging and computed tomography showed explosive L1 fracture with severe SCI. **(C)** Postoperative radiograph.

improve. To improve the quality of life and self-care ability, she opted for acupuncture.

Diagnosis

The patient underwent a detailed clinical examination after her first visit. No obvious abnormalities were observed in each joint of both lower extremities. To evaluate the muscle strength of each key muscle in both lower limbs, muscle fiber fibrillation can be seen in the iliopsoas muscle and the quadriceps muscle eye, but no movement can be formed. The tibialis anterior, extensor, and gastrocnemius muscles were completely paralyzed, and muscle contractions were invisible or undetectable. Blood circulation in both lower extremities was somewhat poor. Taking into account the previous baseline, we decided to apply a different intervention. Informed consent was obtained from the patient for publication of this case report.

Intervention

The intervention proposed included stimulation of the sacral nerve with ultrasound-guided EA, combined with a water-drinking program and intermittent catheterization to improve urinary retention in the bladder; furthermore, ultrasound-guided EA stimulation of the spinal cord and head could improve muscular dystonia in the lower extremity.

The application of ultrasound-guided EA stimulation was based on anatomical structure. In this case, an electrical current was applied to the acupuncture needles placed close to the nerve. Using ultrasound imaging, peripheral nerves could be visualized based on relevant research. Invasive therapies like neural blocks can be made more precise and accurate using this technology (18).

Ultrasound-guided EA stimulation of the sacral nerve

After spinal joint looseness training, respiratory training, lumbar-integrated exercise training, and paraplegic limb training, EA stimulation of the sacral nerve was performed. In 2005, an article described a case report of sacral nerve stimulation, which located S3 and S4 nerves for electrical stimulation to treat neurogenic bladder urinary retention (19). According to that article, the four therapeutic EA electrodes (HUA CHENG.30 mm × 75 mm) were located in the S3 and S4 foramen connected with an electro stimulator (sd Z-III electroacupuncture instrument, Hwato brand, China) at 20 Hz with 220 ms wave width, which is similar with the sacral nerve stimulator (Figures 2A,B). The amount of stimulation was increased until the patient developed flexion reflex of the great toe or rectal traction (20, 21). And the range of intensity was 100-120 mV, five times a week; the treatment was terminated until the patient's residual urine volume was maintained below 100 ml. Each stimulation lasted about 1 h, supplemented by a water-drinking program and intermittent urethral catheterization. Daily drinking time and quantity were fixed.

Ultrasound-guided EA stimulation of the spinal cord and the head

We used a Doppler ultrasonic-diagnostic apparatus (SonoScape®, China) at 12 MHz. The spinal nerve was imaged in transverse cross-sectional (a short axis) and longitudinal (a long axis) views between T12 and L1 to locate the electrical stimulation (Figure 2C). We used a kind of acupuncture needle for carrying an electric current (HUA CHENG.30 mm × 40 mm). The first and second needles were

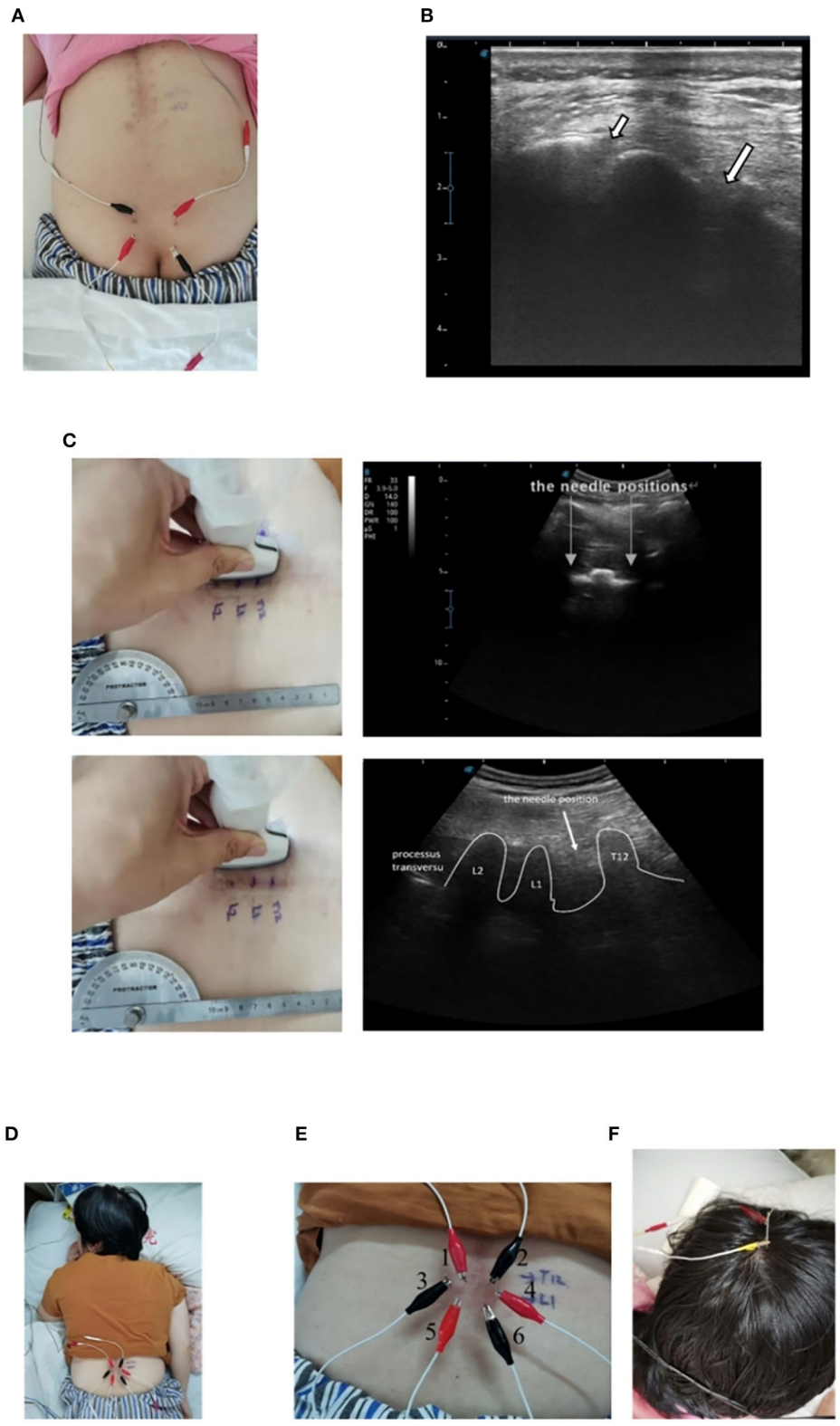

FIGURE 2
Schematic of EA stimulation. **(A)** Sacral nerve EA stimulation on the patient. **(B)** Ultrasonographic images of the S4 (a short arrow) and S3 (a long arrow) foramen. **(C)** Ultrasonographic images of the T12 to the L2 vertebrae. **(D)** Spinal nerve EA stimulation on the patient. **(E)** EA distribution of spinal nerve stimulation. **(F)** EA stimulation of the head on the patient.

located between T12 and L1. The third and fourth needles were located at the left and right nerve roots of L1, and the fifth and sixth needles were located between L1 and L2. The six needles were arranged in a hexagonal pattern to create an electric field stimulus at the affected area (Figure 2D). The depth of EA is about 3.5 cm, not more than 1/2 of the ligamentum flavum. When inserting the EA electrode, it is necessary to prevent it from passing through the ligamentum flavum and causing secondary injury to the spinal cord. Six needles were left in place at six points connected to an electro stimulator (SdZ-III electronic acupuncture therapy instrument, Hwato brand, China) to apply a continuous waveform, at 50 Hz and with 220-ms wave width for 1 h (22) (Figure 2E). The intervention was repeated five times/week until discharge.

The patient received another intervention stimulation of the head during the session. The EA electrode was inserted 1.5 cm in front of the central sulcus and extended along with the skull to the front of the forehead (Figure 2F). The program was performed five times/week.

Outcomes

The results of nearly a 1-year period are presented in this report. A significant improvement in the patient's condition was noted after treatment.

For urinary retention in the bladder, we simultaneously applied clean intermittent catheterization and sacral nerve EA stimulation. We found that voiding volume by the patient herself has been increasing; meanwhile, the volume of the urethral catheter decreases. Hence, we reduced the urethral catheterization times from five to zero. After the urethral catheter was removed, the residual urine volume was detected, which was only 80 ml, proving that urinary retention in the bladder had improved (Figure 3A).

In terms of lower-limb muscle tone, the patient could only walk with a Walkabout orthosis in May 2020 (Figure 4A); she was able to walk with an ankle-foot orthosis in September 2020 (Figure 4B). Next, we compared the neurological level according to the American Spinal Injury Association (ASIA) scale (Supplementary Table 1). We did not find any difference between the ASIA neurological level and the sensory level, but we did find that both the impairment scale and the motor level were better than before. We further compared the scores from the ASIA scale from November 28, 2019 to November 11, 2020. The ASIA scale showed that there was no significant increase in the sensory score and the motor score from the beginning of rehabilitation to the beginning of sacral electrical stimulation. There were no significant changes in sensory scores (156 to 160) when sacral electrical stimulation was initiated. However, the motor scores increased from 58 to 64 after sacral electrical stimulation. When a combination of the spinal cord and head stimulation was added, the motor score (64 to 73) and the sensory score (160 to 186) both showed significant change (Figure 3B).

The results of comparison of the motor score and the sensory score suggested function recovery speed. We found that the slope value of the motor score showed little difference before and after spinal cord stimulation (Supplementary Table 2). However, the sensory score increased significantly after spinal cord stimulation. In the FIM score, the value did not change significantly before sacral EA stimulation (67 to 81) but increased significantly (81 to 114) after sacral EA stimulation (Figure 3C). The slope value increased slowly at first, but its increase rate was rapid after the sacral stimulation. The rate did not slow down with increasing time after spinal cord stimulation (Supplementary Table 3). The imaging data of patient after rehabilitation in Supplementary Figure 1.

Discussion

The physical therapy methods and clinical reasoning of a patient with traumatic SCI are described in this case report. According to the clinical examination, ultrasound-guided EA stimulation was used to target the nerve in this patient. This is a new type of intervention approach targeting the nerve. The stimulation points we selected and the traditional Chinese medicine acupoints have some similarities. For example, the position for the S3 and S4 foramen is similar to Baliao (23, 24). However, compared with acupoints, the points we selected based on the principles of EA stimulation of the sacral nerve, and the stimulation position used in our patient was deeper and more precise.

Sacral nerve EA for the treatment of urinary retention is an improvement based on SNM in our case. The mechanism of sacral nerve EA in the treatment of urinary retention is unclear, but it is similar to the mechanism of SNM in the treatment of SCI, that is, the bladder responds to nerve stimulation with an initial rapid contraction, followed by a slow, sustained relaxation. Shi et al. (25) revealed that SNM could decrease uninhibited detrusor contractions and peak bladder pressures during bladder filling in an experimental animal model of complete SCI. An animal model of complete spinal cord transection caused a decrease in β-adrenergic relaxation responses, and the results were shown to be mutated by SNM *in vitro* (26). The clinical results from humans demonstrated the effects of SNM. All patients who received SNM experienced incontinence, compared to 100% of the control group. The patients with SNM had fewer UTIs (.5/year vs. 3.8/year) and several readmissions. However, the limitation of SNM is obvious. Pain at the implant site and lead migration were the most common adverse events reported. Another health technology investigated the costing factors of patients to SNM. This investigation showed that the cost-effectiveness between SNS and incontinence supplies is essentially identical. This can

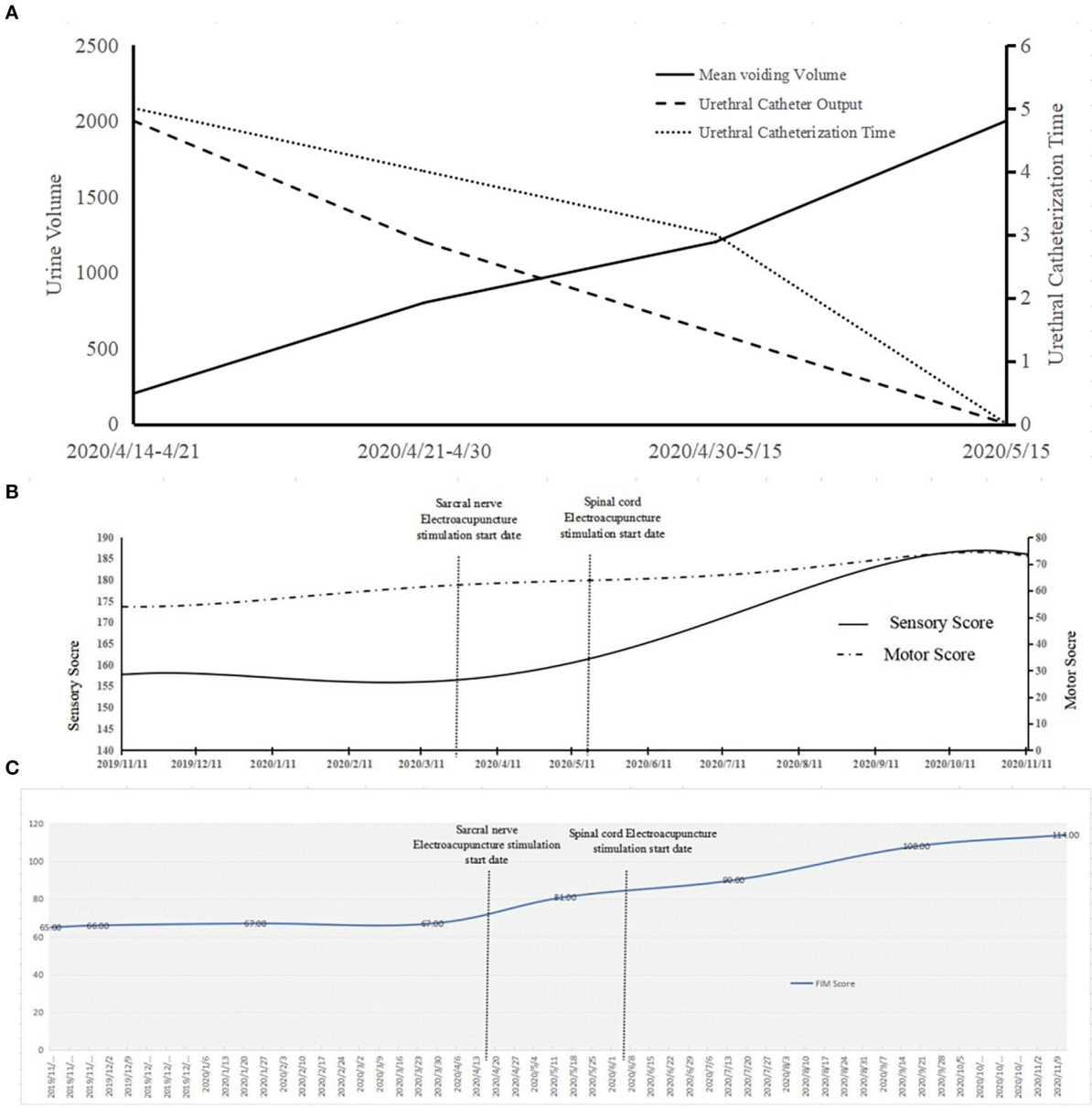

FIGURE 3
The changes of the patient's function during the study period. **(A)** The results show the voiding volume and the volume of the urethral catheter. The right coordinate axis shows the voiding volume and urethral catheter output. The left axis displays the times of urethral catheterization times. **(B)** The ASIA score curve of the patient. **(C)** The FIM score curve of the patient.

be attributed to the adjustments required to make the device most effective and the cost of the procedure. SNS also had a positive impact on the quality of life (27).

In traditional Chinese medicine, the sacral nerve is stimulated with acupuncture needles through the S3 and S4 foramen for the treatment of urinary tract diseases. This way, we used the acupuncture needle to module SNS based on its basic electrical stimulation parameters. The ultrasound-guided EA also increased the voiding volume and reduced the volume of the urethral catheter (Figure 3A). Despite it is not as effective as Bladder Stumilator it is. Compared with sacral nerve electrical stimulation, EA is minimally invasive and avoids the risk of secondary surgery due to battery depletion and electrode movement. Overall, its effects are very promising, and the cost of operation is low. We aim to explore the optimum parameters of the electrical needle in future studies. This treatment approach will likely be relevant and helpful for people with SCI with heavy economic burden, especially in undeveloped countries.

FIGURE 4
Photos of the patient walking before and after treatment. **(A)** Before treatment, walk with the help of walkabout orthosis. **(B)** After treatment, walk with the help of ankle-foot orthosis.

Epidural electrical stimulation is an emerging method for treating SCIs. Human studies have observed that EES triggers alternating rhythmic muscle activity patterns (28, 29), with a reduction in spasticity among patients with incomplete SCI and an increase in the amplitude of voluntary movements in paralyzed limbs (30). Spinal electrical stimulation using electrodes implanted in the epidural space is used to treat SCI (31). However, spinal epidural stimulation may lead to infection of the incision after surgery, spinal epidural hematoma, rejection of the implanted electrode, and a high cost of treatment. Owing to its minimally invasive nature, ultrasound-guided EA stimulation intervention used in our patient reduces the risk. Studies have shown that TCS has a significant effect on motor function in patients with SCI when compared to sham stimulation (32). Furthermore, some studies on transcranial electrostimulation in rats have shown that peripheral craniospinal sensory nerves play a significant role in mediating pulsed electrical stimulation's antinociceptive effects (33). In this study, the antinociceptive effect of stimulation was blocked by local anesthetics applied to the stimulation electrodes injected subcutaneously. Based on these results, it appears that the effects of low-intensity intracranial AC stimulation may be enhanced in brainstem centers by stimulating peripheral cranial nerves (CN1 through CN7), as well as craniospinal nerves (C1–C3) (34). We used the needle inserted into the scalp (precentral gyrus of body surface projection) to stimulate the CNS *via* the peripheral nervous system. The activation from the brain and the brainstem will then be transmitted to the lower motor neurons in the spinal cord, forming a combined effect with electrical stimulation of the spinal cord.

Although data from randomized clinical trials are necessary to further explore the clinical effects of ultrasound-guided EA, in this case report, we present preliminary evidence regarding the potential effectiveness of ultrasound-guided EA stimulation. It is interesting to note that the patient had been injured for 6 months at the time of initiating EA treatment, which is well beyond the prime time of treatment. However, after the first course of treatment, the patient reported regaining motor function, meaning that ultrasound-guided EA stimulation could produce a beneficial effect on both the motor and sensory systems.

This report has some limitations. First, although a few case series have shown promising effects of ultrasound-guided EA stimulation for subjects with neurogenic bladder retention and lower limb dystonia in patients with SCI, this intervention

has not been sufficiently studied in literature. It should be noted that some discrepancies in the methodology, especially the material and insertion depth of acupuncture needles, and the duration of the electrical stimulation can be observed between previous studies and the current one—for example, Wilson et al. implanted permanent electrodes near the nerve (35). Second, the application parameters of electrical stimulation refer to the corresponding parameters of percutaneous electrical stimulation, but the best parameters need to be determined by an active electrical stimulation simulation experiment. Third, neither of the procedures have any psychometric properties (positive or negative likelihood ratios, specificity, or sensitivity data). To further identify the effectiveness of ultrasound-guided EA stimulation in lower limb dystonia, randomized controlled trials need to be conducted. Fourth, because this is a single case report, we eliminated the effects of chance. Randomized controlled trials with large sample size are needed to further determine the efficacy of ultrasound-guided EA in the treatment of dystonia of the lower extremity.

Conclusions

This case report describes the successful rehabilitation of a patient with SCI. Physical therapy intervention included the use of ultrasound-guided EA on S3 and S4 nerves, supplemented by a water-drinking plan and intermittent urethral catheterization, and the use of spinal electroacupuncture on T12-L1, combined with anterior central EA therapy of the head. After 10 months of treatment, there were significant improvements in sensory conduction, nerve function, and muscle strength, and clinically significant changes in the patient's functional status.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Tianjin Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TL, Y-TC, R-XL, M-WG, and Q-WL were involved with the conception and design. X-SG and DM revised the manuscript critically. The first draft of the manuscript was written by X-LC and X-ZS. The final draft of the manuscript has been approved by all the authors.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.903207/full#supplementary-material

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Multi-modal fMRI and TMS follow-up study of motor cortical stroke caused by hyaluronic acid filler: A case report

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Background: Blindness and stroke resulting from hyaluronic acid (HA) fillers are not frequently reported complications. Reports on stroke recovery after HA injection are limited. In the current study, the recovery process, task-based functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and neurophysiological changes of a patient with monocular blindness and ipsilateral motor cortical stroke after forehead injection of HA are explored.

Case-report: The study comprised a 34-year-old female patient who presented with left eye blindness and a stroke after receiving an HA injection a month before admission. The lesion was mainly limited to the left precentral gyrus, and the patient had pure arm monoparesis. For 3 weeks, the patient received conventional rehabilitation treatments and ten sessions of repetitive transcranial magnetic stimulation (rTMS) intervention. Clinical assessments, neurophysiological evaluation, task-based fMRI, and DTI examinations were conducted to assess her motor improvement and the possible neuro mechanism.

Clinical rehabilitation impact: The patient's right upper limb motor function was almost completely restored after receiving rehabilitation therapy. However, the vision in her left eye did not show significant improvement. The neurophysiological evaluation showed partial recovery of the ipsilesional motor evoked potentials (MEPs). DTI results showed that the ipsilesional corticospinal tract (CST) was intact. Task-based fMRI results indicated that the activation pattern of the affected hand movement was gradually restored to normal.

Conclusion: A case of good motor recovery after stroke due to HA injection with a lesion mainly restricted to the precentral gyrus but without CST damage is presented in the current study. Further studies should be conducted to explore the efficacy and the mechanisms of rehabilitation and neuromodulation approaches to motor cortical stroke.

KEYWORDS

hyaluronic acid filler, cortical stroke, rehabilitation, fMRI, TMS

Introduction

Medical cosmetology application has significantly increased recently, resulting in several reports of severe vascular complications caused by the facial injection of soft tissue fillers such as hyaluronic acid (HA) and autologous fat. Vision loss and cerebral infarction are rare but severe complications of these injections and can lead to disability and significant effects on the patient's daily life (1). It is challenging to assess the incidence of these complications due to very few case reports and case series. The proposed mechanism of vision loss and cerebral infarction after HA filler injection into the glabella and forehead is the induction of embolism of the terminal blood vessels of the ophthalmic artery and middle cerebral artery by the intra-arterial embolus of filler either anterogradely or retrogradely (2). Previous studies report that facial vascular compromise and neurologic symptoms related to stroke after HA filler injection can be fully or partially abrogated. However, the prognosis of complete vision loss due to an ophthalmic artery or central retinal artery occlusion is often poor (3, 4). Several studies have been published in the journals of ophthalmology and neurology, and most of them mainly report the description and treatment of HA injection complications. Few studies focus on the rebabilitation of patients with stroke caused by HA injection. In this study, the recovery process, task-based functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and neurophysiological changes of a patient with monocular blindness and ipsilateral hemisphere stroke after forehead injection of HA are reported. The lesion was mainly limited to the left precentral gyrus. The patient had pure arm monoparesis, an uncommon stroke presentation with a reported frequency of <1% of all ischemic strokes (5, 6). Currently, very few studies have explored motor function remodeling and the therapeutic effect of repetitive transcranial magnetic stimulation (rTMS) on motor recovery of pure cortical stroke patients. The present case study sought to explore the possible motor remodeling pattern and recovery mechanism of the patient with precentral gyrus stroke.

Case description

Patient

The patient included in the present study was a 34-year-old Asian woman without any medical history related to the present case. The patient reported receiving a 1 mL HA filler injection into her glabella and forehead using a hollow-bore needle at a local private beauty salon. The procedure was conducted by a nurse practitioner without the presence of a physician on July 2, 2020. The patient complained of left periocular pain and complete left eye vision loss shortly after receiving the HA injection. She immediately received a hyaluronidase injection into the left glabella and forehead. The patient presented with nausea, vomiting, headache, and lost consciousness within 10 min. She was taken to a local hospital 1 h post-injection and was admitted to the intensive care unit. She gradually developed muscle weakness in her right limbs. Diffusion-weighted imaging was performed 3 h after the HA injection, which revealed an acute embolic infarction involving the left frontal and parietal lobes. The patient was stable after 2 weeks of conservative medical treatment. The patient was moved to a local rehabilitation center as she presented with right hemiplegia, where she underwent physiotherapy, occupational therapy, and acupuncture for 2 weeks. Her right lower limb muscle strength was restored to normal, and she could walk independently without abnormal gait. However, the motor function in her right upper limb was not significantly improved. The stability and flexibility of her right upper limb and hand were poor, making it difficult for her to hold items with her right hand. Consequently, she was admitted to our rehabilitation center on August 5, 2020, for further observation (Timeline Figure 1, full details in Supplementary material).

Rehabilitation assessments and treatments

The patient was alert and conscious at the time of admission. MRI showed that the lesion was mainly confined to the left precentral gyrus (Supplementary Figure 1). Clinical assessments, neurophysiological measurements, task-based fMRI, and DTI examinations were performed at different time points to design an individualized neuromodulation protocol and track the process of motor recovery and functional remodeling. The first evaluation, including clinical assessments and neurophysiological analysis, was performed on August 5, 2020 (t0), when the patient was admitted to the rehabilitation center about 1 month after receiving the HA injection. The second evaluation, including clinical assessments, task-based fMRI, and a DTI examination, was performed on August 10 (t1). The third evaluation only comprised clinical assessments and was performed on August 26 (t2) after the patient had undergone conventional rehabilitation treatments for 3 weeks and ten sessions of rTMS intervention on discharge. The fourth evaluation comprised clinical assessments, neurophysiological measurements, and task-based fMRI and was performed on September 28 (t3). The final evaluation included clinical assessments, neurophysiological measurements, task-based fMRI, and a DTI examination and was performed on May 19, 2021 (t4).

Clinical assessments

Brunnstrom Stages (BS), Barthel Index (BI), upper limb Fugl-Meyer (UPFM) scale, and Action Research Arm Test

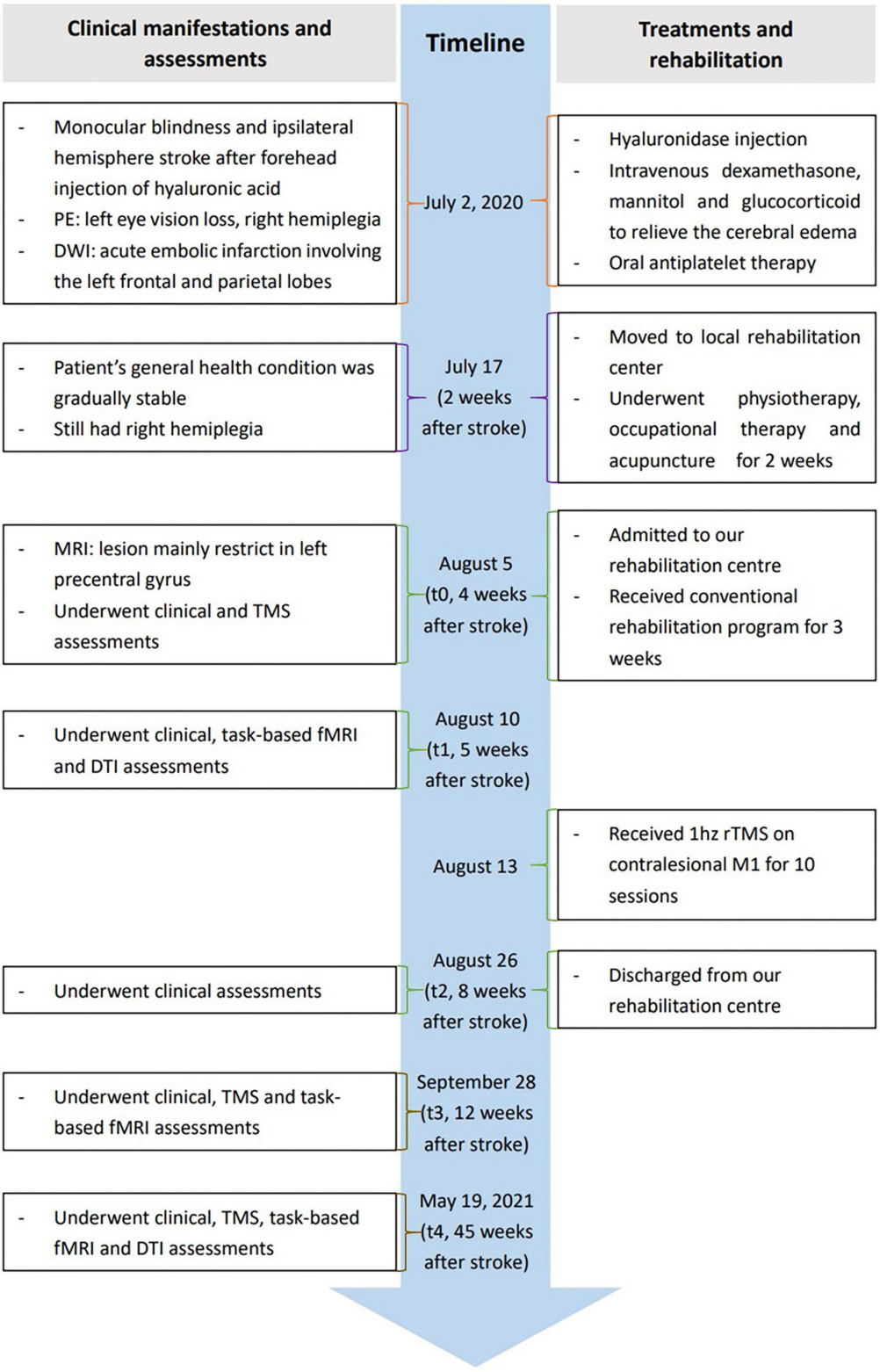

FIGURE 1
Timeline of relevant data, interventions, and outcomes.

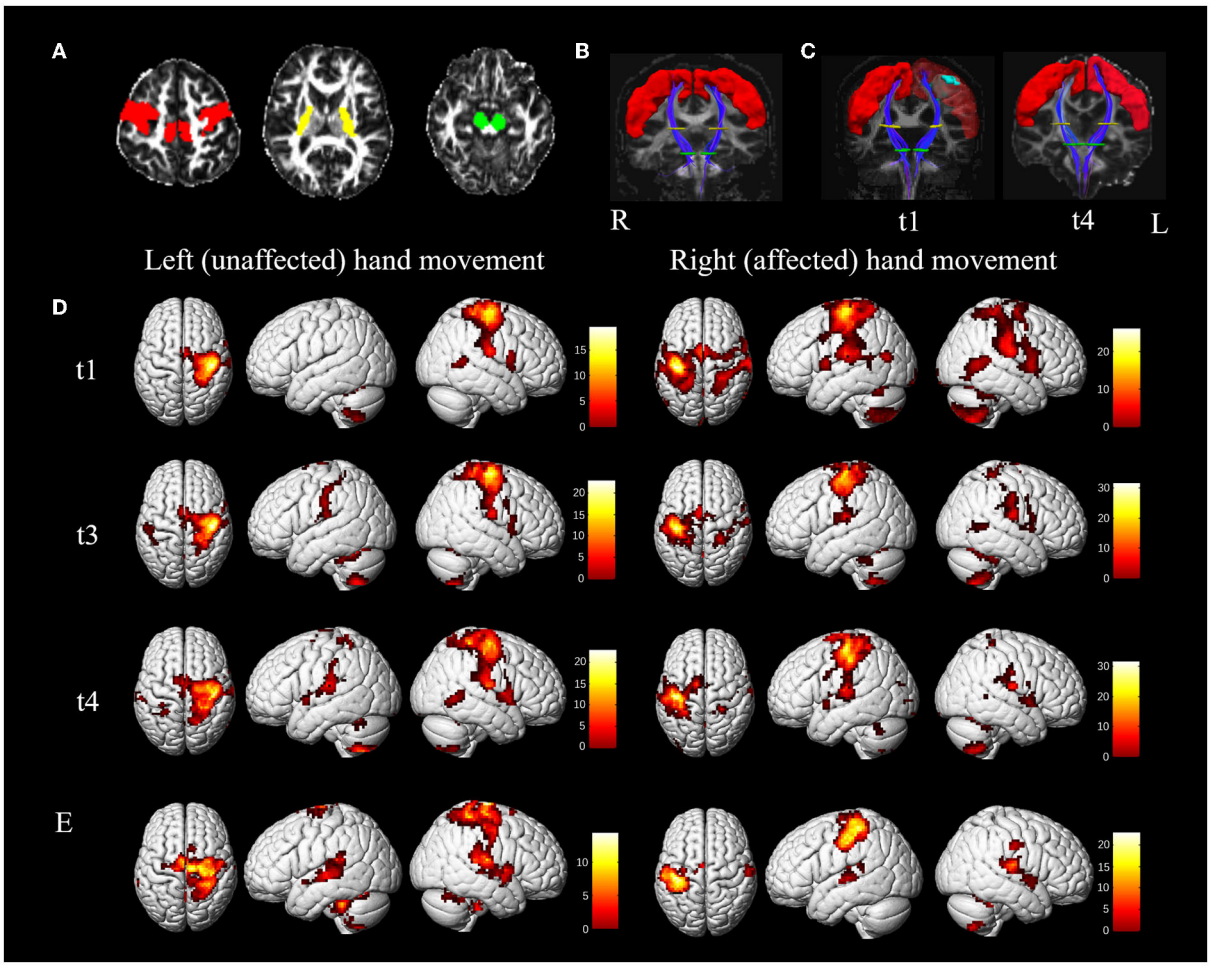

FIGURE 2
MRI results. **(A–C)**, diffusion tensor tractography of the corticospinal tract (CST). **(A)** Regions of interest (ROI) for reconstructing the CST are located at the precentral gyrus (red color, obtained from the AAL90 template), the posterior limb of the internal capsule (yellow color), and the cerebral peduncle (green color) on the fractional anisotropic (FA) map. **(B)** A coronal view of the bilateral CSTs (blue color) from the healthy control. The red, yellow, and green areas represent the ROI of the precentral gyrus, the posterior limb of the internal capsule, and the cerebral peduncle. **(C)** A coronal view of bilateral CSTs from the patient at t1 (5 weeks) and t4 (45 weeks). On the left of the C map (t1), the cyan region is the lesion registered from T1 space to FA space. **(D,E)** activation during passive unaffected (left) and affected (right) hand movements of the patient and healthy control. **(D)** Activation of passive movement of the patient at t1, t3 (12 weeks), and t4; **(E)** activation of passive movement of healthy control. Color bar = *t*-value. The left side indicates the left hemisphere. L, left; R, right.

(ARAT) clinical assessments were conducted at five different time points to monitor rehabilitation effectiveness and outcomes, as mentioned above.

Neurophysiological analysis

Neurophysiological analysis was performed using single-pulse TMS. TMS was conducted using the Yiruide CCY-II TMS instrument (Wuhan, China) with a round coil. Surface electromyography (EMG) was performed by attaching a pair of Ag-Ag/Cl electrodes to the first dorsal interosseous (FDI) muscle of the hand of the patient to assess motor evoked potentials (MEPs). The resting motor threshold (RMT) was determined before stimulation. MEPs were recorded using the self-contained MEP recording system in the Yiruide transcranial magnetic stimulator and analyzed with a coupled MEP-analysis software (Wuhan, China). Ten consecutive MEPs in the cortical representation area of FDI muscles in both hemispheres were recorded as described previously (7). The central motor conduction time (CMCT) for FDI was also recorded (see Supplementary material for further details).

fMRI and DTI procedures

High-resolution T1-weighted anatomical images, fMRI BOLD images for affected and unaffected passive finger

flexion-extension tasks, and DTI data were acquired using a Siemens Prisma fit 3.0 Tesla MRI scanner (Siemens, Erlangen, Germany) at the Shanghai Key Laboratory of Magnetic Resonance, East China Normal University (Shanghai, China). Details are provided in the Supplementary material.

Deterministic fiber tracking was conducted after preprocessing using a fiber assignment based on a continuous tracking algorithm with an angle threshold of 30°. Three regions of interest (ROIs) were placed at the precentral gyrus, the posterior limb of the internal capsule, and the cerebral peduncle to reconstruct the corticospinal tract (CST) of interest. The precentral gyrus was extracted from the AAL90 template (8) and spatially registered to an individual fractional anisotropic (FA) map. The individual axial FA map indicated the posterior limb of the internal capsule and the cerebral peduncle (Figure 2A). Tractography was performed on healthy control (Figure 2B) and a t1 and t4 scan of the patient (Figure 2C).

Individual statistical analyses were performed in a matrix design using parameter estimates (based on a general linear model), and contrasts were defined (passive movement vs. rest in the current study). Statistical parametric maps (SPM) of the t statistic were generated and stored as separate images for each subject. The results were analyzed at $p < 0.05$ and corrected for multiple comparisons (voxelwise FWE corrected) across the whole brain. In this study, we pre-defined the ROIs by the AAL template (8), including bilateral precentral gyrus, postcentral gyrus, supplementary motor area (SMA), cerebellum (Cb), and parietal lobe (PL) (combining superior and inferior lobe), and premotor cortex (PMC) (combining dorsal premotor cortex and ventral premotor cortex) from the high-resolution sensorimotor area tract template (HMAT) (9). The number of significant active voxels for each pre-defined ROI during passive movement of the left and right hand was obtained. The lateralization index (LI) of the primary sensorimotor cortex (SMC), which includes the precentral gyrus and postcentral gyrus, was used to determine the interhemispheric balance.

Rehabilitative treatments

The patient was subjected to a conventional rehabilitation program comprising 60-min physiotherapy (PT) sessions, 45-min occupational therapy (OT), 20-min acupuncture treatment, 20-min neuromuscular electrical stimulation, and 20-min pneumatic gloves for 5 days a week between August 5 and August 26 (t0 to t2). A targeted rTMS protocol was designed for the patient according to the results of the first fMRI and DTI conducted on August 10 (t1). The patient received ten sessions of 1 hz rTMS intervention applied to the contralesional right primary motor cortex (M1) for 10 days between August 13 and August 26. A total of 1,000 stimuli were administered as ten trains of 100 stimuli, with an intertrain interval of 20 s in each session. The stimulation intensity was 100% of RMT.

Outcomes of rehabilitation

Comprehensive rehabilitation treatments induced a gradual increase in right upper limb motor function and caused a satisfactory functional recovery in the present case. The patient's strength in all upper limb muscles was fully restored (grade 5/5) at discharge on August 26, about 3 weeks after admission to the rehabilitation center. In addition, she could write with her right hand, but her left eye vision had not improved.

Clinical scores

Clinical assessment results are presented in Table 1. The BS of the patient increased from 5-4-6 at admission to 6-6-6 at discharge. Moreover, her BI increased from 90 to 100 points. The hand function of the patient improved significantly, as indicated by the ARAT score, which increased from 27 to 54 points. Furthermore, the UPFM score increased from 43 to 61 points, primarily in the distal components of UPFM (wrist and hand), which increased from 10 to 23 points.

Neurophysiological measures

The ipsilesional MEPs of the patient's FDI were absent at t0 on admission. However, it was induced at the follow-up t3 and t4. The average amplitude of the ipsilesional MEPs increased by 90 μV at t4 compared with that at t3, and the average ipsilesional CMCT at t4 decreased by 0.31 ms. RMT-asymmetry, which was calculated as the ratio of ipsilesional RMT and contralesional RMT, decreased from 1.233 at t3 to 1.111 at t4. The average amplitude of the ipsilesional MEPs at t3 and t4 was significantly lower than the contralesional ones. However, the ipsilesional RMT was higher than the contralesional RMT at t3 and t4. Furthermore, the average CMCT of the affected hemisphere was significantly longer than that of the contralesional hemisphere at t3 and t4. Detailed information is provided in Table 1.

Task-based fMRI and DTI measures

CST originating from the precentral gyrus and reaching the cerebral peduncle through the posterior limb of the internal capsule showed no significant difference between the ipsilesional side, the contralesional side of the patient, and the bilateral sides of the healthy control. The mean FA of CST of the healthy control and patient obtained 5 weeks (t1) and 45 weeks (t4) after presenting with stroke are presented in Supplementary Table 1.

The brain activation pattern of passive movement of unaffected hands of the patient was similar to that of healthy control, showing dominant contralateral activation and less ipsilateral activation (Figures 2D,E). However, compared with the passive movement of the unaffected hand of the patient and bilateral hand movement of the healthy control, that of

TABLE 1 Scores on clinical scales and neurophysiological evaluation results.

Clinical assessments	t0	t1	t2	t3	t4	Neurophysiological analysis	t0	t3	t4
UPFM	43	48	61	66	66	Ipsilesional MEP (μV)	/	562	652
UPFM (W/H)	10	12	23	24	24	Ipsilesional RMT (%)	/	53	50
ARAT	19	27	54	57	57	Ipsilesional CMCT (ms)	/	9.35	9.04
BS	5-4-6	5-5-6	6-6-6	6-6-6	6-6-6	Contralesional MEP (μV)	1194	1118	1572
BI	90	95	100	100	100	Contralesional RMT (%)	52	43	45
						Contralesional CMCT (ms)	8.32	8.27	8.14
						RMT ratio	/	1.233	1.111

UPFM (max 66), upper limb Fugl-Meyer Assessment; UPFM (W/H) (max 24), Wrist/Hand component of UPFM; ARAT (max 57), Action Research Arm Test; BS (max 6), Brunnstrom Stages; BI (max 100), Barthel Index; MEP, Motor Evoked Potential (in μV); RMT, Resting Motor threshold (in %, max 100); CMCT, central motor conduction time (in ms); RMT ratio = Ipsilesional RMT/Contralesional RMT.

the patient's affected hand consistently displayed more bilateral and wider activation in the primary and secondary sensorimotor cortices. The numbers of significantly active voxels in each ROI during passive movement of the patient and the healthy control are shown in Table 2. The LI of the affected hand movement was 0.19 at t1. The total voxel number of activations of bilateral SMC decreased slightly, and the LI of the affected hand movement increased to 0.35 at t3. Bilateral activations of the affected hand movement were continuously reduced, and the LI of the affected hand movement showed a significant increase (LI = 0.61) at t4. The LI value of the unaffected hand movement at t1, t3, and t4 was 0.99, 0.91, and 0.92, respectively (Table 2), which showed slightly higher than healthy control (LI = 0.88 and 0.84 for the left and right-hand movement, respectively). Notably, bilateral PMC, SMA, PL, and Cb showed hyperactivation at t1 during affected hand movement, and the activation decreased with motor recovery, especially the over-activation of the ipsilateral areas of the secondary motor cortex and non-motor cortex, which almost returned to normal at t4.

Discussion

The present case was a 34-year-old female patient who presented with left eye blindness and a stroke after receiving an HA injection. The lesion was mainly limited to the left precentral gyrus, and the patient showed right arm monoparesis. She underwent 3 weeks of conventional rehabilitation treatment and ten sessions of rTMS intervention in our rehabilitation center 1 month after the stroke onset. The results from clinical assessments showed that the motor function of the patient's right upper limbs was almost completely restored. Neurophysiological analysis showed partial recovery in the ipsilesional MEPs. Task-based fMRI results showed the activation pattern of the affected hand movement was almost restored to normal. The DTI examination showed that the ipsilesional CST of the patient was intact.

Changes in task-based fMRI and DTI results

Structural and functional MRI results showed that the recovery mechanism of the patient with a lesion mainly restricted to the precentral gyrus would be associated with a complete CST and the recovery of the task-state activation pattern. The activation pattern of the affected hand movement changed from a bilateral pattern to a contralateral one, thus restoring the normal condition. Specifically, this patient's recovery pattern focused on activation in the contralateral SMC with a continued increase in the LI of SMC, accompanied by a decreasing number of over-activated voxels in both hemispheres. This recovery pattern has been reported in the previous study, and another pattern of recovery found in more patients is the continued increase in contralateral SMC activation in subcortical stroke (10). The recovery would be optimal when M1 is not only preserved structurally, as after subcortical as opposed to cortical stroke, but is also capable of enhanced workload (11). However, patients in this study with pure precentral gyrus lesions obtained good recovery through the pattern of progressive focusing. Consistent with previous studies, widespread bilateral recruitment of the secondary motor areas and non-motor cortex occurs first, such as PMC, SMA, and PL, which also happens after cortical stroke (12). Accordingly, the amount of overactivation of these areas declined to normal as recovery took place. In normal subjects, these areas are also involved in hand movement. Thus, bilateral over activation of non-SMC may reflect excess recruitment of a preexisting large-scale distributed motor network rather than genuine reorganization (11). Considering that we applied 1 Hz rTMS to the contralesional M1 to help suppress the over activation of the contralesional hemisphere in this study. As expected, the clinically significant improvement in the patient's hand function was observed after 3 weeks of rehabilitation and ten sessions of targeted rTMS intervention. Notably, although the lesion was mainly located in the precentral gyrus, it was not involved in the original area of the CST pathway in the precentral gyrus, which may also account for the patient's complete CST. Previous studies reported that higher retention of CST leads

TABLE 2 Number of significantly active voxels in each neural region during passive movement for patient and healthy control.

ROI	Left (unaffected) hand movement				Right (affected) hand movement			
	Patient			HC	Patient			HC
	t1	t3	t4	/	t1	t3	t4	/
C_PreCG	478	484	491	400	341	292	196	191
C_PostCG	636	655	647	407	750	550	552	649
C_SMC	1,114	1,139	1,138	807	1,091	842	748	840
C_PMC	221	288	313	180	243	90	92	43
C_SMA	178	179	154	117	318	167	123	111
C_PL	50	60	186	38	301	88	199	198
C_Cb	0	141	70	17	523	305	59	58
I_PreCG	0	0	0	5	136	52	1	0
I_PostCG	4	129	49	48	608	343	157	51
I_SMC	4	129	49	53	744	395	158	51
I_PMC	0	3	1	16	285	81	2	1
I_SMA	46	119	157	120	232	56	7	26
I_PL	0	31	54	34	173	10	0	5
I_Cb	494	597	415	230	956	664	464	282
LI-SMC	0.99	0.80	0.92	0.88	0.19	0.36	0.65	0.89

The LI is calculated for the sensorimotor cortex, defined as the combination of the precentral and postcentral gyrus.
C, contralateral hemisphere to the passive hand movement; I, ipsilateral hemisphere to the passive hand movement; PreCG, precentral gyrus; PostCG, postcentral gyrus; SMC, primary sensorimotor cortex; PMC, premotor cortex; SMA, supplementary motor area; PL, parietal lobe; Cb, cerebellum; LI-SMC, laterality index of SMC.

to better recovery of upper limb function (13–16), and strokes characterized with cortical lesions often have better motor recovery outcomes compared with those with lesions at other sites (17, 18). Structural damage of CST originating from M1 is highly correlated with motor impairments (19), and patients with severe structural pathway damage have lower chances of recovery of upper limb function (20). Therefore, this study's findings may indicate that intact CST would be an essential precondition for good motor recovery. We also suspect that the pattern of recovery and the potential for motor recovery might vary depending on the specific location of the lesion in the precentral gyrus. However, these aforementioned hypotheses are not conclusive enough to be generalized before recruiting more patients with motor cortex lesions and conducting extensive research in the future.

Role of rehabilitation and rTMS intervention

Rehabilitative training plays an essential role in remodeling modified representation hand function within the perilesional area (21–23). Notably, rTMS may enhance this adaptive plasticity process (24). We observed a progressive recovery of the patient's hand function during 3 weeks of conventional rehabilitation therapy combined with ten sessions of rTMS intervention. In particular, although the ipsilesional MEP of the patient was not initially observed at t0, it was detected at t3 and was observed with a higher average amplitude at t4. Additionally, the ipsilesional CMCT and the RMT-asymmetry of the patient at t4 were lower than those at t3. These results indicated a partial recovery of the ipsilesional central motor conduction velocity and the rebalancing of the interhemispheric excitability. The assumption is that the rehabilitation treatment and 1 Hz rTMS over the contralesional M1 might help the patient regain her motor function through the remodeling of ipsilesional M1 and the restoration of the interhemispheric balance. However, this causality could not be confirmed in this case report. Indeed, in a recent literature review of filler-induced cerebral embolism, it was reported that nearly half of the patients recovered (4.65%) or exhibited improved neurologic manifestations (44.19%), while rehabilitative training as well as the additional rTMS intervention were not involved or mentioned in most cases (25). Moreover, very few studies have explored the application of neuromodulation interventions on pure motor cortical stroke patients. Due to the limitations of our magnetic equipment, we did not test the interhemispheric inhibition (IHI), which is largely mediated by the transcallosal pathways (26), to further explore the interhemispheric asymmetry and inter-cortical inhibition after the rTMS intervention. It would also be interesting to investigate the effects of other neuromodulation protocols, such as cortico-cortical paired associative (ccPAS), which may regulate synaptic strength and induce spike-timing-dependent plasticity in sensorimotor circuits (27–29), on the

recovery of motor function after cortical stroke and how these interventions modify the process of cortical plasticity.

Limitations

This study did not include a control patient who had not undergone rehabilitation. Therefore, the possibility of natural recovery in the progress of the patient's motor recovery could not be ruled out. In addition, the time of the initial neurophysiological evaluation was 5 days before the first fMRI and DTI examinations, and DTI was not conducted at t3.

Conclusion

In this case report, the patient who presented with motor cortical stroke after a HA filler injection and suffered from hemiplegia obtained an almost complete restoration of her motor function. However, further research is needed to investigate the real benefits and the underlying mechanisms of rehabilitation and neuromodulation approaches to cortical motor stroke.

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 Huashan Hospital Affiliated to Fudan University Institutional Review Board (HIRB). The patients/participants provided their written informed consent to participate in this study.

Author contributions

XT and QY wrote the first draft. XT collected data, performed the literature search, and prepared Figure 1 and Table 1. QY performed data analysis and interpretation and prepared Figure 2 and Table 2. YP and MG prepared Supplementary material. FL, JZ, and KY provided scientific input and clinical support. MF conducted data interpretation and supervised the study. LS conceived the study, was involved in data interpretation, and revised the final manuscript. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.903648/full#supplementary-material

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Case report: Significant relief of linezolid-induced peripheral neuropathy in a pre-XDR-TB case after acupuncture treatment

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The revised WHO guidelines on multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) include linezolid in the core drug group. Common adverse events of prolonged linezolid use are bone marrow suppression and peripheral neuropathy (PN). Available measures against linezolid-induced PN (LIPN) often have insignificant effects, leading to linezolid discontinuation and a decline in the success rate of MDR/RR-TB treatment. Acupuncture treatment is a symptomatic treatment measure from traditional Chinese medicine (TCM) to relieve pain with overall very low evidence and has never been reported in LIPN. The pilot use of acupuncture in a pre-extensively drug-resistant (XDR)-TB (a more severe form of MDR/RR-TB) patient exhibited significant improvements in LIPN and thus maintained linezolid in the regimen for a longer period.

KEYWORDS

multidrug-resistant tuberculosis, linezolid, peripheral neuropathy, acupuncture, adverse reactions

Background

According to WHO reports and guidelines, multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) is defined as TB that is resistant to rifampicin with or without the co-occurrence of isoniazid resistance, while pre-extensively drug-resistant (XDR)-TB is TB that fulfills the definition of MDR-TB with additional resistance to any fluoroquinolones (FQs). XDR-TB means there is resistance to at least one additional group A drug in addition to pre-XDR-TB (1, 2). In group A, the oxazolidinone linezolid appears to be effective. However, linezolid is associated with considerable adverse effects (AEs), especially when used at a high dosage for a long duration (3). With the common use of linezolid in MDR/RR-TB treatment, peripheral neuropathy (PN) is likely to occur

more frequently and causes long-term functional impairment that impacts the quality of life (4), against which symptomatic treatments are far from bridging the curative gap, despite the efforts being made to shorten the duration and decrease the dose of linezolid (5).

Neuropathic pain is challenging to treat due to its complex natural history, unclear etiology, and insufficient response to standard physical therapy interventions. A multimodal approach to neuropathic pain has been advocated and includes combinations of pharmacological, physical, and cognitive interventions (6). Acupuncture is a traditional Chinese medicine (TCM) treatment modality that is becoming increasingly popular around the world, and some rehabilitation professionals may be trained to provide acupuncture treatment. However, the benefits and harms of acupuncture for linezolid-induced PN (LIPN) have never been reported.

Here, we present a case of a man diagnosed with pre-XDR-TB who developed PN after 4 months of treatment with a linezolid-based regimen and received a series of acupuncture treatments.

Case report

A 26-year-old man, who weighed 48 kg and was 183 cm, was presented to a local respiratory department in Shenzhen, China, after 4 days of fever (up to 38.8°C) and right chest pain, which was accompanied by headache, myalgia, and weakness without cough, sputum, night sweats, weight loss, cutaneous rash, diarrhea, or arthralgia. Other vital signs were within normal limits. The patient had a history of antituberculosis treatment with first-line drugs initiated in 2018 and achieved treatment success in 2019, leaving a cyst in the right upper lung lobe. There were no recent vaccinations or histories of chronic illness, except for 20 years of chronic hepatitis B with normal liver function. On physical examination, the patient appeared thin but did not have cachexia. Breath sounds in the right lung were weakened, but rales were not heard. Routine blood test results were within normal limits. Sputum and blood cultures were negative. A computed tomography (CT) scan of chest of patient showed an enlargement of the cyst, the emergence of a liquid plane in it, and patchy lesions around it. Antibiotic treatment was ineffective, and he was transferred to thoracic surgery and underwent resection of the right upper lope. However, this was not alleviated after the surgery. Further antibiotic treatment and subsequent second surgery to repair the lung were failed to control the fever, but a substantial surgery wound was left on the right chest wall that would not self-heal.

Pleural effusions were emerged after the surgery, and GeneXpert *Mycobacterium tuberculosis*/resistance to rifampicin (MTB/RIF) showed positive TB-DNA and resistance to rifampicin. The rapid molecular test was failed because of paucibacillary samples of sputum and pleural effusion. The patient came to a specialized tuberculosis hospital and received a regimen of bedaquiline, linezolid, moxifloxacin, cycloserine, and clofazimine against RR/MDR/RR-TB. Thereafter, MTB culture from bronchoalveolar lavage (BAL) and pleural effusion were positive, and the minimum inhibitory concentration (MIC) showed resistance to FQs, isoniazid, rifampicin, pyrazinamide, and ethambutol and susceptibility to bedaquiline, linezolid, cycloserine, clofazimine, protionamide, and second-line injections, which met the definition of pre-XDR-TB. Thus, we substituted moxifloxacin for protionamide. In addition to chemotherapy, the patient needed to change the dressing daily on the surgical wound of the right chest wall and was waiting for a suitable time to undergo the right chest wall repair.

After 4 months of MDR/RR-TB treatment, the patient complained of numbness and pain in the lower limbs and progressive worsening, without anemia, leukopenia/neutropenia, thrombocytopenia, diarrhea, or visual problems. The drug that was likely responsible for PN was linezolid. Notably, other markers of linezolid toxicity, such as bone marrow suppression, were absent (7). B vitamin complexes containing vitamin B6, B1, and mecobalamin; painkillers, such as pregabalin, gabapentin, and tramadol; and a subsequent reduction in the linezolid dose to 300 mg daily for weeks were ineffective in relieving the pain. By 6 months, symptoms of the patient had progressed and worsened, and the pain had spread to his legs. In his own subjective opinion, the feeling was acute, frequent disabling, and burning pain, and he also felt numbness in his legs every day, especially in the lower extremities. Continuous insomnia during the day and night was almost unbearable. His electromyography showed that the sensory conductivity of the bilateral superficial gastrocnemius muscle nerves was decelerated and that the sensory nerve action potential (SNAP) amplitude was low so that the conductivity function of the bilateral superficial gastrocnemius muscle nerves was slightly affected. Half a month later, he was diagnosed with PN, and analgesic drugs were added to alleviate the symptoms. However, the problem could not be solved.

As a last resort and after being fully informed, the patient accepted acupuncture treatment once a day at the Acupuncture and Physiotherapy Department 18 times during hospitalization. We assessed the pain pre-, post-, and during the treatment. The intensity of pain was measured with the short form of the McGill Pain Questionnaire (SF-MPQ), which includes three items (8). This questionnaire included the pain rating index (PRI), visual analog scale (VAS), and present pain intensity (PPI). The PRI is used to evaluate pain sensation and emotion, with scores of 0 (no pain), 1 (mild pain), 2 (moderate pain), and 3 (severe pain). The PPI and VAS in SF-MPQ were also used to assess overall pain status.

When evaluating item 1, we asked the patient each question and marked the corresponding level of pain according to the patient's response. For item 2, the length of the line segment in the figure was 10 cm, and the scale was determined in mm.

The patient was asked to mark corresponding points on the line segment with a pen according to his own pain feeling. For item 3, we marked the corresponding score according to the subjective feelings of the patient. Finally, the PRI, VAS, and PPI were evaluated. The higher the score was, the more severe the pain was.

A senior acupuncturist performed the therapeutic acupuncture sessions. The patient was first placed in a comfortable supine position. The acupuncture technique used to treat LIPN pain is in accordance with the "Zang-fu" and meridian system involved in the disease. The point locations for the acupuncture session are those used when treating painful conditions in the lower limbs. The main points were located in the meridians of the lower limb, such as the stomach, spleen, and kidney, for lower limb pain and the nourishing yin point and acupuncture points for the relief of pain. Subsequently, the acupuncturist used the Bilateral Zusanli (ST 36), Sanyinjiao (SP 6), Taixi (KI 3), Yongquan (KI 1), and Bafeng (EX-LE10) points (9) (Figure 1).

The acupuncturist used 0.30 × 25 mm and 0.18 × 13 mm sterile acupuncture needles (Huacheng, Beijing Keyuan Medical Device Manufactory Co., Ltd., Beijing, China). The depth of acupuncture at ST 36, SP 6, and KI 3 was 0.5–0.8 cun and that of the other points was 0.3–0.5 cun. After the insertion, the needles were manipulated to achieve Deqi (10), and the needles at SP 6 and KI 3 were connected to electroacupuncture equipment for 30 min, as shown in Figure 1. The waveform was selected as a continuous wave. Stimulation intensity was determined by the patient's endurance. The acupuncturist added TCM fumigating treatment to promote blood circulation during the acupuncture sessions.

After 18 rounds of treatment, the patient felt much better, indicating an important pain reduction and improved physical function, particularly in the lower limbs. There were significant changes in the scores of the SF-MPQ (PRI decreased from 19 to 7, VAS decreased from 9 to 4, and PPI decreased from 5 to 2; Figure 2). After nearly 3 weeks of treatment, he reported significant improvement in every aspect of his pain, numbness, insomnia, distress, and the reduction in painkiller intake. Thus, linezolid was increased to a dose of 600 mg daily and endured by the patient. After discharge, the patient no longer received acupuncture treatment but continued to adhere to the TCM fumigation treatment.

The PRI, VAS, and PPI scores remained low before a slight increase at 8 months after pre-XDR-TB treatment, while pleural effusion in the left chest had occurred and was drained. After a 3-month remission period until the 10th month, the patient was hospitalized again with an LIPN problem. The PRI score was increased from 8 to 11, the VAS score was increased from 2 to 5, and the PPI score was decreased from 3 to 2. After 10 acupuncture treatments and TCM fumigation, the PRI was decreased from 11 to 5, the VAS score was decreased from 5 to 4, and the PPI score did not change. The patient's lower limb pain and other symptoms were not significantly relieved, and he could not tolerate linezolid anymore; therefore, it was discontinued. Trends in pain assessment over the course of treatment are shown in Figure 2.

Discussion

To the best of our knowledge, this is the first report on the efficacy and safety of acupuncture treatment for LIPN. This case report demonstrates that the development of PN is probably caused by linezolid treatment and its resolution following early detection and appropriate management with acupuncture. With the increasing use of linezolid for MDR/RR-TB, the management of PN in prevalent MDR/RR-TB settings is likely to be a frequent occurrence. The improvement in neuropathy following the application of acupuncture and the avoidance of immediate cessation of linezolid in our patient is encouraging.

On a larger scale, chemotherapy-induced PN (CIPN) is a common and dose-limiting toxicity that negatively affects both quality of life and disease outcomes. To date, there is no proven preventative strategy for CIPN (11). Although multiple randomized trials have evaluated a variety of pharmacologic interventions for the treatment of CIPN, no agent has shown sufficient solid beneficial evidence to be recommended for the treatment or prophylaxis of CIPN. The standard of care for CIPN includes dose reduction and/or discontinuation of chemotherapy treatment. The management of CIPN remains an important challenge, and future studies are warranted before recommendations for the use of supplements can be made (12). In the field of MDR/RR-TB treatment, when pain following LIPN is severe, a change to less effective chemotherapy agents may be needed or patients may choose to discontinue treatment. Medications used to alleviate LIPN often lack efficacy and/or have unacceptable side effects. Hence, the unmet medical need for novel treatments for the relief of this painful condition has driven our establishment of acupuncture therapy for LIPN.

In an individual patient data meta-analysis that assessed 12,030 patients treated for MDR/RR-TB, linezolid and some other agents were found to be associated with greater treatment success and reduced death (13). However, adverse events and discontinuation of linezolid were common, affecting up to 22.6% (141/624; 11 studies) of participants in the nonrandomized studies as described in a Cochrane review (3). PN usually begins in the lower limbs and is the sensory-motor axonal type. Common symptoms include pain, numbness, tingling, burning, and allodynia, usually occurring in a glove- and stocking-like distribution. While optic neuritis due to linezolid has been shown to be reversible in many instances, the reversibility of PN has been described as limited.

The patient had received linezolid for 4 months prior to developing features of PN, which gradually developed into intolerable suffering at 6 months. Three steps were taken to

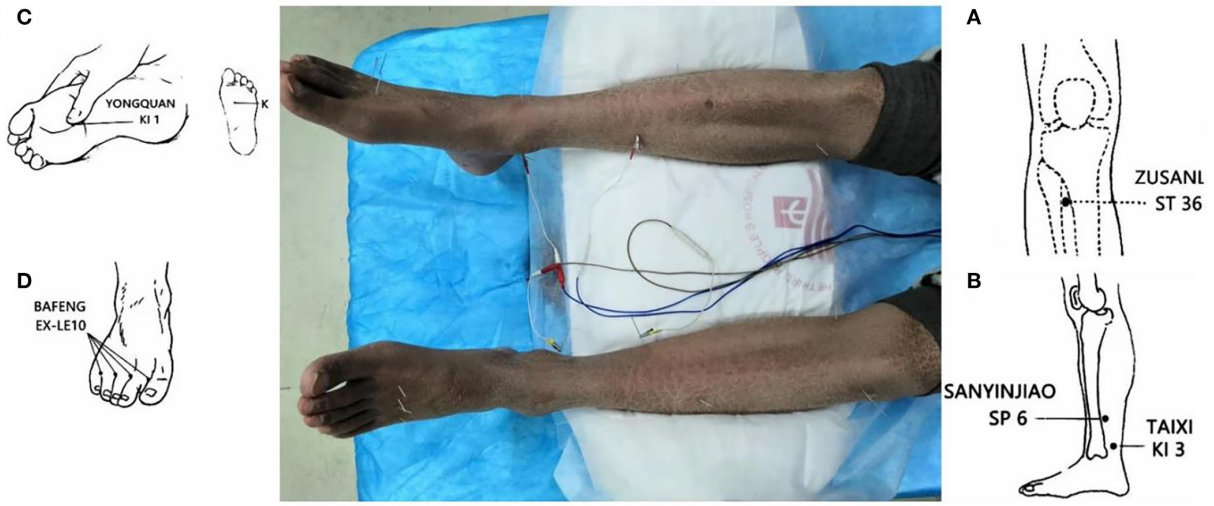
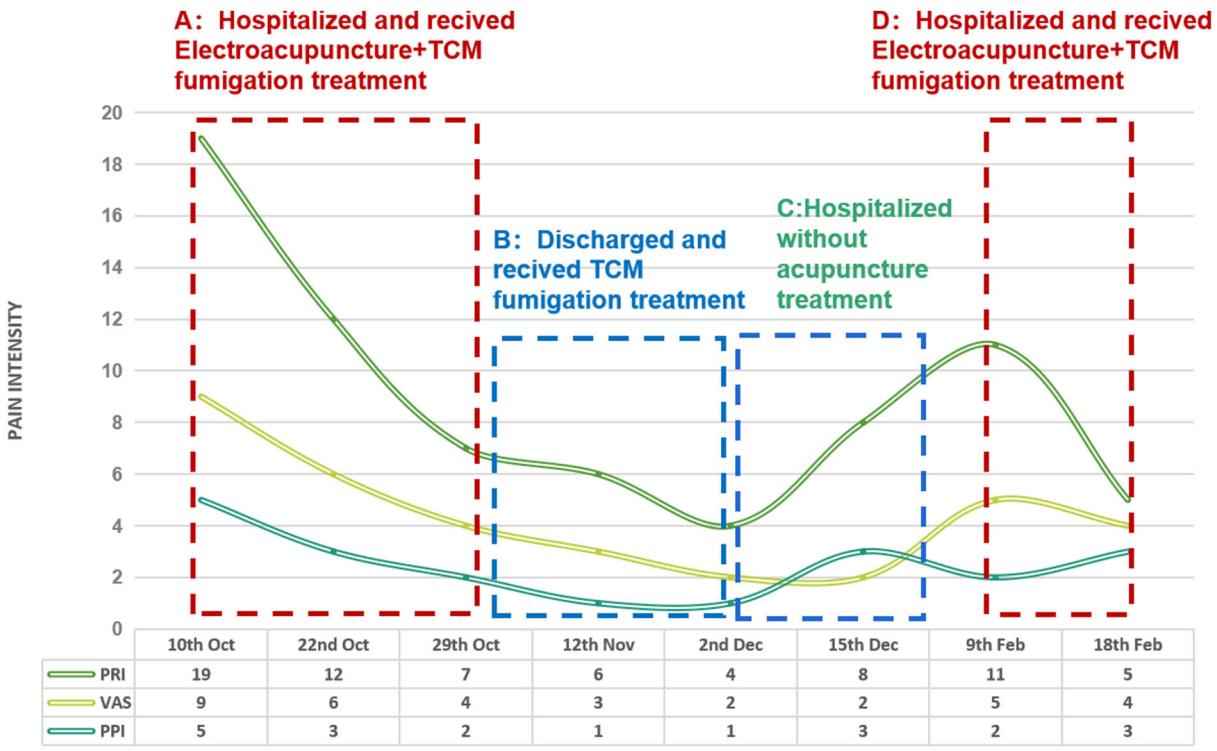


FIGURE 1
The patient on acupuncture. (1) The main acupoints for the patient, bilateral Zusanli [ST 36, **(A)**], Sanyinjiao [SP 6, **(B)**], Taixi [KI 3, **(B)**], Yongquan [KI 1, **(C)**], Bafeng [EX-LE10, **(D)**]. SP 6 and KI 3 were connected to electroacupuncture equipment for 30 min. (2) Brownish skin pigmentation and chapped skin due to prolonged use of clofazimine were observed.



	10th Oct	22nd Oct	29th Oct	12th Nov	2nd Dec	15th Dec	9th Feb	18th Feb
PRI	19	12	7	6	4	8	11	5
VAS	9	6	4	3	2	2	5	4
PPI	5	3	2	1	1	3	2	3

FIGURE 2
SF-MPQ Trend Chart. The evaluation process: **(A)** From 10-Oct-2021 to 29-Oct-2021, hospitalized and treated with electro-acupuncture+TCM fumigation. **(B)** 12-Nov 2021, return visit 2 weeks after discharge, TCM fumigated at home. **(C)** From 2 Dec 2021 to 15 Dec 2021, hospitalized but without acupuncture treatment. **(D)** From 9 Feb-2022 to 18 Feb-2022, hospitalized and treated again with electro-acupuncture+TCM fumigation.

address the PN, but little effect was obtained. First, the prior and prolonged use of vitamin B6 for the purpose of preventing cycloserine side effects did not stop LIPN from happening, while the subsequent use of vitamin B1 and mecobalamin did not improve LIPN. A mini review on B vitamin complexes for CIPN showed that they may play a role in CIPN prevention (14), but little is known about LIPN. Based on the clinical practice in our hospital, a regional TB reference hospital, B vitamin complex has little effect on LIPN, especially those with grades 3–4 AEs. Some mild cases are gradually relieved with the help of these nutrients, but the placebo effect cannot be ruled out, while patients with moderate and severe LIPNs often cannot recover from it. Second, regarding analgesic drugs for CIPN, the best available data support a moderate recommendation for treatment with duloxetine, while the CIPN trials are inconclusive regarding tricyclic antidepressants (such as nortriptyline), gabapentin, and some other agents. Again, in our practice, gabapentin and other painkillers have shown limited efficacy for LIPN-related pain, although we did not approach LIPN exactly according to the cancer pain criteria. Third, the reduction in linezolid dosage to 300 mg daily for weeks did not reverse the LIPN pain either, indicating that medication dosage reduction has no apparent effect on immediate pain relief and therefore is not a favorable strategy for this purpose, although it may work for grades 1–2 LIPN pain in our practice. Halving the dosage of linezolid is one of the commonly used measures, but it may lead to reduced antituberculosis efficacy and an increased risk of treatment failure, not to mention the discontinuation of linezolid, especially during the intensive phase of treatment. In contrast, shortening the duration may be a favorable option. ZeNix's study explored the optimal course of linezolid, suggesting that a 2-month linezolid dosage of 600 mg daily was as effective as a 6-month dosage in pretomanid- and bedaquiline-containing regimens (15). Usually, after all the methods mentioned above were tried and failed, the only option left was to discontinue linezolid until acupuncture was introduced, at least in this case. PN has also been mentioned as a rare but possible AE of other second-line drugs, such as cycloserine and prothionamide (16), which were ultimately excluded as the cause in this case based on the response to AE management.

Acupuncture is a nonpharmacological treatment option for multiple diseases and symptoms. Although numerous studies have been performed on the efficacy of acupuncture, there have been only a few landmark high-quality randomized controlled trials (17). Acupuncture treatment is a symptomatic treatment measure to relieve pain, for which the overall quality of evidence is very low and conflicting due to study limitations (high risk of performance, detection, and attrition bias, and high risk of bias confounded by small study size) or imprecision, indicating that acupuncture was not superior to sham acupuncture or other placebos (18, 19), although it is a pain management method recommended by the Food and Drug Administration (FDA) for chronic low back pain. To date, there are no reports about acupuncture treatment for LIPN except the current one. The patient responded well to acupuncture treatment with improved SF-MPQ, sleep, and mobility scores. After treatment with acupuncture and fumigation, dose reduction and discontinuation of linezolid were avoided for a period of time. These results support the effectiveness of acupuncture as part of a multidisciplinary approach to improve LIPN pain and other symptoms.

In terms of measurements, LIPN may include numbness, pain in the extremities, and vision loss. There is no specialized scale for LIPN pain, so we used a commonly used scale for adult pain, the SF-MPQ, and other methods. For numbness descriptions, we lack an assessment scale, and the Michigan Neuropathy Screening Instrument (MNSI) can be referenced in some circumstances (20), although numbness was insignificant in this case. Vision loss can be assessed by an ophthalmologist or self-measurement, with an absence of vision loss in this case.

With regard to the choice of acupuncture sites, in TCM theory, pulmonary tuberculosis is a chronic wasting disease with the weakness of healthy Qi, the infection of MTB, and the erosion of lungs, influencing each other (21, 22). TB is the cause, and vital Qi deficiency is the basis (23). TB is located mainly in the lung and is most closely related to the spleen and kidney. According to the five-element theory for acupuncture in TCM, the lung will affect other organs, such as the spleen and the kidney, when it is in poor condition (24, 25). In this case, because the patient had no symptoms, such as cough or phlegm, when he came to our department, the acupoints of the lung meridian were temporarily not chosen, and we selected SP 6 in Spleen Meridian of Foot-Taiyin, KI 1 and KI 3 in Kidney Meridian of Foot-Shaoyin to nourish yin, invigorate kidney, and strengthen the spleen, followed by ST 36 in Stomach Meridian of Foot-Yangming to enhance health, and finally SP 6 and KI 3 were connected to electroacupuncture to increase the stimulation intensity to achieve the optimal effect. Additionally, EX-LE10 was selected to dredge meridians and collaterals and relieve pain. These acupoints were chosen on the basis of experience. Numbness and pain, as the clinical manifestations of PN, were considered to belong to the category of "arthromyodynia" in TCM, which was associated with the body's "deficiency and blood stasis," namely, blood deficiency-induced numbness and malnutrition-induced pain. Therefore, acupuncture could be combined with TCM fumigation to promote blood circulation, remove blood stasis, and warm meridians and collaterals (26).

There are several limitations of this case report. First, the mechanistic basis of CIPN is not entirely clear (27), so the mechanism of acupuncture for relieving the relevant symptoms is also unclear. Instead of targeting the underlying pathological mechanism responsible for LIPN, we addressed the LIPN symptoms themselves (11). There are several defined mechanisms of nerve damage that take place along different areas of the peripheral nervous system, and in the near future, we

plan to examine the basic science and pathobiology of LIPN (28, 29), such as whether acupuncture can promote the recovery of nerve injury. Second, for measurement, symptoms and feelings were described or scored with scales from relevant fields. In the next step, it would be better to develop a feasible scoring scale for LIPN, which requires accumulation of a large number of cases and clinical verification. In addition, through follow-up, we found that the patient's symptoms would recur if linezolid was maintained and acupuncture was discontinued. Given the grades 3–4 aggravating AEs in this case, only short-term efficacy was observed before linezolid was ultimately withdrawn, while long-term efficacy, such as MDR/RR-TB treatment success and recurrence, of the intervention of acupuncture still needs to be observed. It is also interesting to observe whether acupuncture performs better for those left with LIPN after treatment completion.

Acupuncture treatment prolonged the availability of linezolid and gained time for antituberculosis treatment, which is of great value for this patient with pre-XDR-TB awaiting chest wall reconstruction. Before recommendations for MDR/RR-TB regimens suggest shorter durations or decreased dosages of linezolid or alternative agents to replace linezolid (30), acupuncture to treat LIPN may have certain applicability in some scenarios.

Conclusion

The common presence of PN with prolonged linezolid-containing regimens against MDR/RR-TB and the ineffectiveness of current adjunctive symptomatic treatments should alert physicians to strive for optimal AE control to minimize the risk of linezolid discontinuation and for optimization of the chances of recovery from MDR/RR-TB. In this pre-XDR-TB case, the pilot application of acupuncture from TCM ensured appropriate management to reduce chronic painful neuropathy and avoid immediate cessation of linezolid, encouraging further explorations of the indications and optimization of acupuncture treatment, given the lack of effective LIPN interventions worldwide.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) and/or minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

The manuscript was drafted and substantially revised by YPM and LF. Inform consent and registration was prepared by ZZ. Acupuncture treatments were administered by YPM, JT, JHW, XCC, and MH. ZZ is responsible for outcome assessment. LF, PZZ, and GFD sought funding, diagnosed and treated primary disease, and observed the effects of the treatments. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Case report: A complicated course of Collet-Sicard syndrome after internal carotid artery dissection and lenticulo-striatal artery infarction

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A 40-year-old Caucasian man presented with sudden onset of left-sided hemiparesis associated with dysphonia, dysphagia, and right-sided weakness on shoulder elevation and head rotation. The clinical examination revealed deviation of the tongue to the right, absence of right-sided gag reflex, right-sided palatal and vocal cord paresis, and weakness of the right trapezius and sternocleidomastoid muscles; all were in addition to left-sided brachiocephalic-accentuated hemiparesis. The diagnostic examination revealed dissection of the right carotid artery with occlusion of the middle cerebral artery and infarction in the lenticular-striatal artery territory. Mechanical thrombectomy with stent angioplasty of the right internal carotid artery was performed. The paresis of the left side of the body completely regressed within a week after symptom onset, but the dysphonia, weakness of the right trapezius and sternocleidomastoid muscles, and especially dysphagia persisted and regressed slowly but gradually. The patient required percutaneous gastric tube feeding for the next 12 weeks, possibly because of involvement of subcortical white matter tracts. The constellation of symptoms and clinical findings were consistent with Collet-Sicard syndrome, an extremely rare disorder caused by direct compression of the caudal cranial nerves at the base of the skull.

KEYWORDS

carotid artery dissection, dysphagia, dysphonia, skull base pathology, dysphagia and rehabilitation

Introduction

Collet-Sicard syndrome is a very rare clinical condition characterized by combined paralysis of cranial nerves IX through XII (1, 2). The syndrome is usually caused by mass lesions at the base of the skull involving the jugular foramen and hypoglossal canal (1, 2). Usually, sympathetic fibers are spared. Neoplasms or traumas are the most common cause of Collard-Sicard syndrome (3), whereas dissection of the internal carotid artery is a very rare cause (4).

Case report

A 40-year-old left-handed Caucasian man was admitted with sudden onset of moderate left hemiparesis, hoarseness, dysphagia, and weakness on lifting the right shoulder and turning the head to the left. There was no evidence of Horner syndrome. The medical history was unremarkable. He was not taking any regular medications. He reported no major or minor head or neck trauma and no recent infection.

The clinical examination revealed left-sided hemiparesis, most pronounced in the arm and face, right-sided tongue weakness, right-sided palatal and vocal cord paresis, right-sided palatal hyposensitivity, and paresis of the right trapezius and sternocleidomastoid muscles. Aphasia was not present. The computed tomography of the brain 3 h after symptom onset was unremarkable (Figure 1a). Additional computed tomography-angiography of the cerebral vessels revealed an incomplete, filiform occlusion of the right internal carotid artery ~1.5 cm distal to the carotid bifurcation (Figure 1c) and thrombus in the middle cerebral artery. These findings were confirmed by conventional angiography (Figure 1d). Transverse computed tomography scans showed wall swelling of the right internal carotid artery due to extensive intramural hematoma (Figures 1e–g). The transverse T1-weighted magnetic resonance imaging with fat suppression 10 weeks after symptom onset confirmed the mural hematoma of the right internal carotid artery (Figure 1h). Intravenous thrombolysis, followed by stent implantation within the right internal carotid artery, followed by mechanical thrombectomy was performed (Figure 1i). The detailed anamnestic re-evaluation revealed no causative evidence of carotid artery dissection. One day after the onset of symptoms, the computed tomography of the brain showed an incomplete ischemic lesion in the right lenticulostriatal arteries (Figure 1b), which was confirmed by magnetic resonance imaging with attenuated inversion recovery 10 weeks after the onset of symptoms (Figure 1j).

Fiberoptic examination of swallowing function was performed on admission. Penetration and aspiration of liquids and all foods were noted. Within 7 days of symptom onset, the left-sided hemiparesis regressed, leaving only mild deficits in the fine motor function of the hand. The dysphagia, dysphonia, hyposensitivity of the palate, and moderate weakness of the right trapezius and sternocleidomastoid muscles persisted but gradually regressed. Ten weeks after the onset of symptoms, the patient was still fed *via* a percutaneous gastric tube. Twelve weeks after the onset of symptoms, the swallowing function was restored and the percutaneous feeding tube was removed. Limited tongue mobility and mild hoarseness with nasal speech were still present.

Discussion

Lesions of the cranial nerves occur in up to 12% of extracranial dissections of the internal carotid artery (4). Collet-Sicard syndrome is a rare clinical condition characterized by combined palsy of the lower cranial nerves, namely, the glossopharyngeus, vagus, accessorius, and hypoglossus nerves, in the absence of ipsilesional miosis, ptosis, or enophthalmus as sympathetic nerval structures are spared (1, 2). The patho-anatomical mechanism most likely to result in combined lower cranial nerve palsy after internal carotid artery dissection is direct compression due to an intramural haematoma at the level of the jugular foramen, where all nerves run through the upper carotid artery sheath (4, 5). Sympathetic nerve fibers also travel through the upper carotid artery sheath at this level, and in case combined lower cranial nerve palsy is associated with signs of Horner's syndrome, the clinical condition should be named Villaret syndrome (6). Therapeutic strategies for Collet-Sicard syndrome should focus on treatment of the underlying pathology as it primarily determines outcome (4, 5).

The prognosis of lower cranial nerve impairment in Collet-Sicard syndrome is generally considered good to excellent (5) but depends on the underlying pathology and additional lesions responsible for dysphagia. In our case, the impact of acute stent implantation on the submandibular portion of the internal carotid artery required for mechanical recanalization remains unclear (7, 8). In patients with stroke and dysphagia, it is generally debated whether one hemisphere is more dominant than the other within the complex bilateral neural network responsible for swallowing. Also, in addition, several lesion sites can potentially cause dysphagia, including the insula, basal ganglia, somatosensory and motor cortices, and internal capsule (9, 10). In our case, infarction of the right basal ganglia occurred in a left-handed person. It may be speculative, but the central lesion may have been responsible for the prolonged recovery of the dysphagia aspect of Collet-Sicard syndrome.

Additional neurophysiologic studies such as electromyographic examination of the muscles innervated by the inferior cranial nerves (trapezius, tongue muscles, and laryngeal muscles) or functional MRI were not performed in our case but could have provided additional information about the nature and severity of the peripheral nerve fiber damage and the brain lesion.

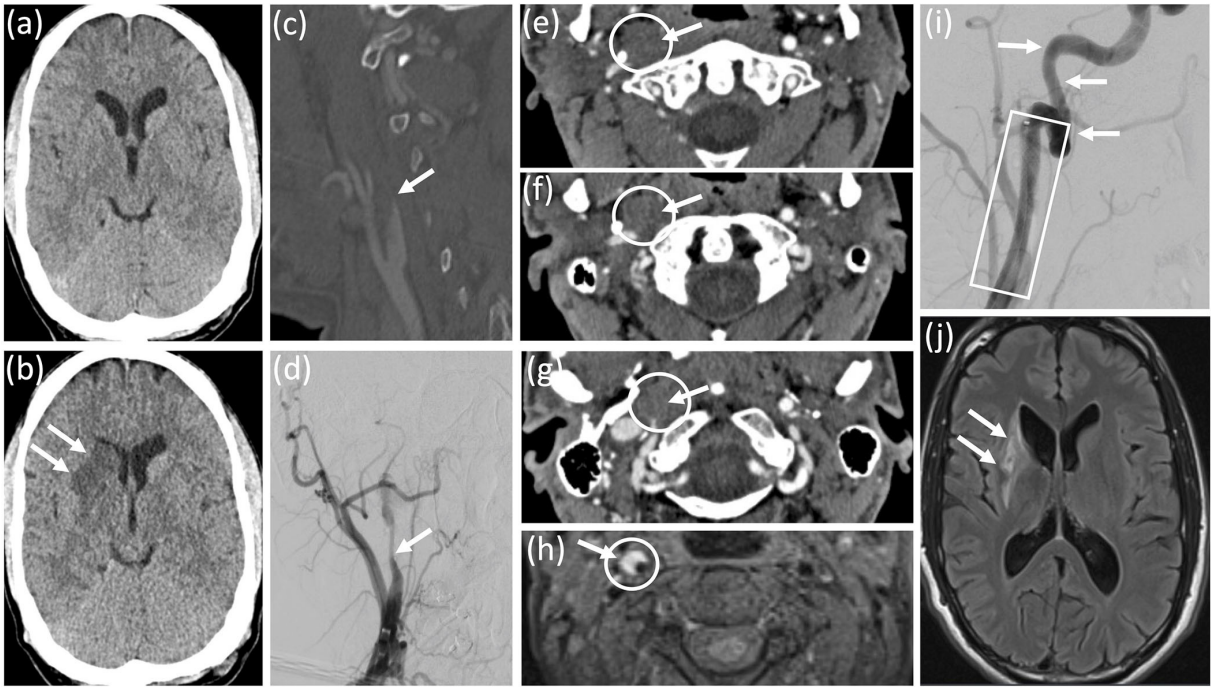

FIGURE 1
Diagnostic work-up and follow-up. **(a)** Initial computed tomography of the brain was unremarkable. **(b)** Computed tomography of the brain 24 h after symptom onset revealed an incomplete ischemic lesion within the territory of the right lenticulo-striatal arteries. Computed tomography angiography **(c)** and conventional cerebral angiography **(d)** revealed a filiform stenosis of the right internal carotid artery about 1.5 cm from the carotid bifurcation. **(e–g)** transversal computed tomography scans showed an intramural haematoma of the right internal carotid artery. **(h)** Transversal T1-weighted magnetic resonance imaging with fat suppression confirmed mural haematoma of the right internal carotid artery. **(i)** Conventional angiography after intra-arterial mechanical thrombectomy and stent implantation illustrated no residual stenosis of the right internal carotid artery. **(j)** Fluid attenuated inversion recovery magnetic resonance imaging 10 weeks from symptom onset revealed the ischemic lesion within the territory of the right lenticulo-striatal arteries, but no additional infarction.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

DN and FS drafted the manuscript. RL, PA, VS, KS, and CW added clinical data and revised the manuscript. All authors contributed to the article and approved the submitted version.

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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Case report: Physical findings, physical therapy practice, and characteristics of disability of activities of daily living caused by obturator nerve palsy after neurotmesis

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The obturator nerve originates from the lumbar plexus and innervates sensation in the thigh and movement of the adductor muscle group of the hip. Reports on physical therapy for patients with obturator nerve injuries have been limited due to insufficient injuries, and there have been no reports on rehabilitation after neurotmesis. Furthermore, there are no reports on the status of activities of daily living (ADL) and details of physical therapy in patients with paralysis of the adductor muscle group. In this study, we reported on a patient with adductor paralysis due to obturator neurotmesis, including the clinical symptoms, characteristics of ADL impairment, and effective movement instruction. The patient is a woman in her 40's who underwent laparoscopic total hysterectomy, bilateral adnexectomy, and pelvic lymph node dissection for uterine cancer (grade-2 endometrial carcinoma). During pelvic lymph node dissection, she developed an obturator nerve injury. She underwent nerve grafting during the same surgery by the microsurgeon. Donor nerve was the ipsilateral sural nerve with a 3-cm graft length. Due to obturator nerve palsy, postoperative manual muscle test results were as follows: adductor magnus muscle, 1; pectineus muscle, 1; adductor longs muscle, 0; adductor brevis muscle, 0; and gracilis muscle, 0. On postoperative day 6, the patient could independently perform ADL; however, she was at risk of falling toward the affected side when putting on and taking off her shoes while standing on the affected leg. The patient was discharged on postoperative day 8. Through this case, we clarified the ADL impairment of a patient with adductor muscle palsy following obturator neurotmesis, and motion instruction was effective as physical therapy for this disability. This case suggests that movement instruction is important for acute rehabilitation therapy for patients with hip adductor muscle group with obturator neurotmesis.

KEYWORDS

obturator nerve, peripheral nerve injury, activities of daily living, rehabilitation, case report

1. Introduction

The obturator nerve arises from the anterior part of the ventral branches of the second, third, and fourth lumbar nerves of the lumbar plexus, and provides sensory innervation of the hip joint and mid-thigh, and motor innervation of the adductor muscles (1). The obturator nerve is often damaged by surgery, hemorrhage, tumor compression, and sports-related trauma (2–7). Symptoms include pain in the medial groin area, loss of sensation in the medial thigh, and weakness of the ipsilateral adductor muscle (2).

The severity of nerve damage, regardless of whether it is an obturator nerve, is divided into five grades by the Sunderland classification (8). While treatment and prognosis after nerve injury depend on injury severity, rehabilitation is often provided for all. Reports on rehabilitation in obturator nerve injury are limited. Yikilmaz et al. reported hospital discharge within 5–9 days of occurrence in three patients with clipping, one incomplete cut, and two complete transection obturator nerve injuries. However, details regarding activities of daily living (ADL) status or rehabilitation were not described (9). The most severe type of injury (grade V: the epineurium is torn, and nerve continuity is severed) is not expected to recover spontaneously, and thus, requires nerve repair or nerve grafting, and has the most severe functional disability (8, 10).

In this report, we describe a patient with a grade-V obturator nerve injury, with the characteristics of ADL impairment in the early disease stages, and details of effective physical therapy.

2. Case report

The patient was a woman in her 40's. Her body mass index was 23.9 kg/m^2. Her current medical history included an infertility-associated hysteroscopy at a community hospital in 2008. During the procedure, a polyp was discovered and resected, and she was diagnosed with endometrial carcinoma G1 *via* pathological examination. She was referred to our university hospital for endometrial curettage, and no findings suggestive of hyperplasia or cancer were determined. In December 2021, she experienced excessive and prolonged menstruation. She presented to a regional hospital, where a transvaginal echocardiogram revealed endometrial polyp-like lesions, and she was referred back to our hospital for further examination and treatment. In January 2022, her tumor marker carbohydrate antigen 125 was normal at 7.4 U/mL. Imaging studies showed a borderline lesion with minimal or no myometrium invasion. She was diagnosed with stage IA, a low-risk recurrence group with absent distant metastasis, and was admitted to our hospital in March 2022 for surgical management of uterine cancer. The following day, she underwent laparoscopic total hysterectomy, bilateral adnexectomy, and pelvic lymph node dissection. She sustained a right obturator nerve transection (Sunderland classification: grade-V injury) during lymph node dissection and was referred to the orthopedic microsurgeon who performed a right sural nerve grafting (the defect of the obturator nerve was 3 cm, and the sural nerve grafting was performed in a cable graft manner). Three days after surgery, the patient was referred to our department for rehabilitation. Physical therapy was initiated on the same day.

Abbreviations: ADL, Activities of daily living.

TABLE 1 Postoperative changes in manual muscle testing (MMT) scores.

	POD1	POD5	POD9
FIM	54	125	126
MMT			
Pectineus	1	1	1
Adductor longs	0	0	0
Adductor brevis	0	0	0
Adductor magnus	1	1	1
Gracilis	0	0	0

FIM, functional independence measure; MMT, manual muscle testing; POD, postoperative day.

Vital signs at the initiation of rehabilitation were as follows: blood pressure, 101/69 mmHg; heart rate, 85 bpm; and SpO_2, 97%. Her ocular conjunctivae were pallor-free, and no heart murmurs or pathological lung sounds were noted. Postoperative white blood cell count and C-reactive protein level were 10,380 μL and 5.85 mg/dL, respectively. The Glasgow Coma Scale was E4V5M6 (11, 12). Since the patient was bedridden on the first postoperative day, the evaluation was performed in bed. Patient-controlled analgesia was placed in the back, a wound drain in the abdomen, and an indwelling bladder catheter was inserted. Endoscopic and sural nerve harvesting wounds were visible in the lower abdomen and posterior right lower leg, respectively. The range of motion was confirmed to be 90° hip flexion and 10° abduction, and no other significant limitations were observed. No further motion was performed to avoid stretching the sutured nerves. Manual muscle testing (13) showed that the adductor muscles on the side of the obturator nerve injury were 1 for the adductor magnus and pectineus muscles and 0 for the adductor longs, adductor brevis, and gracilis muscles (Table 1). Sensory perception was not decreased in the obturator nerve area; however, there was sensory insensitivity and abnormal sensation in the sural nerve area. In the hip flexion exercise and straight leg raising on the bed, as compared with the healthy side (Figure 1A), hip abduction and external rotation occurred with hip flexion on the affected side (Figure 1B). The patient was unable to perform hip adduction at 0° hip extension and was gradually repositioned into adduction by flexing the knee joint during hip external rotation, followed by hip internal rotation and knee extension as a compensatory action. The functional independence measure was 54 points due to bed rest (Table 1). The patient was instructed to perform ankle pump exercises to prevent deep vein thrombosis (Figure 2).

On postoperative day 2, after the resting level was changed to unrestricted, and hip range of motion exercises were unrestricted. Therefore, the patient was weaned off bed rest. The sitting position was stable and possible. The patient was able to stand independently; however, the hip joint on the affected side was mildly abducted and externally rotated (Figure 1C). The patient was able to walk unsupervised and experienced mild discomfort in the hip joint. To prevent secondary complications, such as deep vein thrombosis, bowel obstruction, and pneumonia, gait training was the focus of the early postoperative period. Then, low load aerobic and resistance training were gradually added, depending on the patient's condition (Figure 2).

On postoperative day 5, all routes were removed and the patient became independent. Muscle strength remained unchanged

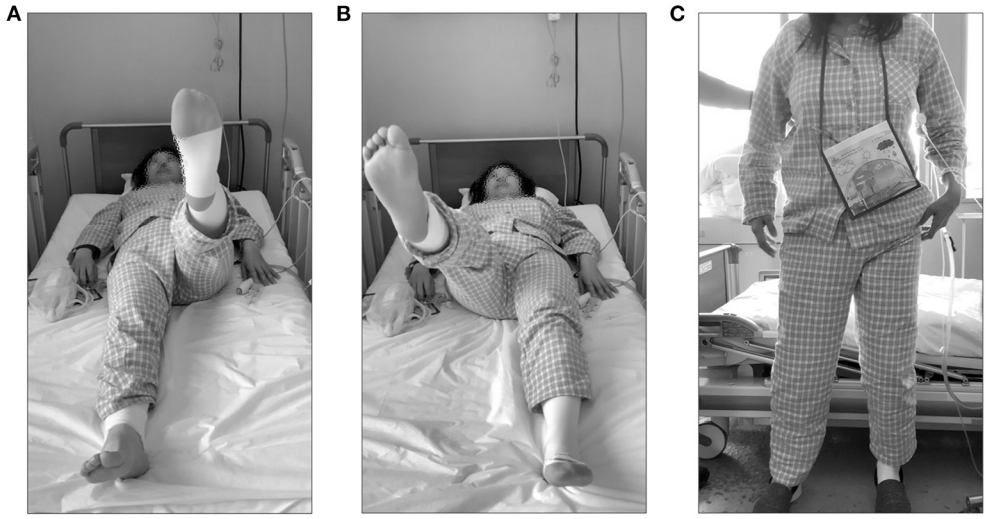

FIGURE 1
Visual examination due to obturator nerve injury. Visual examination performed on day 1 of postoperative intervention. **(A)** Straight leg raising with the healthy lower limb. **(B)** Straight leg raising with the affected lower extremity. **(C)** Standing posture with hip abduction and external rotation.

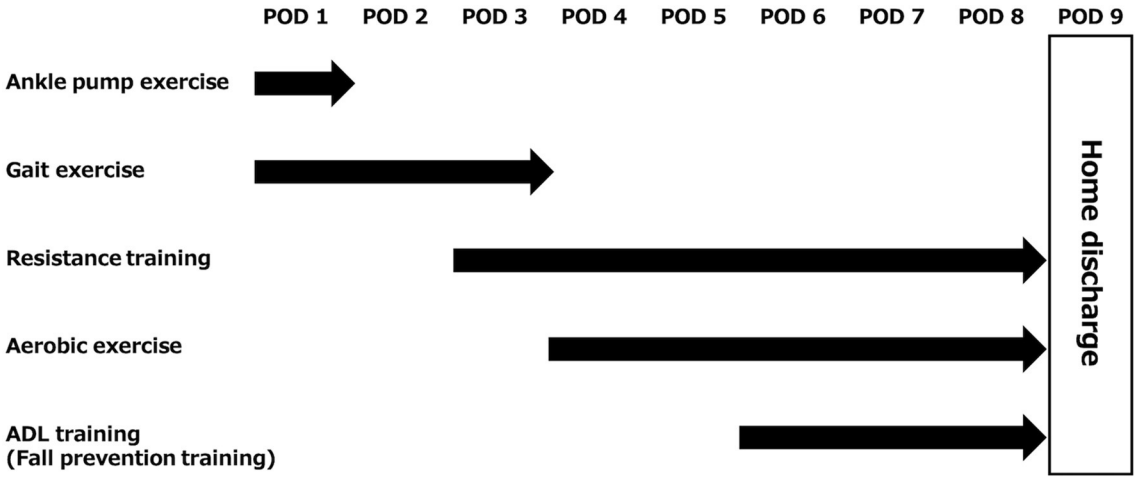

FIGURE 2
Description of rehabilitation for this case. The flow from rehabilitation initiation to home discharge was presented. ADL, activities of daily living; POD, postoperative day.

(Table 1). However, the hip abduction and external rotation that occurred during hip flexion on the bed were no longer present. The stairs also required handrails, and the functional independence measure was 125 points (Table 1). Thereafter, exercise therapy consisted of aerobic exercise on an ergometer at a moderate load, with additional stair climbing training. Resistance training consisted of squats with a ball between the legs, as well as heel raises, leg presses, bridges, and forward lunges (Figure 2).

On postoperative day 6, the patient's movements were reviewed in preparation for home discharge and ADL training was then initiated (Figure 2). There was no risk of falling during basic activities. During one-leg standing, the unaffected side could hold the position for more than 15 s. However, on the affected (right) side, the trunk was flexed to the right within 2 s and she almost fell to that side. At that time, the manual muscle testing of the midline muscles was 5-/5. The patient's manual muscle testing was 5-/5 at the time of the injury. When the motion was reviewed, there was a similar risk of falling to the right side. In this case, she flexed her trunk to the right, abducted her left upper and lower limbs, and internally rotated her ankle joint (Figure 3A), to maintain her center of gravity inside the axis of motion of her hip joint; however, she still fell. To understand the degree to which the body's center of gravity did not exceed the axis of motion of the hip joint, the patient was additionally trained to shift her weight to the right in a one-legged standing position. The duration of the one-leg standing position was prolonged, yet the risk of falling remained. The patient was instructed to move the pelvis to the right and flex the trunk slightly to the left (Figure 3B).

On postoperative day 8, the patient was able to stand on one leg, change clothes, and put on and remove shoes. Finally, when the patient was about to fall, stepping was reviewed. Stepping was possible in the front, back, left, and right.

On postoperative day 9, all sutures were removed from the lower abdomen and right lower leg wounds. Muscle strength was unchanged (Table 1). Her functional independence measure was 126

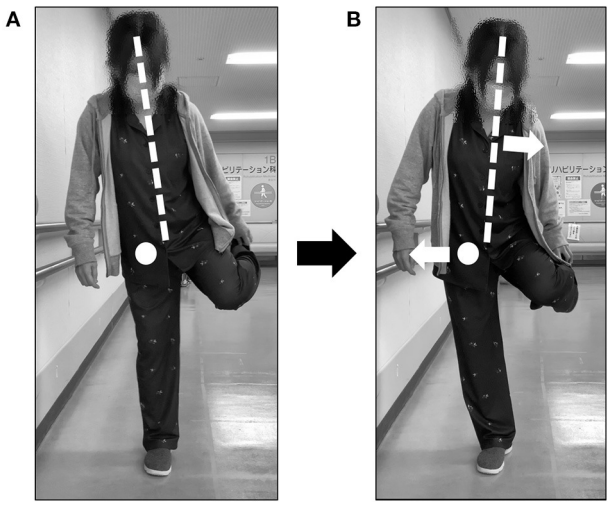

FIGURE 3
Points for which motion instruction was provided. **(A)** A posture with a risk of falling was indicated. **(B)** The posture of the patient after movement instruction was given. Trunk alignment was indicated by a dotted line and the hip axis was indicated by a circle. Arrows indicated the movement direction from the posture before the change **(A)**.

points, and she was discharged home (Table 1). Additionally, loxoprofen was administered for pain, but no medication was used to improve the patient's recovery. In this case, an obstetrician/gynecologist and an orthopedic surgeon were scheduled to see the patient every 2 months and every 6 months, respectively, at our clinic. Therefore, we had the rehabilitation department come in each time to palpate the patient and examine the situation in her home. At the first time, there was no improvement in paralysis, but we were able to confirm that the patient was independent in all aspects of home life, with no falls.

3. Discussion

In this study, we highlighted ADL impairment seen in patients with obturator nerve injury, including the risk of falling, in activities that require one-leg standing and showed an effective method of motion instruction for these patients. To our best knowledge, there are no reports on the rehabilitation treatment of patients with sural nerve transplantation for a grade-V obturator nerve injury. This case report is the first to describe in detail the implementation of rehabilitation therapy in a patient with adductor muscle group paralysis due to an obturator nerve injury.

The patient had obvious postoperative paralysis of the adductor muscle group due to an obturator nerve injury that occurred during obstetric and gynecological surgery. In addition, the patient required compensatory movement for adduction on the bed. As rehabilitation treatment progressed, the risk of falling toward the paralyzed side was higher in movements that required standing on the leg of the paralyzed side. However, there were no reports investigating the risk of falling in patients with obturator nerve injury. When shifting from a bipedal to a one-leg standing posture, it is necessary to shift the position of the body's center of gravity to the stance leg side and maintain that position in the basal plane of support (14). Pelvic shift or trunk lateral bending is required to shift the center of gravity to the stance side. In our case, the patient was responsive and unable to maintain the one-leg upright posture. Therefore, she was at risk of falling to the one-leg upright side. This might result from excessive hip abduction torque generated by the continued shift of the body's center of gravity to the stance leg side (lateral), which moved the hip joint outward from the axis of motion. In healthy subjects, the hip adductor muscles of the stance leg side contract to maintain the one-leg standing position, producing hip adduction torque that can antagonize the hip abduction torque caused by the outward shift of the center of gravity (15). However, our patient was unable to generate hip adduction torque due to adductor paralysis, leading to a risk of falling to the paralyzed side. Therefore, as rehabilitation treatment, we instructed the patient to move in a posture that reduces hip abduction torque by utilizing the position of the body's center of gravity (Figure 3B). Soon after movement instruction, the patient's time in the one-legged standing position was prolonged, and 2 days later, she was able to move in the one-legged standing position. She was discharged home with a reduced risk of falling after movement instruction as acute rehabilitation treatment was provided. However, in order for the aforementioned instructions to be properly implemented, the patient must be able to maintain the abductor muscle strength of the paralyzed side of the hip, have no range of motion limitations in the hip, and be able to properly understand the instructions. Elderly patients often show muscle weakness with aging and have limited range of motion due to osteoarthritis. Additionally, their cognitive function is often impaired, and the instructional content may not be appropriate as in this case. In such cases, instructing the patient to hold a cane on the paralyzed side to antagonize the hip abduction torque may be one option. Furthermore, having the patient hold the luggage or other weights with the healthy upper extremity can also reduce the occurrence of abduction torque on the affected hip because the body center of gravity is shifted more medially. Thus, therapists need to choose appropriate instructional content for the subject.

In this case, a sural nerve graft was used for a grade-V injury of the obturator nerve. A sural nerve graft is commonly used because of its low sequelae after harvesting (16). A previous report concluded that the sural nerve was a good grafting material, as it demonstrated functional recovery during a follow-up period of 2 years when 12 nerve grafts were performed using a sural nerve (17). Conversely, a 71-year-old man with an obturator nerve transection and thermal injury who underwent sural nerve grafting reported reduced adductor muscle weakness after 6 months. Additionally, persistent sensory disturbance and muscle atrophy were observed in the lower limbs (9). Recent reviews have identified microsurgical techniques, patient age, lesion level, associated disease, and mechanism of injury as determinants of outcomes after nerve reconstruction (16, 18), and older age and more complex injury mechanism were poor prognostic factors. Because the patient was young and had no associated diseases, and the mechanism of injury was a sharp amputation, her prognosis was considered good. As the nerve recovery rate is 1–4 mm per day (19) and the distance from the injury site to the neuromuscular junction in this case was approximately 30 cm, recovery was expected to take more than half a year. Therefore, strengthening the residual muscles is necessary as a rehabilitation treatment. In the acute phase, when there is little functional improvement after a grade-V injury, it is important to provide movement guidance to avoid the risk of falling.

Further periodic examinations should be conducted to confirm that the patient is maintaining the instructional program and is not falling down. Then, as soon as contraction of the obturator nerve innervating muscles is confirmed, a new rehabilitation treatment program should be offered to improve function.

Patients with obturator nerve injury were at risk of falling when moving in a one-leg standing position with a paralyzed hip adductor muscle group, indicating the requirement for motion guidance to reduce hip abduction torque using the center of gravity during movement. This study shows that movement instruction is important for acute rehabilitation treatment of patients with obturator nerve injury, due to a grade-V injury.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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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Effects of sequential inhibitory and facilitatory repetitive transcranial magnetic stimulation on neurological and functional recovery of a patient with chronic stroke: A case report and literature review

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Background and purpose: The effects of conventional protocols of repetitive transcranial magnetic stimulation (rTMS) in the chronic phase of stroke are limited. This study aimed to apply the sequential inhibitory and facilitatory rTMS for upper limb motor dysfunction post-stroke to observe the efficacy and explore the possible neurophysiological mechanism. We hypothesize that this protocol would both enhance the excitability of affected M1 and promote connections among motor areas.

Case description: We reported a 55-year-old female patient with a 1-year chronic stroke and right-sided hemiplegia, who underwent the 14-session rTMS with seven sessions of low frequency (LF) and with seven sessions of high frequency (HF). Clinical scales mainly including Fugl-Meyer Assessment of Upper Extremity (FMA-UE), Action Research Arm Test (ARAT), neurophysiological measures, and functional near-infrared spectroscopy (fNIRS) were assessed before (T0), at the midpoint (T1), and after the intervention (T2).

Outcomes: The patient exhibited post-intervention improvement in upper extremity function. There was increased excitability in the ipsilesional hemisphere and the opposite in the contralesional hemisphere. The interhemispheric inhibition (IHI) ratio increased from 2.70 to 10.81 and finally decreased to 1.34. Oxy-Hb signal was significantly decreased in affected M1 and mildly decreased in unaffected M1, while that of PMC and SMA on the affected side increased significantly.

Conclusion: The sequential inhibitory and facilitatory rTMS significantly promoted motor recovery in the patient. Related mechanisms include upregulation of excitability in the ipsilesional hemisphere, return of interhemispheric balance, and neuroplasticity-induced cortical reorganization.

KEYWORDS

stroke, motor recovery, transcranial magnetic stimulation, neuroplasticity, case report

Introduction

Stroke is an important cause of mortality and disability in adults (1), which places a heavy burden on families and societies around the world (2). Motor impairment is one of the most common complications post-stroke. More than half of the survivors with an initial paretic upper limb will still have problems with arm function months to years after their stroke (3), largely damaging activities of daily living. Repetitive transcranial magnetic stimulation (rTMS)

is one of the non-invasive electrophysiological methods for the treatment of hemiplegia post-stroke, which can promote cortical reorganization and synaptic plasticity (4). Based on the interhemispheric competition model, numerous studies demonstrated that inhibition of the contralesional hemisphere by low-frequency rTMS (LF-rTMS; <1 Hz) (5) or facilitation of the ipsilesional hemisphere by high-frequency rTMS (HF-rTMS; >5 Hz) (6) can significantly improve upper limb motor function in patients with post-stroke (7–9), but the effects of conventional protocols in the chronic phase are limited (10). Patterned or complex coupled stimulation protocols might potentiate the efficacy of stimulation (11).

In this study, we introduce a coupled treatment initiated with seven-session 1 Hz rTMS over the contralesional primary motor cortex (M1) and followed by seven-session 10 Hz rTMS over the ipsilesional M1. Previous studies reported similar protocols in patients with subacute and chronic stroke with promising results (12, 13). On the one hand, this protocol could inhibit the excitability of the unaffected hemisphere at low frequency and thus enhance the excitability of M1 on the affected hemisphere based on the theory of transcallosal inhibition (14, 15). On the other hand, 10 Hz-rTMS has been shown to induce a long-lasting increase in glutamatergic synaptic strength, accompanied by structural remodeling of dendritic spines (16), thereby promoting the connection between affected M1 and the premotor cortex (PMC), the supplementary motor area (SMA), the primary motor cortex (M1), and other brain areas (17, 18) and regulating the neuroplasticity of the affected hemisphere. We hypothesize that the efficacy of stimulation could be potentially enhanced with this protocol. The sequential rTMS was applied to a 55-year-old woman with a chronic stroke of 1 year with a satisfying treatment effect; we now report the case below and explore the possible neurophysiological mechanism through functional near-infrared spectroscopy (fNIRS) and transcranial magnetic stimulation (TMS) assessments.

Case description

The Ethics Committee of Huashan Hospital affiliated with Fudan University (No. KY2021-1005) approved the study protocol and intervention, and informed consent was obtained from the patient before enrolling in the study.

The 55-year-old female patient was right-handed and graduated from senior high school. She was retired with good financial and family support. She has a history of hypertension, type 2 diabetes, and coronary heart disease, controlled by daily medication. There was no relevant genetic or psychosocial history in her family. At the time of stroke onset in January 2021, she presented with complete right hemiplegia without unconsciousness, and then, she was immediately transferred to the local District Central Hospital in Shanghai. Her blood pressure was 140/80 mmHg and her heart rate was 80 beats per min. Based on diffusion-weighted imaging (DWI) of magnetic resonance imaging (MRI) with a high-intensity area in the left basal ganglia, the patient was diagnosed with cerebral infarction and received conservative antiplatelet therapy and butylphthalide infusion therapy to improve cerebral circulation. One-hour bedside rehabilitation was offered to her every day. When she was discharged 12 days after onset, she had a Brunnstrom Staging (BS) of 1/1/3 (upper extremity/hand/lower extremity) in her right extremity, with a muscle strength of 0 in the upper extremity and 1–3 in the lower extremity. She was able to stand and walk with support but was unable to initiate movement in the paretic upper limb. Then, the patient was transferred to a general rehabilitation hospital for multidisciplinary rehabilitation including limb positioning, passive stretching, sit-to-stand, muscle strength exercises, balance training, hand function training, acupuncture, massage, electrical stimulation, and so on. The recovery in the affected upper limb continued gradually along a proximal-distal mode. During the enrolment in March 2022, she could flex and extend her elbow obviously and flex weakly but not extend her fingers on the affected side. Muscle strength of the right upper limb was grade 3/3/2/2 (shoulder flexion/elbow flexion/wrist flexion/finger flexion), and muscle tone was grade 1/1+/1 (shoulder adduction/elbow flexion/wrist flexion), with BS reaching 3/3/3.

Intervention

rTMS were conducted using MagTD (YIRUIDE Company, Wuhan, China) connected with a 90-mm figure-of-eight coil. The coil was positioned tangentially on the scalp with the handle pointing 45° posterolaterally. Stimulation intensity was gradually increased, and coil position was shifted slightly until we determined the optimal stimulation site ("hot spot") where the largest motor-evoked potential (MEP) could be consistently elicited from the contralateral abductor pollicis brevis (APB) (9, 19). The "hot spot" served as the target for the rTMS modulation. The stimulation intensity was set at 120% of the resting motor threshold (RMT) of APB (7, 20). If stimulus intensity exceeds maximal stimulator output (MSO), 100% MSO will be adopted. The patient accepted seven-session 1 Hz rTMS (a 20-min train of 1 Hz rTMS, a total of 1,200 pulses in one session) over the non-lesional hemisphere (13, 21) followed by seven-session 10 Hz rTMS (9, 22, 23) (1-s trains of 10 Hz with 9-s inter-train intervals over 12 min, total 1,200 rTMS pulses in one session) over the lesional hemisphere. Besides, she also received conventional rehabilitation programs, such as task-oriented training, range-of-motion exercise, muscle exercise, gait training, and acupuncture, for 150–180 min daily during the study period. Medical treatment was also provided to her, including dapagliflozin, insulin lispro, and insulin glargine for blood sugar control, losartan and levamlodipine for blood pressure control, aspirin and clopidogrel for antiplatelet therapy, and atorvastatin for lowering lipid levels.

Assessments

Clinical outcome measures

Assessments were acquired at baseline (day 0, T0), in the middle of the intervention (day 7, T1), and after treatment (day 14, T2). Clinical scales included the Fugl-Meyer Assessment of Upper Extremity (FMA-UE), the Action Research Arm Test (ARAT), the Modified Ashworth Scale (MAS), the BS, the Barthel Index (BI), and the Mini-Mental Score Examination (MMSE).

Neurophysiological measures

Motor cortical excitability was evaluated by single-pulse TMS, and interhemispheric inhibition (IHI) was evaluated by paired-pulse TMS. First, we tested the RMT, which was defined as the

lowest stimulus intensity that produced MEPs >50 μV in at least five out of 10 trials when the target muscle (APB) was at rest (24). MEP amplitude and latency were measured as peak–peak (μV) of the mean MEP and the time (ms) from the onset of the stimulus to the beginning of the MEP, respectively. Central motor conduction times (CMCT) were calculated by deducting the peripheral conduction time (PMCT) from MEP latency, and PMCT was obtained by stimulating the brachial plexus. When it comes to IHI, we delivered a conditioning pulse (110% RMT) to the hotspot of one hemisphere followed 10 ms later by a test pulse (120% RMT) to the hotspot on the opposite hemisphere. Besides, a single test pulse to the target hemisphere was also delivered, and we calculated the ratio of the average amplitude of paired-pulse MEPs to the average amplitude of single-pulse MEPs for both hemispheres, expressed as $IHI_{Ipsi-to-Contralesional}$ and $IHI_{Contra-to-Ipsilesional}$, respectively (25, 26). The lower the value, the stronger the IHI. IHI ratio was determined by the inhibition of the ipsilesional to the contralesional hemisphere divided by that of the contralesional to the ipsilesional hemisphere, which was defined as: IHI ratio = $(1 - IHI_{Ipsi-to-Contralesional})/(1 - IHI_{Contra-to-Ipsilesional})$ (26). This ratio provided us with a normalized and quantitative parameter to assess the nature of IHI, and the ratio of >1 implied larger inhibition from the affected to unaffected hemisphere compared to that from the unaffected to affected hemisphere. The above operations were repeated 10 times each.

fNIRS data acquisition and analysis

fNIRS data were acquired using a 41-multichannel fNIRS instrument (BS-3000, Wuhan Union Technology Co., Wuhan, China). The fNIRS data were sampled with a frequency of 20 Hz. A customized brain cap consisting of 32 probes (16 sources and 16 detectors) was placed on the head of the patient. Referring to the international EEG 10–20 system, all the source probes and detector probes were, respectively located over the bilateral prefrontal cortex (PFC), the M1, the premotor cortex (PMC), the supplementary motor area (SMA), and the Broca's area, constituting 41 channels. Data were recorded at wavelengths of 690 and 830 nm. Here, we used a block paradigm design consisting of 60-s rest at baseline, 20-s task, and 20-s rest three times. The patient was instructed to sit in a comfortable position in a chair with the upper extremities relaxed at rest condition. During the task, the patient was asked to perform repetitive movements of flexion and extension of the paretic elbow at a comfortable speed, with 1 kg carried on the forearm (27).

The fNIRS data were exported to MATLAB (R2013a, MathWorks, USA) for further data processing and analysis, and the HbO_2 signal was chosen as the marker of neural activity in the study. The data were analyzed in Homer2 (28). The raw fNIRS signals were first transferred into hemodynamic signals according to the modified Beer–Lambert law. After removing the invalid channels, the visible motion artifacts, and physiological noise, a Butterworth band-pass filter between 0.01 and 0.1 Hz was applied to filter the HbO_2 signals to eliminate slow drift and cardiac pulsation. To identify the task-related cortical activation, the changes in concentration of HbO_2 (ΔHbO_2) were computed as follows: $\Delta HbO_2 = HbO_{2task} - HbO_{2baseline}$. $HbO_{2baseline}$ was defined as the average value of the HbO_2 signals at the last 10 s during the resting-baseline period. The HbO_{2task} was defined as the average value of the HbO_2 signals derived from a 6-s window around the peak of the most positive deflection within the 20 s following task onset (29). The ΔHbO_2 of all channels in each cortical area was averaged to represent cortical activation. To evaluate the interhemispheric asymmetry of cortical activation, we calculated the laterality index (LI) of each cortical region (30). The values of LI were between −1 and 1, with positive LI indicating greater activation in the ipsilesional than in the contralesional hemisphere and vice versa. LI was calculated as follows:

$$\begin{aligned} LI = & \left(\Delta HbO_2 \left(\text{ipsilesional hemisphere}\right)\right. \\ & \left. - \Delta HbO_2 \left(\text{contralesional hemisphere}\right)\right) \\ & / \left(\Delta HbO_2 \left(\text{ipsilesional hemisphere}\right)\right. \\ & \left. + \Delta HbO_2 \left(\text{contralesional hemisphere}\right)\right). \end{aligned}$$

TABLE 1 Details of clinical scales.

Item	T0	T1	T2	Change (T1−T0)	Change (T2−T0)
FM-UE	17	19	23	2	6
ARAT	3	6	9	3	6
MAS-shoulder	1	0	0	−1	−1
MAS-elbow	1+	1+	1	0	−0.5
MAS-hand	1	1	1	0	0
BS-UE	3	3	3	0	0
BS-HAND	3	3	4	0	1
BI	85	85	90	0	5
MMSE	30	30	30	0	0

T0, baseline; T1, day 7; T2, day 14; FM-UE, Fugl-Meyer of Upper Extremity; ARAT, Action Research Arm Test; MAS, Modified Ashworth-Scale; BS, Brunnstrom stages; UE, lower extremity; BI, Barthel Index; MMSE, mini-mental state examination.

Outcomes

The test was smooth and the patient completed the 14-day rTMS sessions without adverse side effects during the treatments and assessments.

Clinical scores

Clinical scales for the patient are presented in Table 1. The scores of both the FMA-UE and ARAT showed progress at both measurement points after starting treatment. Spasticity relief was demonstrated from MAS value from 1 to 0 at shoulder-joint and 1+ to 1 at elbow-joint with no change for hand. BI increased by 5 points from T1 to T2, and the patient could walk independently without any assistance. Notably, the BS of the hand progressed from level 3 to 4, and her thumb could be slightly pinched and loosened with the remaining four fingers extended actively in a small range. In addition, the patient's MMSE score remained at 30 and she had good cognition throughout the treatment.

TABLE 2 Changes in neurophysiological measures and cortical asymmetry as evaluated by fNIRS.

Item	T0	T1	T2	Change (T1–T0)	Change (T2–T0)
Neurophysiological measures					
AH					
MEP amplitude (μV)	112.44	105.27	124.36	−7.17	11.92
MEP latency (ms)	29.24	27.53	28.07	−1.71	−1.17
RMT (%)	95%	90%	90%	−5	−5
CMCT (ms)	13.39	13.17	13.45	−0.22	0.06
UH					
MEP amplitude (μV)	245	118.55	177	−126.45	−68
MEP latency (ms)	23.62	22.05	25.95	−1.57	2.33
RMT (%)	50%	60%	50%	10%	0
CMCT (ms)	8.14	6.83	11.63	−1.31	3.49
IHI					
$IHI_{Ipsi-to-Contralesional}$	0.19	0.13	0.24	−0.06	0.05
$IHI_{Contra-to-Ipsilesional}$	0.7	0.92	0.43	0.22	−0.27
IHI ratio	2.7	10.81	1.34	8.11	−1.36
LI					
M1	−0.05	/	−0.49	/	−0.44
PMC	0.28	/	0.58	/	0.3
SMA	−0.14	/	0.88	/	1.02

T0, baseline; T1, day 7; T2, day 14; fNIRS, functional near-infrared spectroscopy; AH, affected hemisphere; UH, unaffected hemisphere; MEP, motor evoked potential; RMT, resting motor threshold; CMCT, corticomotor conduction time; IHI, interhemispheric inhibition; Ipsi, ipsilesional; Contra, contralesional; LI, laterality index; M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area.

Neurophysiological measures

We elicited MEPs of the affected limb from the ipsilesional hemisphere of this patient. As illustrated in Table 2, ipsilesional RMT and MEP latency decreased, and MEP amplitude increased after treatment. There was little change in ipsilesional CMCT. As for the contralesional hemisphere, the RMT was increased by 10% at the mid-intervention and returned to 50% post-therapy. The values of MEP latency and CMCT decreased slightly at T1 and increased significantly after treatment beyond the initial value. MEP amplitude was decreased by 126.45 μV from T0 to T1 and increased by 58.45 μV to T2. Excessive IHI from the ipsilesional to the contralesional hemisphere was observed at baseline, and the value did not change significantly throughout treatment. $IHI_{Contra-to-Ipsilesional}$ increased at T1 and decreased significantly at T2, even below baseline, which led to an increase in the IHI ratio from 2.70 to 10.81 and finally to 1.34.

Activation of cortical core motor regions

At baseline, the patient exhibited activation of bilateral motor cortices during the movement of the paralyzed upper extremity (Figure 1, Table 3). After 14-day treatment, the oxy-Hb signal was significantly decreased in affected M1 and mildly decreased in unaffected M1, which resulted in a decrease in LI of M1. However, cortical activation showed a significant increase in affected PMC and SMA, increasing the LI of PMC and SMA.

Discussion

Two weeks of sequential inhibitory and facilitatory rTMS significantly facilitated motor performance and recovery in the patient with chronic subcortical stroke. Related mechanisms include upregulation of excitability in the ipsilesional hemispheric, return of interhemispheric balance, and neuroplasticity-induced cortical reorganization.

The cortical reorganization in ipsilesional PMC and SMA and contralesional M1

In our study, the MEPs of the APB could be elicited on the affected side indicating that the structure of ipsilesional CST was reserved. After the 14-day intervention, there was increased excitability in the affected hemisphere. In the fNIRS assessment, we found decreased activation of ipsilesional M1 and significantly increased activation of ipsilesional PMC and SMA during the movement of the paretic upper extremity after treatment. The stimulus intensity we took on ipsilesional M1 was close to MSO, and the site we stimulated in the affected hemisphere was probably the premotor areas, thereby activating the CST from those areas and causing some of the effects we observed.

Functionally, PMC and SMA are involved in motor planning, control, and learning, as they project to M1 for movement execution (31–33). In patients with significant functional disruption of the corticospinal system, task-related brain activation shifts from primary to secondary motor networks (34). Our findings align well with previous studies showing that the plastic reorganization of ipsilesional PMC and SMA contributes to functional recovery (35–38). The abovementioned phenomenon can be explained by the mechanism that movements might be directly controlled by the increased corticospinal pathways originating from PMC and SMA (39–42). Fridman et al. (43) reported that, in well-recovered chronic stroke patients with lesions located in the internal capsule, motor potentials evoked by TMS stimulation of the ipsilesional PMC were larger and of shorter latency than those evoked by stimulation of the ipsilesional M1. Subsequently, an fMRI study (39) confirmed that the integrity of the PMC-derived CST correlates with grip strength.

In the contralesional hemisphere, RMT increased at T1 and decreased to baseline at T2, indicating a gradual return to normal excitability after HF-TMS, but increased contralesional CMCT and MEP latency and decreased MEP amplitude suggested decreased excitability compared to baseline. Considering that there was a clear decrease in LI of M1 in the fNIRS assessment, we speculate that for this patient, the ipsilateral CST derived from the contralesional M1 was considered as a possible mechanism for motor improvement (44, 45). Even in a subset of well-recovered patients, activation of contralesional M1 was effective for motor recovery (46). Patients with more severe impairments of ipsilesional CST might rely more on contralesional hemisphere activity (47).

Taken together, effective functional recovery should fully utilize ipsilesional and contralesional resources, and the cortical

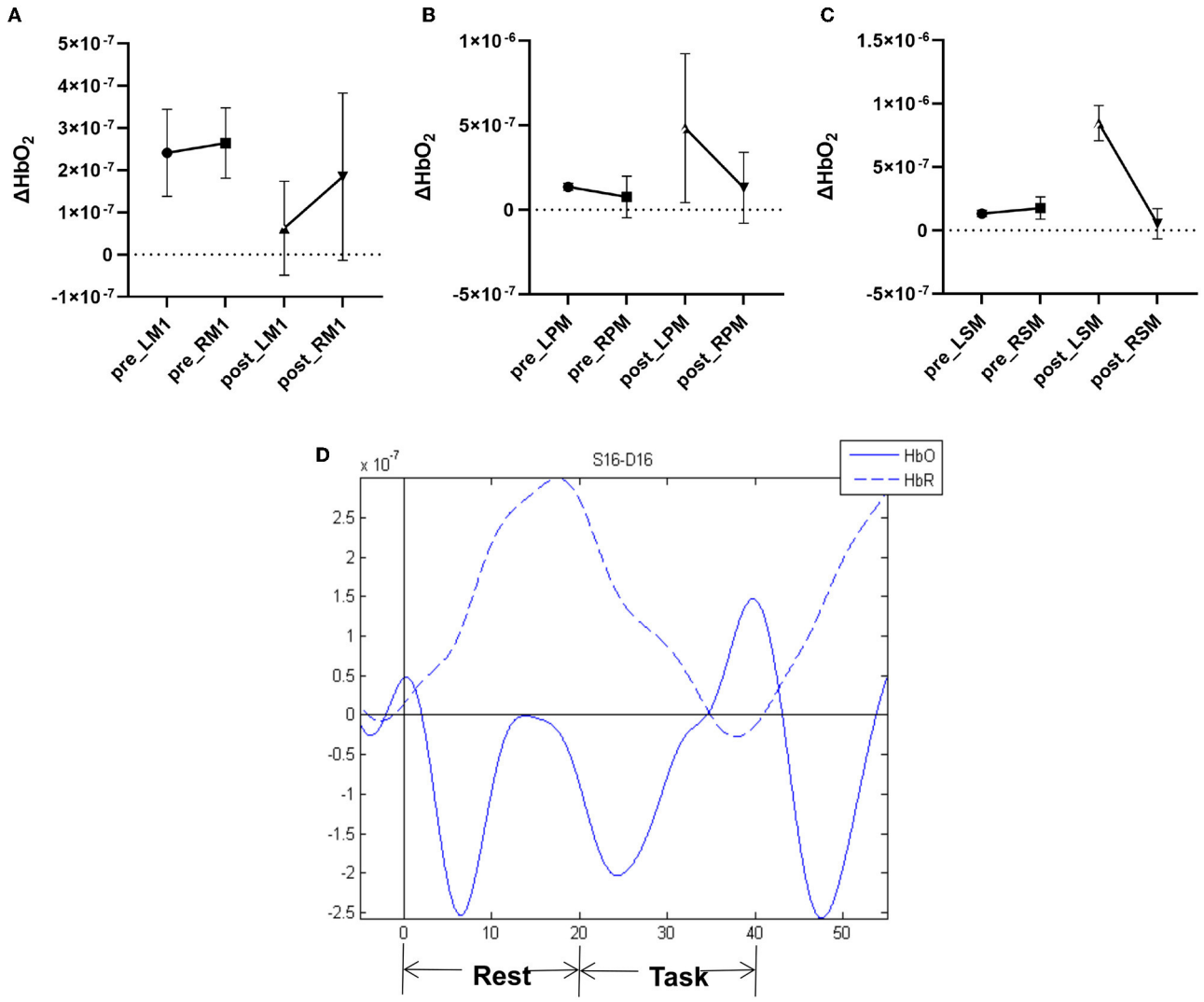

FIGURE 1
Pre- and post-therapy oxygenated hemoglobin (oxy-Hb) concentration measured by fNIRS during movement of the paretic upper limb in **(A)** M1 primary motor cortex, **(B)** PM premotor cortex, and **(C)** SMA supplementary motor area. **(D)** Example of hemodynamic response function (HRF) time series.

TABLE 3 Changes of HbO_2 concentration in cortical core motor regions.

Channels	Cortical region	ΔHbO_2 ($*10^{-6}$) (T0)	ΔHbO_2 ($*10^{-6}$) (T2)
28, 29, 32	Ipsilesional M1	0.241	0.063
27, 30	Ipsilesional PMC	0.136	0.484
31, 33	Ipsilesional SMA	0.132	0.846
34, 35, 36	Contralesional M1	0.264	0.185
40, 41	Contralesional PMC	0.077	0.130
38, 39	Contralesional SMA	0.176	0.052

T0, baseline; T2, day 14; M1, primary motor cortex; PMC, premotor cortex; SMA, supplementary motor area.

reorganization in ipsilesional PMC and SMA and contralesional M1 played an important role in the recovery of motor function throughout the intervention. As for the different changes in the IL of M1 and PMC/SMA, we considered that it might be due to the limited CST originating from ipsilesional M1. Sequential rTMS would lead to neural remodeling in ipsilesional PMC/SMA to promote functional recovery, and the increased activation of ipsilesional PMC/SMA might contribute to abnormally increased neural activity in the contralesional motor areas (48).

Restoration of interhemispheric balance

It is noteworthy that, at baseline, $IHI_{Ipsi-to-Contralesional}$ was much lower than $IHI_{Contra-to-Ipsilesional}$, suggesting that the affected M1 had a stronger inhibitory effect on the healthy M1, and we consider it as a maladaptive process. After the 14-day sequential rTMS over affected M1, there was a significant decrease in $IHI_{Contra-to-Ipsilesional}$ and a slight increase in $IHI_{Ipsi-to-Contralesional}$, reducing the IHI ratio from 2.70 to 1.34 and leading to a balance between two hemispheres. It has been demonstrated that chronic patients with more impairment (FM-UE $\leq$ 43) have stronger IHI from the contralesional to the ipsilesional hemisphere with greater motor performance, while patients with less impairment (FM-UE $>$ 43) show the opposite (49). The former is manifested in our

patients. The negative impact of the ipsilesional motor areas on the contralesional M1 has been confirmed to normalize gradually with functional recovery (50). In combination with TMS and electroencephalography (EEG), Casula et al. (51) have found that in patients with chronic stroke, the better the strength of the affected hand is restored, the closer the interhemispheric balance is to 1. Combined with the abovementioned studies and this case, we can conclude that the better the recovery of motor function, the more stable balance between the two hemispheres.

The advantages of sequential rTMS

A previous randomized controlled study has shown that 10 sessions of 1 Hz rTMS followed by 10 sessions of iTBS could improve FMA-UE of patients with chronic stroke by about three points (12), which was lower than the increase in this case. rTMS can maximize metaplasticity effects to induce or restore synaptic plasticity (52). HF-rTMS and LF-rTMS can result in strengthening (long-term potentiation/LTP) or weakening (long-term depression/LTD) of synaptic connections and efficacy, respectively (53), and the efficacy of LTD or LTP depends on the integrity of the corticospinal pathway (54). Therefore, priming the intact hemisphere first would be more conducive to promoting synaptic plasticity. LF-rTMS over unaffected M1 can effectively reduce RMT and increase MEP amplitude in unstimulated M1 (15). The increased cortical excitability in the lesional hemisphere might be related to the increased intrinsic excitability of the excitatory interneurons responsible for glutamatergic non-NMDA receptors, and these changes are likely mediated by interhemispheric callosal connections (55). In addition, the effects of LF-rTMS can be continued into the next session, thus enhancing the effectiveness of subsequent high-frequency transcranial magnetism (12), as reflected in the FM-UE and ARAT results and distal upper limb function. Compared to LF-rTMS, HF-rTMS over the ipsilesional M1 could be more conducive to the functional connectivity reorganization of the ipsilesional motor network (17). Moreover, HF-rTMS can enhance the interhemispheric connection both anatomically and functionally (56–58), providing the basis for restoring interhemispheric inhibitory balance regardless of which hemisphere has a stronger IHI.

Conclusion

In this study, we have proposed a protocol of sequential inhibitory and facilitatory rTMS that significantly improved motor performance in the patient with chronic subcortical stroke, and explored the neurophysiological mechanism through fNIRS and TMS. Further randomized controlled trials are needed to confirm the effectiveness of sequential rTMS for motor function improvement in patients with chronic phase and to explore possible underlying mechanisms of interhemispheric balance and cortical reorganization.

Limitations

First, the study lacked fNIRS mid-term assessment and long-term follow-up of the patient, so we are unsure about the cortical activation after LF-TMS and the duration of the effect after treatment. Second, we did not use DTI to assess the structural integrity of the pyramidal tract and the contribution of the CSTs from ipsilesional premotor areas and contralesional M1 to motor recovery.

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 authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Huashan Hospital affiliated to Fudan University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

NC did the intervention, collected data, and wrote the paper. XQ analyzed the data. YH evaluated the patient. JH and YB revised the literature and offered the grant support. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1064718/full#supplementary-material

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Case report: Dysphagia after COVID-19 infection in a stroke patient—Is neurostimulation a potential management?

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A 90-year-old man with stroke was weaned from tube feeding 4 months after stroke onset. However, he had a coronavirus disease 2019 (COVID-19) infection after 2 months and suffered from drastically worsened oropharyngeal dysphagia that required a reinsertion of the nasogastric tube. A videofluoroscopic swallowing study revealed poor bolus oral transit, significantly delayed swallowing reflex, reduced pharyngeal movements, and insufficient cough response. Repetitive transcranial magnetic stimulation and neuromuscular electrical stimulation were applied, in addition to conventional swallowing training. The feeding tube was removed after 20 treatment sessions. Clinicians should be aware of the risk of dysphagia after COVID-19 infection in patients with underlying neurological diseases. The management of post-COVID-19 dysphagia has not yet been fully established. Repetitive transcranial electrical stimulation combined with neuromuscular electrical stimulation may be used as an auxiliary intervention in specific cases.

KEYWORDS

COVID-19, dysphagia, repetitive transcranial magnetic stimulation, brain plasticity, neurostimulation

Introduction

As of September 2022, there had been over 600,000,000 confirmed cases of the coronavirus disease 2019 (COVID-19) and over 6,500,000 deaths, according to the World Health Organization (1). The severity and clinical manifestation of the disease vary widely among individuals (2, 3). Dysphagia has been reported as a sequela of COVID-19 (4, 5). Identified risk factors include pneumonia, acute respiratory distress syndrome, intubation, and old age (6). However, dysphagia can develop in non-intubated patients (7). A questionnaire screening found that 7% of non-critical, hospitalized patients with COVID-19 expressed self-perceived dysphagia after the acute phase (8). The exact mechanism of dysphagia development and persistence after COVID-19 is yet to be determined, in addition to the concerns with uncertainties in appropriate management.

Dysphagia is a common comorbidity of stroke and is associated with aspiration, pulmonary complications, malnutrition, prolonged length of hospital stay, increased healthcare expenditure, and even mortality (9–11). Conventional dysphagia training includes sensory stimulation, oral/facial/pharyngeal muscle strengthening, and swallowing

maneuver education. Newer therapeutic techniques aimed at promoting neuroplasticity and recovering swallowing function have received considerable attention. Repetitive transcranial magnetic stimulation (rTMS) targets the central oropharyngeal cortex, whereas neuromuscular electrical stimulation (NMES) excites the peripheral nervous system (12). The respective and combined efficacy of these two approaches in improving poststroke dysphagia has been demonstrated (13, 14).

We present the case of a patient with stroke who experienced drastically worsened oropharyngeal dysphagia following COVID-19 infection. After conventional swallowing training, rTMS, and NMES, excellent patient outcomes were achieved.

Case report

A 90-year-old man with hypertension, type 2 diabetes, and chronic kidney disease had cerebral infarction in the left medial temporal lobe on January 2, 2022. The patient was admitted for poststroke rehabilitation 3.5 months after onset. Prior to the stroke, the patient was able to walk independently in the community with a single cane and did not report any symptom of dysphagia. On admission (March 16, 2022), the patient had clear consciousness, but was bedridden due to right hemiplegia. The breathing pattern was smooth without supplemental oxygen. The patient was fed through a nasogastric tube with a functional oral intake scale (FOIS) score of 1. Clinical swallowing evaluation revealed reduced tongue motor skills, weak spontaneous cough, and grade I right central-type facial palsy. The gag reflex was normal bilaterally and velar elevation was symmetric. Mildly delayed swallowing reflex with a cough response was recorded during the 3-ounce water swallowing test. Two weeks after the patients was admitted (March 22, 2022), a fiberoptic endoscopic evaluation of swallowing test reported no aspiration of liquid or soft foods, but residue of soft foods in the vallecula. One week after (April 1, 2022), a videofluoroscopic swallowing study (VFSS) demonstrated a delayed swallowing reflex and premature leakage (Supplementary Video 1). The patient aspirated thin barium with a cough response. There was a slight bolus retention in the vallecula and piriform sinuses. The tests indicated that the patient had adequate swallowing ability with only minimal aspiration of thin liquid; therefore, his nasogastric tube was removed on April 1, 2022 and a modified diet was prescribed. On discharge, the patient could finish a meal by himself and consume adequate thickened liquid (FOIS: 5).

The patient had a fever of 38°C, cough with sputum, and rhinorrhea on June 19, 2022 (2 months after discharge), and tested positive for COVID-19. Oral antiviral molnupiravir 800 mg every 12 h was given for 5 days (June 19–June 24, 2022), and oxygen *via* a nasal cannula was provided temporarily. Fever subsided since June 22. However, owing to frequent choking and coughing, the nasogastric tube was reinserted 1 week after the patient contracted the virus. By 3 weeks after the COVID-19 infection, the patient was free of upper respiratory symptoms except for coughing when choked on his own saliva or small sips of water. The patient was admitted to our rehabilitation ward 1.5 months after the COVID-19 infection (August 2, 2022) for swallowing training. Upon admission, the patient exhibited good orientation and engaged in fluent conversations. Brunnstrom's staging and muscle strength of the patient's right limbs remained the same as they were during the previous admission; however, the patient's trunk muscles became weaker, and maintaining an upright sitting position was difficult. Excessive saliva drooling and a wet voice were observed. The patient's swallowing reflex was remarkably delayed. Gag reflexes were diminished bilaterally. Brain magnetic resonance imaging (MRI) showed no new insults (Figure 1). On August 8, 2022, a VFSS revealed severe oropharyngeal dysphagia (Supplementary Video 2). Difficulty in oral phase bolus transfer, premature oral leakage, remarkably delayed swallowing reflex, inadequate hypolarynx complex elevation, large amounts of bolus accumulation in the vallecular/pyriform sinuses, and residue spillage were shown. In addition, the patient aspirated both thin and thick barium. Cough responses although present, were weak.

Swallowing therapy with neurostimulation was afterward initiated. Training sessions began with rTMS. A magnetic stimulator (MagVenture; NeuroStar) delivered 500 pulses of 10 Hz stimulation at a 90% resting motor threshold to bilateral phayngeal cortices using a figure-of-eight coil. The rMT was identified as the intensity that produced motor-evoked potentials of 50 μV at least five out of ten times on mylohyoid electromyographic recordings. The rMT for each hemisphere was determined separately. Coil position was marked on an elastic cap that the patient wore during each session. Immediately after rTMS, the patient received a one-on-one swallowing training with a speech-language pathologist, during which sensory stimulation using NMES (Intelect; VitalStim) were employed along with swallowing muscles strengthening. The VitalStim device consists of four bipolar electrodes and were placed on both sides of the midline of the anterior neck. The top ones were situated at the level of the hyoid bone and the bottom ones at the level of the thyroid notch. The stimulation pulse was set at frequency of 80 Hz and wave amplitude of 12 mA. The 1-h-long program was administered 5 days per week for 2 weeks. The patient showed improved oral movements, with reduced drooling, better laryngeal elevation, and stronger volitional cough. The oral intake of thickened liquids and pureed foods was attempted under supervision. The chin tuck maneuver and supraglottic swallowing were used. We observed less post-swallowing choking and greater swallowing endurance. Therefore, the patient was discharged on August 26, 2022, and the management plan shifted to out-patient rehabilitation. At that time, the nasogastric tube was still necessary for nutritional requirements, which could not be met by oral intake (FOIS: 3).

After returning home, the patient continued the swallowing exercises as instructed by the rehabilitation team, which included effortful swallow, Shaker exercise, chin tuck against resistance, and expiratory muscle strengthening. The patient's swallowing ability improved daily, alongside increased oral intake with fewer choking episodes. Based on improved swallowing function, the patient was readmitted on September 22, 2022 in an attempt to wean the patient from tube feeding. Another 10 sessions of swallowing training, containing rTMS and NMES, were administered. A VFSS performed on October 7, 2022 showed good bolus transit, less premature leakage, delayed swallowing reflex, good hypopharynx elevation, penetration in thin and thick barium, trace aspiration in thin barium, and limited residue

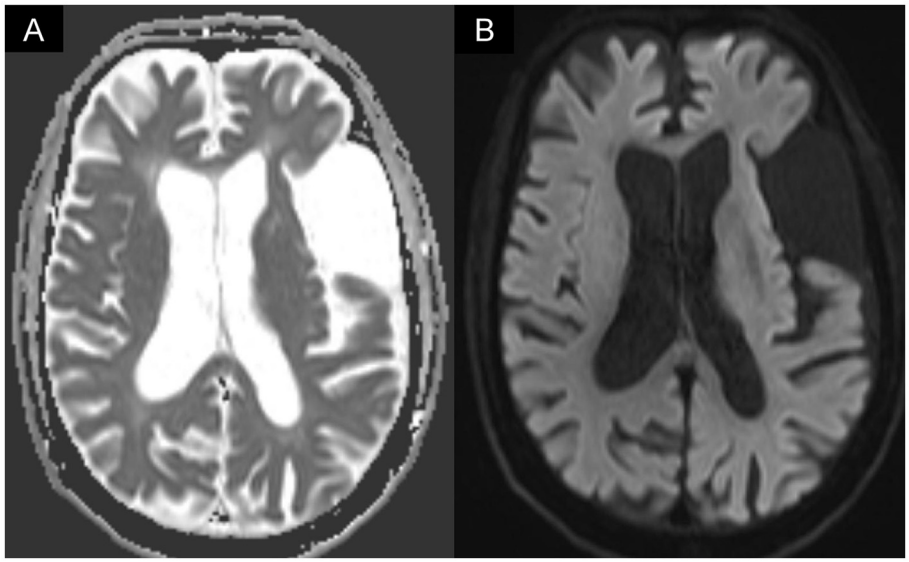

FIGURE 1
Brain MRI showed **(A)** increased signal intensity on diffusion-weighted imaging (DWI) in the left temporal lobe, which corresponded to **(B)** decreased apparent diffusion coefficient (ADC) value. The MRI image was compatible with post-stroke encephalomalacia but found no evidence of new infarction.

(Supplementary Video 3). With satisfactory swallowing function and adequate oral intake, the patient's nasogastric tube was removed on October 7, 2022, which was the 110th day after the patient's COVID-19 infection.

One month after the removal of the nasogastric tube, the patient presented in a healthy state at the follow-up clinic and showed no lung infection. In addition, the patient gained 2 kg weight after the last discharge. The clinical course is summarized in Figure 2, and the major findings of the swallowing assessments are outlined in Table 1.

Discussion and conclusion

In this case report, we presented the development of post-COVID-19 dysphagia in a patient with stroke and the patient's subsequent recovery using several swallowing assessments. The patient was weaned off tube feeding 4 months after the stroke. However, he had COVID-19 infection after 2 months and reported worsened oropharyngeal dysphagia. A nasogastric tube was inserted to maintain safe enteral nutrition. Twenty sessions of swallowing therapy augmented with neurostimulation were administered. The feeding tube was removed 3.5 months after COVID-19 infection.

Newly-diagnosed oropharyngeal dysphagia was found in 35.3% of hospitalized patients with COVID-19 (15). Dziewas et al. (16) postulated several etiologies of COVID-19-associated dysphagia, including encompassing stroke, encephalitis, critical illness neuropathy, Guillain-Barré syndrome (GBS), and skeletal muscle injury. In our case, recurrent stroke was excluded by brain MRI. The patient did not present with limbs twitching, speech disturbance, vomiting, altered consciousness, unusual behaviors or personality changes. Although cerebrospinal fluid analysis and electroencephalography were not performed, encephalitis and non-convulsive seizures were unlikely. Muscle strength and sensation across the four limbs remained constant throughout the disease course, which is incompatible with critical illness neuropathy, GBS or its pharyngeal-cervical-brachial variant which can initially present with swallowing difficulties. Myositis was unlikely because the patient did not have muscle pain and had normal serum creatinine kinase levels.

Cranial nerve dysfunction is a possible explanation for the marked deterioration in swallowing function after COVID-19 infection in our case. Dysosmia and dysgeusia are common complications of COVID-19. The virus enters the human body by binding with angiotensin-converting enzyme II cell receptors, which are expressed in the tongue, oral mucosa, and olfactory epithelium (17). Neurotropism, the direct viral invasion of nerves, is the most reported pathophysiology of cranial nerve involvement in COVID-19 (18). Other speculated causes include involvement of the central nervous system, focal immune response, and inflammatory reaction (18, 19). Gag reflex disappeared and laryngeal sensation reduced after the COVID-19 infection in our patient, which might be a presentation of glossopharyngeal and vagal neuropathies. Damage to the trigeminal and hypoglossal nerves impairs bolus formation and propulsion. Furthermore, breathing-swallowing coordination is fundamental for protecting the lower airway. Symptoms, such as coughing, sneezing, and shortness of breath, can hamper this predetermined rhythm. In addition, malnutrition and deconditioning from an acute infection may play a role in the patient's dysphagia, as the patient had a concurrent decline in physical function. Fatigue can persist after the acute phase of a COVID-19 infection (20). In this patient, eternal nutrition and body weight were promptly supported by tube feeding. Progress in exercise

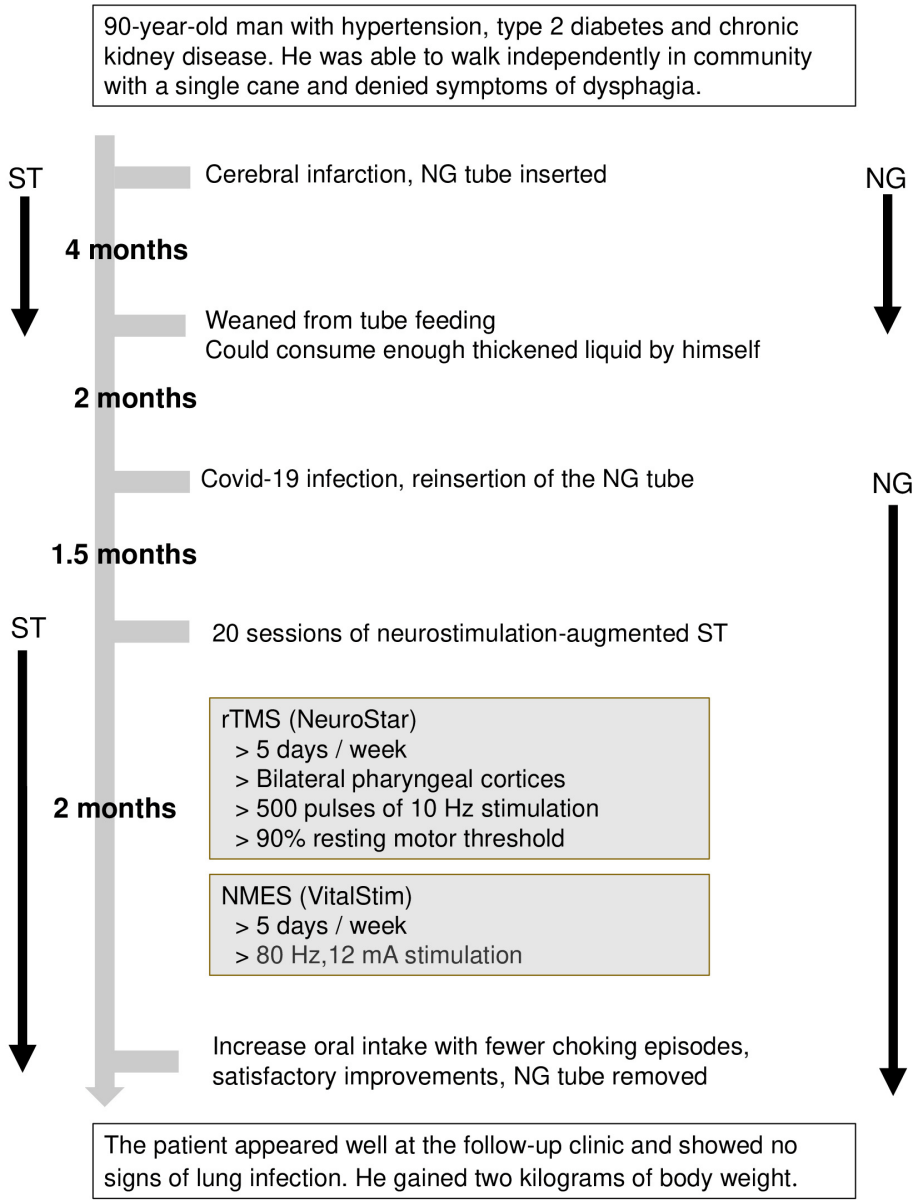

FIGURE 2
Clinical course of the patient. NMES, neuromuscular electrical stimulation; rTMS, repetitive transcranial magnetic stimulation; ST, swallowing therapy.

endurance and transfer skills was made during admission; however, the progress was to a lesser extent compared to swallowing ability.

Dysphagia among non-intubated patients with COVID-19 is generally self-limiting (7). An observational cohort study by Archer et al. (21) found that in 70.7% of patients referred for post-COVID-19-associated swallowing problems, the swallowing problems fully resolved on discharge. However, they also pointed out that patients with preexisting neurologic diagnoses were prone to experience persistent dysphagia in the absence of mechanical ventilation. Lee et al. (22) described that a new-onset swallowing difficulty in a patient with Parkinson's disease was so severe that the patient continued to rely on tube feeding 2 months after the viral infection. In the present case, the patient sustained an infarction and developed poststroke dysphagia. Nonetheless, through rehabilitative endeavors, the feeding tube was successfully discontinued 4 months after stroke onset. The dramatic reduction of swallowing function following COVID-19 infection could be attributed to the failure of compensatory techniques when prior deficits are coupled with COVID-19-related neuromuscular dysfunctions, respiratory distress, and fatigue.

In recent years, neurostimulation has been extensively studied for its ability to modulate neuroplasticity and maximize functional recovery. Changes to the neural network could be induced by applying stimulation directly to the motor cortex (rTMS) or through peripheral somatosensory stimulations (NMES) (23, 24). Promising outcomes were shown in the management of numerous neurological/psychological diseases with rTMS (25). Furthermore,

TABLE 1 Findings of the VFSS studies.

VFSS findings	Before COVID-19 infection (April 1st)			After COVID-19 infection (August 8th)			After swallowing therapy (October 7th)		
	Thin	Thick	Paste	Thin	Thick	Paste	Thin	Thick	Paste
Oral phase									
Oral stasis	(–)	(–)	(–)	(+)	(+)	(+)	(+)	(–)	(–)
Premature oral leakage	(+)	(+)	(+)	(+)	(+)	(–)	(+)	(+)	(+)
Pharyngeal phase									
Hypohyoid elevation	Adequate	Adequate	Adequate	NA	Poor	NA	Adequate	Adequate	Adequate
Vallecular stasis	(+), <1/2	(–)	(–)	NA	(+), >1/2	NA	(+), >1/2	(+), <1/2	(+), <1/2
Pyriform stasis	(–)	(–)	(–)	NA	(+), >1/2	NA	(–)	(–)	(–)
Premature spillage	(+)	(–)	(–)	NA	(+)	NA	(+)	(–)	(–)
PAS	7	1	1	NA	7	NA	8	2	1
Swallow reflex (seconds)	3	8	5	(–)	>10	(–)	>10	4	8

Hypothyroid elevation was defined as adequate when there was complete airway closure during bolus swallow whereas poor hypohyoid elevation indicated incomplete airway closure and protection. Vallecular/pyriform stasis was expressed as more than half (>1/2) or less than half (<1/2) of the space of the vallecular/pyriform sinuses.
PAS, penetration-aspiration scale; NA, not available.

there is growing evidence that it is a validated approach to treat poststroke dysphagia (13). The effectiveness of rTMS is significantly greater when administered alongside conventional swallowing therapy than when being administered as a stand-alone treatment (26). However, stimulation protocols and their respective results are diverse. In particular, a randomized controlled study performed by Park et al. (27) illustrated bilateral stimulation produced better and faster improvements than unilateral stimulation. NMES is effective in treating dysphagia in patients with and without stroke (28, 29). A report found a superior recovery of poststroke dysphagia in the rTMS plus NMES group than in the NMES group (14). No study has mentioned using neurostimulation for the treatment of dysphagia after COVID-19 infection. As both the central and peripheral nervous systems could be involved in prolonged dysphagia in our case, we adopted rTMS and NMES to optimize the patient's recovery. Surprisingly, the results were good. The extent to which neurostimulation contributed to the favorable outcome in our patient was uncertain. The intensity of the neurostimulation protocol (500 pulses of rTMS combined with NMES for 20 days in our case) may be crucial to its effectiveness. Nonetheless, this report may provide some clues to the etiology and treatment of post-COVID-19 dysphagia.

In summary, we emphasized the risk of dysphagia after COVID-19 infection in patients with premorbid neurological conditions and swallowing difficulties. The multifactorial detrimental effects of COVID-19 can have serious consequences in vulnerable populations. Intensive rehabilitation yielded favorable outcomes in this case. The therapeutic potential of neurostimulation in post-COVID-19 dysphagia is worth further investigation.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

S-MY and T-GW contributed to conception and design of the study. T-YL wrote the first draft of the manuscript. S-MY, K-VC, and T-GW reviewed and edited the manuscript. P-CS and S-AL prepared the table, figure, and videos. All authors read and approved the submitted version.

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Conflict of interest

T-YL, P-CS, S-AL, and S-MY were employed by Lo-Hsu Medical Foundation, Inc.

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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1126390/full#supplementary-material

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Long-term effects of the gait treatment using a wearable cyborg hybrid assistive limb in a patient with spinal and bulbar muscular atrophy: a case report with 5 years of follow-up

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Background: Spinal and bulbar muscular atrophy (SBMA) is a progressive neuromuscular degenerative disease characterized by the degeneration of lower motor neurons in the spinal cord and brainstem and neurogenic atrophy of the skeletal muscle. Although the short-term effectiveness of gait treatment using a wearable cyborg hybrid assistive limb (HAL) has been demonstrated for the rehabilitation of patients with SBMA, the long-term effects of this treatment are unclear. Thus, this study aimed to investigate the long-term effects of the continued gait treatment with HAL in a patient with SBMA.

Results: A 68-year-old man with SBMA had lower limb muscle weakness and atrophy, gait asymmetry, and decreased walking endurance. The patient performed nine courses of HAL gait treatment (as one course three times per week for 3 weeks, totaling nine times) for ~5 years. The patient performed HAL gait treatment to improve gait symmetry and endurance. A physical therapist adjusted HAL based on the gait analysis and physical function of the patient. Outcome measurements, such as 2-min walking distance (2MWD), 10-meter walking test (maximal walking speed, step length, cadence, and gait symmetry), muscle strength, Revised Amyotrophic Lateral Sclerosis Functional Assessment Scale (ALSFRS-R), and patient-reported outcomes, were evaluated immediately before and after gait treatment with HAL for each course. 2MWD improved from 94 m to 101.8 m, and the ALSFRS-R gait items remained unchanged (score 3) for approximately 5 years. The patient could maintain walking ability in terms of gait symmetry, walking endurance, and independence walking despite disease progression during HAL treatment.

Conclusion: The long-term gait treatment with HAL in a patient with SBMA may contribute to the maintenance and improvement of the gait endurance and ability to perform activities of daily living. The cybernics treatment using HAL may enable patients to relearn correct gait movements. The gait analysis and physical function assessment by a physical therapist might be important to maximize the benefits of HAL treatment.

KEYWORDS

spinal and bulbar muscular atrophy, wearable cyborg hybrid assistive limb (HAL), gait treatment, walking symmetry, walking endurance

Introduction

Spinal and bulbar muscular atrophy (SBMA) is a progressive neuromuscular degenerative disease characterized by the degeneration of lower motor neurons in the spinal cord and brainstem and neurogenic atrophy of the skeletal muscle (1). SBMA occurs only in adult men (1). The typical symptoms are muscle weakness and atrophy, mainly in the proximal parts of the limbs and ball paralysis (2, 3). Sensory deficits may localize to the distal lower extremities (4). The phenomenon of fibrous bundle contraction is another characteristic finding during the voluntary contraction of the facial and neck muscles (1). The age of SBMA onset is 30–60 years. In most cases, the tremors and painful muscle spasms in the fingers precede the disease onset (5). There was no recovery for SBMA. The disease follows a slowly progressive course, usually requiring a wheelchair for mobility 10–15 years after onset. Respiratory failure is a common cause of death by bulbar paralysis (5). However, the kind of rehabilitation that is effective for patients with SBMA is not clear. A progressive neuromuscular disease places a considerable burden on muscles even with mild exercise (6). For SBMA rehabilitation, it is very difficult to set the amount, frequency, and type of exercise. Thus, there are only a few reports on effective rehabilitation methods for SBMA (7, 8).

The main treatment method of rehabilitation for patients with SBMA is symptomatic therapy (9). Leuprorelin—which inhibits the nuclear transportation of testosterone and abnormal androgen receptors—was clinically demonstrated to improve dysphagia in patients with SBMA (10). However, leuprorelin use was not associated with improvements in ambulatory function (10). Several clinical trials of gait treatment using the wearable cyborg hybrid assistive limb (HAL) have been conducted in patients with neurological problems (11–13). Recently, a physician-initiated clinical trial (NCY-3001 study) on gait treatment with HAL for eight rare diseases, including SBMA, was conducted (14). The NCY-3001 study validated the efficacy and safety of HAL gait treatment for an intractable neuromuscular disease with gait disturbance (14). Gait treatment with HAL has resulted in improved gait ability and balance performance (14). In the NCY-3001 study, HAL gait treatment showed significant improvements in the 2-min walking distance (2MWD), cadence at the 10-meter walking test (10MWT), and total scores of the manual muscle testing (MMT) compared with conventional methods (14). The effectiveness of HAL gait treatment for intractable neuromuscular diseases was proved by this doctor-initiated randomized controlled trial (14).

However, the NCY-3001 study was a short-term randomized crossover trial with nine sessions, up to four per week. Some points were unclear about the effects of HAL gait treatment. Moreover, there are no reports on the long-term efficacy and safety of the gait treatment with HAL and appropriate treatment intervals. In addition, previous studies have shown improvements in 2MWD, cadence at 10MWT, and muscle strength (14), but the effects on other outcomes are unclear, such as gait symmetry, activities of daily living (ADL), and treatment satisfaction of the patient, such as the Japanese version of the Decision Regret Scale (DRS).

We had the opportunity to continue HAL gait treatment in a patient with SBMA with reduced walking endurance for approximately 5 years. Thus, this study aimed to report the results of the long-term effects of HAL gait treatment on a patient with SBMA.

Materials and methods

Patient

The patient was a 68-year-old man who lived with his wife. He was able to perform independently all his ADL before the first course of HAL gait treatment. The patient was not employed, and before SBMA onset, his hobby was going to the museums, which influenced him to draw pictures. The chief complaint of the patient was difficulty walking with the right foot and feeling of fatigue when walking long distances. He hoped to visit museums again using public transportation. The patient wanted to walk more than 500 m without resting, and he wanted to appreciate the museum environment. His height, weight, and body mass index were 168 cm, 55.6 kg, and 20.1 kg/m^2, respectively. As regards his current medical history, the patient had finger tremors at the age of 35 years and painful swelling of the mammary gland since the age of 40. The patient has decreased muscle strength in the right lower extremity from the age of 60, and an abnormal creatine kinase (CK) value was discovered at a nearby clinic. The CAG repeat count of the patient was abnormal at 46 in the Kennedy genetic analysis at the same years; subsequently, the patient was diagnosed with SBMA. He began to experience dyspnea when walking at the age of 62 and became aware of the progression of muscle weakness in the lower limbs (right > left) from the age of 63. The patient has used an ankle-foot orthosis (Gait Solution-Design®: GSD, Pacific Supply, Japan) when walking. He had decreased muscle strength in the upper extremities from the age of 66 and has started regular rehabilitation hospitalization in our hospital for gait treatment with HAL from the age of 68 years (December 2016) (Figure 1). The patient has started leuprorelin acetate once every 12 weeks from November 2017 (ongoing). Regarding his family history, his father has been diagnosed with spinal muscular atrophy and his nephew with SBMA. Medical histories included hypertension and diabetes mellitus.

The neurological findings of the patient before HAL treatment (first course) are as follows: he had a clear level of consciousness and good communication ability. The score of the Japanese version of the Montreal Cognitive Assessment was 28/30. In the MMT, the muscle strength of the lower limbs (right/left) was as follows: hip flexion, 3/4; hip extension, 3/4; knee flexion, 3/4; knee extension, 4/4; ankle dorsiflexion (DF), 4/4; and plantarflexion (PF), 2-/2. The patient had no limitations in the range of motion (ROM); however, there was concave deformation in both legs. The superficial sensation in the sole decreased in the right side dominance, and warm pain and position sensation decreased in the right peripheral limb. The patient's bilateral patellar tendon reflex and Achilles tendon reflex disappeared. The patient had muscle atrophy of the tongue and right lower limb.

The gait ability, gait posture, and gait treatment policy of the patient before HAL treatment (first course) are as follows. The patient was able to walk independently using a Lofstrand crutch in

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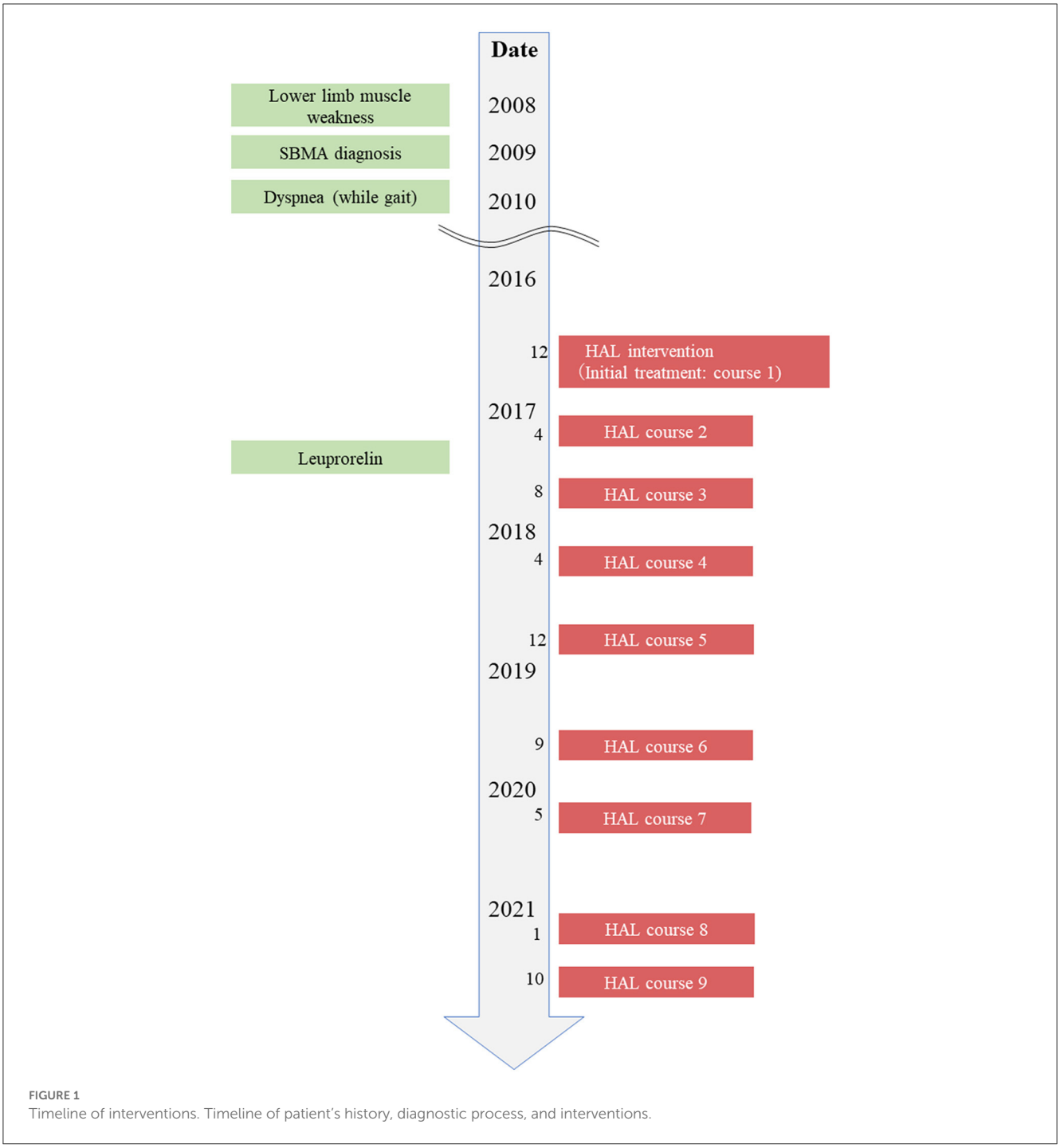

FIGURE 1
Timeline of interventions. Timeline of patient's history, diagnostic process, and interventions.

the right upper limb and wearing a GSD in the right lower limb. The patient showed a slight trunk forward tilt in the mid-stance (MSt) to the terminal stance (TSt) on the right side, and the hip extension motion reached initial contact (IC) on the left side without reaching the extension range. Thereafter, the hip joint heeled off in a mildly flexed position in the right TSt to pre-swing (PSw), and the load shifted to the left (Supplementary Figure S1). The stance time during walking was shorter on the right side than on the left side, and the swing time was shorter on the left side. Consequently, the patient showed a temporal asymmetric gait. The continuous walking distance of the patient was approximately 200 m. When the patient walked more than 150 m, dyspnea occurred, and the muscle spasms of the right lower limb appeared at 200 m. The results showed that the patient has insufficient endurance for walking. A previous study reported that asymmetric ambulatory activity negatively affected energy cost during walking (15). The inefficient gait caused by the shortening of the right-side stance phase perhaps caused the decreased walking endurance. The aim of this treatment using HAL was to acquire an efficient gait by the expansion of the hip joint extension motion in the right-side stance phase and accordingly improve the walking endurance to realize the patient's desire.

Setting and methods of HAL gait treatment

The method of HAL gait treatment was based on a previous study (NCY-3001 study) (14). Gait treatment with HAL was conducted three times per week for 3 weeks, totaling nine times as one course. Fitting was mainly performed according to the HAL-medical leg-type proper-use guide in the initial treatment of each course (16). Fitting was performed by the responsible physical therapist so that the patients received the appropriate assistance. The physical therapist selected the cybernic voluntary control (CVC) mode in all sessions. The CVC means that the assisting torque controls the movement based on the intensity of the bioelectric signals (BES) (16, 17). BES are motor unit potentials on the skin; they correspond to the motor torque required for each joint movement, including the hip and knee, in accordance with the wearer's motor intention (14). Moreover, the physical therapist adjusted the torque tuner and balance tuner based on the alignment, walking observation (gait posture), and body function. The torque tuner indicates the strength of the assistance provided by the four motors at the right and left hip and knee joints, adjustable in 21 levels at each joint (0–20). The balance tuner indicates the balance between the flexion and extension movements of the hip and knee joints and is adjustable in 20 levels at each joint (flexion, FX1–10; or extension, EX1–10). For example, if a physical therapist wants to increase the hip extension assist in a patient's supporting leg, the physical therapist adjusts the balance tuner by one step in the extension dominance (EX1). The patient performed the gait treatment with HAL for approximately 60 min, including setting up, wearing HAL, and break times. The physical therapist selected the task (STAND or WALK) according to the treatment that the patient wanted to perform. The physical therapist selected a task from five levels (WALK 1–5) according to the patient's walking speed. The walking speed is a guide, and the physical therapist adjusted it according to the patient's comfort level when walking faster or slower. In this study, WALK 5 was selected in all sessions. The patient used an all-in-one walker (All in One®, Ropox A/S, Denmark) with an unloading function for fall prevention during the treatment, and the physical therapist measured blood pressure and pulse rate before and after the intervention. The intensity of HAL gait treatment was set to the patient's fatigue level that did not exceed "slightly tight" using the modified Borg score (18). The physical therapist checked the presence or absence of muscular fatigue after treatment and on the next day. The walking distance and time during HAL gait treatment were recorded for each course between December 2016 and October 2021.

Conventional physical therapy

The conventional physical therapy was performed for 40–60 min 3–6 days per week during hospitalization. It included ROM practice, sensory input to the sole, muscle force enhancement training, balance practice, and walking practice. The walking intensity was defined as the distance the patient could walk continuously without rest and was only recorded during courses 1–6.

Outcome measurements

Gait evaluation

Treatment outcome measures were evaluated immediately before and after HAL gait treatment for each course. The primary outcome was 2MWD, and the secondary outcomes were 10MWT (maximal walking speed, step length, and cadence) and muscle strength as measured by MMT. Notably, 2MWD measured before initiating course 1 was compared with that measured after completing course 9 to clarify the long-term effects of HAL treatment. Moreover, we evaluated 10MWT using a portable three-axis accelerometer (Mimamori-Gait ®, LSI Medience Corp, Japan) to determine walking speed, step length, cadence, and swing times of both legs. Furthermore, the symmetry index (SI) was calculated using the left–right swing times to evaluate the detailed symmetry during gait (19) as follows:

$$\text{Symmetry Index (SI)} = \frac{\text{Left swing times} - \text{Right swing times}}{1/2(\text{Left swing times} + \text{Right swing times})} \times 100$$

The swing time indicates the values for each swing time on both legs in the 10-m interval.

If the SI is close to 0, the left and right swing times during walking are equal; that is, walking with bilaterally symmetric leg movements is realized. A negative value also represents a shorter swing time on the left than on the right.

Muscle strength using MMT

The MMT total score (0–60) was calculated by summing the scores of each lower limb (bilateral flexion and extension of hip, knee, and ankle) (14).

Severity of SBMA using the revised amyotrophic lateral sclerosis functional assessment scale (ALSFRS-R) and serum creatinine levels

A previous study conducted by Hasizume et al. assessed the severity of SBMA using the ALSFRS-R (ALS-functional rating scale) and serum creatinine levels (mg/dL) (20). The ALSFRS-R was developed as a comprehensive severity index for patients with ALS and consists of four parts: bulbar function, ADL, respiratory status, and upper and lower extremities (21). A previous study suggested that the serum creatinine level is the most useful blood parameter to detect the severity of motor dysfunction in SBMA. This study also revealed a strong positive correlation between the serum creatinine level and clinical parameters, such as ALSFRS, grip power, and 6-min walking distance (6MWD) at baseline (20). Therefore, we measured the ALSFRS-R and serum creatinine as disease indices of SBMA. Both the ALSFRS-R and serum creatinine level were calculated for the annual decline rate based on the previous studies: [(follow-up data) – (baseline data)/observational period (years)] (20).

Patient-reported outcomes (PRO) using the Japanese version of the DRS

The Japanese version of the DRS analyzes patients' feelings of loss of expectations after treatment; thus, we measured the effects of long-term HAL use using this scale after course 9. The DRS is a self-administered rating scale; there were five question items, and responses are scored using a Likert scale, ranging from 1 (strongly agree) to 5 (strongly disagree), with scale scores ranging from 0 to 100. Positive questions (questions 1, 3, and 5) are drawn 1 from the response number, whereas negative questions (questions 2 and 4) are drawn 5 to the response number, and the total score of five questions is multiplied by 5 to calculate the scale score. The higher the score, the higher the decision regret (22).

Results

Change in the primary outcome measure (2MWD)

2MWD improved in each course after HAL gait treatment (Figure 2). The improvement rates of 2MWD for each course were as follows: course 1, +21.1%; course 2, +30.0%; course 3, +18.8%; course 4, +13.8%; course 5, +6.5%; course 6, +5.5%; course 7, +17.0%; course 8, +10.0%; and course 9, +12.1%. The result of 2MWD was less than the baseline for the first time in course 7 before the assessment. Thereafter, 2MWD in course 8 and course 9 pre-assessments were also less than the baseline; however, all were higher after HAL treatment. The improvement rate of 2MWD was +8.3% compared with course 1 pre-initiation and course 9 termination, showing an improvement in 2MWD within 5 years.

Changes in walking capacity and HAL adjustments accordingly to the gait posture

The maximal walking speed, step length, cadence, and SI were improved pre- and post-HAL treatment for each course (Table 1). The patient's condition had worsened daily, therefore the physical therapist adjusted HAL assistance according to the gait posture of the patient during the 5 years of HAL gait treatment. Detailed changes for the gait posture and adjustments for HAL assistance are as follows:

Course 1

The mild trunk forward-leaning of the patient was observed in MSt to TSt on the right side before the initiation of HAL gait treatment and hip extension movements in TSt reached IC on the left side without reaching the extension range of the hip. The right hip joint remained in a mildly flexed position from TSt to PSw, and in that state, weight-bearing was shifted to the left leg (Supplementary Figure S1A). The swing time during walking was 0.52 s on the left side, whereas it was 0.59 s on the right side. The swing time on the left side was short. Regarding the HAL setting, the physical therapist adjusted the torque tuner of the right hip joint to 2 and the balance tuner to EX5. The EX5 of the balance tuner means that the motion assistance of HAL provided more support on hip extension than on hip flexion. The physical therapist visually checked the symmetry of the gait of the patient and adjusted the motion assistance from HAL to bring the patient's gait closer to normal. The patient could keep in the mid-trunk position from the right MSt to TSt at course 1. The motion of the right hip extension was expanded in the right stance phase, and the

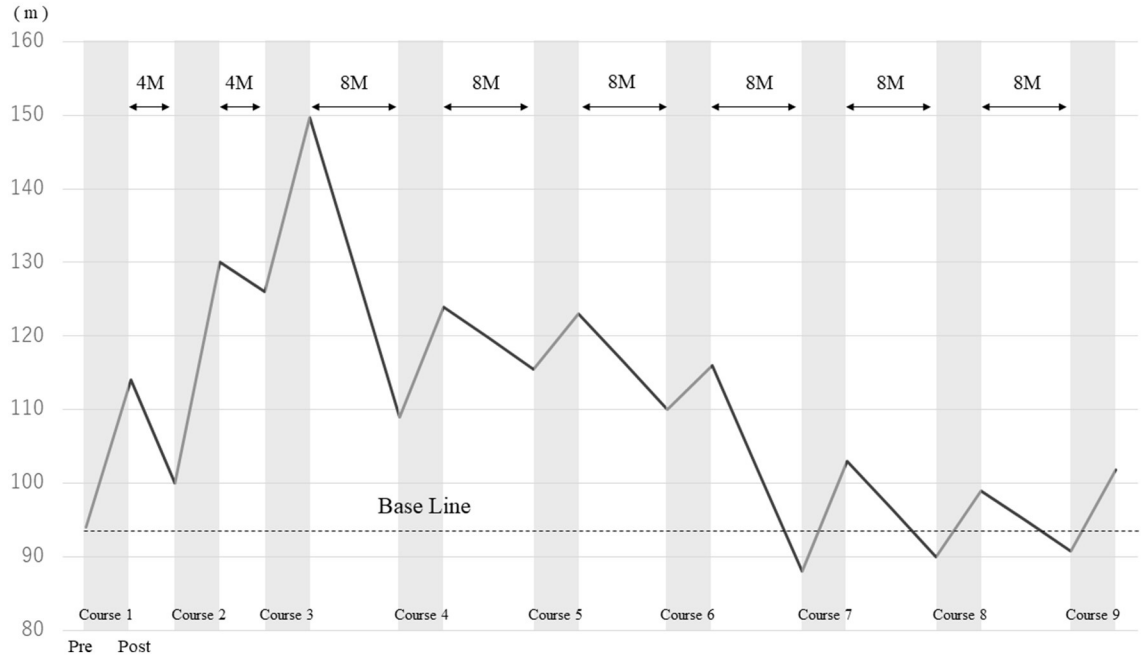

FIGURE 2
Comparison of the 2-min walking distance before and after HAL gait treatment in each course.

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TABLE 1 Change in the walking ability and total muscle strength before and after HAL gait treatment in each course.

	Course 1		Course 2		Course 3		Course 4		Course 5		Course 6		Course 7		Course 8		Course 9	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Velocity (m/s)	0.87	1.07	1.08	1.17	1.15	1.23	1.10	1.12	0.98	1.14	0.90	1.08	0.60	0.89	0.70	0.73	0.86	0.96
Cadence (steps/min)	1.79	1.93	1.93	2.02	1.99	2.08	2.00	2.03	1.87	2.03	1.85	1.95	1.60	1.71	1.50	1.45	1.82	1.92
Step length (cm)	49.0	55.6	54.0	58.3	58.0	59.3	55.3	55.3	52.3	56.0	48.6	55.6	42.0	53.6	47.0	50.0	47.6	51.2
Rt step time (s)	0.59	0.51	0.56	0.49	0.49	0.48	0.50	0.49	0.56	0.50	0.53	0.54	0.60	0.58	0.63	0.65	0.64	0.62
Lt step time (s)	0.52	0.51	0.56	0.50	0.50	0.48	0.49	0.49	0.49	0.49	0.50	0.52	0.65	0.61	0.70	0.72	0.71	0.68
Symmetry index	−12.6	0.0	0.0	2.0	2.0	0.0	−2.0	0.0	−13.3	−2.0	−5.8	−3.8	8.0	5.0	10.5	10.2	10.4	9.2
Muscle score (total)	40	40	42	42	42	42	42	42	41	41	41	41	39	39	39	39	36	36

motion of the left hip flexion was expanded in the left swing phase (Supplementary Figure S1B). The swing times of both legs were 0.51 s, and the SI changed from −12.6 to 0. The patients acquired symmetric gait after HAL treatment.

Courses 2–4

The walking ability of the patient was maintained after HAL treatment for course 1, and no significant side-to-side differences were found in the left and right swing times before and after HAL treatments for courses 2–4. The balance tuner was changed to EX1.

Course 5

The right hip extension movement decreased from the right MSt to the TSt, and the swing time of the left leg decreased. The SI at this time was −13.3, and the side-to-side difference was recognized. The balance tuner was set to EX3. The motion of the right hip extension in the right stance phase was expanded, and the SI improved to 2 after the gait treatment with HAL for course 5.

Courses 7–9

Regarding the disease progression, muscle weakness around the left hip (Table 1), bilateral sensory impairment, and progression of muscular atrophy were observed before HAL treatment for courses 7–9. As a result, the patient had knee joint instability in the left stance phase, shortening the left-side stance time, causing asymmetric gait, and lowering the endurance. The torque tuner was increased to EX2 of the left hip joint, and the balance tuner was changed in the extension dominance of both the hip joint (EX1) and knee joint (EX1) to compensate for the instability in the knee joint.

Walking distance of the conventional physical therapy and HAL gait treatment

In conventional physical therapy, the average walking distance was 350.9 m from course 1 to course 6. During gait treatment with HAL, the average walking distance was 1,441.2 m from course 1 to course 6. Moreover, the average walking distance was 1,574.6 m from course 1 to course 9. No adverse events, such as falls or fractures, were noted during the 5-year follow-up period.

Progression of SBMA using the ALSFRS-R and serum creatinine

Table 2 shows changes in the ALSFRS-R score from course 1 to course 9. The annual percentage change in the total score of ALSFRS-R over the 5 years was −1.6. ALSFRS-R items, such as salivation, handwriting, cutting food, handing utensils, dressing, hygiene, turning in bed and adjusting bedclothes, climbing stairs, and dyspnea were gradually decreased. However, there was no change in swallowing, speech, walking, orthopnea, and respiratory insufficiency. The serum creatinine level was 0.36 mg/dL before

TABLE 2 Change in the ALSFRS-R score before and after HAL gait treatment in each course.

	Course 1		Course 2		Course 3		Course 4		Course 5		Course 6		Course 7		Course 8		Course 9	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1. Speech	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
2. Salivation	4	4	4	4	4	4	4	4	4	4	4	4	3	3	3	3	3	3
3. Swallowing	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
4. Handwriting	4	4	4	4	4	4	4	4	4	4	4	4	4	4	3	3	3	3
5. Cutting food and handling utensils	4	4	4	4	4	4	4	4	4	4	4	4	3	3	3	3	3	3
6. Dressing and hygiene	4	4	4	4	4	4	3	3	3	3	3	3	3	3	3	3	3	3
7. Turning in bed and adjusting bed clothes	4	4	4	4	4	4	3	3	3	3	3	3	3	3	3	3	3	3
8. Walking	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
9. Climbing stairs	3	3	3	3	3	3	2	2	2	2	2	2	1	1	1	1	1	1
10. Dyspnea	4	4	4	4	3	3	3	3	3	3	3	3	3	3	3	3	3	3
11. Orthopnea	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
12. Respiratory insufficiency	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Total	44	44	44	44	43	43	40	40	40	40	40	40	37	37	36	36	36	36

ALSFRS-R, revised amyotrophic lateral sclerosis functional assessment scale.

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course 1 and 0.40 mg/dL after course 9, and the 5-year annual percentage change was +0.008.

PRO using the Japanese version of the DRS

The patient answered the following changed points: "the body became straight and gait was stabilized", "the feeling of walking was realized by kicking the ground", "the step length increased", and "the feeling of fatigue decreased and muscle cramps decreased" after HAL gait treatment for course 1. In daily life, the patient answered "increased frequency of going out" and "decreased frequency of rests when going out". The DRS score after course 9 was 5 points. In the DRS questionnaire, the patient stated: "If I had not done HAL treatments, I could not walk in daily living now. Therefore, I have no regrets about HAL gait treatment (high satisfaction)". Regarding HAL treatment, the patient commented, "The time required to wear HAL is too long. As I had to stand while wearing HAL, I already felt a little fatigued before starting the HAL treatment".

Discussion

This case report aimed to determine the long-term effects of HAL gait treatment on gait disorders in a patient with SBMA. Based on the results of the present study, the patient exhibited improved short-term gait symmetry and endurance as well as maintained long-term gait endurance and gait ability for ADL and muscle mass. The results also suggest that the continuous long-term use of HAL in patients with SBMA can help them to maintain their walking ability. In a previous report of a patient with SBMA, the gait function of the patient was improved and maintained without damaging the motor unit, and it was reported that combining leuprorelin with cybernic treatment (i.e., using gait treatment with HAL) may suppress disease progression (23). As reported in the results of the present study, the average walking distance during gait treatment with HAL was approximately 1,500 m per session, which is four times greater than that for conventional gait training without HAL. Moreover, the patient with SBMA could walk long distances without experiencing excessive fatigue. Although we could not report the changes in CK levels over time in the present report, the use of HAL may have prevented the overloading of the remaining muscle tissues as suggested in the previous study (23), thereby resulting in an adequate amount of walking exercise without excessive fatigue.

Short-term effects of HAL gait treatment

This study indicated that the patient with SBMA had improved walking endurance, gait velocity, step length, and gait symmetry after HAL gait treatment in each course. The cybernic treatment with HAL may have been successful as a contributing factor to these results (14, 17). The physical function and gait analysis by a physical therapist before the gait treatment with HAL are essential for cybernic treatment. The physical therapist confirmed decreased superficial and deep sensations in the periphery of the lower extremity and muscle strength in the right lower extremity periphery before HAL treatment (course 1). Therefore, the patient lacked sensory information associated with load shifting during walking.

The extension motion of the hip joint of the patient in MSt to TSt was insufficient because of the lowering muscle strength of the right leg and lowering supportiveness by the hypoesthesia of the periphery. Furthermore, the shortening of the stance phase on the right side of the patient resulted in the shortening of the swing time on the left side; thus, the patient learned incorrectly (mislearning) the asymmetric gait on the over-ground walking without HAL. The physical therapist adjusted the torque tuner of the right hip joint to 2, and the balance tuner was set to hip extension dominance (EX5). Moreover, the physical therapist performed the gait treatment with HAL appropriately while visually checking the gait symmetry. The patient had decreased muscle strength of the left hip joint, bilateral sensory disturbance, and progression of muscular atrophy in both legs in course 7. The worsening muscle atrophy resulted in knee joint instability in the left stance; thus, a shortening of the left-side stance time caused gait asymmetry and decreased walking endurance. The physical therapist increased the amount of torque tuner of the left hip joint and left knee joint, and the balance tuner was set in the extension dominance of both the hip and knee joints. The patient could walk without knee joint instability during the gait treatment with HAL. During the study, the physical therapist recognized decreased physical function, such as decreased muscle strength, muscle atrophy, sensory disturbance and gait ability walking endurance, and walking symmetry. The gait analysis by the physical therapist revealed that the gait and posture based on the evaluation of the physical functions and the use of a wearable sensor indicate that the patient could more comfortably walk each time using HAL. As a result, the patient had improved walking endurance and walking symmetry after HAL gait treatment in every course. A previous study reported that asymmetric ambulatory activity negatively affected the energy costs during walking (15). Therefore, HAL gait treatment (cybernic treatment) may have contributed to the improvement in walking endurance after the patient developed a symmetric gait.

Long-term effects of HAL gait treatment

This study suggested that the long-term continuous use of HAL can maintain the walking ability of patients with SBMA. It was found that 2MWD, ALSFRS-R gait items, and serum creatinine of the patient after courses 1 and 9 of HAL treatment were similar to those at the baseline assessment. In the relevant literature, few studies have reported the natural course of SBMA, which has been found to progress gradually, eventually leading to the need for a wheelchair for mobility. Notably, Atsuta et al. (5) conducted a longitudinal observational study of 223 Japanese patients with SBMA (55.2 ± 10.5 years) to elucidate the natural course of SBMA based on the ADL milestones; they reported that the average time interval between the onset of muscle weakness and becoming wheelchair-bound was 13.2 ± 7.8 years in patients with SBMA and CAG repeat counts of ≤47 (5). However, our patient could still independently walk 13 years after the onset of SMBA.

Hashizume et al. investigated the natural course of the disease in 34 Japanese patients with genetically confirmed SBMA in terms of the annual rate of decline for each endpoint over 3 years (20). They found that the yearly declines in 6MWD, ALSFRS-R, and serum creatinine levels were −20.3 ± 26.0 m, −1.1 ± 0.9, and −0.013 ± 0.03 mg/dL, respectively. 6MWD has been considered the most reliable measure of motor impairment in SBMA owing to its ability to reliably detect a 10% decline in 1 year (24, 25). A previous study reported a strong correlation between 6MWD and 2MWD in patients with neuromuscular disease (26). We measured 2MWD instead of 6MWD in the present study, and we observed an improvement in 2MWD after each HAL treatment; moreover, our patient maintained the achieved 2MWD for over 3 years. Although not directly comparable, 2MWD was expected to decrease by −6.76 ± 8.66 m per year according to a previous study (20). 2MWD was 94 m, the ALSFRS-R score was 44 points, and the serum creatinine level was 0.36 mg/dL before course 1 of HAL treatment. The predicted 5-year prognosis at this time was 2MWD of 60.2 m, ALSFRS-R of 38.5, and serum creatinine level of 0.29 mg/dL based on a previous study (20). In this study, 2MWD was 101.8 m, the ALSFRS-R was 36 (no reduction in walking items), and the serum creatinine was 0.40 mg/dL after course 9 of HAL gait treatment. 2MWD and serum creatinine levels were good compared with the natural course of SBMA.

The total MMT score decreased from 40 to 36 in 5 years. The lower extremity muscle strength decreased in both hip flexion, left hip extension, and both ankle PF and maintained in the right hip extension, both knee extension, and both ankle DF. The ALSFRS-R score decreased beyond prognostic prediction, and in this patient, disease progression may be relatively rapid compared with the natural disease course. However, the score of the gait items in the ALSFRS-R did not change. In addition, the serum creatinine values increased compared with baseline assessment. In general, serum creatinine is associated with whole muscle mass (20). Our results suggested that HAL gait treatment might contribute to improvement in walking endurance and progression of muscle atrophy. Long-term HAL gait treatment for patients with SBMA may maintain and improve gait endurance and gait ability for daily activities; therefore, it may also contribute to the maintenance of muscle mass. In addition, the results of the DRS after course 9 showed that the patient had no regrets (high satisfaction) with HAL gait treatment. HAL gait treatment provided long-term satisfaction for the patient with SBMA.

Study limitations

First, the appropriate interval of the use of HAL gait treatment cannot be mentioned. 2MWD increased progressively during courses 1–3; HAL gait treatment was conducted at 4-month intervals, and the longest 2MWD was reached after course 3. On the contrary, 2MWD gradually shortened after course 4. Indeed, HAL gait treatment was conducted at 8-month intervals after course 3. The decline in walking ability due to the natural disease course is also in the background; however, the effect of HAL gait treatment may change depending on the treatment interval. We think that there is a need to shorten HAL treatment interval as much as possible. Furthermore, the benefits of HAL treatment at 8-month intervals should be carefully assessed. Second, the results of this study are limited to a single case and include limiting factors, such as the ABA design and lack of a control group with respect to treatment intervals. Finally, the effects of conventional physical therapy and medication other than HAL gait treatment may become a confounding factor in terms of the long-term effectiveness of HAL gait treatment. Despite these limitations, only a few reports have evaluated the long-term effects of HAL gait treatment on patients with SBMA. Our results may help researchers set the protocol and outcomes of HAL gait treatment for patients with SBMA. The long-term effects of HAL gait treatment should be evaluated in more individuals with SBMA in the future.

Conclusion

Continuous HAL gait treatment might inhibit disease progression only in terms of mobility items in ADL, walking endurance, and overall body muscle mass in patients with SBMA. The correct HAL settings based on the appropriate evaluation by the physical therapist may be important for efficient HAL gait treatment. We need to reconsider the pretreatment evaluation method for the correct settings in HAL gait treatment and shorten HAL treatment interval as much as possible.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient/participant provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

KI and HW were the major contributors to manuscript writing and literature review. KI administered HAL treatment and collected, analyzed, and interpreted the data. YN, YI, MN, FM, and SH provided valuable comments about the case report. All authors revised the manuscript and approved the final version.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1143820/full#supplementary-material

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Case report: Rehabilitation course in thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly syndrome complicated by cerebral infarction in the left parabolic coronary region

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Although thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly (TAFRO) syndrome was first reported in 2010, its pathogenesis and prognosis are still unknown. Moreover, reports on rehabilitation in patients with TAFRO are limited. In severe cases, dyspnea and muscle weakness could impede improvements in activities of daily living (ADL). However, reports on exercise intensity showed no worsening of TAFRO within the load of 11–13 on the Borg scale. Herein, we describe the rehabilitation and progress in a 61-year-old woman with TAFRO syndrome complicated by cerebral infarction from early onset to discharge. After cerebral infarction onset in the perforating artery, she was admitted to the intensive care unit due to decreased blood pressure and underwent continuous hemodiafiltration. Two weeks following transfer to a general ward, the patient started gait training using a brace due to low blood pressure, respiration, and tachycardia. After initiating gait training, increasing the amount of training was difficult due to a high Borg scale of 15–19, elevated respiratory rate, and worsening tachycardia. Furthermore, there was little improvement in muscle strength on the healthy side after continuous training, owing to long-term steroid administration. On day 100 after transfer, the patient was discharged home with a T-cane gait at a monitored level. The patient had severe hemiplegia due to complications with severe TAFRO syndrome delaying early bed release and gait training; tachycardia; and respiratory distress. Additionally, delayed recovery from muscle weakness on the non-paralyzed side made it difficult for the patient to walk and perform ADLs. Despite these issues, low-frequency rehabilitation was useful. However, low-frequency rehabilitation with gait training, using a Borg scale 15–19 orthosis, did not adversely affect the course of TAFRO syndrome.

KEYWORDS

thrombocytopenia anasarca fever reticulin fibrosis/renal failure organomegaly syndrome, stroke, rehabilitation, Borg scale, case report

1. Introduction

Thrombocytopenia, anasarca, fever, reticulin fibrosis/renal failure, and organomegaly (TAFRO) syndrome is a systemic inflammatory disease with a currently unknown cause (1, 2). Treatment of TAFRO includes steroids and immunosuppressive therapy (3). Additionally, its complications include cerebral infarction due to an abnormal blood coagulation system, interstitial lung lesions, and dilated cardiomyopathy (4, 5). According to the 2019 diagnostic criteria, TAFRO is diagnosed based on: (i) fluid retention (pleural effusion, ascites, and generalized edema); (ii) thrombocytopenia (100,000/μl); (iii) fever of unknown origin >37.5°C or serum C-reactive protein (CRP) concentration of 2 mg/dl. Moreover, the minor criteria for establishing this diagnosis comprise Castleman's disease-like findings on lymph node biopsy; bone marrow fibrosis; mild organ enlargement (hepatosplenomegaly or lymphadenopathy); and progressive renal involvement.

The disease severity is rated on a 3-point scale regarding each of the four categories: asthenia including pleural effusion and ascites; thrombocytopenia; fever and inflammation; and renal failure. Depending on the total score, severity is classified as: 0–4 points, mild (grade 1); 5–6 points, moderate (grade 2); 7–8 points, somewhat severe (grade 3); 9–10 points, severe (grade 4); and 11–12 points, very severe (grade 5) (6).

Although reports describing rehabilitation in patients with TAFRO syndrome are limited, dyspnea caused by thoracoabdominal effusion and muscle weakness is thought to impede rehabilitation progress. Improvement in activities of daily living (ADL) is also challenging to achieve in severe cases (7, 8). Furthermore, aerobic and strength exercises within the Borg scale rate of perceived exertion (RPE) of 11–13 do not appear to cause adverse events or exacerbate pathological conditions (8). The guidelines for cerebrovascular disorder treatment recommend early release from bed and early gait training with orthotics for rehabilitation (9). However, to date, there are no reports on early rehabilitation in patients with TAFRO syndrome complicated by cerebral infarction. In addition, whether gait training with orthotics exacerbates the condition remains unclear.

In this study, we attempted gait training using an orthotic device in a patient with severe right hemiplegia due to perforator artery infarction with severe TAFRO syndrome to wean the patient from continuous hemodiafiltration (CHDF) and reacquire gait. We assessed the contents of training and difficulties in practicing in each stage of the disease; progress of improvement in motor function and ADL, and whether early rehabilitation had any adverse effects on TAFRO syndrome based on blood test results.

2. Case report

The patient was a 61-year-old woman with no remarkable medical history and independent ADL before her illness. She experienced coronavirus disease 2019 and was admitted to a community hospital, after which she was discharged home. However, the patient was admitted again on suspicion of cholecystitis and transferred to our university hospital due to a persistent inflammatory reaction and acute renal failure. The patient was treated with steroids (1,000 mg/day) and hemodialysis (HD). Moreover, physical therapy was initiated the following day after admission. Only indoor rehabilitation was provided to prevent post-coronary infection. On day seven after admission, we observed fluid retention (pleural and ascites effusions, generalized edema; Figures 1A, B), platelet loss (PLT), fever, high CRP levels, and bone marrow fibrosis: the essential diagnostic criteria for TAFRO syndrome. Creatinine (Cre) levels, an indicator of renal dysfunction, were also elevated. The patient was diagnosed with TAFRO syndrome secondary to bone marrow fibrosis, mild organ enlargement, and progressive renal impairment. On day 12 after hospitalization, another pulse of steroids was administered (1,000 mg/day). However, the symptoms did not resolve. On day 13, chest pain appeared (no enzyme excursion or abnormal electrocardiogram), and pleural effusion increased.

After 14 days, she developed branch atheromatous disease (BAD; Figure 2) in the perforating artery of the left radio coronary artery. The patient was treated conservatively but was admitted to the intensive care unit (ICU) on day 15 for CHDF due to low blood pressure (BP). In the ICU, the patient received CHDF, range-of-motion training of the limbs while in bed due to the low BP, as well as muscle-strengthening exercises of the limbs of the healthy side. Additionally, on day 19, the patient was weaned from CHDF, transferred to HD, and discharged from the ICU.

On discharge from the ICU, the patient's TAFRO syndrome severity classification was grade 4 (severe) (6), with resting heart rate (HR; 108), BP (111/82), and oxygen saturation (SpO_2; 96%). Physical examination revealed abdominal distention due to pleural effusion and marked edema in the trunk, both lower extremities, and right upper extremity. Although the patient was conscious and had good communication without obvious higher brain dysfunction, she had difficulty articulating. Muscle strength on the manual muscle testing (MMT) (10) was 0 in the right upper and lower limbs (no muscle contraction at all) and 4 in the left upper and lower limbs (full range of motion overcoming gravity even with some resistance), with severe right hemiplegia and muscle weakness on the non-paralytic side. The patient required heavy-to-full assistance when getting up, sitting on the edge, or standing up. Her HR also increased over 130 while sitting and standing. Although there was no evidence of tachycardia or decreased SpO_2, she could only maintain sitting in a wheelchair for ∼5 min with or without assistance due to respiratory distress and tachypnea (upper 20 to lower 30 per min). She was administered 45 mg of methylprednisolone as a steroid. The goal of physiotherapy was to improve the patient's endurance in a wheelchair position and start gait training rehabilitation with an orthosis promptly. Rehabilitation consisted of sitting for 5 min, standing for 1–2 min, and 5–10 min in the wheelchair transfer position. The patient's tachycardia and dyspnea gradually decreased, and she could sit in a wheelchair for ∼20 min.

On day 27 after admission, the patient was transferred for gait training using a long leg brace (LLB). She started walking on the parallel bars. However, after ∼5 min, her HR increased from 100 to 150 beats/min, her resting respiratory rate increased from 15 to 30 beats/min, experiencing severe respiratory distress. The patient's subjective exercise intensity was Borg RPE 15 (hard)−19 (very hard; Figure 3A). The patient could perform only four sets of 10 m walk over 60 min of training. The patient was transferred to a

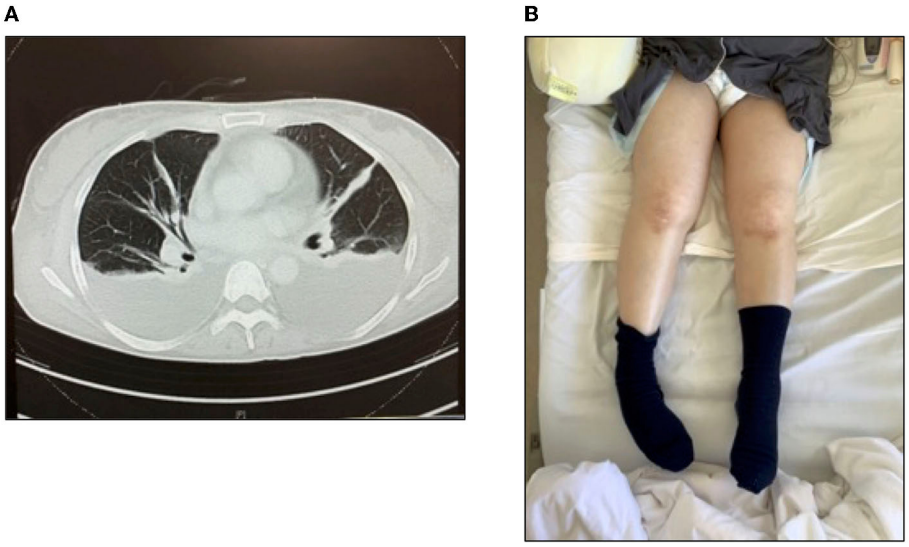

FIGURE 1
Thoracic ascites and generalized edema and the diagnostic criteria for TAFRO syndrome. **(A)** Computed tomography image of the chest and **(B)** generalized edema.

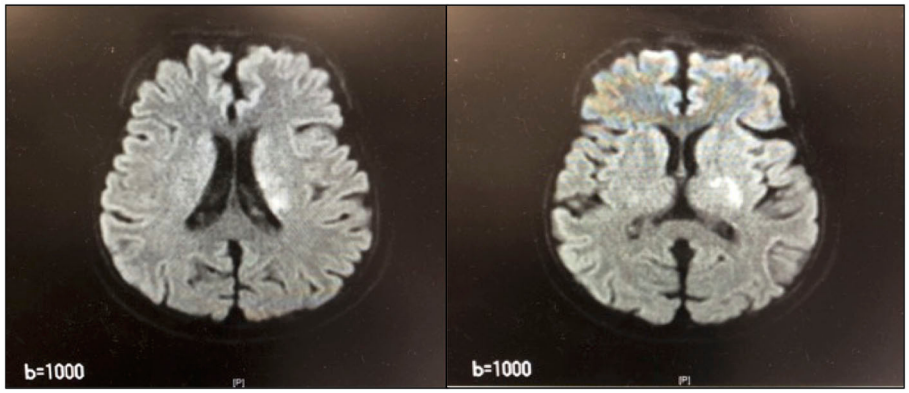

FIGURE 2
Magnetic Resonance Imaging of the head. High-signal area from the left parabasal corona to the inner retrosternal leg.

community hospital on day 56 due to tachycardia and respiratory distress. Gait training could not be gradually increased. At the time of transfer, her gait training consisted of three sets of 10 laps on parallel bars (three sets of 60 m) and three sets of 15 m continuous T-cane walking (Figure 3B). The steroid dose was also reduced to 30 mg of prednisolone (PSL).

On day 71, she was transferred back to our hospital due to hemorrhage from a rectal ulcer and underwent surgical suturing. After 75 days, the Hematology Department requested rehabilitation, and walking training was resumed on day 76. The patient's muscle strength in the right lower limb did not recover to MMT 0. Therefore, she was provided with walking assistance using LLB. On day 77, her respiratory rate was over 30 after ∼100 m of continuous T-cane walking. On day 86, there was no significant change in motor paralysis of the right limbs. The patient was in a state of light transfer and moderate walking assistance. Assuming the patient would live at home, LLB was cut down and gait training with a short-leg orthosis began. During a 60 m T-cane assisted walk, the patient's HR was over 120, respiratory rate was ∼20 breaths/min, and Borg RPE was 12–13. On day 100, the patient was discharged home.

On discharge, PLT (23.8 × 104 μl), CRP (0.02 mg/dl), and renal impairment improved, without pleural or ascites effusion. The patient was classified as grade 1 on the TAFRO syndrome severity scale (6). Additionally, resting HR was in the 70s, MMT was 1 in the right limbs (slight muscle contraction was observed) and 4 in the left limbs. However, muscle weakness persisted on the healthy side. The patient's basic activities were independent getting up and transferring to a wheelchair using a motorized bed, independent T-cane walking with minimal assistance, and continuous walking distance of ∼100 m. The subjective exercise intensity was Borg RPE 13 (slightly severe), HR was 110–120

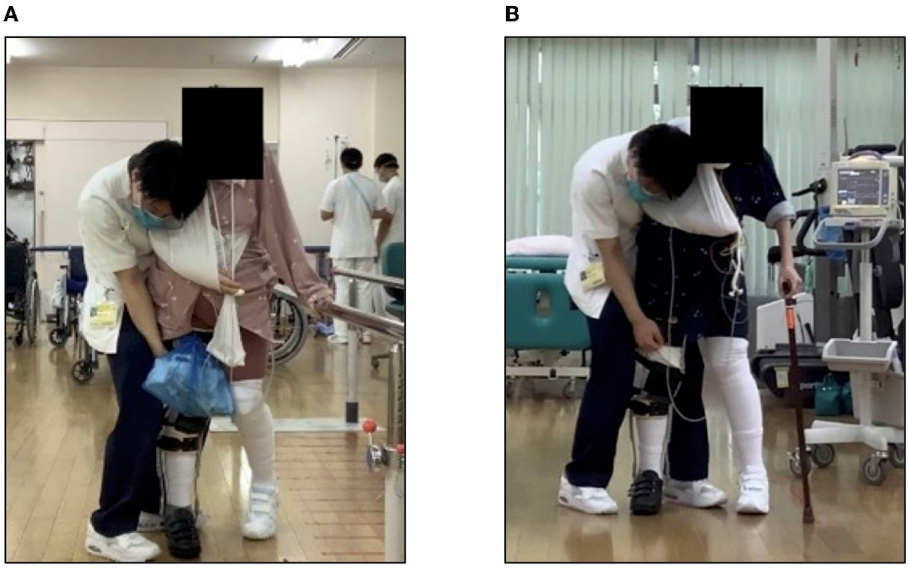

FIGURE 3
Gait training using long leg brace. **(A)** Walking with parallel bars and **(B)** walking with a T-joint cane.

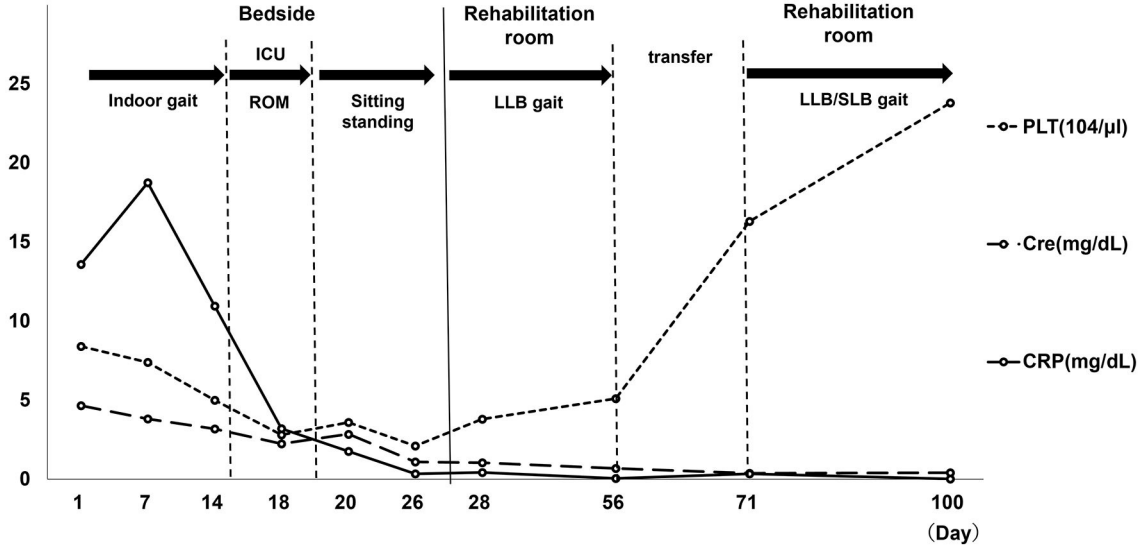

FIGURE 4
Blood collection item. PLT, platelet; Cre, creatinine; CRP, C-reactive protein; ROM, range of motion; LLB, long leg brace; ICU, intensive care unit. Day 1: hospitalization, Day 7: TAFRO diagnosis, Day 14: Cerebral infarction Onset. Day 19: Start of bed release, Day 27: Start of LLB gait, Day 56: hospital transfer. Day 100: discharge from hospital.

during exertion, and respiratory rate was 15–20 breaths/min: improvement was observed. The functional independence measure (FIM) was 47/126 at intervention, 58/126 at transfer, and 82/126 at discharge. Moreover, the PSL dose at discharge was 12 mg. A summary of the blood test results throughout the patient's admission time is shown in Figure 4.

When first diagnosed with TAFRO syndrome, CRP and Cre levels were elevated, and her PLT levels had decreased. Elevated CRP levels persisted after the onset of cerebral infarction. When released from the hospital ward, blood samples showed worsening of PLT, CRP, and Cre levels. Moreover, when starting gait training using LLB, her Borg RPE was 15–19 and HR over 150. She continued rehabilitation with HR over 150 and tachypnea (30 breaths/min). However, there was no deterioration in blood test results by the day 56 after hospital transfer. Thereafter, no further deterioration in blood test results was noted until discharge home on day 100.

Written informed consent was obtained from the patient's family to publish this case report. This study conforms to all case report guidelines.

3. Discussion

This study reported the rehabilitation progress in a patient with severe TAFRO syndrome and right hemiplegia due to BAD. The patient had difficulty in early release from bed and participating in rehabilitation due to tachycardia, low BP, and respiratory distress. In addition, the patient had prolonged muscle weakness on the healthy side, making it difficult to resume ADL. Furthermore, the rehabilitation load after the patient could leave bed was considered high-intensity based on the HR and Borg RPE results. However, providing a high-intensity exercise load at a low frequency did not seem to adversely affect the patient's general condition or blood test results. To our best knowledge, this is the first case report to describe, in details, the content and course of rehabilitation treatment in a patient with TAFRO syndrome complicated by cerebral infarction.

In a previous study on patients admitted to the ICU, those out of bed within 24 h after admission had a significantly shorter time to gain standing and walking abilities than did those in the standard physical therapy group. Furthermore, their ADL improvement at discharge was also significantly better (11). Out of bed within 24 h has been reported to increase ADL improvement in patients with cerebrovascular disease at the time of transfer to an acute care hospital and 6 months later, with most improvements in exercise abilities (12, 13). Therefore, early release from the ICU is recommended for patients with a cerebrovascular accident, even under ICU management However, the rehabilitation expert consensus recommends withholding active exercise in the case of unstable cardiac rhythms and supplemental circulation, such as an intra-aortic balloon pump, or if BP was too low, even with high doses of inotropic and hypertrophic drugs (14).

TAFRO syndrome is associated with cardiomyopathy. Echocardiography has shown decreased wall motion of the left ventricle, which may require inotropic therapy or left ventricular assist (4). Cytokine storms caused by TAFRO syndrome have been also reported to cause systemic edema and intravascular dehydration associated with cardiac complications (15). In the present case, after complications of BAD, echocardiography showed no decrease in wall motion (ejection fraction, 59 %). However, BP was low due to systemic edema and intravascular dehydration. Additionally, the patient's circulatory and general condition was severe enough for the ICU, including CHDF. Moreover, the Japanese stroke treatment guidelines recommend gait training with orthotics at an early stage (9). Even after discharge from the ICU, the patient had tachycardia and dyspnea, considered TAFRO syndrome symptoms, and took ∼2 weeks before being able to sit in a wheelchair and begin gait training in a rehabilitation room. A previous study reported that in terms of TAFRO severity, patients with thoracoabdominal effusion, respiratory distress, tachypnea, and abdominal distention appeared even in a gaggle-up sitting position, which inhibited the progress of rehabilitation (7). This case is similar to previous research, and it appears that patients with severe TAFRO syndrome might have a significant delay in appropriate training, such as bed release and gait training.

A large amount of rehabilitation is recommended for improving ADL according to the Japanese guidelines for people with cerebrovascular disorders (9). Previous studies have reported a correlation between total daily rehabilitation time and functional improvement, with longer time contributing to the improvement in total FIM scores (16). However, in the present case, tachycardia and respiratory distress appeared even after the start of gait training. Therefore, it was difficult to secure the time and distance for gait training. According to the criteria for discontinuation of rehabilitation in Japan, a pulse rate exceeding 140 beats/min is considered a threshold for termination in the middle of a rehabilitation program (17).

At our hospital, physiatrists may examine patients with cerebral infarction and continue gait training even with tachycardia exceeding 140 beats/min after risk management. However, in the present case, the patient had tachycardia of 150 beats/min during a 5 m assisted walk, and thoracoabdominal effusion due to TAFRO syndrome, with a respiratory rate exceeding 30 beats/min, resulting in respiratory distress and Borg RPE 15–19. In addition, it took 5–10 min for the respiratory rate and Borg RPE to return to a resting level, and the total walking distance was extremely short compared with patients with stroke in our hospital. Previous reviews reported that the 5-year survival rate of patients with TAFRO is severe (66.5%). Thus, timely diagnosis and rational treatment remain a major challenge for clinicians, and the prognosis and course of TAFRO syndrome are unclear (18). Even in those who respond well to drug treatment, symptoms can take at least one year to subside (19). Additionally, in severe TAFRO syndrome, it may be difficult to titrate the training dose over a long period of time due to the time required to recover from symptoms such as tachycardia and tachypnea. In patients with TAFRO syndrome and BAD, low BP, tachycardia, and respiratory distress may delay the start of early weaning and gait training. Moreover, difficulties may persist after initiation to maintain walking distance, shorten rehabilitation time, and improve ADLs.

The current patient still had muscle weakness in the healthy limbs at the time of discharge from the hospital, suggesting that disuse muscle weakness occurs due to the inability to secure a large amount of activity due to edema and respiratory distress. In addition, muscle weakness also may be due to steroid use (20, 21). Furthermore, prolonged muscle weakness on the healthy side may exacerbate delays in ADL recovery.

The effects of exercise on systemic inflammation and organ function in patients with TAFRO syndrome are unknown. In previous physical therapy, the most severely ill patients were trained to perform 10–20 consecutive Borg RPE 11–13 muscle strengthening exercises and walking endurance training. Adjusting the walking distance to 11–13 on the Borg RPE scale also resulted in improvement in bedridden state with a Barthel Index score of 0 to walking independently with an ankle-foot orthosis without adverse events or condition worsening (7). In the current case, the patient experienced cerebral infarction. Additionally, when orthotic-assisted gait training was performed, the exercise was Borg RPE 15–19. Compared with previous reports, high-intensity exercise did not exacerbate the symptoms of TAFRO syndrome if performed at a low frequency with long rest periods.

TAFRO syndrome is a relatively new disorder, first reported in 2010 (1). Therefore, the pathogenesis and prognosis remain unclear. Furthermore, since this study is a case report, it

is difficult to generalize the course in this patient to other patients with TAFRO syndrome. However, this report may provide valuable information on rehabilitation and progress in patients with TAFRO syndrome complicated by cerebral infarction.

4. Conclusions

In this case of severe hemiplegia due to BAD combined with severe TAFRO syndrome, the patient was in a serious condition, with delayed early bed release and gait training initiation. In addition, delayed recovery from muscle weakness on the non-paralyzed side of the body made it difficult for the patient to walk and perform ADLs. However, the results suggest that low-frequency rehabilitation with Borg RPE 15–19 orthotic gait training did not have an adverse effect on the condition and could be useful for treating such patients.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TH and YN conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. TK, KM, MK, and YU designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. FT designed the data collection instruments, coordinated and supervised the data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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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.

Publisher's note

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Case report: "Proust phenomenon" after right posterior cerebral artery occlusion

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Odors evoking vivid and intensely felt autobiographical memories are known as the "Proust phenomenon," delineating the particularity of olfaction in being more effective with eliciting emotional memories than other sensory modalities. The phenomenon has been described extensively in healthy participants as well as in patients during pre-epilepsy surgery evaluation after focal stimulation of the amygdalae and post-traumatic stress disorder (PTSD). In this study, we provide the inaugural description of aversive odor-evoked autobiographical memories after stroke in the right hippocampal, parahippocampal, and thalamic nuclei. As potential underlying neural signatures of the phenomenon, we discuss the disinhibition of limbic circuits and impaired communication between the major networks, such as saliency, central executive, and default mode network.

KEYWORDS

olfaction, limbic system, stroke, medial temporal lobe, hippocampus, emotional regulation

Introduction

The French literate Marcel Proust, an eponym to the phenomenon, observed that olfactory stimuli are prone to spontaneously elicit vivid and intensively felt autobiographical memories. He meticulously described how the exposure to the smell of a tea-soaked biscuit elicited the sudden rising of a lively childhood memory closely linked to a feeling of intense joy (1). Research has investigated the capacity of olfactory stimuli to trigger emotion and memory effectively. Indeed, most studies in humans, although few in number, pointed at the capacity of odors to serve as significant context cues underlying the formation and later retrieval of content-dependent odor-evoked autobiographical memories (2, 3). Furthermore, odor-evoked memories were found to be particularly emotional as measured by both self-report and heightened heart rate responses, especially in comparison to memories elicited by other modalities (visual, tactile, and auditory) (1, 4–6). These characteristics have been related to the specific connectivity between olfactory and limbic structures, permitting the integration of olfactory information and mnemonic processes in a way that affective, visceral, and motor responses to odors can be generated congruously (3, 7–9). The neural structures implied in olfactory processing are the primary olfactory (piriform) cortex, the amygdalae, the hippocampus and the surrounding cortex, the anterior insulae, the orbitofrontal cortices, and parts of the medial thalamus. In contrast to other sensory information, olfactory signals have a dual route to the neocortex: one relaying to parts of the medial thalami nuclei and one projecting directly from the bulbs to the primary olfactory cortices and limbic structures (2, 3, 10, 11).

Direct cortical stimulation during pre-surgical exploration in patients suffering from epilepsy offered more insight into the potential neural underpinnings of the "Proust phenomenon," reporting the induction of the phenomenon via focal electrical stimulation of the amygdalae. Indeed, the stimulation of the basolateral nuclei of the left amygdala in a patient led to the sudden reminiscence of a smell of burnt wood evoking a campfire scene associated with the feeling of intense joy. The patient herself did not suffer from olfactory hallucination or déjà-vu before the stimulation, the semiology of her seizures being complex motor semiology since the age of 5, following a small lesion of the left frontal lobe (10, 12). Furthermore, a study of bilateral amygdala stimulation evinced that both positive and negative valence could be linked to a scenic memory when stimulating the left amygdala, while stimulation of the right amygdala resulted only in negatively valenced reminiscence (13, 14). A divergence is conjectured to be the result of asymmetrical processing of visceral signals in the insular cortices, which are structures with which the amygdalae are known to interact closely (2, 12, 15, 16).

Furthermore, the effectiveness of olfactory stimuli in triggering emotive memories becomes relevant in patients suffering from post-traumatic stress disorder (PTSD), especially of the non-dissociative type, where odor-evoked aversive autobiographical memories are a particularly debilitating issue. The neural structures facilitating olfactory processing overlap with those known to have altered functionality in patients with PTSD, where a threat triggered unexpectedly by an odor may be discrepant with the actual danger of the present situation and results in involuntary intrusions and flashbacks (2, 3, 17). Even healthy veterans display changes in processing the intensity of aversiveness related to contextually relevant odors, such as diesel or rubber (18), suggesting that the pairing among odor, arousal, and valence in becoming a relevant threat may be gradual, may even be time-limited, and possibly responsive to context-dependent learning *via* interoceptive and exteroceptive cues (19).

To the best of our knowledge, the appearance of a "Proust phenomenon" has not yet been described following a stroke.

Case

A 64-year-old male patient was presented to the emergency ward with left-sided hemiparesis, sensory hemisyndrome, homonymous hemianopia, as well as left spatial neglect. The initial cerebral MRI showed an ischemic lesion in the territory of the right posterior cerebral artery (PCA) with occlusion of the P2-segment. Areas affected were the right gyrus parahippocampalis, right hippocampus, and posterior-medial thalamus without signs of hemorrhage. Endovascular treatment was administered including intra-arterial lysis, leading to complete recanalization of the right PCA (TICI 3). The follow-up MRI showed demarcated subacute ischemic lesions in the PCA territory, complicated by the hemorrhagic transformation of the right medial and posterolateral thalamus, right cuneus, precuneus, complete hippocampus, and gyrus parahippocampalis (see Figure 1). Stroke etiology was considered cardiac with a permeable foramen ovale as seen in the trans-esophageal echocardiography and a risk of paradoxical embolism (RoPE score) of 5, in the absence of other causes. The patient had been absolved from primary school and then worked as a farmer. His wife died 6 years before his stroke. An intensive inpatient neurorehabilitation with physical, occupational, speech therapy, and neuropsychology was initiated on the 7th-day post-stroke.

During the clinical examination at the neurorehabilitation onset, the patient showed a left sensorimotor hemisyndrome with dysesthesia, homonymous hemianopia, severe topographagnosia, and deficits in visuo-construction, as well as deficits in the executive domain. Furthermore, the patient reported the sudden upcoming of a scenic childhood memory including rotten piglets at the farm he grew up on when smelling the odor of meaty dishes, associated with a feeling of strong repulsion and disgust. That odor-evoked autobiographical memory was unknown before the stroke but only triggered when smelling meaty substances and was always reported as highly aversive. However, the patient could taste, smell, and distinguish properly different odors on Sniff tests,[1] a clinical olfactory assessment. He had no psychiatric or neurological condition before the stroke onset, no history of drug abuse, long-term medical treatment, no current psychosocial stress factors, and no pronounced commitment to vegetarianism or veganism. Furthermore, the reminiscence was context-dependent and never occurred without the specific olfactory stimulus. These odor-evoked memories impaired the patient considerably, leading to a reduced appetite, weight loss of ∼13 pounds, and an important psychological strain. The severity of the "Proust phenomenon" regressed moderately under therapy with selective serotonin reuptake inhibitors as well as pregabalin, food counseling, and neuropsychological therapy. After discharge, aversive memories could still be triggered by the smell of meaty substances but were not experienced as debilitating.

Discussion

Our patient started presenting the "Proust phenomenon" after the stroke to the right PCA territory. He never witnessed intrusions or odor-triggered memories before the incident. Hence, we suggest that stroke lesions must have disrupted the network integrity and communication of olfactory limbic circuitry resulting in the attribution of negatively valenced salience to formerly neutral olfactory stimuli. In particular, we think that lesions in the right hippocampal structures may have disrupted the functional integrity at the circuit and network level, thereby facilitating signal processing in olfactory limbic circuits.

In our patient, the complete right hippocampus was damaged (see Figure 1B). Anterior and posterior subregions of the hippocampus have distinct functional and structural connections, with the anterior hippocampus being active when the context is evaluated and the posterior hippocampus when precise spatial location is assessed (20). Furthermore, the anterior hippocampus, structurally linked to the amygdalae, the limbic prefrontal areas,

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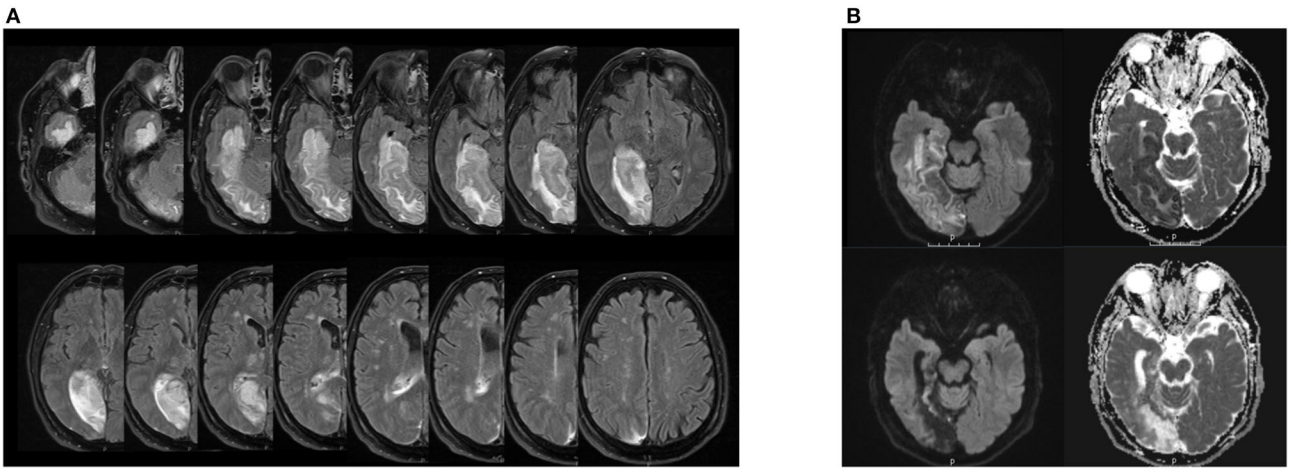

FIGURE 1
(A) Lesion extension in patient EP in the follow-up MRI after acute treatment. Right hemisphere is on the left side of the each image respectively. FLAIR sequence from a cerebral magnetic resonance imaging, 3 Tesla, with on the upper left side of the image the inferior and the lower side of the image the upper bound of lesion estension. The hyperintense signal displays the demarcated subacute ischemic and hemorrhagic transformations in the right PCA-territory encompassing the right thalamus, cuneus, hippocampus, gyrus parahippocampalis and the precuneus as well as the right medial and posterolateral thalamus. **(B)** Hippocampal lesion in patient EP in the follow-up MRI after acute treatment (upper images) and 3 months after symptom onset (lower images). Right hemisphere is on the left side of each image respectively. DWI sequence from a cerebral magnetic resonance imaging, 3 Tesla, on the left side b 1,000 and the ride side the ADC map. On the upper images, the diffusion restriction encompasses the hippocampus, the gyrus parahippcampalis and the temporo-occipital lobes depicted. Note the cortical diffusion restriction of the ventral hippocampus. On the lower pictures 3 months after symptom onset, we find the post-ischemic parenchymal lesion of the formerly diffusion restricted regions with evacuo configurartion of the temporal ventricle and loco regional subarachnoid space.

and the hypothalamic-pituitary axis, has been shown to be active in emotional memory (21) and reward-directed behavior (22). The posterior hippocampus is connected with cingulate areas, notably the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and precuneus (23), and contributes to the default mode network (DMN). Importantly, the amygdalae and their projections to the orbitofrontal and insular cortices, structures of the central olfactory matrix, were preserved in our patient. Thus, direct and bilateral processing of olfactory stimuli by the amygdalae and further cortical projections remained intact.

We propose that the lesion of the right anterior hippocampus in our patient and its consecutive hypoactivation may have disrupted the connectivity between the anterior hippocampus and the amygdala, facilitating the disinhibition of olfactory-limbic processing and associative learning mechanisms driven among others by the amygdalo-insular pathways. Hypoactivation may have ensued in a lesser ability to disambiguate the context when exposed to the smell of meat, henceforth triggering repulsive childhood memories, the clinical presentation of the "Proust phenomenon."

Earlier research in PTSD highlights the importance of the hippocampus–amygdala circuit for further emotion regulation in autobiographic memories and lends support for our interpretation. Patients with PTSD without dissociative symptoms may re-experience events vividly through salient olfactory stimuli (6). Studies suggest that those patients are not necessarily displaying a globally enhanced fear expression when exposed to salient stimuli but rather an impaired capacity to use contextual information to disambiguate potential safety and threat. As we previously highlighted, the process of disambiguating stimuli is known to be a hippocampus and parahippocampus-dependent process. Indeed, Garfinkel showed that PTSD patients were less effectively using the safety context to suppress fear memory than a danger context to enhance it (19). Furthermore, studies revealed that in addition to displaying reduced hippocampal neuronal integrity, patients with PTSD showed increased amygdala activity, suggesting enhanced fear signal processing (19). Taken together, we postulate a meaningful neurobiological similarity between the disinhibited amygdala-insular pathways due to anterior hippocampal lesion in our patient compared to the hippocampal under activity and amygdalae hyperactivity in patients with PTSD and non-dissociative symptoms when exposed to salient olfactory stimuli, leading to the "Proust phenomenon."

Furthermore, the negative valence of the emotion associated with the triggered autobiographical memory in our patient is not arbitrary as earlier research in the "Proust phenomenon" has shown that hemispheric laterality mattered for the valence attributed to the evoked autobiographical memory after stimulation of the amygdalae, with right amygdala stimulation ensuing in negatively evoked memories and left amygdala stimulation in both positively and negatively valenced evoked memories (10, 13, 15). As smell has been linked to precipitating fear- and anxiety-related memories in PTSD patients without dissociative symptoms, it is worthwhile highlighting here that deficits in intrinsic sensory inhibition have just recently been found to contribute to intrusive trauma re-experiencing mediated by olfactory memory (17). Additionally, the olfactory cortex and its extended circuit encompass the amygdala, hippocampus, orbitofrontal cortex, insula, and the ACC, which receive a significant bottom–up input from the primary olfactory cortex when triggered by an odor (3), areas left untouched by lesions in our patient. Although neural communication in patients with PTSD is still poorly understood, especially in the domain of olfaction, studies found increased functional connectivity between

the right anterior insula and amygdala among PTSD patients at rest (24) as well as when repeatedly exposed to traumatic memory (25). Furthermore, particularly the anterior insula, the ACC, and their functional coupling within the salience network are active in the evaluation of disgust and consecutive avoidance behavioral (15, 26) symptoms that our patient witnessed when exposed to the smell of meaty substances.

Interestingly, facilitated olfactory-limbic processing results in a heightened activity of regions that constitute key components of the distributed salience network. This network, including the bilateral anterior insulae, ACC, amygdalae, and hippocampi, is involved in the detection of homeostatically relevant inputs, i.e., the detection, learning, and modulation of salient events and the promotion of appropriate behavioral adjustment with strong functional coupling to the motor system (15, 27). Furthermore, the salience network is thought to arbitrate the functional dynamics between the central executive network (CEN) and DMN (28). In patients with PTSD without dissociative symptoms, functional neuroimaging studies indicated an at-rest overactivity and hyper-connectivity of the salience network eventually resulting in a low threshold for perceived salience, facilitated bottom-up processing, and an inefficient DMN-CEN modulation (17, 29, 30). Indeed, our patient's repeated and effective olfactory-induced, repulsive memories share many features clinically with the olfactory intrusions reported by patients suffering from PTSD without dissociative symptoms most likely facilitated by the overactivity and hyper-connectivity of the salience network.

Notably, we observed that the lesions of higher visual areas, the visual tract, and the precuneus may have complicated stimulus reappraisal in our patient as exteroceptive updating through visual pathways of relevant olfactory cues (19) was less available. Indeed, research in healthy participants showed that an intact amygdala–precuneus connectivity correlated positively with eye-tracking measures of successful attentional deployment suggesting that diverting attention away from arousing information depends on the functional relationship between limbic and parietal structures, essential for emotion regulation strategies (31, 32).

Finally, preserved amygdala integrity allowed the ultimately efficacious behavioral therapy approach in our patient with reconditioning the formerly neutral stimulus of a meaty dish (32, 33).

Conclusion

While perceptual disorders often develop after stroke (34), we here report for the first time a "Proust phenomenon" following a right posterior cerebral artery stroke. The putative underlying mechanisms encompass aberrant processing in olfactory-limbic networks and their deficient integration with larger neural ensembles, such as the salience and default mode networks. In our patient, we hypothesize deficient contextualization of the olfactory stimulus due to lesions in the right anterior hippocampus, thereby disinhibiting negatively valenced olfactory limbic processing and associative learning mechanisms. Understanding the circuit- and network-level structural and effective connectivity (35, 36) of neurocognitive and behavioral phenomena is crucial as it enables the development of efficacious and individualized treatment options in neurorehabilitation. Close interaction and interdisciplinary interpretation of the observed phenomena in neurology and psychiatry also appear indispensable as the behavior often relies on similar or overlapping circuits (37, 38).

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SB wrote the manuscript. AS and RM commented and proof-corrected it. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Case report: Self-restraint in a patient with alien hand syndrome following cerebral infarction involving the anterior cerebral artery territory

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Frontal alien hand syndrome (AHS) presents as impulsive grasping and groping and compulsive manipulation of environmental objects that can affect the dominant or nondominant hand. A few reports have shown improvements in neuropsychological scores over time when self-restraint of the right hand AHS was enforced. A 72-year-old woman presented with right-handed involuntary instinctive grasping reactions and compulsive manipulation of tools after an infarction of the frontal lobe and corpus callosum (CC). She was diagnosed with cerebral infarction involving the anterior cerebral artery territory and a frontal variant of AHS. At AHS onset, the patient was unaware that her right hand was moving against her will; she was only aware that her right hand was moving when the therapist pointed it out to her. Later, she began to recognize that her right hand was involuntarily moving, and she could restrain the movement of her right hand with her left hand. Approximately 5 months following AHS onset, the patient could voluntarily restrain her AHS symptoms by telling her right hand not to move against her will in her head. Most neuropsychological scores improved by 5 months following AHS onset. However, the patient showed disruptions in the genu and midbody of the left cingulate cortex, as shown via diffusion tensor imaging (DTI), and the sensation of the "right hand moving by itself" remained even 5 months after AHS onset. Although damage to the CC fibers was evident on DTI at 5 months following onset, the patient exhibited no sensory deficits and demonstrated good hand ownership as well as early improvement in attention and cognitive dysfunction. Therefore, the patient recognized her AHS symptoms, which included her hand moving against her will, and was able to consciously restrain her hand movement.

KEYWORDS

cerebral infarction, corpus callosum, alien hand syndrome, diffusion tensor imaging, self-restraint

1. Introduction

Alien hand syndrome (AHS) is characterized by the involuntary and autonomous activity of the affected limbs and includes frontal, callosal, and posterior variants (1, 2). Frontal AHS presents with impulsive grasping and groping and compulsive manipulation of environmental objects in the presence of frontal-release signs and can affect the dominant or nondominant hand (3). Although the long-term course of frontal AHS symptoms has been described, to the best of our knowledge, the disease course including the results of neuropsychological tests has not been reported, and no cases of patients who were able to self-restrain abnormal movement related to AHS symptoms have been reported.

Herein, we describe a case of right-handed AHS after cerebral infarction in the left anterior cerebral artery region whose symptoms improved neuropsychologically over time and enabled the self-restraint of right-handed AHS. Diffusion tensor imaging (DTI) of the patient is shown and the basis of fiber contacts in the corpus callosum (CC) at 5 months after onset is discussed. The following case is presented in accordance with the CARE reporting checklist.

2. Case presentation

A 72-year-old right-handed woman was admitted to our hospital with a history of hypertension and diabetes mellitus (DM). The patient had been diagnosed with hypertension and diabetes 2 years before the current hospital admission and attended a specialized clinic where her condition was controlled using medications for the respective illnesses. The patient took Valsartan 80 mg for hypertension and Glimepiride 1 mg for DM. She had no other medication history or relevant family history. Informed written consent for the publication of the clinical details of this case was obtained from the patient. After falling at the entrance of her house, the patient could not walk and had required external support to walk. The patient was admitted to our hospital's neurology department owing to poor response and difficulty in standing the next day. She was diagnosed with cerebral infarction involving the anterior cerebral artery territory and a frontal variant of AHS. On admission, hematological tests including a complete blood count and coagulation fibrinolysis examination revealed no obvious abnormalities (white blood corpuscle, $4.7 \times 10^3/\mu l$; red blood corpuscle, $461 \times 10^4/\mu l$; hemoglobin, 14.1 g/dl; hematocrit, 41.8%; platelet count, $10.9 \times 10^4/\mu l$; fibrinogen, 296 mg/dl; and triglycerides, 70 mg/dl), with items related to blood glucose levels in biochemical tests alone being elevated (albumin, 4.2 g/dl; glucose, 124 mg/dl; and hemoglobin A1c, 6.4%). The patient was conscious and had Brunnstrom stage V in her right upper and lower limbs. The Romberg test was negative. The Babinski and Chaddock signs in her right lower extremity and the Hoffmann reflex in her right upper extremity were negative. She had mild right facial paralysis and was alert and oriented with nonfluent speech and slight dysarthria. The palate was asymmetrical on phonation, and the tongue was slightly shifted to the left. Coordination was slightly worse on the right upper extremity, as assessed using the finger–nose–finger test and pronation–supination test. Superficial and deep sensations were normal. No diagnostic dyspraxia was observed. The patient was administered aspirin antiplatelet therapy (100 mg QD) for the treatment of her cerebral infarction. She could not release another person's arm or object after grasping them once with her right hand and pressed all the buttons of the elevator and the nurse call with her right hand involuntarily. The patient's Hasegawa's Dementia Scale-Revised (HDS-R) score was 11, Mini-Mental State Examination (MMSE) score was 17, Frontal Assessment Battery (FAB) score was 5, Praxis as one subscale in the Western Aphasia Battery (WAB) score was 43 for the right hand and 35 for the left hand (Table 1), and there was no apraxia in her daily life.

Magnetic resonance imaging (MRI) of the brain 2 days after AHS onset revealed a high-intensity signal in the left anterior cerebral artery region (the left genu to midbody of CC) on admission (Figure 1A), and a low-intensity signal in the same regions 5 months following onset (Figure 1B). Computed tomography and MRI did not reveal any hemorrhages or exudates. Magnetic resonance angiography (MRA) images revealed a vessel occlusion of the left A2 (Figure 1A). The vital signs of the patient were as follows: pulse, 52/min and blood pressure, 163/96 mm Hg. Her heart rate and rhythm were regular. Echocardiography revealed mild aortic, mitral, and tricuspid regurgitation but no organic change. No left ventricular hypertrophy or primary pulmonary hypertension was observed, and left ventricular contraction was normal. A transcranial Doppler study revealed a normal direction of blood flow with mean flow velocities and spectral waveform within normal limits in all insolated segments of the circle of Willis. In addition, DTI was performed at 5 months after onset.

As the patient had mild motor paralysis in the upper and lower limbs from AHS onset, therapy included walking and exercise of daily living to help the patient live independently in the ward. The patient was able to stand and walk without physical assistance. The patient underwent physical and occupational therapy for the upper limbs, focusing on bimanual movements and object manipulation exercises to treat her AHS. When compulsive manipulation of tool use and/or instinctive grasping reactions appeared, the therapist provided verbal instructions, and the patient shifted to verbal statements by herself over time.

A month after onset, score improvements were observed in the HDS-R, MMSE, and FAB and score reduction was observed in the BIT-total in "Figure and shape copying" and "Representational drawing." The Trail Making Test (TMT)-part A took 147 s and she made two errors; the TMT-part B could not be completed (Table 1). The patient's instinctive grasping reaction to the handrail remained involuntary, and she also continued to repeatedly press the nurse call button and push the elevator buttons. Furthermore, she wrote her name with her right hand against her intention when a pen was placed in front of her. However, the abnormal movement of the right hand could be corrected by verbal instructions from the therapist or other interventionists.

Three months following AHS onset, compared with a month after onset, there were further improvements in the scores of the HDS-R, MMSE, and FAB as well as improvements in performance in the TMT-A and -B. At this time, there was no apraxia on the WAB, and performance on the Kohs block-design test was low

TABLE 1 Changes in the scores of the neuropsychological tests over time from admission to discharge.

	Admission	1 month	2 months	3 months	4 months	5 month (discharge)
HDS-R (/30)	11	18	22	26	28	28
MMSE (/30)	17	22	26	28	28	30
FAB (/18)	5	10	11	16	15	13
WAB (right) (/60)	43	60	58	59	60	60
WAB (left) (/60)	35	58	58	60	60	60
TMT-part A (sec) (errors)		147 (2)	139 (0)	77 (0)	79 (0)	87 (0)
TMT-part B (sec) (errors)		–	316 (5)	235 (2)	181 (3)	183 (4)
BIT-total (/146)		132	141	142	144	139
Kohs block-design test (IQ)				64	64	57.8

HDS-R, Hasegawa's Dementia Scale-Revised; MMSE, Mini Mental State Examination; FAB, Frontal Assessment Battery; WAB, Praxis as one subscale in Western Aphasia Battery; BIT-total, Behavioral Inattention Test.

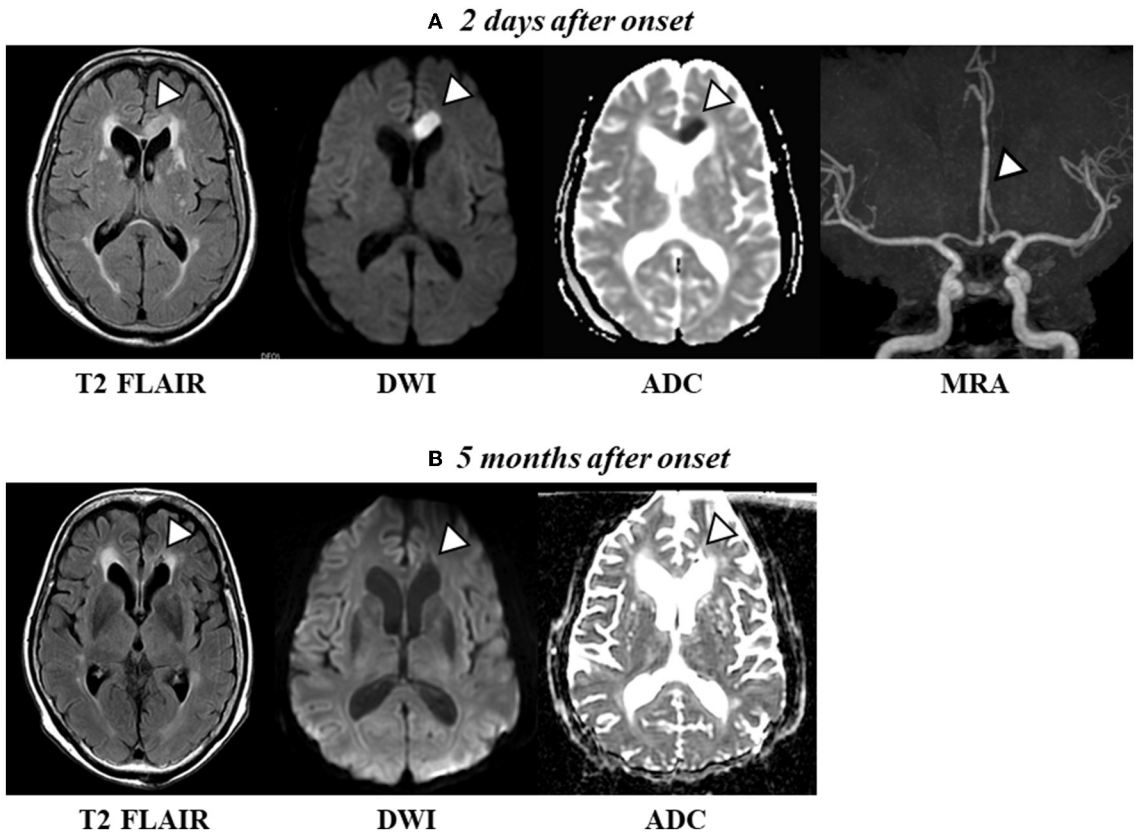

FIGURE 1
(A) Axial T2 FLAIR scan and diffusion-weighted imaging (DWI) revealed a high-intensity signal [apparent diffusion coefficient (ADC) shows a low signal intensity, indicating acute cerebral ischemia] in the left frontal lobe and midbody of the CC 2 days after onset. Magnetic resonance angiography (MRA) images revealed a vessel occlusion of the left A2. **(B)** Axial T2 FLAIR and DWI show a change to a low-intensity signal (conversely, ADC shows a high-intensity signal, indicating a chronic phase) in the left frontal lobe and the midbody of the CC 5 months after onset.

(Table 1). The patient was able to restrain her right hand with her left hand, although she still repeatedly pressed the nurse call button and the elevator buttons.

Five months after AHS onset, the patient made a statement that "the right hand moves on its own," but "I can prevent the right hand from moving in my head before it starts to move," and the number of right hand movements against her intention decreased. The scores of the FAB, TMT-A and -B, BIT-total, and Kohs block-design test decreased (Table 1); however, these tests were conducted just before discharge; thus, it was possible that her mental agitation affected these tests.

MRI was performed using a 3.0 Tesla MRI scanner (Discovery MR750; GE Healthcare, Milwaukee, Wisconsin). The patient was scanned in the supine position using a GEM Head & Neck coil. DTI

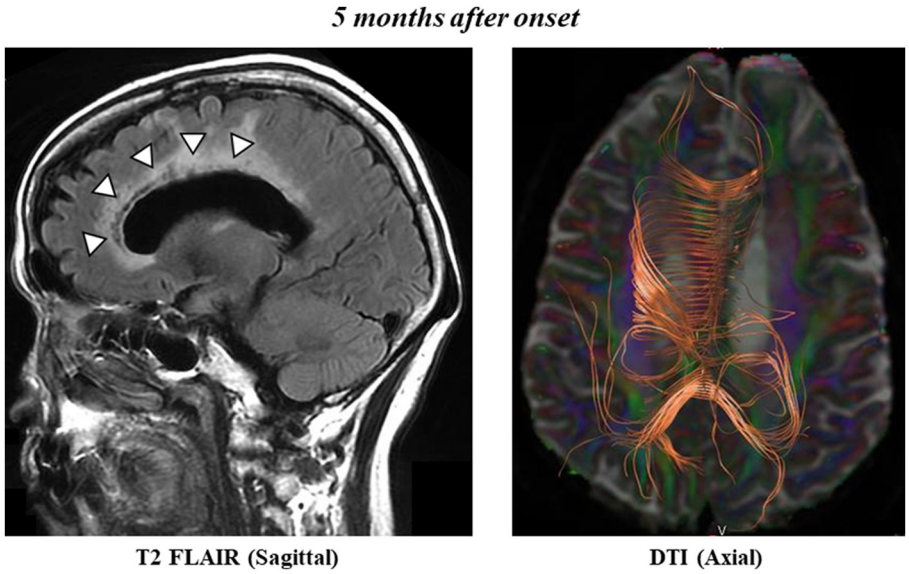

FIGURE 2
Sagittal T2 FLAIR scan shows postinfarct necrosis in the left frontal lobe, genu, and midbody of the CC 5 months after onset **(left panel)**. Axial diffusion tensor tractography of the CC 5 months after onset **(right panel)**.

was performed using a special sensitivity array encoding protocol, with factor = 2, chemical shift-selective suppression, and an echo-planar imaging sequence. An image without diffusion encoding (*b* value = 0 s/mm^2) was acquired to register the diffusion-weighted volume during analysis. The following imaging parameters were used: *b* value = 1,000 s/mm^2, motion probing gradient, 15 directions, time to repetition/echo time = 8,500/109.6 ms, flip angle = 90°, axial slice orientation, slice thickness = 3.6 mm with no interslice gap, field of view = 260 × 260 mm, 128 × 128 matrices, 40 slices, number of acquisitions = 2, and a 4-min and 40-s scan time. The regions of interest were manually selected separately on sagittal fractional anisotropy colormaps for each of the bilateral genu, midbody, and splenium of the CC, and the fractional anisotropy (FA) values were calculated as the mean of the individual values obtained from each region of interest.

MRI T2-FLAIR revealed low-intensity signals and enlarged left cerebral ventricles 5 months after onset (Figure 2, left panel). DTI showed disruptions in the genu and midbody of the left CC (Figure 2, right panel), which were bilaterally connected to the frontal and parietal cortices, respectively. We also observed CC fibers in the splenium of the CC. The FA values were 0.64 for the genu of the right CC, 0.29 for the genu of the left CC, 0.67 for the midbody of the right CC, and 0.46 for the midbody of the left CC, consistent with the values of the infarcted region. The FA values in the splenium of the CC were 0.80 and 0.72. These results confirm that the cerebral CC fibers had not recovered even after 5 months.

3. Discussion

We presented the case of a patient with cerebral infarction in the left anterior cerebral artery region who presented with AHS due to damage from the left genu to midbody of the CC. Although motor paralysis and sensory impairment were very mild, AHS symptoms, including instinctive grasping reaction and compulsive manipulation of tools, were observed. With time, the patient was able to restrain the unintended movements of her right hand.

Feinberg et al. (3) reported compulsive tool use as a characteristic symptom of frontal AHS. Frontal AHS lesions are usually located in the medial frontal lobe (supplementary motor area, anterior cingulate gyrus, and medial prefrontal cortex) and the anterior part of the CC, including the genu (4–6). In this case, MRI revealed an ischemic lesion in the left supplementary motor and medial frontal cortices. In addition, the patient's compulsive manipulation of tools, such as repeatedly pushing the nurse call and elevator buttons regardless of the patient's intention, was confirmed, suggesting a high probability that the patient had frontal AHS. Kikkert et al. (6) reported that AHS symptoms decreased in 68% of patients within 1 year of onset. Herein, the postinfarct necrosis of the genu and midbody of the CC was confirmed 5 months after onset via MRI, and the patient still had the sensation of the "right hand moving by itself" at the time of hospital discharge, suggesting that AHS was still present 5 months after onset.

DTI data at 5 months revealed that the left genu and midbody of CC were disconnected from the left and right sides of the hemispheres, consistent with the data of the infarcted region, resulting in lower FA values. FA values represent the degree of directionality of microstructures, such as axons, myelin, and microtubules, and the tract number is determined by counting the number of voxels contained within a neural tract (7, 8). Herein, the connection in the genu and midbody of the CC did not recover, indicating that AHS had not resolved. Therefore, the DTI data in this case strongly support the introspection of the "right hand moving by itself" at 5 months after onset.

The patient restrained AHS over time, although she still exhibited AHS symptoms. At onset, the patient was unaware that her right hand was moving against her will; she was only aware that her right hand was moving when the therapist pointed it out to her. Later, she began to recognize that her right hand was moving without her intention, and she could restrain the movement of her right hand with her left hand. Approximately 5 months after onset, the patient was able to voluntarily restrain the AHS symptoms by telling her right hand not to move against her will in her head. The patient exhibited little motor paralysis and sensory impairment compared with that at onset, and the sense of her right-hand ownership remained. The scores of the neuropsychological tests improved early during the disease course; however, the AHS symptoms persisted until the patient was discharged from the hospital, although the patient was able to control herself using her left hand (contralateral to the upper limb where symptoms appeared) or via her own will.

4. Conclusion

Although damage to the CC fibers was evident on DTI at 5 months after onset, the patient exhibited no sensory deficits and showed good hand ownership as well as early improvements in attention and cognitive dysfunction. Therefore, the patient could recognize the AHS symptoms (hand movement against her own will) and was able to consciously restrain this movement. However, the direct causal relationship between the scores of the neuropsychological tests and AHS remains unclear. Further investigation focused on the relationships between cognitive functions and AHS prognosis is warranted.

Data availability statement

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

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

KS performed manuscript writing. KS, TT, YK, and RF performed literature reviews. TT, MT, and IF were involved in patient care. KH conducted and operated the MRI. All authors approved the final version of the manuscript.

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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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Postoperative ecchymoma of eyelid after botulinum toxin injection for hemifacial spasm: a case report

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Hemifacial spasm (HFS) is a rare movement disorder characterized by involuntary muscle contractions on one side of the face. Compared to the high therapeutic effect, adverse effects of botulinum toxin treatment for HFS occurred rarely. However, managing HFS patients who are also taking antithrombotic drugs poses a challenge. Here, we present a case of postoperative ecchymoma of the eyelid following a botulinum toxin injection in a patient receiving daily vinpocetine and aspirin antiplatelet therapy. This case highlights the importance of considering the potential risks and formulating a treatment plan that maximizes benefit while minimizing complications in HFS patients undergoing botulinum toxin injections and taking antithrombotic medications. To the best of our knowledge, this is the first reported case of postoperative ecchymoma of the eyelid following a botulinum toxin injection. Further research and additional case reports are needed to better understand the management strategies for this patient population.

KEYWORDS

postoperative ecchymoma, eyelid, botulinum toxin injection, hemifacial spasm, case report

Introduction

Hemifacial spasm (HFS) is a rare movement disorder characterized by involuntary muscle contractions on one side of the face (1). Primary HFS has proven to be a neurovascular compression syndrome of VII cranial nerves by aberrant arteries. The mean annual incidence is 0.81 per 100,000 women and 0.74 per 100,000 men (2). And the mean age at disease onset is 55 years. Usually, HFS initially involves the orbicularis oculi muscle, followed by gradually spreading to other parts of the face, which causes significant negative impact on the quality of life in HFS patients (3). Without proper therapy, the symptoms may last for lifetime, and the spasms progress gradually in terms of intensity and frequency (2). Pharmacological treatments, including carbamazepine, clonazepam, baclofen as well as other anticonvulsive drugs such as gabapentin, can be beneficial in some patients, but such treatments can be limited in severe and disabling cases by serious side effects (4). Botulinum toxin (BTX), produced by *Clostridium botulinum*, is a neurotoxin that paralyses muscles by irreversibly blocking the cholinergic signal transmission at the presynaptic nerve endings (5). For a long time, BTX has only been used in

cosmetic dermatology. Since the 1980s, botulinum toxin type A (BTXA) has been used to treat HFS and provide symptom relief and improved quality of life in about 85 to 95% of the cases (6). Recently, botulinum toxin A (BTXA) has been introduced as a safe and effective therapeutic option for HFS (7). Most patients achieve moderate or marked relief by accepting BTXA therapy, although the injection must be repeated every 3 to 6 months. The intramuscular injections may cause various adverse effects including mild facial paresis, diplopia, allergy, pain, lid ptosis, brow ptosis, or hematomas. However, the available evidence suggests that hematoma at injection sites occur in less than 3% of BTXA injections (8) and no serious systemic side effects of the therapy have been reported yet (9).

In this case report, we describe an elder patient who was treated with aspirin and vinpocetine, showing ecchymoma once BTX injected. We aim to raise the question whether the antiplatelet or anticoagulant drugs should be discontinued before the BTXA therapy.

Case report

A 60-year-old man, previously diagnosed with posterior circulation ischemia, had a 7-year history of right-sided HFS. Initially he had intermittent involuntary contractions of the right eyelid, which resulted in forced closure of the eye, and the spasms gradually spread to muscles of the lower part of the face. Ultimately, these muscles on the right side were affected nearly all the time. The distinct spasm of the orbicularis oculi muscle impaired his homolateral vision, which severely impacted his ability to read. The severity of HFS was assessed by the standard of Shorr et al. (10). Grade 0: no spasm; gradeI: increased frequency of blink caused by external stimulus; gradeII: mild spasm, slight tremor of eyelid and no dysfunction; grade III: obvious spasm and mild dysfunction; gradeIV: severe spasm and severe spasm and dysfunction (unable to read and drive, etc.). In this case, prior to treatment, the severity was assessed at graded IV. Moreover, he used aspirin 100 mg daily to prevent ischemic stroke. He was referred to the Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology for the treatment of both posterior circulation ischemia and HFS. A computed tomography scan of the brain and angiography obtained normal results. Routine laboratory tests, including blood test, urine test, electrolytes, liver-function and renal-function tests, and erythrocyte sedimentation rate measurements all showed normal results, apart from mildly elevated total cholesterol and low density lipoprotein levels. Coagulation function test parameters were also negative.

Based on the clinical picture, the patient was being treated continuously with aspirin 100 mg and vinpocetine 30 mg daily. Furthermore, the patient was willing to receive the BTXA injection to relieve the spasm. BTXA (Botox, 100 U of clostridium botulinum type A neurotoxin complex) was acquired from Allergan Inc., the United States. BTX-A was dissolved in 2 mL of saline (0.9%) to 50 U/mL, as recommended by the manufacturer. 1 mL syringe with a 26-gauge needle was used for the injection procedure. On the right side, the dosage of BTXA per injection site was 2.5 to 5 units, including orbicularis oculi (5 points, 5 units per points), corrugator supercilii (1 point, 5 units), zygomaticus (1 point, 2.5 units) orbicularis oris (3 points, 5 units per points) and the muscle mentalis (1 point, 2.5 units) (10). To keep the balance, a half of the BTXA dosage was injected to a variety of muscles on the left side. A total of 50 units of BTXA were administered. Considering the patient's history of antiplatelet medication, we conducted pre-injection aspiration by gently withdrawing the syringe plunger to check for the presence of blood. Additionally, we administered the BTXA injection slowly and with precise control to minimize tissue trauma and the potential risk of bleeding. We closely monitored the injection site for any signs of bleeding or hematoma formation. However, the patient developed an ipsilateral periocular swelling and eyelid hematoma the following morning, approximately 12 hours after receiving the injection (Figure 1; Supplementary Video S1). The patient was referred to an ophthalmologist for counseling. The periorbital swelling and eyelid ecchymoma were absorbed in 7 days after injection gradually (Supplementary Video S2) and disappeared 14 days later. Meanwhile, we observed mild eyelid muscle tremors without any functional impairments such as whistling, blowing, frowning, or chewing (Supplementary Video S2). The Shorr scale assessment decreased to gradeII. Moreover, the severity of spasm decreased to grade 0 after BTX treatment.

Based on our follow-up, complete remission was observed for a duration of 4 months, with symptoms gradually returning to the pre-injection level after 2 months. Notably, to prevent hematoma formation, we implemented specific techniques, including careful aspiration prior to injection and a slow and controlled injection process. Additionally, we opted for smaller insulin syringe needles, specifically a 30-gauge size, to minimize tissue trauma. Post-injection, we applied ice packs to the injection site and surrounding area to facilitate cold therapy and mitigate the risk of hematoma formation. Treatment was then repeated with the same dosage (50 units) injected in the same muscles, resulting in a similar marked improvement. Now the patient is receiving the injection every 6 months regularly and reaches satisfied remission without eyelid ecchymoma.

Discussion

The ecchymoma of eyelid is a relatively rare and late complication after the botulinum toxin therapy for HFS. There are few reports about

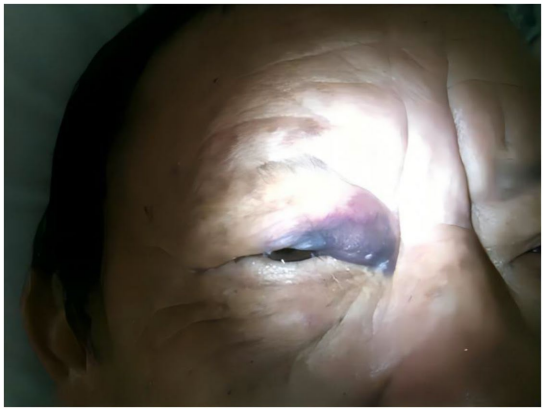

FIGURE 1
The extensive eyelid ecchymoma of the patient 12 hours after the BTXA injection.

this issue at home and abroad. In this case, the patient developed a postoperative hematoma characterized by tardive ecchymoma, which refers to a time delay between the initial occurrence and its manifestation. The onset of ipsilateral periocular swelling and eyelid hematoma was observed the morning after receiving the botulinum toxin injection, which occurred 12 hours prior. While the majority of tardive hematomas in cosmetic procedures or facial surgeries typically manifest within 24 h to several days after the procedure, the occurrence of a hematoma 12 h after the injection may not strictly align with the clinical definition of a delayed hematoma (11, 12). Therefore, we have chosen to categorize this hematoma as a "postoperative hematoma" rather than a "tardive hematoma".

To our knowledge, this is the first report of postoperative ecchymoma of eyelid after botulinum toxin injection. Nevertheless, patients are recommended to discontinue nonsteroidal anti-inflammatory agents such as aspirin and also tocopherol or even gingko biloba, 10 days before BTXA injections (13). In this case, the patient presented a marked ecchymoma, which may attribute to: (1) The elders usually have loose eyelid tissue and periorbital tissue which blood can easily permeate into; (2) The patient was being treated with aspirin and vinpocetine which may have increased the risk of ecchymomsis complications; and (3) Some delayed immune rejections related to the neutralizing antibodies *in vivo*. Specifically, the immune response triggered by BTXA injection can lead to the production of neutralizing antibodies, which can interfere with blood clotting mechanisms (14). These antibodies may bind to proteins involved in clotting, such as coagulation factors and platelets, impairing platelet aggregation and inhibiting coagulation factor activity. In addtion, they can induce inflammation and damage to blood vessel walls, increasing the risk of bleeding. Although the development of neutralizing antibodies in response to botulinum toxin injections is uncommon, long-term and repetitive treatment may increase this likelihood (15).

Owing to demographic characteristic changes with an aging population, the number of patients with antiplatelet or anticoagulant drugs is predictable to rise. Additionally, daily aspirin therapy is recommended by key guideline agencies for the prevention of cardiovascular and cerebrovascular events in the elderly (16). At the same time, the aged people composed a significant part of the patients who need BTX therapy (17). The elderly are more prone to bleeding in this case to some extent within the injections. In addition, the interruption of antiplatelet therapy may increase the risk of cerebral infarction or myocardial infarction leading to life-threatening, disabling, and costly consequences.

The dilemma obviously exists in patients who are receiving antiplatelet or anticoagulant therapy and still require surgery. In order to help clinicians make a decision, the American College of Chest Physicians has made cautious suggestions after considering the risk of cardiovascular events and the risk of thrombosis after the operation (18). This provides us with ideas to solve the problem. Because of the severe consequences of cardiovascular and cerebrovascular events we should evaluate the risk of discontinuing the antiplatelet therapy. For those high-risk patients, we should analyze the situation, and take into consideration the suffering ecchymoma and the risk of infarction, then formulate a treatment course to ensure maximum benefit. As for the patients who have taken anticoagulants for a long time, we are required to avoid food of high vitamin K and check coagulation function regularly. The most important thing is that the dose should be adjusted to prevent over-coagulation, if anticoagulants are used in combination with other drugs. Whether we choose the injection with discontinuing or continuing antiplatelet therapy, we should be informed of the potential risk to the patients.

Besides, efficient preparation and preventive measures are crucial in minimizing the occurrence of ecchymoma. Efficient preparation and preventive measures are crucial in minimizing the occurrence of hematoma. During injections, meticulous aspiration, slow and controlled injection techniques are important measures. Immediate pressing at the injection site after each injection have been identified as effective preventive measures against hematoma. Previous studies have also recommended the use of smaller needle sizes of appropriate length to reduce bleeding complications associated with BTX administration (19). Additionally, ultrasound guidance has shown superior therapeutic efficiency compared to relying solely on anatomical palpation (20). These measures collectively contribute to reducing the risk of hematoma formation. However, in cases where hematoma occurs, for instant application of cold compresses to the injection site can help alleviate swelling and reduce inflammatory responses (21). It is important to avoid massaging or manipulating the injection site to prevent further irritation and spreading of the hematoma. Additionally, maintaining a slightly elevated head position can reduce blood flow to the injection area and alleviate the severity of the hematoma. Close observation and monitoring of the hematoma's changes and associated symptoms, such as swelling degree, color changes, pain, or discomfort, are necessary.

Since few literatures are available to help us make a decision, the problem that BTXA injection with discontinuing antiplatelet therapy or not should attract more attention to make a marked standard. We recommend giving due consideration to the occurrence of tardive ecchymoma and the risk of infarction by devising a treatment plan that maximizes its benefits. Furthermore, future research should aim to explore additional strategies for the prevention and management of postoperative ecchymoma.

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

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KG, JH, GL, HoL, and NX contributed to the conception and design. KG, JL, XW, HaL, QY, GK, and NX took care of collecting the clinical information. XH, KG, JL, JH and NX interoperated the images and videos. XH, KG, JL, ZL, and NX coordinated and helped to draft

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Conflict of interest

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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.2023.1171303/full#supplementary-material

SUPPLEMENTARY VIDEO S1
The eyelid ecchymoma twelve hours after the BTXA injection.

SUPPLEMENTARY VIDEO S1
The ecchymoma seven days after the BTXA injection.

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Case report: Neural timing deficits prevalent in developmental disorders, aging, and concussions remediated rapidly by movement discrimination exercises

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Background: The substantial evidence that neural timing deficits are prevalent in developmental disorders, aging, and concussions resulting from a Traumatic Brain Injury (TBI) is presented.

Objective: When these timing deficits are remediated using low-level movement-discrimination training, then high-level cognitive skills, including reading, attention, processing speed, problem solving, and working memory improve rapidly and effectively.

Methods: In addition to the substantial evidence published previously, new evidence based on a neural correlate, MagnetoEncephalography physiological recordings, on an adult dyslexic, and neuropsychological tests on this dyslexic subject and an older adult were measured before and after 8-weeks of contrast sensitivity-based left–right movement-discrimination exercises were completed.

Results: The neuropsychological tests found large improvements in reading, selective and sustained attention, processing speed, working memory, and problem-solving skills, never before found after such a short period of training. Moreover, these improvements were found 4 years later for older adult. Substantial MEG signal increases in visual Motion, Attention, and Memory/Executive Control Networks were observed following training on contrast sensitivity-based left–right movement-discrimination. Improving the function of magnocells using figure/ground movement-discrimination at both low and high levels in dorsal stream: (1) improved both feedforward and feedback pathways to modulate attention by enhancing coupled theta/gamma and alpha/gamma oscillations, (2) is adaptive, and (3) incorporated cycles of feedback and reward at multiple levels.

Conclusion: What emerges from multiple studies is the essential role of timing deficits in the dorsal stream that are prevalent in developmental disorders like dyslexia, in aging, and following a TBI. Training visual dorsal stream function at low levels significantly improved high-level cognitive functions, including processing speed, selective and sustained attention, both auditory and visual working memory, problem solving, and reading fluency. A paradigm shift for treating cognitive impairments in developmental disorders, aging, and concussions is crucial. Remediating the neural timing deficits of low-level dorsal pathways, thereby improving both feedforward and feedback pathways, before cognitive exercises to improve specific cognitive skills provides the most rapid and effective methods to improve cognitive skills. Moreover, this adaptive training with

substantial feedback shows cognitive transfer to tasks not trained on, significantly improving a person's quality of life rapidly and effectively.

KEYWORDS

timing deficits, magnocellular deficits, cognitive remediation, cortical plasticity, reading/attention/memory/executive control networks, perceptual learning

1. Introduction

The brain needs to orchestrate and integrate the activity of different cortical areas that are involved in a particular task. This is accomplished by boosting synchronized oscillations that occur between these cortical areas. The neural timing deficits that are found in a wide range of brain disorders, affecting these synchronized oscillations are not well understood. Much evidence has now accumulated to suggest that a fundamental deficit in developmental dyslexia (1–5) atypical, in older adults (6–10), and in traumatic brain injury (TBI) (11–13) is impaired operation of the visual timing functions mediated by the magnocellular system (14). Moreover, this review concludes: "These studies suggest that a paradigm shift from phonologically-based to visually-based methods is required for the treatment of dyslexia. In older adults and following a concussion, the same paradigm shift is also called for. Moreover, this adaptive training, with substantial feedback and rewards, shows cognitive transfer to tasks not trained and can thus help to improve a person's quality of life rapidly and effectively. The critical issue is that regardless of input modality, effective treatments must address neural timing deficits."

We will describe additional evidence showing that neural timing deficits that are prevalent in many different types of cognitive impairments, including developmental disorders, like dyslexia where reading is difficult, normal aging, and concussions, reported previously (15), are remediated rapidly by visually-based movement-discrimination exercises, significantly improving cognitive abilities, so that a person's quality of life improves rapidly, when other methods have been unsuccessful. We will show that a paradigm shift for treating visual timing deficits found in a wide range of different of cognitive disorders is crucial.

The movement-discrimination intervention used in this study is believed to improve the precision in timing of visual events, and thus accelerate reading progress by increasing processing speed, selective and sustained attention, and working memory span (16–20). It achieves this by improving the function of the dorsal stream, boosting magnocellular relative to parvocellular activity, thereby improving inhibitory and excitatory circuits, in feedforward and feedback pathways, taking advantage of the brain's neural plasticity (21). Visually-based movement-discrimination exercises in both normal participants (16, 22–27), dyslexics (14–16, 18, 19, 25), and after a TBI (15) have demonstrated neuroplasticity in domain of processing speed by practicing these exercises over a short period of time. These studies found that the more movement-discrimination was practiced, the more motion sensitivity, attention, memory, and reading skills improved, indicating that timing deficits are a key factor preventing normal cognitive function in dyslexia, aging, and after a TBI. Movement-discrimination exercises were not only more effective, but also were completed 2–8 times faster than other reading and cognitive interventions (14). We provide additional evidence showing that reading, attention, processing speed, problem solving, and memory problems involve neural timing deficits in visual system's dorsal stream. These deficits in the dorsal stream affect both feedforward and feedback pathways between visual, parietal, and frontal areas.

The visual system has been hypothesized to exploit the dichotomy of a fast magnocellular channel (dorsal visual stream) together with a slower parvocellular channel (ventral visual stream) for the purpose of selective attention (28–30). The major dorsal stream attentional pathway, receiving predominantly magnocellular input is specialized for processing the location and movement of objects in space, whereas the ventral stream receives both magnocellular and parvocellular inputs and is specialized for extracting the details related to an object's color and shape (31–33).

The dorsal visual stream provides the input to the attention networks (28–30). The control of spatial attention in early visual cortex is likely to be directed by regions of the Posterior Parietal Cortex (PPC) and dorsal lateral Prefrontal Cortex (dlPFC) (28–30, 34–37). Top-down attentional feedback occurs in the PPC where increased gamma activity is shown to be linked to visual attention and planned saccadic eye movements (38). The parvocellular neurons in the ventral stream subsequently use the coupled alpha-gamma oscillations regulated by the pulvinar for sequential processing (39), as a starting point for deciphering the individual letters (18, 19, 28–30, 40, 41). Sequential processing also uses the functional anatomy of the claustral connections of items being processed serially, such that cross-frequency coupling between low frequency (theta) signals from the claustrum and higher frequency oscillations (gamma) in the cortical areas is an efficient means for the claustrum to modulate neural activity across multiple brain regions in synchrony (42). The timing, period, envelope, amplitude, and phase of the synchronized coupled theta-gamma oscillations are modulating the incoming signals to the striate cortex, and have a profound influence on the accuracy and the speed of reading (30). It is likely that the dyslexic reader's deficit in attentional focus (43, 44) is a consequence of slow magnocells preventing the linked parvocellular neurons from being able to isolate and sequentially process the relevant information that is needed for reading (28, 29, 45). Cross-frequency theta-gamma coupling enables sensory areas of the brain which capture language stimuli to communicate rapidly with higher-order brain areas for real-time processing of language input (38, 46), playing a crucial role in mediating working memory and in enabling learning (47, 48). Both claustral connections (42) and the pulvinar complex (39) regulate synchronous information transmission between cortical areas based on attentional demands.

Contrast sensitivity-based movement-discrimination training employing figure/ground discrimination improved not only magnocellular function and attention, but also improved magno-parvo integration, figure/ground discrimination, and feedback measured by the strength of coupled theta/gamma activity for the test patterns

moving at 6.7 and 8 Hz and coupled alpha/gamma activity for test patterns moving at 10 and 13.3 Hz (14, 15, 18, 19, 25, 27). Moreover, feedback in the dorsal stream from middle temporal cortex (MT), the specific cortical region vital for movement discrimination (31), to V1 improves figure/ground discrimination (49) a task used when reading by discriminating the letters in the word from the remaining text, or discriminating direction of movement relative to a background (50). Furthermore, feedback from MT has its strongest effects for low salience stimuli (49), such as low contrast patterns having less than 10% contrast, i.e., those patterns that maximally activate magnocellular neurons (51, 52). When movement-discrimination training was done using patterns optimal for activating the V1-MT network (49, 53, 54) visual timing deficits were remediated for those with a TBI, causing attention, reading fluency, processing speed, and working memory, all high-level cognitive functions, to improve significantly (15). These results were also found for those with dyslexia (14, 19, 27, 50) and older adults (55).

The scientific premise for using contrast sensitivity-based movement-discrimination training is that remediation of a fundamental visual timing deficit affecting motion discrimination at a low level of cognitive processing generalizes to high level cognitive skills (attention and working memory) reliant upon motion processing as a foundation. Sluggish motion cells make it difficult to locate the beginning and end or identify the order of letters in a word, causing confusion, mis-sequencing, and hence slow reading. Thus, slow neural pathways cause the brain to misdirect visual attention, confuse what the eye sees, and reduce the ability to remember the visual forms of words (14, 15, 19, 27). The movement-discrimination training enhances coupled theta/gamma and alpha/gamma oscillations, improving both the feedforward and feedback attention and executive control networks conveyed by the dlPFC and PPC to modulate attention in MT and striate cortex (V1), enabling a wide range of cognitive skills to improve. This theory of change is validated further by the results of this study: MEG imaging showing the improvements in these networks, and the improvements in cognitive skills found following short period of movement-discrimination training. Contrast sensitivity-based left–right movement-discrimination exercises is the first visually-based intervention that was found to improve both low-level movement-discrimination in the dorsal stream and high-level cognitive functioning. This has been demonstrated both behaviorally and using MEG brain imaging, improving the attention and executive control networks in dyslexics (14, 56) and after a TBI (15). Since contrast sensitivity-based movement-discrimination neurotraining is so rapid and effective, it offers a new approach that represents a paradigm shift in the treatment of dyslexia, one that is based on improving visual timing instead of targeting higher level phonological timing (14, 19).

MagnetoEncephaloGraphy (MEG) brain source imaging, providing a neural correlate, was conducted to determine the brain areas that increase in function for an adult dyslexic following these left–right movement-discrimination exercises. This neural correlate for dyslexia shows for the first time that these left–right movement-discrimination exercises improve the function of the motion area: MT in the first 300 ms, improving the sensitivity and neural timing of magnocells in the dorsal stream. Improvements in cognitive skills were also measured for an older adult with a battery of neuropsychological tests of cognitive skills, for the first time.

TABLE 1 Dyslexic pre-post standardized percentiles and reading scores.

Standardized tests	Pre-test	Post-test
Reading speed	154 wpm	437 wpm
IVA+ focusing attention	1%	54%
IVA+ sustained attention	10%	82%
IVA+ impulsivity	18%	62%
WAIS processing speed	23%	50%
TIPS visual working memory	6%	99%
TIPS delayed recall	1%	25%

2. Methods

2.1. Participants

A 29 years-old dyslexic Caucasian man answered an ad to improve cognitive skills that was posted by UCSD. He had been finding his quality of life was limited by his dyslexia and was interested in any methods to improve his cognitive skills. A healthy 71 years-old Caucasion woman, having a PhD in physics, referred by a professor at UCSD, enrolled in this study, since she wanted to improve her ability to remember. Lately, she found her vision and memory were not as reliable, increasingly reducing her quality of life, especially when driving during dawn or dusk.

The subjects had tried many different interventions that were all unsuccessful. When asked, neither subject could recall the names of these interventions. These vision and cognitive deficits were not experienced by other family members, so not likely to be genetic in origin. Behavioral pre-tests, shown in Tables 1, 2, confirmed both subjects concerns about their cognitive abilities. The inclusion criteria consisted of: wanting to improve their visual and cognitive skills, agreeing to complete two sessions of PATH training twice a week for 8 weeks, at the same time of day, around 11 am, so they were not tired, and agreeing to follow PATH training with at least 30 min of cognitive exercises. Since there was no control condition, there was no blinding in this study.

Both participants, who lived in the San Diego area, signed informed consent forms, the dyslexic subject's consent form approved by UCSD Institutional Review Board, and the older adult's consent form approved by SolutionsIRB, a full service private Institutional Review Board registered with OHRP. This informed consent form assured the subject their data would be anonymous. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by each IRB. The intervention exercises were conducted in a room devoted to this task at either UCSD, Perception Dynamics Institute, or once learned at home.

2.2. Intervention: visual movement-discrimination task- PATH to Reading™ (PATH) neurotraining

The patented (16, 17) visual timing intervention[1] uses dim grayscale patterns optimal for activating magnocellular (magno)

1 https://pathtoreading.com

TABLE 2 Older adult pre-post standardized percentiles and reading scores.

Standardized tests	Pre-tests	Post-tests after 8 weeks	Post-tests 4 years later
ADT visual processing	Markedly Below Normal	Above Normal	Above Normal
ADT phonological processing	Mildly Below Normal	Above Normal	Above Normal
WRAT reading	75%	87%	87%
WRAT spelling	58%	61%	73%
WRAT math	73%	95%	92%
Reading speed	229 words/min	541 words/min	430 words/min
WAIS processing speed	42%	77%	87%
DKEFS attention	81%	87%	81%
DKEFS cognitive flexibility	81%	87%	81%
TIPS visual working memory	34%	86%	87%
WAIS auditory working memory	55%	97%	90%

neurons to retrain the brain's pathways (15–19), see Figure 1 and https://youtu.be/HgCZn9uVdS0. These patterns are designed to activate motion pathways (by using left–right movement) relative to the pattern pathways by using a stationary background that entrains motion discrimination (23, 24). Each pattern is presented for less than half a second, increasing from slow theta movement (6.7–8 Hz) to faster alpha movement (10–13.3 Hz) every 4 complexity levels. Only the contrast of the center stripes (the test spatial frequency) in the fish shaped pattern that moves left or right relative to a stationary striped background is dimmed until the direction can no longer be seen. The low contrast (0.1–5%) test frequency was set to either 0.25, 0.5, 1, or 2 cyc/deg., being an octave apart. The five stationary vertical background gratings for each test frequency bracket the test frequency, having a fundamental frequency equal to the test frequency or ±1 or 2 octaves from it. Only when movement-discrimination is done relative to a structured background, do all types of dyslexics exhibit motion discrimination deficits (18, 19, 25, 26).

The subject sat 57 cm in front of a 13-inch MacBook Pro computer monitor, with a display similar to the ones in Figure 1. During the presentation, the bars in the "fish-shaped" window in the center of the screen formed by a sinusoidal grating, moved left or right very briefly (<= 450 ms). The fish-shaped pattern subtended 4 deg. visual angle, and the structured background subtended a 16 deg. visual angle. When the screen went blank, the subject reported which way the center pattern moved by pushing the left or right arrow key (Figure 1C). A brief tone was presented after incorrect responses. The program adaptively changed the contrast of the test pattern in order to keep the subject at 79% correct. There are also levels of difficulty introduced by making the background pattern more similar to that in the fish, see center pattern in Figure 1A, and by increasing the pattern's complexity level (Figure 1B). The complexity level increases: (1) the number of sinewave components in the background from one (Figure 1A) to three harmonically related frequencies having a difference frequency equal to the test frequency (Figure 1B), shown previously to facilitate movement discrimination (23, 24) by providing a wider background frame of reference, (2) the background contrast from 5 to 10 to 20%, to increase the amount of parvocellular activity, since magno-cells saturate at 10% contrast (51), and (3) the pattern's speed of movement after every 4 complexity levels, increasing from 6.7 to 8 Hz (in theta range) to 10 to 13.3 Hz (in alpha range), so that the subject was challenged as the training progressed. Faster speeds of movement, 10 Hz to 13.3 Hz, were too fast to be trained on until slower speeds of movement had been trained.

At the start of a session, both the test and background gratings were set to 5% contrast to ensure that the contrast of the test pattern is in the middle of the magnocellular contrast range (51). The mean luminance was approximately 120 cd/m^2, measured using a Pritchard 1980A Spectra photometer. Each time the subject correctly identified the direction the fish stripes moved, the contrast of the test grating was lowered one step until the subject answered incorrectly. Following the first incorrect response, a double-staircase procedure (22) was used to measure the movement-discrimination contrast threshold. Lowering a subject's contrast threshold is what increased a subject's sensitivity to motion discrimination. This staircase procedure estimates the contrast threshold by using the most sensitive, repeatable measurements of contrast sensitivity possible (57). Each contrast threshold required 20-40 trials. A full training cycle of the movement-discrimination task required 20 contrast threshold determinations: for each of the four test spatial frequencies (0.25, 0.5, 1, and 2 cyc/deg) paired with each of the five background spatial frequencies (equal to test frequency or ±1 or ±2 octaves from the test frequency), patterns chosen to optimally active magno-cells, see Figure 1A. After each contrast threshold measurement, a score was given to make the training more game-like. The lower the contrast threshold, the higher was the score. Other motivational strategies in PATH training included earning a fish for each low contrast threshold (<= 1% contrast), showing a graph at end of each training cycle displaying original, current, and optimal contrast sensitivity function for each test frequency, and a star for each complexity level completed. This training was adaptive in response to the subject's performance, and incorporates cycles of feedback and reward at multiple levels, ranging from positive and negative feedback on a trial-by-trial basis, as well as cumulative block and session feedback. Such feedback greatly accelerates learning (58, 59). This interactive training procedure (15–19, 25, 26) and feedback motivated the user to continue to improve. Motion direction-discrimination was trained for between 15 and 20 min to complete one training cycle, twice a week for 8 weeks. Initially this intervention was administered one-on-one by staff. After the intervention was learned, it was completed by each subject at their home unsupervised. This training was followed by at

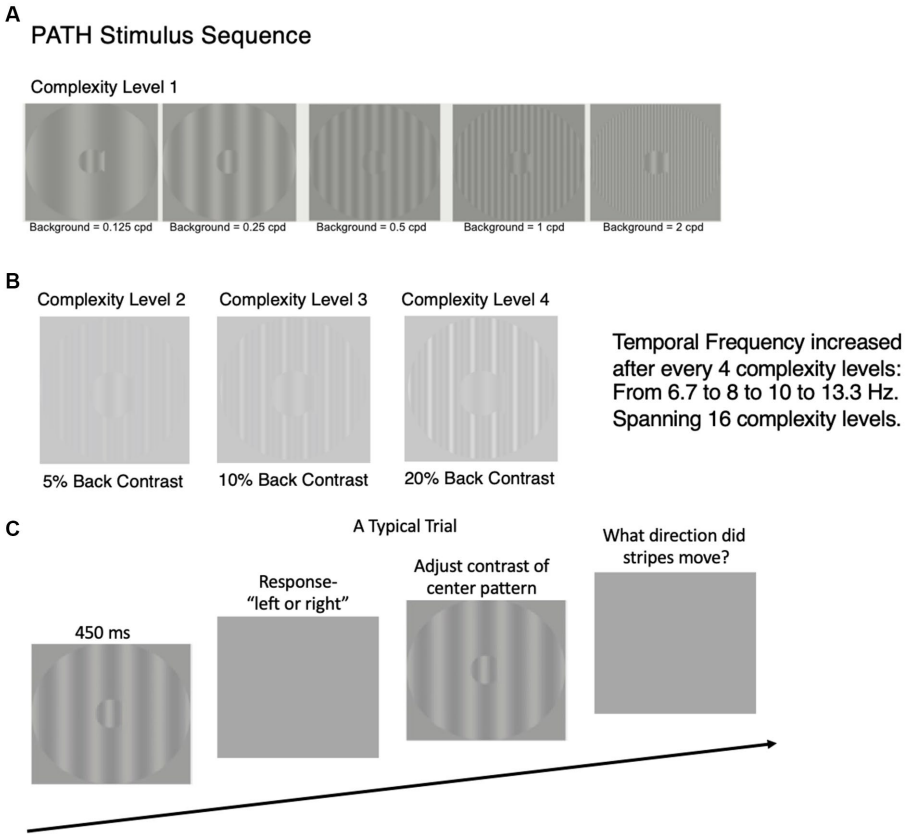

FIGURE 1
Time sequence for study design. After subjects were enrolled in study, a battery of visual and cognitive skills standardized tests were administered at the beginning and end of this study, results reported in Tables 1, 2. After standardized tests were administered, the PATH neurotraining program was administered for 8 weeks. The details of the PATH neurotraining program are presented in **(A–C)** and in the video (https://youtu.be/HgCZn9uVdS0). **(A)** Sample patterns for intervention at Complexity Level 1 for a background two octaves lower in spatial frequency than the test frequency, one octave lower in spatial frequency than the test frequency, equal in spatial frequency to the test frequency, one octave higher in spatial frequency than the test frequency, and two octaves higher in spatial frequency than the 0.5 cyc/deg. "fish shaped" test pattern. This same set of backgrounds was presented in this order for each of the 4 test spatial frequencies (0.25, 0.5, 1, and 2 cyc/deg). **(B)** Complexity levels 2, 3, and 4 display multifrequency backgrounds for center pattern in 1.A (0.5, 0.5 cyc/deg), having the same fundamental frequency as in complexity level 1, with a difference frequency equal to the test frequency, increasing the background contrast from 5 to 10 to 20% contrast. **(C)** A typical trial for *PATH to Reading* /Insight intervention. Pattern flashes on screen for <= 450 ms while center stripes move left or right. Screen goes blank, waits for left or right arrow key to be pushed. If incorrect, short tone sounds. As soon as left or right key pressed, next pattern with same or different contrast flashes on screen while center stripes move left or right. This sequence of patterns is presented continuously until the contrast threshold for this pattern is measured (20–40 trials). At the end of each contrast threshold measurement, a fishnet appears with a fish for each pattern having a contrast threshold <= 1% contrast, personal best score, current score, and number of patterns remaining. Then the next pattern combination is presented to measure next contrast threshold until all 20 *PATH neurotraining* patterns were presented, and the program says 'Thank You', presents a star for each level of complexity completed, shows a graph with the contrast threshold function (optimal, current, initial) for each test frequency with its 5 background patterns, and quits.

least 30 min of reading an interesting story (dyslexic) or cognitive exercises (older adult), helping this training to generalize to high-level cognitive skills.

2.2.1. Fidelity of implementation

Contrast threshold data was collected using the most sensitive, repeatable measurements of contrast sensitivity (57). All contrast threshold data with date and time stamps was stored in individual and summary files, and collected automatically by the computer. Therefore, there was no means for tampering with the data collection. Data in summary files showed each subject's contrast thresholds, and how long it took to complete each threshold. This summary data was examined weekly to ensure the subject was completing one training cycle twice a week and seeing left–right movement dimly. Compliance was never a problem.

2.3. Neural correlate: MEG source imaging

Two MEG exams were performed for the dyslexic subject: one before and another after 8-weeks of the movement-discrimination intervention to evaluate whether he had significant improvements in brain functioning after intervention training. A structural MRI used for superimposing the functional activity on top of the brain anatomy was done before initial MEG recording. MEG responses evoked by a 2.5% contrast 1 cyc/deg. sinewave grating moving left or right at 10 Hz relative to a 5% contrast 1 cyc/deg. background, using the same time sequence, as described above and in Figure 1C, was collected using the VectorViewä whole-head MEG system (Elekta-Neuromag, Helsinki, Finland) with 306 MEG channels. The movement-discrimination task entails on-line monitoring, updating, and manipulation of remembered information. During this task, the subject was required to monitor the

direction of movement. A fixation cross was presented during the 3,000 ms interstimulus interval. The subject was instructed to push a right button if the test pattern moved right relative to the background and push a left button if the pattern moved left relative to the background. About 50 trials per load condition were collected for this subject. Performance was recorded using an MEG-compatible response pad, in which index finger blocks-and-unblocks a laser-beam.

The dyslexic subject, who did not have metals objects in his brain, was seated in an upright position inside a multi-layer magnetically-shielded room at the UCSD MEG Center. MEG data were sampled at 1000 Hz and were run through a high-pass filter with a 0.1 Hz cut-off, and a low-pass filter with a 330 Hz cut-off. Eye blinks and eye movements were monitored using two pairs of bipolar electrodes with one pair placed above and below the left eye, and the other pair placed on the two temples. Heart signals were monitored with another pair of bipolar electrodes. Precautions were taken to ensure head stability; foam wedges were inserted between the subject's head and the inside of the unit, and a Velcro strap was placed under the subject's chin and anchored in superior and posterior axes. Head movement across different sessions was about 2–3 mm on average. Analysis of MEG sensor waveforms were described previously (15, 60–62).

2.4. Behavioral measures used before and after intervention (pre-post tests)

Improvements in cognitive skills were measured using a battery of neuropsychological tests, described below, administered by trained staff before and after intervention training in the middle of the day around noon so subject was not tired or hungry. These tests were chosen since they are considered the gold standard for assessing impairments in cognitive function (15). Based on subject's raw score and age, a standard score that was converted into a standardized percentile score was assigned. Visual skills were measured using tests of near visual acuity (Good-Lite acuity card held 16 inches away), and measuring the eyes' convergence near-point (distance where 1 cm letter 'A' blurs or becomes two).

The tests of cognitive skills that were completed are:

1. Adult Dyslexia Test (ADT), https://www.good-lite.com/products/482700, to measure reading proficiency evaluated whether a subject's visual processing and phonological processing was above normal, normal, borderline, mildly below normal, moderately below normal, or markedly below normal.
2. Wide Range Achievement Test (WRAT) measures Reading: number of words read correctly, Spelling: number spelled correctly, and Math: number math problems solved correctly in 15 min.
3. Computer-Based Reading Speed test determined speed needed to read six consecutive words in story, *Wrinkle in Time* by Madeleine L'Engle, on computer screen, at increasing speeds to measure two reading rate thresholds (16–19, 25–27, 63).
4. Attention tests measured using either: Integrated Visual and Auditory Continuous Performance Plus (IVA + Plus) Tests from *BrainTrain* to measure attentional focus, sustained attention, or inattention, hyperactivity, and impulsivity by measuring the accuracy and reaction time of different responses to different tasks that are scored and converted to standardized percentile scores by the IVA+ computer program, Or Delis-Kaplan Executive Function System (DKEFS) Color-Word Interference test, where subject says printed color of words that denoted a different color (Stroop Attention test), and Attention Switching (Cognitive Flexibility), switching between color of word and what word says when surrounded by a rectangular box. The standardized percentile is reported in Tables 1, 2 (Attention and Cognitive Flexibility) since these are the most meaningful scores to understand attention levels pre and post intervention training.
5. Wechsler Adult Intelligence Scale (WAIS)-4 Processing Speed required two subtests: (1) the WAIS Symbol Search subtest which required subjects to scan a target group (two symbols) and search a group of 5 symbols, indicating whether one of the target symbols appeared in the search group, and (2) WAIS Digit Symbol Coding subtest, where the subject filled in boxes below digits with symbols that were paired with them in a key at the top of the page. Both of these subtests were timed for 2 min each. The scaled scores from each subtest were combined to create an overall Processing Speed Index score, that was converted to a standardized percentile score.
6. WAIS-4 Working Memory Index to measure Auditory Working Memory (AWM) required two subtests: (1) the Digit Span subtest, where the subject had to repeat a list of spoken numbers, requiring the subject to remember subsequently more numbers: in the correct order, backwards, and in numerical sequence on three different subtests, and (2) the Letter-Number Sequencing subtest which required sequencing subsequently more numbers and letters in the correct numerical and alphabetic sequence. Presentation of the numbers and letters were timed for one second each for these working memory tests.
7. Visual Working Memory (VWM) using the Test of Information Processing Skills (TIPS), provided by WPS: *WesternPsychologicalServices*. The subject recalled a sequence of letters presented visually one at a time for 2 s each, for sequences of from 2 up to 9 letters right after seeing the entire sequence of letters. Short Term VWM was assessed by recalling the correct sequence of letters after counting from 1 to 10 numbers in sequence, starting at different initial numbers, slowly, and after repeating a short sentence with an animal subject for VWM. Delayed Recall was assessed by remembering all animal names in repeated sentences 3 min after finish the VWM test.

All of these cognitive assessments, which were age-appropriate, took 1.5 h to complete.

3. Results

Both MEG brain imaging, see Figure 2, and neuropsychological behavioral tests, see Tables 1, 2, found substantial improvements in the visual, attention, and executive control networks after PATH to Reading™ training. The dyslexic subject read *A Wrinkle in Time* for 30 min after each training cycle (2 sessions), whereas the older adult practiced cognitive exercises, either math problems or playing chess, for 30 min following each training cycle, since previous research (14) found that practicing on what one needs to improve is essential for PATH neurotraining to be effective. Both subjects found the intervention to be easy to complete, noticing the improvements right

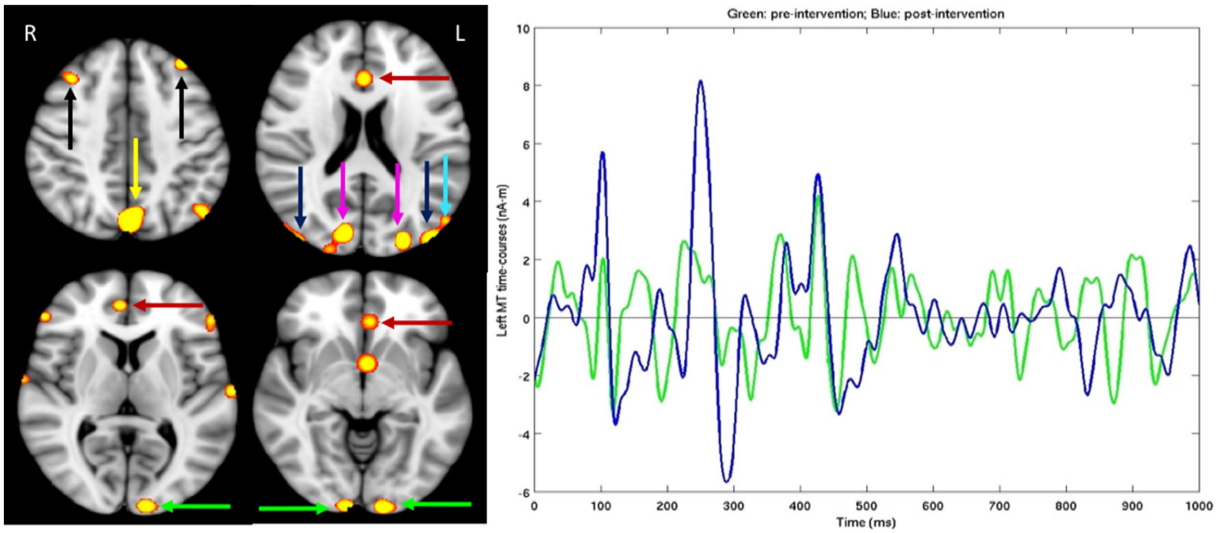

FIGURE 2
For dyslexic subject, after standardized tests were administered MEG brain imaging before and after the PATH neurotraining intervention was completed. Left Panel: Different slices from the left (L) and right (R) sides of the brain. Hot spots showing significant MEG source magnitude (i.e., root-mean-square measure) signal increases were computed from mean square measure of MEG signal increases for the 0–1,000 ms time interval following the stimulus onset in post- versus pre-intervention exams, for an adult male dyslexic aged 29 years. Familywise error was corrected for multiple comparison across spatial voxels using standard cluster analysis. For those hot spots, the corrected value of *p* thresholds were at $p = 0.01$ for red, and $p = 0.001$ for bright yellow color. Green arrows: Visual Area 1 (V1); Blue arrows: Middle Temporal (MT) cortex; Magenta arrows: visual Area 3 (V3); Cyan arrow: Medial Superior Temporal (MST) cortex; Red arrows: Anterior Cingulate Cortex (ACC); Yellow arrow: precuneus/Posterior Cingulate Cortex (PCC); Black arrows: dorsal lateral Prefrontal Cortex (dlPFC); Right Panel: MEG source time-courses from left MT area during post-intervention (Blue line) and pre-intervention (Green line) exams in the figure above.

away, and had no trouble completing the intervention on their own, after initial training at UCSD or Perception Dynamics Institute.

3.1. Dyslexic adult improved in reading, attention, processing speed, and memory

MEG brain imaging, Figure 2, right panel, shows that improvements in MT (difference between pre-and post- MEG exams) happen in the first 300 ms. Showing that this training sped up magnocells in visual dorsal pathways. The details of the evoked potentials in MT are shown (right panel), whereas the data from other regions were not chosen, because MT is the main region of interest for improving the function of the dorsal stream that has been shown previously not to be responsive in dyslexics (64, 65). The improvements in MT reveal improvements in P1 and N1, showing that the post-intervention signal is increased in sensitivity for both excitatory and inhibitory signals, at durations between 80 and 150 ms that result from *alpha activations* (10–13.3 Hz), and in P2 and N2 at durations between 240 and 300 ms from *theta activations* (6.7–8 Hz), improvements in N1 and N2 known to be enhanced by selective attention (66) were found for older adults following twice as much perceptual training (67). Different slices from the left (L) and right (R) sides of the brain are shown in the left panel since the brain exhibits asymmetrical functioning in the two sides of the brain, with dyslexics showing more cognitive deficits in the left side of the brain (68). Hot spots showing significant MEG source magnitude (i.e., root-mean-square measure) signal increases were computed from mean square measure of MEG signal increases for the 0–1,000 ms time interval following the stimulus onset in post- versus pre-intervention exams, for an adult male dyslexic aged 29 years. Familywise error was corrected for multiple comparison across spatial voxels using standard cluster analysis. For those hot spots, the corrected value of p thresholds were at $p = 0.01$ for red, and $p = 0.001$ for bright yellow color. Substantial MEG signal increases (left panel) in visual Motion Networks [V1, V3, MT, Medial Superior Temporal cortex (MST)], Attention Networks [Anterior Cingulate Cortex (ACC) and precuneous/Posterior Cingulate Cortex (PCC) areas] and Memory Networks (dlPFC) were observed following a short period of training on contrast sensitivity-based movement-discrimination, the same improvements found after a TBI (15).

Behavioral tests, shown in Table 1, found that his reading speed improved almost 3-fold, and his processing speed improved from much lower than average (23%) to average (50%). Moreover, his attention skills improved markedly. His performance in IVA+ Focusing Attention improved from the lowest 1% to just above average (54%), his IVA+ Sustained Attention improved from the lowest 10% to 82% (i.e., better than 82% of his peers), and his IVA+ Impulsivity improved from much lower than average (18%) to above average (62%). His working memory skills improved markedly as well. His visual working memory improved from the lowest 6% to 99% (better than 99% of his peers), and his delayed recall improved from the lowest 1% to 25%. He also improved in visual skills, markedly reducing his convergence insufficiency: his near point of convergence was reduced from 9 cm down to 3.5 cm and his visual acuity improved from 20/20 to 20/16. In addition to these improvements, his quality of life also improved remarkably, doing activities that previously were too overwhelming to consider: getting married, starting a business helping dyslexics, finishing college, and becoming an electrician, being very grateful. These improvements were retained years later, this subject reported.

These improvements in cognitive skills found for dyslexics following contrast sensitivity-based movement-discrimination training were not found by targeting higher level phonological skills like FastForWord, nor linguistic-based training like Learning-Upgrade (19), nor computer-based repeated reading (14, 27, 69) which was 4-fold less effective. These improvements were also found in 6–8 year-old typically-developing children (25–27, 50), which is the age when the temporal lobe shows peak synaptogenesis (70). These findings support the hypothesis that visual magnocellular pathways provide the gateway for attentive processing (28–30) and reading (71–73), since timing impairments can be reduced following training using contrast sensitivity-based left–right movement-discrimination exercises (19, 27). Research finds that there is an imbalance between magno- and parvo-cellular systems in dyslexics (74). These results confirm the causal role of visual motion sensitivity and faulty synchronization of parvocellular with magnocellular visual pathways in the dorsal stream as a fundamental cause of dyslexic reading problems.

3.2. Older adult improved in reading, attention, processing speed, and working memory

The older adult's contrast sensitivity function for movement-discrimination for each test frequency, when averaged across the five background patterns at each level of complexity, is shown in Figure 3. These contrast sensitivities are amongst the highest yet recorded, showing age was not a limiting factor. The contrast sensitivities for the widest bars, 0.25 cyc/deg., were much lower than for other test frequencies, supporting the hypothesis that information from several spatial-frequency neural channels must be combined for movement-discrimination, making this task so difficult. The highest contrast sensitivities were found for 2 cyc/deg. test frequency, detected using a single spatial-frequency channel (75). A similar pattern of contrast sensitivities for movement-discrimination in older adults was found previously (55).

After 8 weeks of movement-discrimination training, and practicing cognitive exercises, either math problems or playing chess, for 30 min following each training cycle, large improvements in working memory (VWM: from 34 to 86%, AWM: from 55 to 97%) were found for the older adult who was already adept at paying attention, yet still improved after training, see Table 2. Moreover, her processing speed improved from 42 to 77%. Her reading skills improved markedly, more than doubling in reading speed, dyslexia improving to above normal, and WRAT Reading, Spelling and Math improving substantially, as shown in Table 2. These results show that not only reading, attention, processing speed and working memory skills, but also problem-solving skills improved markedly, showing cognitive transfer to untrained tasks. When this older adult was tested on these behavioral tests 4 years and 2 months later, when she was 76 years old, having had no additional cognitive training, the remarkable cognitive improvements were still evident, showing that the improvements in cognitive skills after PATH training are sustained over time. Remarkably, some cognitive skills were even higher 4 years later, see Table 2, including processing speed, now 87% (improving 10% more), VWM, now 87%, and Spelling now 73%. AWM was still high at 90%, as was problem solving at 92%. Not only cognitive skills improved, but her visual skills also improved, improving from a near point of convergence of 25 cm down to 15 cm. Her visual acuity of 20/32 did not change. These results validate the reported improvements in cognitive skills found previously (55) using robust neuropsychological tests. Since coupled alpha-gamma activity is reduced in older adults with mild cognitive impairments (76), these

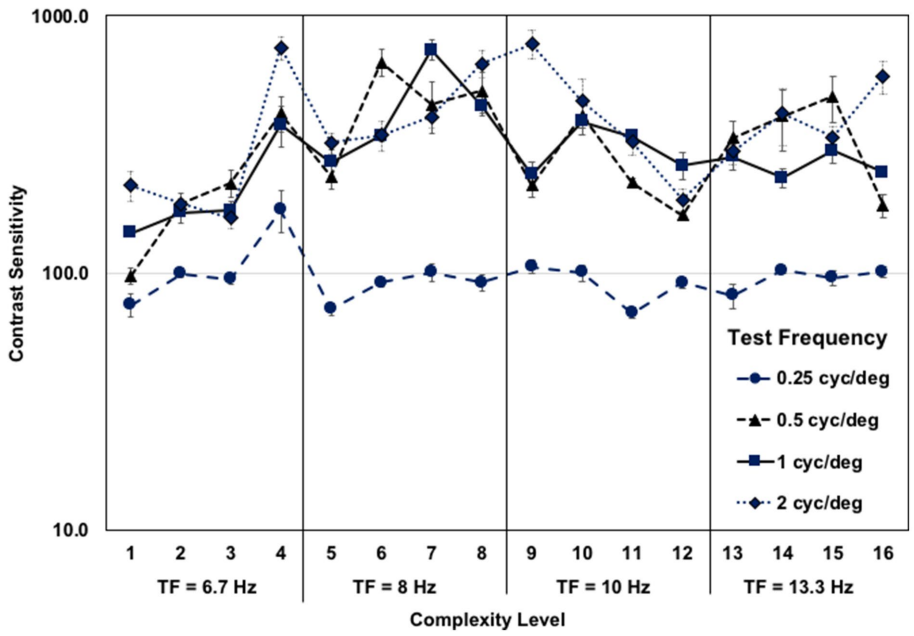

FIGURE 3
Older adult mean contrast sensitivity function for left–right movement discrimination at each complexity level, for each test frequency, when averaged across the five background patterns, each 4 complexity levels having a faster test frequency temporal frequency (TF). The first eight complexity levels trained coupled gamma/theta oscillations (6.7–8 Hz) and the second eight complexity levels trained coupled alpha/gamma oscillations (10–13.3 Hz), showing similar contrast sensitivities for both.

improvements in processing speed and working memory provide more evidence movement-discrimination training improves coupled alpha-gamma activity.

Following contrast sensitivity-based left–right movement-discrimination training, this older adult's quality of life improved remarkably. She reported "My memory, reading speed, ease of understanding, processing speed, ability to multitask, concentrate, and pay attention have improved remarkably in just a few months. Since doing PATH training, I find that driving is much easier, and I am able to attend to a much wider region, allowing me to see street signs more easily. I am now able to distinguish the other car movements at dawn and dusk much better improving my driving skills. These improvements in remembering, concentrating, and reading have made life much easier and more enjoyable. I have noticed that everyday activities are so much easier to complete and are more enjoyable. I hope that you are able to help other older adults so that forgetting and everyday activities are no longer difficult." This subject reported that these improvements have not degraded over time, and are really appreciated.

These results demonstrate neuroplasticity in the domain of visual motion sensitivity and timing, processing speed, reading speed, attention, working memory, and problem solving using a short period of practice on discriminating moving patterns that optimally activate magnocells, relative to a stationary background that optimally activates parvocells. We found, using MEG source imaging and behavioral neuropsychological tests, that speeding up these motion cells improves not only the visual pathways, but also the attention and executive control networks of both young adults who are dyslexic, and older adults with mild cognitive impairments. The dramatic improvements are reliable and cannot be due to practice effects, since none of the test items nor their order of presentation could be memorized. These improvements are also verified by patient reports at the end of the study and years later. Subjects experienced no adverse effects, only benefits.

4. Discussion

This study supports our working hypothesis (14, 15, 19, 27) that magnocellular neurons in dorsal visual pathway (V1-MT) of dyslexics are sluggish, causing visual timing deficits at lower levels of visual processing that disrupt processing at higher levels of dorsal stream processing, including the development of these visual, attention, and executive control pathways. Considerable evidence confirms that many dyslexic readers demonstrate impairments in motion perception that rely upon magnocellular functioning. People with dyslexia have been found to have motion perception deficits at each of the processing levels in the magnocellular stream (14). These visual timing deficits limit reading acquisition in dyslexics. These results suggest a strong relationship between dorsal stream processing and reading ability, such that poor dorsal stream processing caused by sluggish magnocells is associated with slower timing and poorer reading skills (14, 16–20, 25–29, 63, 71–73, 77–80). Dyslexics lack the ability to process sequential information quickly and accurately, causing deficits in both reading speed and comprehension. These findings show that just by doing rapid brain exercises that improve a person's ability to discriminate left–right movement relative to a stationary background pattern, improving the brain's timing, one's ability to read rapidly and accurately can be improved significantly.

These improvements indicate that remediation of visual timing deficits (visual motion networks), via PATH training, generalizes to high level cognitive abilities, improving the function of not only the hubs of the attention networks (ACC, precuneus/PCC) but also the hub of the executive control network, dlPFC, where working memory is analyzed (81). Notice that the left cortical areas V1 and MT showed more improvements than the right V1 and MT, which is consistent with previous imaging studies showing that dyslexics have reduced activations in the left temporal, parietal, and fusiform regions (68). These improvements in visual, attention, and memory networks are also validated behaviorally. Only by improving low-level skills (movement-discrimination) do high-level cognitive skills such as attention, processing speed, working memory and reading improve.

The MEG results from both an adult dyslexic and after a TBI (15) corroborate these findings, showing that the timing and sensitivity of magnocells in MT improve significantly after a short period of contrast sensitivity-based movement-discrimination training. Moreover, finding P1, N1, and P2, N2 MT signals improved markedly after only 5 h of training on movement-discrimination indicates that attentional signals driven by coupled alpha/gamma and theta/gamma oscillations, respectively, are enhanced (67). Furthermore, there is evidence that improvements in the cognitive skills of dyslexics after this movement-discrimination training that is more rapid and effective than the competition are sustained over time (14, 18, 19, 27), as also shown for the older adult in this study.

The data from this study provides new evidence that deficits in attentional focus, working memory, and navigation experienced by older adults result from timing deficits in the dorsal stream that are abated rapidly following training on contrast sensitivity-based movement-discrimination. Slower processing speeds and more effortful attention were found to explain a large part of age-related memory loss (82–84). This mental slowing can lead to inefficient processing based on strategies where further elaboration is required (85). Since this study found that improving bottom-up timing improved high-level cognitive skills, requiring coupled theta/gamma and alpha/gamma oscillations, this indicates bottom-up processing is the limiting factor in cognitive skills declining as we age. This conclusion is supported by the neural plasticity underlying visual perceptual learning in aging following training on a movement-discrimination task designed to activate MST (67). This perceptual training of older adults (67) produced large improvements in speed and accuracy, but no improvements in cognitive skills validated by neuropsychological tests, like those shown in Table 2, were reported. It is likely that contrast sensitivity-based movement-discrimination training, activating magnocells at both early and late levels of dorsal stream processing is more effective in improving cognitive skills in older adults.

4.1. Study limitations

This study has limitations since only two subjects were studied. The purpose of a case report is to demonstrate phenomena worthy of future investigation. Since those who completed PATH training, including dyslexics, older adults, and following a concussion experienced improvements in their visual and cognitive skills (14, 15, 17–20, 27, 50, 55, 56), we expect the improvements in visual and cognitive skills reported in this case report to be found when a larger group of subjects is studied. Additionally, due to sample size standard statistics showing whether these improvements are statistically significant cannot be assessed. Further limitations come from the relatively small number of trials in the imaging paradigm (approximately 200 at pre- and post- test, each). Future studies

could improve the strength of the MEG signal with a larger number of experimental trials. However, the magnitude of improvements seen in the two cases presented are certainly promising. Currently, PATH training is used by some therapy centers, since some, like Stowell Learning Center, have found it rapidly remediates attention deficits that are not addressed by any other intervention. Future studies are planned to provide MEG neural correlates showing that coupled theta/gamma and alpha/gamma oscillations increase following PATH neurotraining.

5. Conclusion

Since this study found that a short period of movement-discrimination training improved dyslexic and older adult's cognitive skills, both behaviorally and using a neural correlate, MEG physiological brain recordings, this data provides irrefutable evidence that improving low-level dorsal stream activity by increasing the timing and sensitivity of magnocells enhances coupled theta/gamma and alpha/gamma oscillations that enable improving both low- and high- level cognitive functions. Other cognitive training programs: (1) had little effect on improving the executive functions and attention in TBI (86, 87), (2) had results from brain training that were neither robust nor consistent, with transfer and sustained effects which were limited (88), and (3) improved only the task being trained on, and do not generalize to tasks not trained on or everyday cognitive performance (59). Currently, there are no proven solutions to improve attention and working memory in TBI patients (86, 89–91). We propose that rehabilitative treatments fall short because visual timing issues, persistent in individuals with a TBI (15, 92), with dyslexia (14, 17–20, 27–30, 50, 71–73), and older adults (55, 67, 82), are not being addressed. This study found that remediating visual timing deficits, via PATH training, generalizes to high level cognitive abilities not trained on, improving not only attention and memory, improving the functioning of the executive control network (81), but also processing speed and reading speed, behavioral measures of timing, after a short period of movement-discrimination exercises. By using a broad battery of pre-post neuropsychological tests, as well as pre-post MEG recordings, in this study and previously (15), the data indicate that PATH training improvements transfer to a broad range of cognitive abilities. These improvements were found for all users of PATH neurotraining (14, 17–20, 27, 50, 55, 56), also verified by testimonials on https://pathtoreading.com/testimonials. Recovering these cognitive skills will substantially improve a person's quality of life. These studies indicate that a paradigm shift for remediating dyslexia and in treating attention, processing speed, memory, problem solving, and reading impairments in older adults, and after a concussion is needed.

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 UCSD Institutional Review Board and SolutionsIRB. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TL and M-XH contributed to conception and design of the study. JS-T and M-XH performed the statistical analysis. TL wrote the first draft of the manuscript. TL, JS-T, and M-XH wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

TL has a potential conflict of interest, since she is the developer of PATH to Reading/Insight program (https://pathtoreading.com), and was employed by Perception Dynamics Institute. The role of this author was to design the behavioral study, recruit and train staff, run daily operations and help write the article. She had no part in collecting or analyzing the data, however, thereby having no influence over the results that were obtained.

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.

Publisher's note

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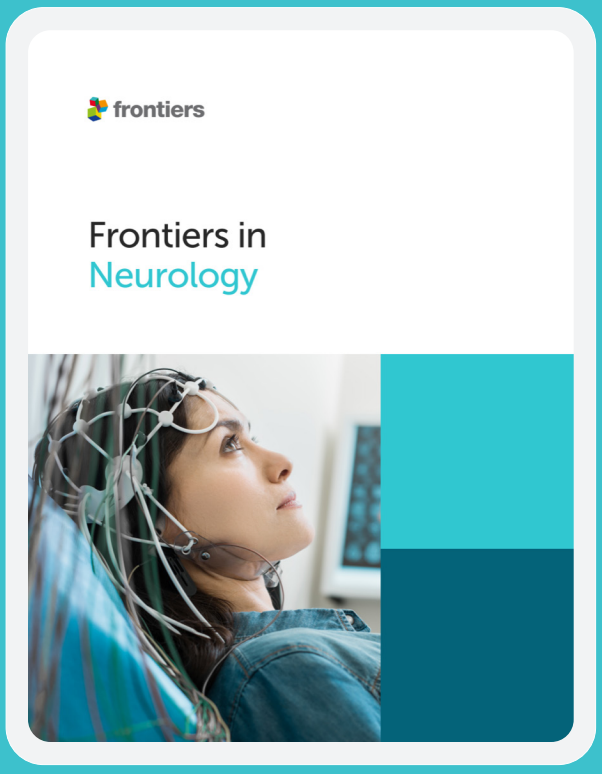

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