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Epilepsy – case report collection 2022

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CASE REPORT
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Case Report: Stereoelectroencephalography and Stereoelectroencephalography-Guided Radiofrequency Thermocoagulation in Familial Lateral Temporal Lobe Epilepsy

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Familial lateral temporal lobe epilepsy (FLTLE) is genetic focal epilepsy usually characterised by auditory symptoms. Most FLTLE cases can be controlled by anti-seizure medications, and to our best knowledge, there are no previous reports about stereoelectroencephalography (SEEG) used for patients with FLTLE. In this report, we present two patients with FLTLE in one family and their SEEG performances, together with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET and MRI results. In case 1, fast activities originated from the right superior temporal gyrus and spread rapidly to the right anterior insular lobe and hippocampus. In case 2, there were two seizure patterns: (1) The fast activities or sharp slow waves were identified at the left superior temporal gyrus, then, sharp waves and spike waves spread in the left superior temporal gyrus; (2) There were fast activities and slow-wave oscillation originated in the left superior temporal gyrus, then, the fast activities spread in the left superior temporal gyrus and finally spread to the other sites. An SEEG-guided radiofrequency thermocoagulation was performed for both patients and one of them underwent resection surgery. Seizures are well-controlled and the patients are very satisfied with the therapeutic effects.

Keywords: superior temporal gyrus, stereoelectroencephalography-guided radiofrequency thermocoagulation, stereoelectroencephalography, familial lateral temporal lobe epilepsy, case report

INTRODUCTION

Familial lateral temporal lobe epilepsy (FLTLE) is genetic focal epilepsy usually characterised by auditory symptoms. Despite the complexity of FLTLE, it is generally considered as a benign epilepsy syndrome and routinely used anti-seizure medications can usually control seizures (1).

Stereoelectroencephalography (SEEG) is a methodology for presurgical invasive evaluation and SEEG-guided radiofrequency thermocoagulation (RFTC) can be used as an alternative to resection surgery. Using stereotactically implanted electrodes, SEEG provides neuronal electrical activities

recordings in the deep brain (2) and helps locate epileptogenic zone for thermocoagulation or resection surgery (3). Most FLTLE seizures can be controlled by anti-seizure medications, and there are no previous reports about SEEG being used in the treatment of patients with FLTLE. Here we report two refractory FLTLE cases in one family. SEEG and SEEG-guided RFTC were performed for both patients and one of them underwent resection surgery. Seizures are well-controlled and the patients are very satisfied with the therapeutic effects.

CASE REPORT

Case 1

A 47-year-old woman, with her grandmother and her son, was diagnosed with FLTLE. Seizures firstly occurred when she was 22, with the symptoms of a sudden loss of consciousness, daze, delayed movements, chewing, and hand groping-like movements. Genetic tests were refused.

In scalp electroencephalogram (EEG), interictal spikes and intermittent slow waves were observed in the bilateral anterior temporal region and sphenoidal electrode. Seizures were characterised by initial attenuation of background activity followed by low-voltage fast activity in the right temporal-occipital lobe, then, quickly spread to the right and left temporal lobe.

No abnormality was found in 3.0T T1-weighted (voxel space $= 2 \times 2 \times 2$ mm^3, TR $= 381$ ms, TE $= 2.3$ ms), T2-weighted (voxel space $= 2 \times 2 \times 2$ mm^3, TR $= 3{,}000$ ms, TE $= 100$ ms) or fluid-attenuated inversion recovery (FLAIR) (voxel space$=2 \times 2 \times 2$ mm^3, TR $= 4{,}800$ ms, TE $= 411.7$ ms) MRI. The ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET results were characterised by hypometabolism in the right superior temporal gyrus, right medial temporal lobe (**Figure 1**), and right insular lobe. The SEEG was performed, and the positions of electrodes were shown in **Figure 2**.

The SEEG in the interictal period showed obvious fast activities in the right superior temporal gyrus and the right anterior insular lobe. In the ictal period, fast activities originated from the right superior temporal gyrus (N1-8) and spread rapidly to the right anterior insular lobe (I3-8) and hippocampus (H1-3, B1-3) (**Figure 1B**).

The SEEG-guided RFTC was performed at electrodes N1-8 (**Figure 1B**), but there was no significant seizure decrease after the RFTC. She underwent the right anteromedial temporal lobe and insular lobe resection. The postoperative T1-weighted MRI results are shown in **Figure 3A**. Follow-up results showed that in the next 2 years, only one seizure occurred in 3 months after the operation.

Case 2

Case 2 was a son of case 1, with normal delivery and no nervous system injury. The first seizure occurred at the age of 19, with limb tonic seizures at the frequency of about once a month. When he came to our hospital at 24, he felt dizzy and cannot understand other people's language, then, he experienced consciousness loss, bilateral upper limbs flexion, and elicited mouth movements. Genetic tests showed an abnormality in the microtubule-associated protein tau (MAPT) gene and linked it to chr17:44060593.

Scalp EEG showed that the epileptiform activities mainly occurred in the left sphenoidal electrode and frontotemporal region. Ictal EEG was characterised by initial attenuation, followed by rhythmic 5–6 Hz activities in the left sphenoidal electrode and frontotemporal region.

No abnormality was found in MRI results with the same scanning parameters as in case 1. The PET results suggested hypometabolism in the left superior temporal gyrus, left supramarginal gyrus, and inferior central gyrus (**Figure 4A**).

The SEEG in the interictal period showed obvious abnormal discharges in the left superior temporal gyrus, which then affected the lateral temporal lobe. Two types of seizure patterns were identified.

In the first seizure pattern, the patient felt dizzy and had auditory hallucinations. The seizures were then followed by daze, wink, and chewing. During this pattern, fast activities or sharp slow waves were identified at the left superior temporal gyrus (N'3-5), then, sharp waves and spike waves spread in the left superior temporal gyrus (N'2-8, W'5-10, X'4-8), as shown in **Figure 4B**.

The second seizure pattern was characterised by feeling uncomfortable, groaning, right and then both upper limbs tonic seizures, right-turning head, and, finally, secondarily generalised tonic-clonic seizures. There were fast activities and slow-wave oscillation at the left superior temporal gyrus (N'3-5), then, the fast activities spread in the left superior temporal gyrus (W'2-9, N'2-6) and, finally, spread to the other sites (**Figure 4C**).

The RFTC was performed at electrodes W'1-10, N'1-8, and X'1-10. The T1-weighted MRI results after the RFTC are shown in **Figure 3B**. According to the last follow-up at 18 months after the RFTC, he remained seizure-free (Engel 1A).

DISCUSSION

Familial temporal lobe epilepsy (FTLE) can be subdivided into lateral and mesial forms by clinical and genetic characteristics, and FLTLE is characterised by auditory auras (1). Several protein mutations were considered to be associated with temporal lobe epilepsy, such as axon guidance proteins, leucine-rich glioma inactivated 1 protein, microtubular protein, pore-forming, chromatin remodelling, and chemokine proteins (4). Hyperphosphorylated tau protein has been identified in patients with refractory temporal lobe epilepsy and might be the cause of the cognitive decline in these patients (5). Given that there were no other genetic abnormalities detected in case 2, we suppose that MAPT mutation played a role in the case of FLTLE. However, such supposition still needs further verification.

For patients with FTLE, most of the reports mentioned that they had a good response to anti-seizure medications, and the disease would be gradually controlled with the increase of age. Cendes et al. (6) reported 36 FTLE cases, including eight with refractory epilepsy who underwent surgery. Fabera et al. (7) also reported two FTLE cases that underwent left

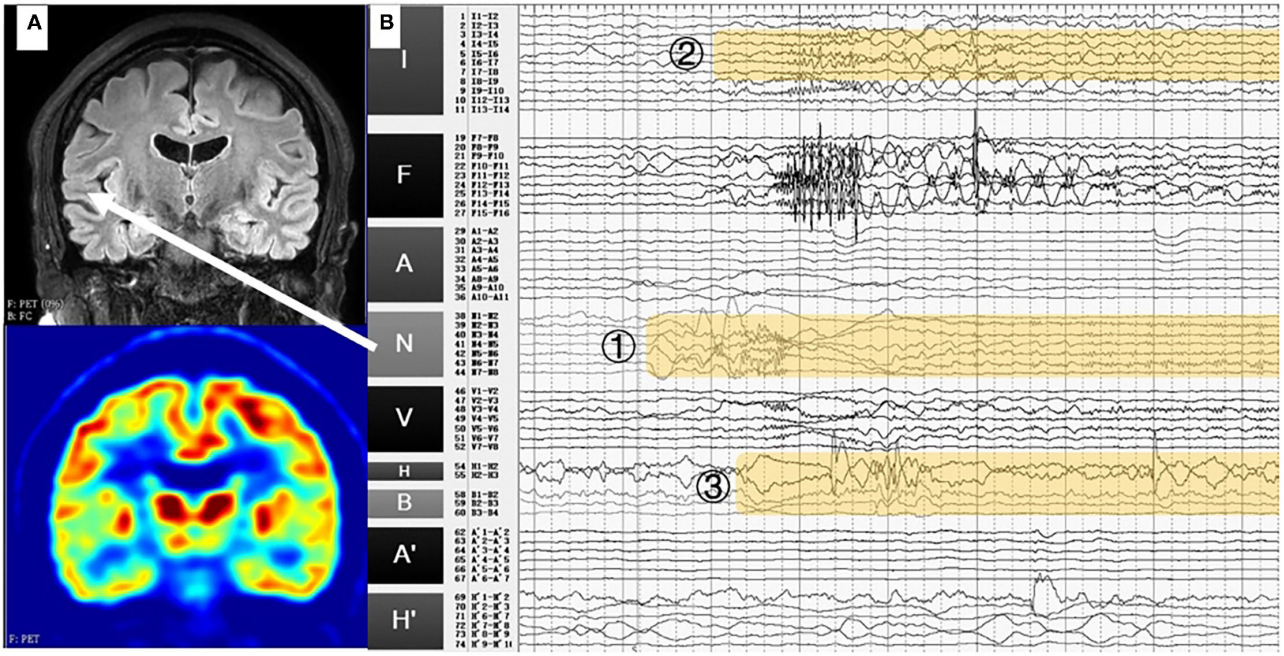

FIGURE 1 | (A) T1-weighted MRI and PET results of case 1. No abnormality was found in MRI, while hypometabolism was identified in the right superior temporal gyrus. **(B)** Stereoelectroencephalography (SEEG) signals in the ictal period. Fast activities originated from the right superior temporal gyrus ① (N1-8) and spread rapidly to the right insular lobe ② (I3-8) and hippocampus ③ (H1-3, B1-3). White arrow: the location of the electrodes N in MRI (right superior temporal gyrus).

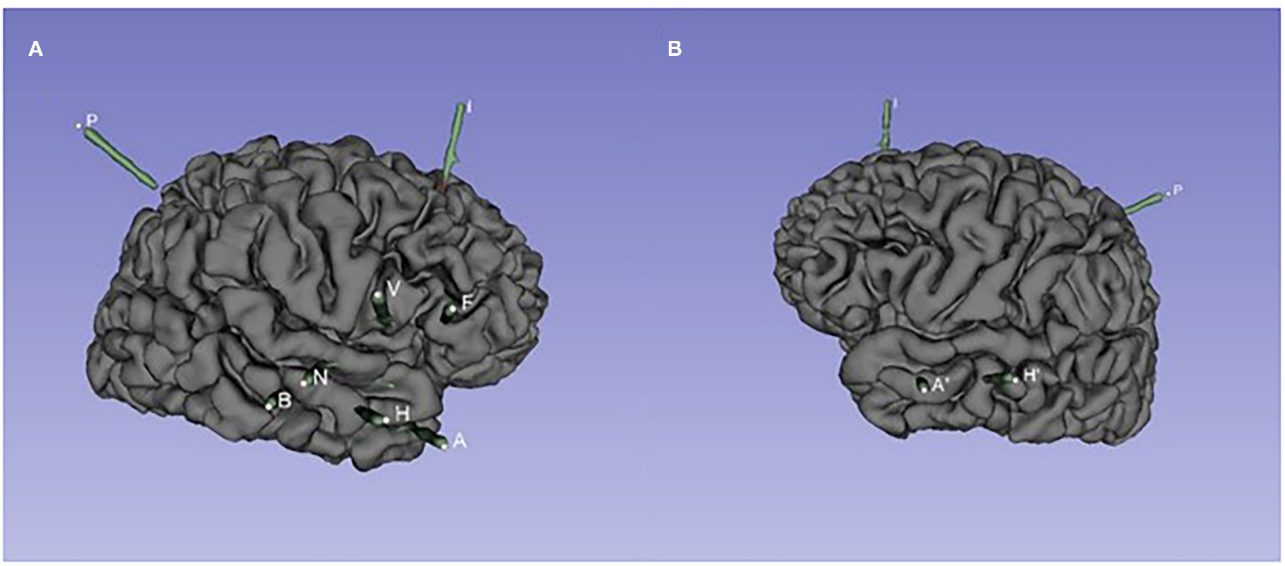

FIGURE 2 | The spatial position of SEEG electrodes of case 1. **(A)** Right hemisphere. Entry points to target points: A: the middle temporal gyrus to the amygdala; H: the middle temporal gyrus to the head of the hippocampus; B: the middle temporal gyrus to the middle of the hippocampus; N: the superior temporal gyrus to the posterior insular gyrus; V: opercular partis to the short gyri of insula; F: pars triangularis to anterior cingulated cortex; I: the middle frontal gyrus to the accessory gyrus; P: the supramarginal gyrus to the anterior insular gyrus. **(B)** Left hemisphere. Entry points to target points: A′: the middle temporal gyrus to the amygdala; H′: the middle temporal gyrus to the head of the hippocampus.

anteromedial temporal lobectomy. Koizumi et al. (8) reported five refractory epilepsy cases in one family. Among them, four patients underwent bilateral subdural electrode implantation and resection, two patients underwent standard anterior temporal lobectomy and two underwent lateral temporal lobectomy, and all of them were rated as Engel 1 after the operation. The cases

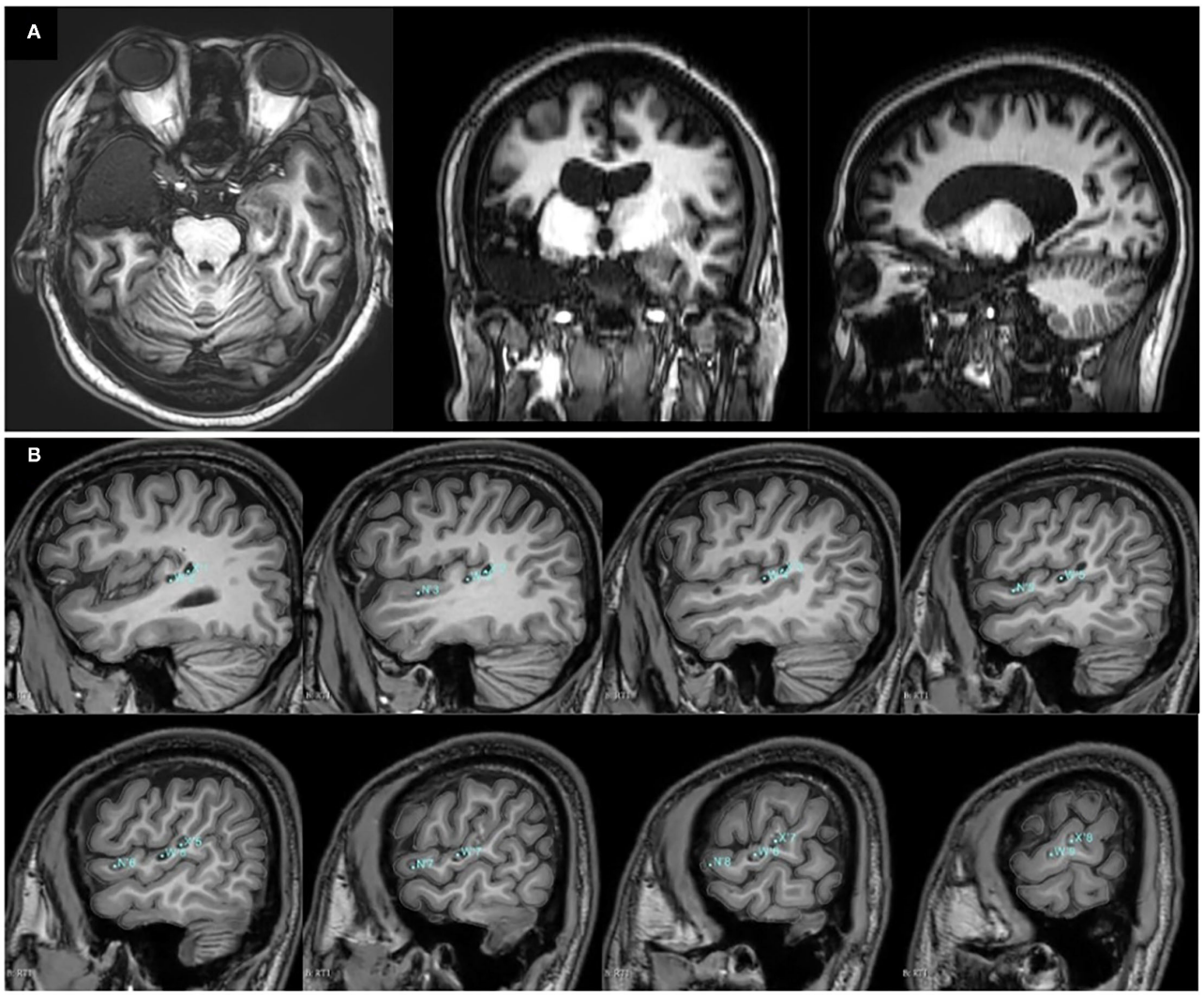

FIGURE 3 | Postoperative T1-weighted MRI results. **(A)** T1-weighted MRI results of case 1 after the right anteromedial temporal lobe and insular lobe resection. **(B)** T1-weighted MRI results of case 2 after SEEG-guided radiofrequency thermocoagulation (RFTC). The locations and labels of the electrodes for the thermocoagulation were marked in blue.

reported in this paper also showed that surgery has a good effect on patients with refractory FLTLE.

According to the results of SEEG and clinical information, the superior temporal gyrus was confirmed as the onset area, and SEEG-guided RFTC was performed. However, only case 2 had a significant curative effect. The SEEG signal can provide effective information to locate the epileptogenic zone, but by the limited number of electrodes and the range of thermocoagulation, SEEG-guided RFTC may easily miss the epileptogenic zone. Koizumi et al. (8) reported two cases, whose epileptic focuses were located in the superior temporal gyrus by electrocorticographic results, one case in the lateral temporal lobe (including the superior temporal gyrus) and the other in the inferior temporal gyrus and fusiform gyrus. Whether these results suggest that the epileptic focus of FLTLE located in the superior temporal lobe still needs more clinical results to confirm. We identified three different seizure spreading patterns: (1) pure superior temporal gyrus with auditory symptoms; (2) mesial temporal lobe with automatisms; and (3) frontal lobe with movement symptoms.

Interestingly, the epileptic focus in case 1 is located in the right superior temporal gyrus, whereas the one in case 2 is located in the left superior temporal gyrus. In the FLTLE family reported by Koizumi et al., the three patients' epilepsy focuses were located on the left side and one on the right (8). The invasive EEG monitoring results suggest that, although FLTLE is an autosomal dominant genetic disease, the side of epileptic focus is not fixed.

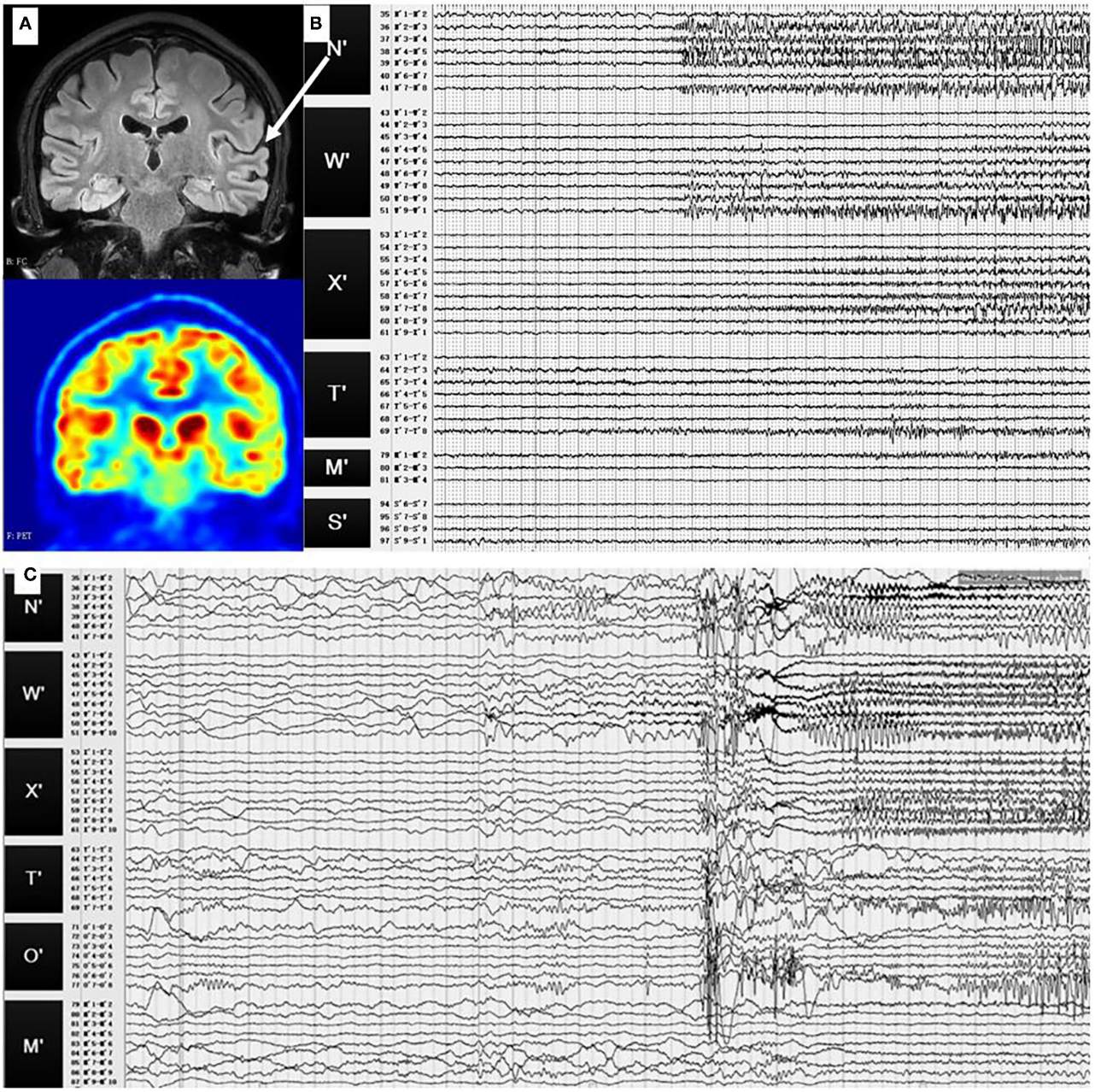

FIGURE 4 | (A) Preoperative T1-weighted MRI and PET results of case 2. No abnormality was found in MRI, while hypometabolism was identified in the left superior temporal gyrus. **(B)** SEEG signals of the first seizure pattern. During this pattern, fast activities or sharp slow waves were identified at the left superior temporal gyrus (N′3-5), then sharp waves and spike waves spread in the left superior temporal gyrus (N′2-8, W′5-10, X′4-8). **(C)** SEEG signals of the second seizure pattern. There were fast activities and slow-wave oscillation at the left superior temporal gyrus (N′3-5), then the fast activities spread in the left superior temporal gyrus (W′2-9, N′2-6), and finally, spread to the other sites. White arrow: the location of the electrodes N′ in MRI (left superior temporal gyrus).

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ruijin Hospital Luwan Branch Ethics Committee, Shanghai Jiao Tong University School of Medicine. 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

QL, XY, CW, and JX designed and implemented the treatment and provided clinical information. ZW, PZ, and JZ summarised relevant researches and wrote and revised the case report. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Macroglossia Associated With Clobazam Administration: A Case Report and Literature Review

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Clobazam is a benzodiazepine derivative used as an antiepileptic agent for the treatment of focal and generalized seizures and drug-resistant epilepsy associated with Lennox-Gastaut Syndrome. While somnolence and mood-related side effects are commonly observed, acute macroglossia following initiation of Clobazam therapy has not been previously reported in the medical literature. In this case report, we present a female pediatric patient who developed significant tongue swelling with protrusion beyond the oral cavity after initiation of Clobazam for treatment-resistant epilepsy. Symptoms were unresponsive to antihistamines and steroids but resolved gradually in the days following discontinuation of Clobazam with no lingering sequelae.

Keywords: antiseizure drug, Clobazam, epilepsy, macroglossia, pediatric neurology

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INTRODUCTION

Macroglossia is defined as a painless enlargement of the tongue that presents either congenitally in association with a wide variety of inherited disorders (e.g., Down Syndrome, Hunter and Hurler Syndromes, Beckwith-Wiedemann Syndrome) or acquired as a result of inflammation, amyloidosis, and endocrine and metabolic disorders. In rare cases, severe tongue swelling causing upper airway obstruction presents as a medical emergency requiring reduction glossectomy, which is indicated in an estimated maximum of 10% of cases of macroglossia (1). Frequently, acquired macroglossia resolves spontaneously with treatment of the underlying cause, and corticosteroids have also shown effectiveness in reducing glossal edema associated with trauma and mechanical injury (2).

Macroglossia secondary to angioedema is commonly observed in the setting of drug hypersensitivity reactions, in which drug-antigen presentation causes crosslinking of IgE immunoglobulins on the surface of mast cells with subsequent degranulation of intracellular contents. The release of vasoactive substances such as histamine and bradykinin leads to increases in the permeability of submucosal and subcutaneous capillaries, resulting in fluid shifts into the interstitial environment that cause localized tissue swelling. The onset of glossal swelling following the administration of Clobazam therapy for refractory epilepsy has not been previously reported in the literature and the pathophysiology by which these symptoms occur is currently unknown. In this case report, we present a pediatric patient who developed significant tongue swelling with protrusion beyond the oral cavity in the days after initiating Clobazam therapy for treatment-resistant epilepsy and whose symptoms resolved gradually following discontinuation of the drug.

Day 1	Lorazepam and Fosphenytoin doses given in ED, Midazolam drip started in PICU
Day 2	Clobazam administered
Day 3	
Day 4	Antibiotics discontinued
Day 5	Tongue swelling first noted, Furosemide given
Day 6	Tongue swelling worsens, Diphenhydramine given
Day 7	
Day 8	Tongue swelling continues to worsen, Clobazam discontinued
Day 9	Dexamethasone started
Day 10	
Day 11	Dexamethasone discontinued due to lack of improvement
Day 12	Tongue swelling unchanged, patient intubated due to concern of airway loss
Day 13	Tongue swelling improves, patient extubated
Day 14	Tongue swelling continues to improve
Day 15	Complete resolution of symptoms

FIGURE 1 | Timeline of patient hospitalization events.

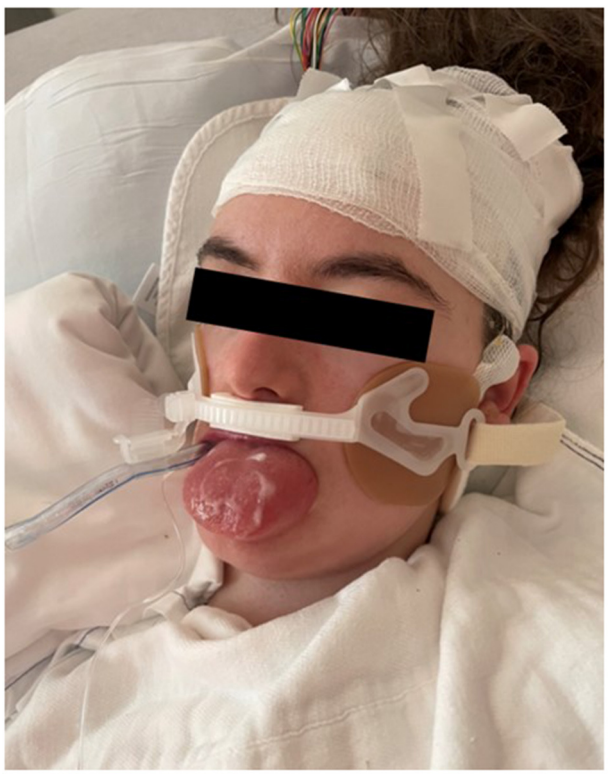

FIGURE 2 | Patient with notable tongue enlargement and protrusion from oral cavity.

CASE PRESENTATION

A 17-year-old Caucasian female, born at 34 weeks *via* Cesarean section, presented to the emergency department (ED) with status epilepticus. Her past medical history was significant for unbalanced chromosome 6 and 21 translocation, gross developmental delay, polymicrogyria, low-lying cerebellar tonsils, arachnoid cyst, micrognathia, scoliosis, and multifocal drug-resistant epilepsy since age 5 (managed on Levetiracetam, Lacosamide, and rectal Diazepam as needed). At baseline, the patient experiences four seizures per day lasting between 30 and 60 s and the parents report the patient maintains good compliance with her antiseizure drug regimen. In the 24 h prior to admission, the father estimated that she had ∼80 breakthrough seizures with episodes of head deviation and whole body stiffening and shaking each lasting between 30 and 120 s in duration. No significant improvement was observed after giving extra doses of Levetiracetam and Lacosamide. The family denied any recent history of fever, upper respiratory infection, nausea, vomiting, urinary symptoms, trauma, or travel. Previous attempts to control the patient's seizures using Topiramate, Sodium Valproate, Oxcarbazepine, Zonisamide, and Lamotrigine were ineffective. **Figure 1** represents the timing of events in the patient's hospital course by day of admission.

Lab results showed leukocytosis (WBC, 15.1 $\times$ 10^9/L) with neutrophils 59.9% and lymphocytes 32.0%, and reactive thrombophilia (482 $\times$ 10^9/L). Comprehensive metabolic panel was significant only for anion gap elevation (16 mmol/L) and low bicarbonate (15 mmol/L) which resolved over the following days. Ceftriaxone was started for empiric coverage; initial blood cultures grew Staphylococcal species and Vancomycin was added. The patient's seizures were terminated by Lorazepam and Fosphenytoin loading in the ED. She was continued on her home antiseizure medications and continuous video electroencephalography (EEG) was started. The patient was stabilized in the ED and transferred to the pediatric floor. Overnight, the patient began to have seizures again and EEG detected epileptogenic sharp waves over the left hemisphere. Due to continued seizures, the patient was subsequently transferred to the pediatric intensive care unit (PICU), started on a Midazolam drip, and required endotracheal intubation for airway protection. Clobazam 5 mg BID was initiated on Day 2 of hospital admission for further seizure control. Head CT and brain MRI

were negative for acute intracranial pathology. Antibiotics were discontinued on Day 4 following negative blood, urine, and cerebrospinal fluid cultures, and the patient's seizures were reported to be adequately controlled at this time. On Day 5 of PICU admission, the patient was noted to have mild tongue swelling; this was initially thought to be secondary to fluid overload and the patient was started on Furosemide given her overall volume status. While her volume status notably improved, her tongue swelling continued to worsen, with inability to manually retract the tongue and protrusion beyond the oral cavity over the following day (**Figure 2**). No signs of infection or trauma were noted within the oral cavity on inspection. Trial of Diphenhydramine did not improve the tongue swelling. Given that Clobazam was the only new medication that she had not previously received, it was suspected to be the offending agent and replaced with Clonazepam on Day 8 of hospitalization. No recurrence of seizures were noted and EEG was discontinued. On the following day, a steroid course with Dexamethasone was initiated for the patient's macroglossia. Serum complement panel demonstrated normal C4 levels (39.6 mg/dL) and elevated C1 esterase inhibitor (53 mg/dL). Further inquiry into family history was also negative for angioedema. On Day 12, following 72 h of steroid administration, the patient's tongue was noted to still be edematous and protruding. Intubation and mechanical ventilation had been maintained due to concern of airway loss from macroglossia. On Day 13, she started to show improvement with tongue swelling and was successfully extubated with no complications. Complete resolution of macroglossia was observed on Day 15 of hospitalization, seven days following the discontinuation of Clobazam.

DISCUSSION

Clobazam is a benzodiazepine antiepileptic agent used to treat a range of focal and generalized seizure disorders, as well as drug-resistant seizures associated with syndromes such as Lennox-Gastaut Syndrome and Dravet Syndrome. Its mechanism of action is through its binding to γ-aminobutyric acid-A (GABA-A) receptors and potentiation of GABA action by increasing the channel conduction of chloride ions in response to ligand binding, thereby increasing the seizure threshold (3). Clobazam differs from typical benzodiazepines due to placement of its two

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
TOTAL SCORE:				+6

FIGURE 3 | Naranjo adverse drug reaction probability scale (9). Score was calculated as "+6" due to the patient's adverse event appearing following administration of Clobazam, improvement of symptoms following discontinuation of the drug, other causes for the patient's tongue edema ruled out, and the results of the patient's presentation and work-up confirmed with neurology, immunology, and otolaryngology consults.

nitrogen atoms at the 1st and 5th positions of the diazepine ring resulting in partial agonism of the GABA-A receptor, rather than the 1st and 4th ring positions of other benzodiazepines which act as full agonists (3). This structural variation confers an improved side effect profile and also increases its anxiolytic and antiepileptic properties due to improved binding affinity for the GABA-A $\alpha 2\beta 3\gamma 2$ subtype (4). Common side effects noted in up to 80% of patients during Phase III drug trials included somnolence, pyrexia, lethargy, drooling, and constipation (5). While side effects are generally mild, increased severity has been observed in patients prescribed Clobazam along with cannabinoid agents such as Epidiolex for the treatment of refractory epilepsy (6). Serological studies show cannabidiol use in combination with Clobazam was correlated with a five-fold increase in concentration of N-desmethylclobazam, the active metabolite of Clobazam, due to shared metabolism by the hepatic cytochrome P450 enzyme CYP2C19 (7). Patients with "poor metabolizer" phenotypes due to high rates of polymorphism in the CYP2C19 gene have also been noted to be at a higher risk of adverse drug effects (8). However, the patient described in our case report did not have a history of cannabinoid use and CYP2C19 genotyping had not been conducted.

Our report presents the first published case of acute tongue enlargement in the context of naïve Clobazam exposure. While the patient had also been treated with antibiotics, Lorazepam, Fosphenytoin, and Midazolam during her inpatient course, the patient's previous exposure to these medications, lack of rash or pruritus, and minimal response to Diphenhydramine and corticosteroid therapy likely rule out allergic or inflammatory etiologies. In addition, our findings of elevated C1-esterase inhibitor levels, normal C4 complement levels, and negative family history for angioedema accounted for any possible pathologies related to bradykinin-mediated angioedema. Improvements in macroglossia observed while the patient was still intubated and lack of similar symptoms following previous intubations also make a traumatic cause for the patient's acute tongue swelling less likely. However, calculation of the Naranjo adverse drug reaction probability scale (9) for our patient (represented in **Figure 3**) yielded a score of "+6," which determined a "Probable" drug-related cause for the patient's macroglossia, and it had been noted that Clobazam was the only new medication that the patient had been exposed to during this hospital stay. While isolated tongue swelling has not previously been described in the literature following Clobazam administration, two reports have presented four adult patients (10) and one pediatric patient (11) who developed distal extremity edema associated with chronic Clobazam use (within 1–3 months of therapy) that spontaneously resolved within 2–6 weeks following discontinuation of the drug. In both cases, the pathophysiology was speculated to be due to the disruption of autonomic signaling in the myocardium and peripheral vasculature due to benzodiazepine-mediated increases in chloride channel conduction (12). However, no reports of macroglossia or extremity edema have been reported in the acute setting in the days following initiation of Clobazam therapy.

Notably, acute tongue swelling has been reported in patients receiving barbiturates for sedation. Darshan et al. reported a patient who developed severe tongue swelling with protrusion after placement into a drug-induced coma using Pentobarbital (13). The patient was weaned off Pentobarbital with improvement of his tongue swelling over the following week; however, later in his hospital course, he was administered Pentobarbital again and three days later developed similar symptoms of macroglossia, which again resolved in a few days following discontinuation of Pentobarbital (13). In another report, Parthvi et al. reported a patient who was administered Phenobarbital for agitation related to alcohol withdrawal and also developed isolated tongue swelling that was ruled to not be related to anaphylaxis or angioedema (14). In a similar mechanism of action to benzodiazepines, barbiturates act as positive allosteric modulators of GABA-A receptors by binding to a distinct site from benzodiazepines and increasing GABA-mediated activity. Phenobarbital and Pentobarbital have also been found to be mainly metabolized by hepatic CYP2C19 (15), and patients with genetic polymorphisms resulting in decreased enzymatic activity have been noted to be at higher risk of developing side effects related to barbiturate intake (16). We would hypothesize that in patients with a poor metabolizer phenotype characterized by reduced CYP2C19 activity, elevated drug metabolite levels disrupt autonomic vasoconstriction in the tongue (a highly neurovascular structure) and produce the characteristic macroglossia observed in these patients, though further serological and genotyping studies are required to draw definitive conclusions in this susceptible patient population.

Unresolved macroglossia poses a significant risk for unsuccessful extubation, resulting in obstructive symptoms post-extubation or possible cardiac arrest due to an inability to pass an oral or nasotracheal tube and necessitating emergency tracheostomy. Fortunately, as in the case of our patient, drug-related symptoms of macroglossia have been observed to resolve quickly and spontaneously following discontinuation of the offending agent without any lingering sequelae. In this case report, we hope to increase awareness among clinicians for this possible side effect of Clobazam therapy in order to avoid unnecessary testing and treatment which may prolong a patient's length of stay.

CONCLUSIONS

Macroglossia is a previously unreported side effect associated with initiation of Clobazam therapy for drug-resistant epilepsy. Early recognition of this symptom and discontinuing the offending agent may to lead to spontaneous resolution of macroglossia and can reduce hospital length of stay.

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

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

JZ: drafting the manuscript, editing the manuscript, approving the manuscript, and accountable for manuscript integrity. KN and RP: editing the manuscript and approving the manuscript. OF and AS: project conception, editing the manuscript, and approving the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Newly Diagnosed Hepatic Encephalopathy Presenting as Non-convulsive Status Epilepticus: A Case Report and Literature Review

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Background: Hepatic encephalopathy is characterized by psychiatric and neurological abnormalities, including epileptic seizure and non-convulsive and convulsive status epilepticus. Conventional brain magnetic resonance imaging is useful in supporting diagnosis since it can reveal specific radiological findings. In the literature, there is no description of hepatic encephalopathy onset as non-convulsive status epilepticus; we provide the first report.

Case Summary: We report a case of a 67-year-old woman, without history of cirrhosis, presenting altered mental state, normal brain computed tomography imaging, and electroencephalography suggestive of epileptic activity. We suspected non-convulsive status epilepticus, and we administered diazepam and levetiracetam with clinical improvement. Thus, we made a diagnosis of non-convulsive status epilepticus. A radiological study with brain magnetic resonance imaging showed bilateral hyperintensity on T1-weighted sequences of globus pallidus and hyperintensity of both corticospinal tracts on T2-weighted fluid-attenuated inversion recovery sequences. Blood tests revealed hyperammonemia, mild abnormality of liver function indices, and chronic Hepatitis B and D virus coinfection. Hepatic elastosonography suggested liver cirrhosis. The patient started antiviral therapy with entecavir and prevention of hepatic encephalopathy with rifaximin and lactulose; she was discharged with a normal mental state.

Conclusions: Hepatic encephalopathy can present as an initial manifestation with non-convulsive status epilepticus. Electroencephalography is useful for differentiating non-convulsive status epilepticus from an episode of hepatic encephalopathy, and neuroimaging aids the diagnostic process.

Keywords: hepatic encephalopathy, non-convulsive status epilepticus, brain magnetic resonance imaging, case report, corticospinal tract, globus pallidus

INTRODUCTION

Hepatic encephalopathy (HE) is defined as brain dysfunction caused by liver failure or portal systemic shunting, without considering the etiology (1). The clinical picture comprises neurological or psychiatric abnormalities, ranging from subclinical alterations to coma (1). It is one of the most important complications of liver cirrhosis, contributing to both morbidity and mortality (1). From the pathophysiological perspective, ammonia is, probably, the central player in the pathogenesis of HE (1). Considered a metabolic disorder, it is usually reversible by liver transplantation (1). Although rare, HE can present as epileptic seizure; manifestations vary widely, encompassing tonic-clonic seizure, convulsive (CSE), and non-convulsive status epilepticus (NCSE) (2–6). HE can show typical features on brain magnetic resonance imaging (MRI), namely, the bilateral and symmetric hyperintensity of the globus pallidus on T1-weighted (T1W) sequences, and hyperintensity in cerebral white matter, involving corticospinal tract and subcortical hemispheric white matter on T2 weighted (T2W)—"fluid attenuated inversion recovery" (FLAIR) MRI sequences (7). Herein, we report a case of newly diagnosed HE presented as NCSE, in which conventional brain MRI shows some findings associated with this disease, such as the hyperintensity in the globus pallidus on T1 and the hyperintensity along the corticospinal tract on T2-FLAIR.

CASE PRESENTATION

A 67-year-old woman from Romania presented to our Emergency Department for confusion and subacute ideomotor decline in the previous 5 days. Insomnia, nocturnal awakenings, urinary incontinence, and amnesia for recent events were reported in the last month. The patient had a past medical history of paroxysmal atrial fibrillation, previously treated with amiodarone and apixaban, which were self-suspended 1 year ago, obesity, hypertension, and rectal carcinoma which was surgically treated with an enterostomy. The patient had no

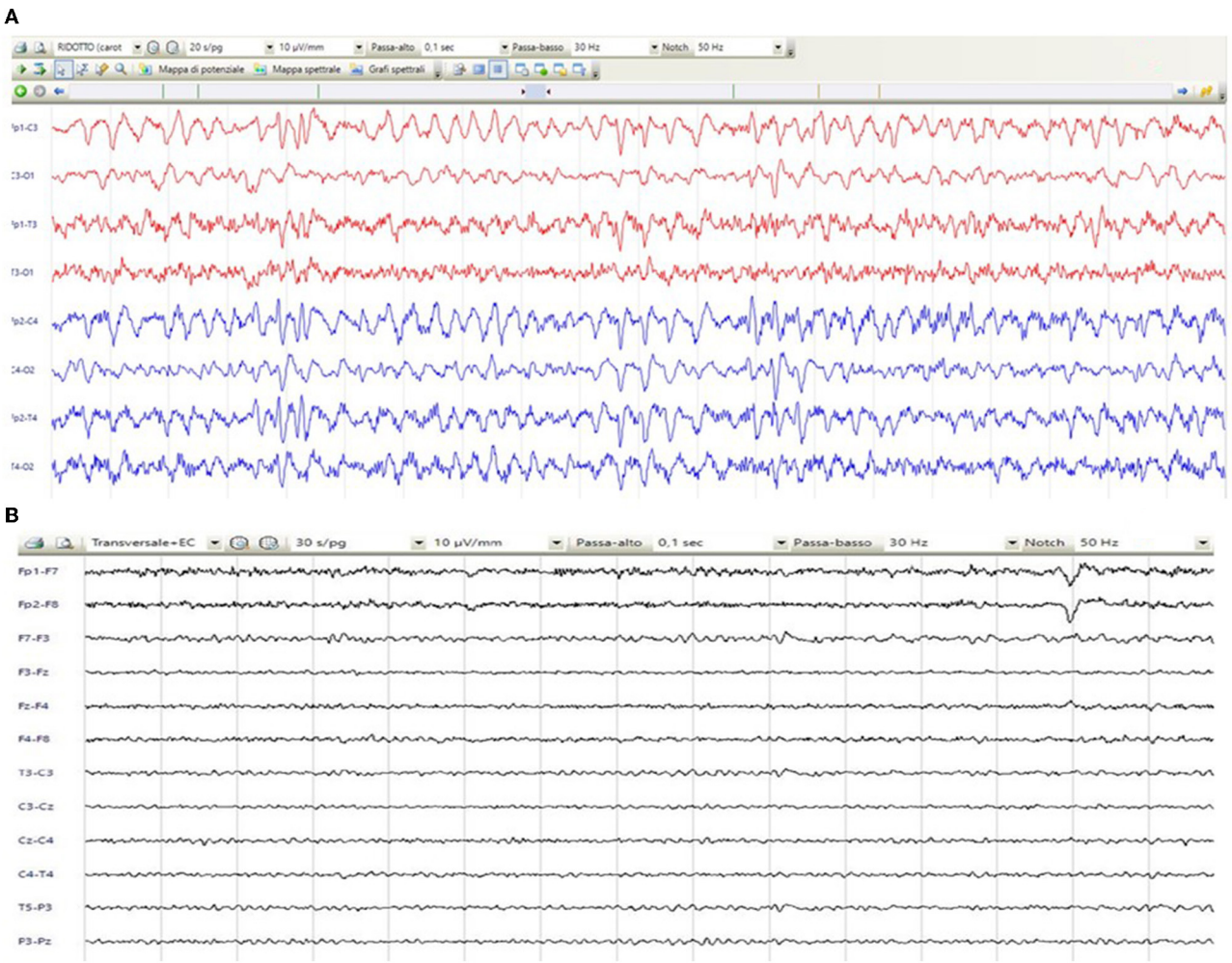

FIGURE 1 | EEG showing status epilepticus **(A)** and resolution after antiepileptic therapy **(B)**.

known history of seizures or other neurological diseases, recent illness, brain trauma, or recent surgical procedures. The chronic therapy encompassed olmesartan, bisoprolol, indapamide, furosemide, amlodipine, acetylsalicylic acid, and ranitidine. The vital parameters were normal, and the Glasgow Coma Scale (GCS) score was 15. The general physical examination did not show pathological items, nor signs of trauma. The chest X-ray was normal, while the electrocardiogram was suggestive of atrial fibrillation. From a neurological point of view, the patient was disoriented in space and time and unable to denominate objects of common use. The pupils were isochoric and reactive to light. The posture was normal and there were no signs of meningism. The cranial nerve examination was normal, except for dubious absence of the menace reflex on the left, not confirmed by a subsequent evaluation. The global strength of the limbs was preserved, as well as tactile sensitivity and coordination. The osteotendinous reflexes were valid, symmetrical in the upper limbs, with a mild prevalence on the right, and weak and symmetrical in the lower limbs. Cutaneous plantar response was mute bilaterally. A stroke was initially suspected, and a neuroimaging study was performed with brain computed tomography (CT), CT angiography, and CT perfusion, which were unremarkable. Because of the persistence of the altered mental state, electroencephalography (EEG) was performed. EEG showed a broadly slowed trace, with a background theta rhythm, which was more expressed on the right. Fast paroxysmal bilateral activity of the type sharp wave was superimposed and more represented on the right and mainly frontotemporal (**Figure 1A**) areas. Herein, NCSE was suspected and 10 mg of diazepam was administered intravenously, with regression of the paroxysmal activity on the synchronous recording of the EEG. Furthermore, antiepileptic therapy with 4,000 mg of intravenous levetiracetam was started, and the mental state progressively improved. The next day, the EEG was repeated, and epileptiform activity did not reappear (**Figure 1B**); levetiracetam was switched to an oral dosage of 2,000 mg daily. The patient was admitted to our Neurology Department with the presumptive diagnosis of NCSE, and a 3 Tesla brain MRI with gadolinium was performed. Bilateral hyperintensity of the lenticular nucleus was detected on T1W sequences (**Figure 2A**), while bilateral hyperintensity of the corticospinal tract signal was displayed on FLAIR (**Figure 2B**). Neuroimaging ruled out an ischemic event and an expansive lesion, with findings suggestive of chronic HE. As a completion, a lumbar puncture with examination of cerebral spinal fluid was performed. It did not show any noteworthy findings, including the real-time polymerase chain reaction for an infectious agent or dosage of autoantibodies associated with autoimmune and paraneoplastic encephalitis. The patient was obese (body mass index = 38.3 kg/m^2) but had no past history of alcoholic abuse. There were no signs of ascites and declining edema. She presented no signs of asterixis. Blood tests performed a few days later revealed: chronic coinfection of Hepatitis B (HBV) and D (HDV) virus, negative Hepatitis C virus (HCV) infection, ammonium 141 umol/L (11.2–48.2 umol/L), albumin 2.7 mg/dl (3.4–4.8), total bilirubin 1.33 (0.12–1.1 mg/dl), INR 1.25 (0.8–1.2), proteins 5.6 g/dl (6.4–8 g/dl), cobalamin 1,121 pg/ml (191–663 pg/ml), and normal levels of folate, transferrin, sideremia, and ferritin. Hepatic elastography recorded values compatible with cirrhosis. Hepatic cirrhosis from mixed etiology, chronic HBV-HDV co-infection, and metabolic syndrome was diagnosed. The clinical picture was considered to be an episode of HE, presenting as NCSE. Anti-HBV therapy with entecavir (0.5 mg daily orally) was started, as well as secondary prevention of HE with lactulose (10 g two times daily orally) and rifaximin (400 mg three times daily orally). On the day of discharge, her mental state was normal, and the patient noted improvement in her general health condition (**Figure 3**). Afterwards, she continued to receive levetiracetam for epilepsy, besides lactulose and rifaximine for secondary prevention of HE; relatives reported no other episodes of mental confusion. Three months later, a brain MRI was repeated, and radiological findings were stable.

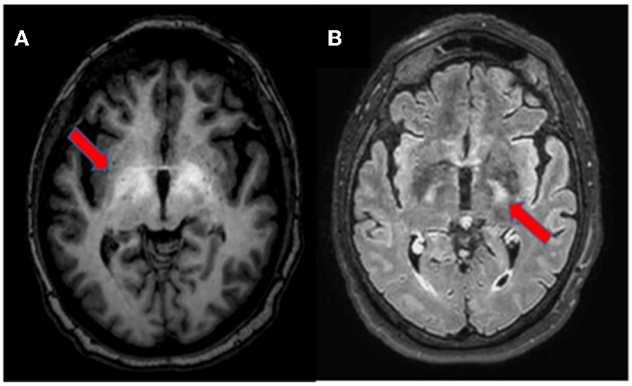

FIGURE 2 | Brain MRI, axial section. T1-weighted imaging showing bilateral symmetrical hyperintensity in the globus pallidus and upper mesencephalon [**(A)**, arrow]. T2-weighted FLAIR imaging depicting hyperintensity of the corticospinal tracts [**(B)**, arrow].

DISCUSSION

HE is one of the main complications of liver cirrhosis, along with variceal bleeding, hepatorenal syndrome, hepatopulmonary syndrome, and ascites (8). Historically, it has been classified into "overt hepatic encephalopathy" (OHE, clinically manifested neurological and psychiatric abnormalities) and "covert hepatic encephalopathy" (CHE, abnormalities on neuro-psychological and electrophysiological tests without or mild clinically detectable neurological-psychiatric abnormalities) (9). According to the recent "International Society for Hepatic Encephalopathy and Nitrogen Metabolism" (ISHEN) consensus, the onset of disorientation and/or asterixis confirms OHE (10). In cirrhotic patients, OHE develops in 30–40% at some time during their clinical course, while minimal hepatic encephalopathy (MHE) and CHE are seen in 20–80% (11). As HE is a manifestation of serious liver impairment, its outcome depends on the severity of underlying liver disease, its clinical course, and its treatment (1). The serum level of ammonia plays a central role in the pathophysiology of HE, helping physicians in ruling out the diagnosis and defining the

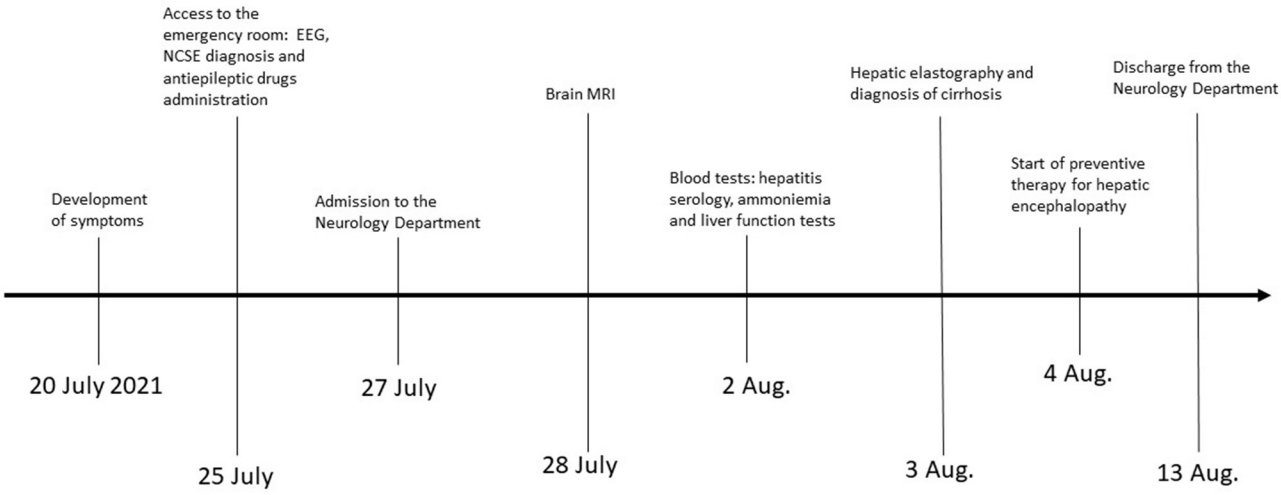

FIGURE 3 | The timeline of the case report.

prognosis; lowering serum ammonia is the main therapeutic goal (1, 9). Apart from hyperammonemia, other pathogenetic factors are implied, such as systemic inflammation, increased blood manganese, circulating bile acids, and lactate (1, 9). Their generation is influenced by common precipitant factors of HE, like malnutrition, infections, electrolyte imbalance, constipation, gastrointestinal bleeding, dehydration, and use of diuretics (1, 9). These pathogenetic factors influence the blood-brain barrier (BBB) by increasing its permeability (1, 9). Anyway, independent of blood-brain barrier status, ammonia passes freely into the brain, which is exclusively removed by astrocytes *via* glutamine synthetase (1, 9). The generation of glutamine renders the astrocyte hypertonic, resulting in swelling, impaired function, and, finally, brain edema (1, 9). Astrocyte swelling causes neuronal dysfunction and clinical manifestations of HE (1, 9). However, as in our case, there may be no clear precipitant factor underlying an episode of OHE (1, 9).

On a neurological point of view, clinical elements are plethoric, encompassing, mostly, the higher cortical functions and the motor system (12). Cognitive findings in patients with chronic HE vary from subtle deficits, not apparent without psychometric and electrophysiological testing (CHE), to clearer findings during periods of decompensation related to higher ammonia levels, such as impairments in attention span, reaction time, and working memory (OHE) (12). Disturbances in the sleep-wake pattern are common initial manifestations of HE and may precede mental state changes or neuromuscular symptoms (13). As HE progresses, patients may develop mood and personality changes, disorientation in time and space, inappropriate behavior, somnolence, confusion, and, finally, the so-called "coma hepaticus" (14). Seizures and status epilepticus are very rarely reported in HE (2). Generally, HE is associated with different EEG patterns, such as delta activity and the more typical triphasic waves (9). In particular, the description of NCSE in HE is anecdotal, probably because cognitive disturbances are shared in the two conditions, and an EEG is not always performed. To the best of our knowledge, just four case reports were previously described, and none of them reported NCSE as the first manifestation of HE (3–6). In our case, NCSE was diagnosed according to Salzburg criteria, since we found epileptiform discharge on the EEG that ceased after antiepileptic drugs administration, associated with a mental state improvement (15). The pathophysiology underlying the development of seizures in the setting of HE remains unknown, although hyperammonemia is likely the most important factor (16). In our case, the patient developed, within a few days, cognitive symptoms of episodical OHE but more likely caused by NCSE secondary to hyperammonemia. Neuroimaging excluded structural causes of seizures, while blood tests showed no other noteworthy metabolic alterations.

Brain MRI is the most useful imaging technique to support the diagnosis of HE in uncertain cases (17). Neuroradiological signs depend on the severity and velocity of development of liver failure, namely, a chronic or acute HE (18). In this case, we observed findings on conventional brain MRI compatible with a chronic form of HE, probably long neglected, not associated with any neurological signs. The bilateral and symmetric T1 hyperintensity involving the globus pallidus and substantia nigra reticulata is characteristic, reported in almost 90% of patients with cirrhosis and likely due to manganese accumulation; it may be associated with Parkinsonism (7, 17). Sometimes, other areas are involved, namely, the subthalamic nucleus, tectal plate, hypothalamus, adenohypophysis, limbic system, and white matter (7, 17, 18). Less commonly, the hyperintensity of both corticospinal tracts is described on T2-FLAIR sequences; it is caused by vasogenic brain edema due to glutamine increase in astrocytes, resulting in loss of organic osmolytes, such as myo-inositol, that accumulate in the extracellular compartment (17). This finding may be associated with subclinical alterations, detectable in electrophysiological studies with motor-evoked

potentials, not performed in the case of our patient (19). Similar abnormalities may also be seen in periventricular white matter, the thalamus, posterior limb of internal capsule, and cortex (18). However, hyperintensity along both the corticospinal tracts may be seen in healthy adults and should be interpreted with caution, especially in 3 Tesla MRI (17, 20). These changes are similar to the signal abnormalities observed in patients with other diseases, such as amyotrophic lateral sclerosis, X-linked Charcot-Marie-Tooth, optic neuromyelitis, metabolic disorders (Krabbe disease and X-linked adrenoleukodystrophy), infectious diseases (*Borrelia* spp. and Human T-cell lymphotropic Virus 1), and primary central nervous system lymphoma (21–28). Other neuroradiological findings include an increase of mean diffusivity of hemispheric brain matter on diffusion weighted imaging (DWI); laminar hyperintensities involving the cortical deep layers; white matter focal lesions; and a low magnetization transfer ratio (MTR) in various white matter regions (17, 29). These radiological findings have been shown to be reversible after liver transplantation (30, 31).

CONCLUSIONS

We reported the first description of NCSE as an initial manifestation of HE. Specific brain MRI findings, namely, bilateral hyperintensity on T1 of the globus pallidus and hyperintensity of both corticospinal tracts on T2-FLAIR, were able to suggest the diagnosis of HE. From a general point of view, NCSE is easily underdiagnosed for lack of clear and univocal clinical signs. It is important to understand the possibility of NCSE in patients presenting an altered mental state; EEG is helpful in ruling it out. Hyperammonemia is a possible pathogenetic factor of NCSE, especially in patients with cirrhosis. The problem arises in differentiating acute alteration of the mental state due to an episode of HE from a real NCSE. Again, the EEG is useful for resolving diagnostic doubt, especially in the case of presumed HE that does not respond to empirical treatment.

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

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

MO: drafted the manuscript for intellectual content and collected and analyzed the data. DG, GCos, DV, and MM: collected and analyzed the data and revised the manuscript for intellectual content. FM, FT, GCon, GPC, and SC: revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Late-Onset Lennox-Gastaut Syndrome Treated With Stereotactic Electroencephalography-Guided Radiofrequency Thermocoagulation Before Craniotomy

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The onset of Lennox-Gastaut syndrome (LGS), a severe epilepsy syndrome, is typically before 8 years of age. Late-onset LGS (with onset in adolescence and adulthood) is relatively rare clinically and has some differences from classical LGS. Herein, we describe the case of a patient with late-onset LGS and provide a literature review of such cases. The patient had focal epilepsy onset at 8 years of age. After a 9-year evolution, he suffered seizures of different types and had a diagnosis of late-onset LGS. Drug treatment was ineffective. Nothing was found on stereotactic electroencephalography (SEEG) and magnetic resonance imaging (MRI) during the course of the disease. After the second presurgical evaluation, we found a suspicious focus on high-resolution structural MRI which was verified by SEEG at last. After SEEG-guided radiofrequency thermocoagulation (RFTC), his seizures were controlled, and his cognitive function and quality of living clearly improved. However, his seizures recurred 2 years later, and he underwent left occipital resection. Thereafter, his seizures have been controlled until now. This case emphasizes the importance of high-resolution structural MRI in the treatment of LGS. Furthermore, it suggests that late-onset LGS may be caused by focal lesions and evolve from focal epilepsy. Thus, characterizing the clinical symptoms and performing individualized electroencephalographic follow-up are both very important. Additionally, the clinical outcome in this case implies the value and limitations of RFTC in patients with epilepsy and a clear focal lesion. Moreover, this case further supports differences between late-onset and classical LGS in terms of clinical manifestation, cognitive changes, prognosis, and treatment.

Keywords: Case Report, refractory epilepsy, late-onset Lennox-Gastaut syndrome, stereotactic electroencephalography, radiofrequency thermocoagulation

INTRODUCTION

Lennox-Gastaut Syndrome (LGS) is a severe epilepsy syndrome, with onset typically before 8 years of age and comprising a variety of seizure types. LGS is often accompanied by specific changes on electroencephalography (EEG) and cognitive impairment. Herein, we describe a patient with late-onset LGS who had onset after 8 years of age. For a comprehensive analysis, previous cases of late-onset LGS were reviewed and compared to this case.

CASE PRESENTATION

Patient Information

A 19-year-old man first experienced a generalized seizure attack without any cause at 8 years of age. Subsequently, he sometimes complained of bright or colorful flashing lights, blurry vision, and distance changes in both visual fields before seizures, especially on the right side. The visual auras usually lasted several min and sometimes occurred alone. At 17 years of age, he experienced transient nodding attacks, frequently without an aura. At 18 years of age, dropping attacks occurred frequently, with accompanying gripped hands and slight forearm flexion. After the attacks, he could stand by himself without an aura or a memory. The nodding and dropping attacks could occur 2–10 times in 4–5 days and in a series. He was diagnosed with refractory epilepsy and underwent presurgical evaluation at another hospital. Magnetic resonance imaging (MRI) scans were considered negative, and he was monitored by stereotactic electroencephalography (SEEG) focusing on the temporal, parietal, and occipital (TPO) regions, especially on the left side, but without lateralization or localization. Although he underwent vagal nerve stimulation (VNS) using five types of antiepileptic drugs, there was no significant improvement. Thus, he was admitted to our hospital for further treatment.

Clinical Findings

His family, perinatal, and growth history, and physical examination results were normal. Wakeful background on video electroencephalography showed 9–10 Hz alpha rhythm in bilateral occipital regions. Interictal EEG showed generalized 2–2.5 Hz slow spike waves (SSWs) during wakefulness and generalized paroxysmal fast activities (GPFAs) during sleep. There were also multifocal independent spikes, especially in the bilateral occipital and posterior temporal regions where the left side was more predominant than the right. Compared with SSWs and occipital discharges, GPFA was more prominent, followed by occipital discharges. Epileptic spasms, tonic seizures, and atypical absence were recorded, which showed EEG onsets with a little localization value. MRI showed a suspiciously unclear gray-white matter boundary around the left calcarine sulcus (**Figures 1**, **2**), which also showed low metabolism on positron emission tomography (**Figure 1**). Neuropsychological tests showed moderate cognitive impairment. No abnormalities were found on genetic testing and perimetry. Accordingly, the clinic diagnoses were as follows: refractory epilepsy, late-onset LGS, possible onset zone at the left occipital cortex, and postoperative VNS.

Therapeutic Intervention

We analyzed his previous SEEG even though the former hospital considered the SEEG result without lateralization or localization value and performed the VNS, but we found there were rhythmic discharges mainly in the left TPO region, which also had the most obviously electrical evolution during tonic and spasm seizures onset. Combining the imaging finding, we considered the seizure onset was most likely to be on the left TPO region and re-inserted six electrodes in total, of which five were focused on left TPO region and one was focused on the left hippocampus. During the SEEG monitoring, there were plentifully rhythmic interictal discharges in the left occipital region and higher frequency of fast activities during spasm and tonic seizures onset, which verified the left occipital lesion as the epileptogenic zone. Radiofrequency thermocoagulation (RFTC) was performed on this lesion and the surrounding region, with five electrodes and 17 contacts in total.

Follow-Up and Outcomes

Following the treatment with RFTC, he did not experience seizures for more than 1 year, but the right visual hemianopsia remained. There were a few spikes on EEG (only one during a 24-h test), and his cognition improved. However, he again experienced tonic seizures 2 years after the RFTC; thus, he underwent left occipital resection. The pathology indicated micro-malformation of cortical development (mMCD) (1, 2). As yet, he has remained seizure-free for 1 year following the occipitectomy.

DISCUSSION

The onset of LGS is typically before 8 years of age, with a peak at 4–5 years (3). Late-onset LGS, occurring in adolescents or adults (> 8 years old), is relatively rare and accounts for 10–15% of all LGS cases (4, 5). Thus, we collected data on all cases of late-onset LGS that have been reported since 1991; the 42 identified cases are summarized in **Table 1** (6–13). The age of seizure onset ranged from 6 weeks to 28 years, while the age at LGS diagnosis ranged from 8 to 64 years, The lag time between seizure onset and LGS diagnosis is mostly due to ictal semiology and electroclinical findings not having been fulfilled, suggesting that electroclinical changes in LGS follow a gradual evolutionary process, as in this case. It generally takes 1–2 years from seizure onset to a definite diagnosis of LGS (14, 15) because of differences in etiology, clinical characteristics, and disease progression between patients. This emphasizes the importance of individual electroclinical follow-up for early diagnosis of LGS. Additionally, for patients with a definite LGS diagnosis, a retrospective analysis of the characteristics of their electroclinical evolution is necessary and useful for precise treatment.

Among the identified 42 cases of late-onset LGS, 13 showed chromosome variations. Of the 29 remaining cases, 17 showed normal cognition and had a disease course of 5–32 years, while 12 showed cognitive impairment (mild cognitive impairment in two cases) and a course of 5–25 years. This indicates that unlike early-onset LGS, cognitive function, and daily viability are relatively preserved in late-onset LGS; additionally, cognitive function is

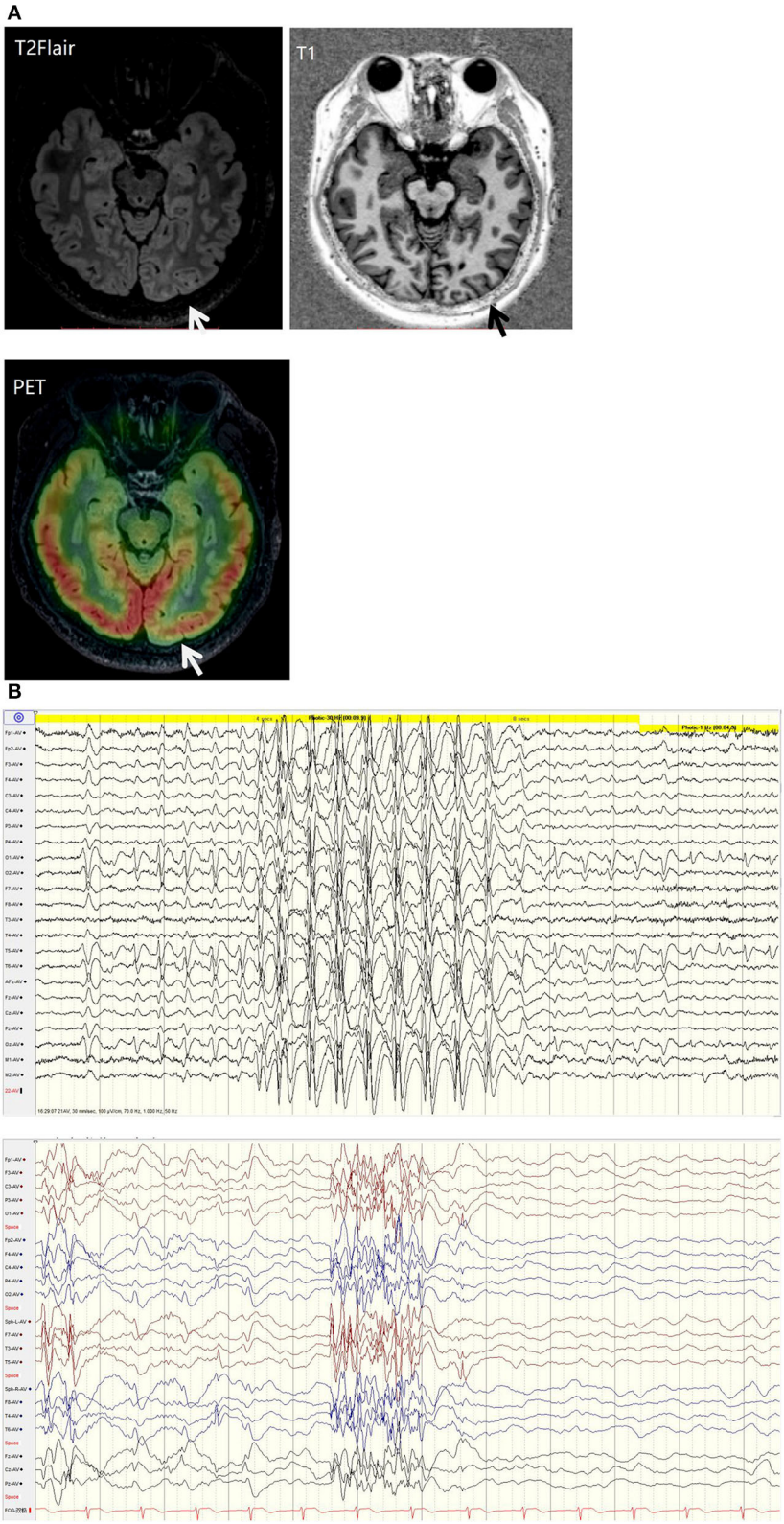

FIGURE 1 | (A) T2 fluid-attenuated inversion recovery (T2-FLAIR) magnetic resonance imaging showing a suspiciously unclear gray-white matter boundary around the left calcarine sulcus (white arrow). T1 magnetic resonance imaging showing a suspiciously unclear gray-white matter boundary around the left calcarine sulcus (black arrow). Positive emission tomography showing low metabolism at the cortex around the left calcarine sulcus (white arrow). **(B)** EEG background: generalized 2-2.5 Hz slow spike waves (SSWs) during wakefulness and generalized paroxysmal fast activity (GPFA) during sleep.

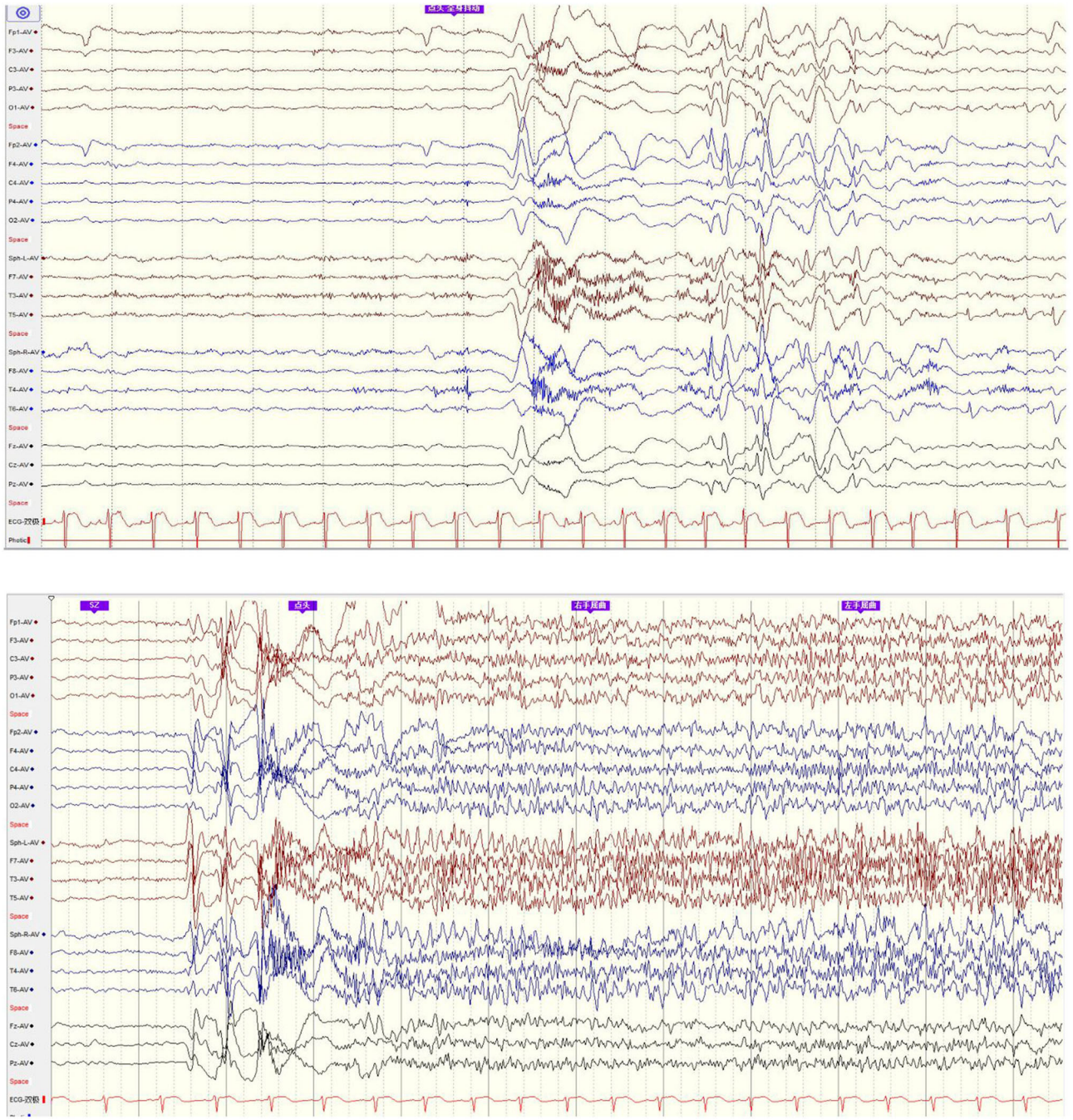

FIGURE 2 | EEG onset: epileptic spasm and tonic seizure involved general EEG onsets with little localization value.

not significantly related to disease course (4, 5, 8). This case had a disease course of 9 years, but the patient's cognitive function had only moderately declined. Furthermore, neurological examination results were mentioned in 38 of the 42 cases, among which four patients had abnormal neurological signs related to intracranial infection, cerebral infarction, perinatal injury, etc. Additionally, the EEG background was mentioned in 16 of the 42 cases, among which 10 showed normal EEG background, and six showed nonspecific slow waves. These findings suggest that late-onset LGS mostly shows no positive neurological signs or special abnormalities in the EEG background, as observed in this case.

Among the 42 cases, MRI findings were negative in 17, nonspecific or subcortical changes were found in 12, local cortical lesions were found in 5, and MRI findings were not mentioned in the remaining 8, suggesting that the cortical

TABLE 1 | Clinical characteristics, EEG and imaging findings, and other case details in 42 cases of late-onset Lennox-Gastaut Syndrome (LGS).

NO.	Sex	Seizure onset (age, y)	Diagnosis (age, y)	Seizure types	Cognition	Living independently	Neurologic exam	EEG background	EEG epileptiform discharges	Imaging	Etiology	AEDS(≥3)	VNS	Prognosis
1	M	14	22	T, AA, GTC	N	N	N	N	GPFA, SSWs	N	/	Y	N	/
2	M	12	17	T, AA, P	N	N	N	N	GPFA, SSWs, MS	N	/	Y	N	/
3	M	17	46	T, P	N	N	N	N	GPFA, SSWs, MS	N	/	Y	N	/
4	M	6w	8	A, AA, T	AB	AB	VI	/	GPFA, SSWs, MS	/	Infection	Y	N	/
5	M	18m	8	A, T	AB	AB	/	/	GPFA, SSWs, MS	/	/	Y	N	Mostly controlled
6	F	9	19	A, GTC	mild	AB	/	Slow	SSWs	/	/	Y	Y	Mostly controlled
7	F	28	28	AA, GTC	mild	AB	LH	Slow	SSWs	Right hemispheric stroke	Stroke	Y	Y	/
8	F	7	32	A, P, SI	AB	AB	/	Slow	SSWs	/	/	Y	Y	/
9	F	13	27	A, T, AA, GTC	N	N	N	N	GPFA, SSWs, GS	N	/	Y	N	/
10	F	12	49	T, AA, A, GTC	N	N	N	N	GPFA, SSWs, GS	N	/	Y	N	/
11	M	17	61	T, AA, M, GTC	N	N	N	N	GPFA, SSWs, GS	N	/	Y	N	/
12	F	12	44	T, AA, A, GTC	N	N	N	N	GPFA, SSWs, GS	N	/	Y	N	/
13	F	16	41	T, A, M, GTC	N	N	N	N	GPFA, SSWs, GS	N	/	Y	N	/
14	M	11	40	T, AA, A, GTC	N	N	N	N	GPFA, SSWs, GS	N	/	Y	N	/
15	F	17	22	T, AA, A, GTC	N	N	N	Slow	GPFA, SSWs, GS	N	/	Y	N	/
16	M	13	26	T, AA, A, GTC	N	N	N	Slow	GPFA, SSWs, GS	N	/	Y	N	/
17	/	20	20	T, AA, A, M, GTC	AB	/	/	/	GPFA, SSWs, MS	N	Brain injury	Y	N	/
18	F	16	16	T, A, GTC	N	/	N	/	GPFA, SSWs, GS	Low-lying cerebellar tonsils just below the foramen magnum level	/	Y	Y	Encephalopathy, DS
19	M	5	32	T, AA, A, GTC	N	/	N	/	GPFA, SSWs, GS	Small probable arachnoid cyst in the left frontal region	/	Y	Y	DS
20	F	9	14	T, AA, A, M, GTC	AB	/	N	/	GPFA, SSWs, GS	Modest ventricular dilatation	ALL with MTX	Y	N	Encephalopathy, DS
21	F	15	26	T, AA, A, M, GTC	N	/	N	/	GPFA, SSWs, GS	N	/	Y	Y	Encephalopathy, DS, SUDEP
22	M	19	19	T, A, GTC	AB	/	N	/	GPFA, SSWs, GS	N	Infection	Y	N	DS
23	F	15	15	T, AA, A, GTC	AB	/	N	/	GPFA, SSWs, GS	Single non-enhancing 6 mm focus in the paramedian inferior left cerebellum	/	Y	Y	VNS partially effective, DS
24	F	11	11	T, AA, A, GTC	N	/	N	/	GPFA, SSWs, GS	Gray matter of heterotopia with transmantle dysplasia	ALL with MTX; MCD	Y	Y	Encephalopathy, DS

(Continued)

TABLE 1 | Continued

NO.	Sex	Seizure onset (age, y)	Diagnosis (age, y)	Seizure types	Cognition	Living independently	Neurologic exam	EEG background	EEG epileptiform discharges	Imaging	Etiology	AEDS(≥3)	VNS	Prognosis
25	F	11	11	T, AA, A, GTC	N	/	N	/	GPFA, SSWs, GS	Cerebellar atrophy	/	Y	Y	Encephalopathy, DS
26	F	11	11	T, A, GTC	AB	/	N	/	GPFA, SSWs, GS	Pachygyria, diffuse bilateral lissencephaly and band heterotopia	MCD	Y	Y	DS
27	F	10	10	T, AA, A, M, GTC	AB	/	N	/	GPFA, SSWs, GS	Mild cerebellar and cortical cerebral atrophy	/	Y	N	DS
28	F	14	64	AA, GTC, A	N	/	N	N	GPFA, SSWs, MS	N	/	Y	N	/
29	F	9	27	T, AA	AB	/	N	/	GPFA, SSWs	Moderate diffuse atrophy	trisomy 21	Y	N	Weekly seizures, SUDEP
30	F	8	12	T, AA, A	AB	/	N	/	GPFA, SSWs	/	trisomy 21	Y	N	DS
31	M	11	14	T, AA, A	AB	/	N	/	GPFA, SSWs	Multiple small subcortical calcification	trisomy 21	Y	N	DS
32	F	12	30	T, AA	AB	/	N	/	GPFA, SSWs	N	trisomy 21	Y	N	Seizures decreased
33	F	8	33	AA, A	AB	/	N	/	GPFA, SSWs	/	trisomy 21	Y	N	Weekly seizures, SUDEP
34	M	5	30	T, GTC	AB	/	LH	/	GPFA, SSWs	/	trisomy 21	Y	N	DS
35	M	12	17	T, AA	AB	/	N	/	GPFA, SSWs	Mild diffuse atrophy	trisomy 21	Y	N	DS
36	M	6	36	T, AA, P, GTC	AB	/	N	/	GPFA, SSWs	/	trisomy 21	Y	N	DS
37	M	16	23	T, AA, GTC	AB	/	N	/	GPFA, SSWs	Moderate diffuse atrophy	trisomy 21	Y	N	DS
38	M	11	12	T, M, P	AB	/	N	/	GPFA, SSWs	Mild diffuse atrophy	trisomy 21	Y	N	DS
39	M	7	11	T, AA, A, GTC	AB	/	N	/	GPFA, SSWs	N	trisomy 21	Y	N	Weekly or monthly seizures
40	M	10	43	T	AB	/	N	/	GPFA, SSWs, MS	Dilation cortical sulci, calcification globus pallidus	trisomy 21	Y	N	DS
41	M	7	34	T, AA	AB	/	N	/	GPFA, SSWs	Mild diffuse atrophy	trisomy 21	Y	N	DS
42	M	9	30	T, AA, GTC	AB	/	slight cerebellar sign	Slow	GPFA, SSWs, MS	Asymmetrical cystic lesions in bilateral parietooccipital regions	Perinatal injury	/	/	/

/, information not available; M, male; F, female; y, year; w, week; m, month; N, normal; AB, abnormal; A, atonic; AA, atypical absence; T, tonic; IS, infantile spasm; GTC, generalized tonic-clonic; P, partial; SI, startle induced; M, myoclonic; VI, visual impairment; LH, left hemiparesis; GPFA, generalized paroxysmal fast activity; SSWs, slow spike waves; MS, multifocal spikes; GS, generalized spike; ALL, acute lymphoblastic leukemia; MTX, methotrexate; MCD, malformations of cortical development; AEDs, antiepileptic drugs; VNS, vagal nerve stimulation; Y, yes, N, none; SUDEP, sudden unexpected death in epilepsy; DS, daily seizures.

structure in late-onset LGS mostly showed no specific changes. However, this substantially differs from previous reports on classical LGS, which indicate that more than 2/3 of patients show cortical structural lesions on MRI (3, 16), including focal, multifocal, and diffuse abnormalities, with static pathological lesions predominating (e.g., focal cortical dysplasia), while progressive or metabolic lesions are relatively rare (17, 18). This may reflect a difference between early- and late-onset LGS, but it may also be related to a case inclusion bias and skill in image reading; thus, this potential distinction needs to be confirmed by accumulating more cases. However, the progression of neuroimaging technology and the quality of MRI scans may also contribute to focal structural lesion identification. In this case, nothing was found in the initial clinical work-up, and the epileptic focus was found during the re-evaluation process by high-resolution structural MRI and later confirmed by SEEG and RFTC, indicating the important role of high-resolution structural MRI in the etiological diagnosis and treatment of late-onset LGS. Routine MRI should include three-dimensional T1, T2 FLAIR, and coronal thin-layer scanning of the long axis of the vertical hippocampus (3).

In the 29 cases without chromosome variations, the prognosis was not mentioned in 6 cases, 11 cases had independent viability, 2 cases had well-controlled seizures, and the remaining 10 cases had a poor prognosis, including frequent seizures, encephalopathy, sudden unexpected death in epilepsy, etc. This indicates that the prognosis of late-onset patients is relatively good. Furthermore, although most of the 42 identified cases had tried more than three antiepileptic drugs, none underwent surgery, which may be related to an unclear etiology. In total, 10 cases had tried VNS, which was clearly mentioned as effective in only 1 case, suggesting that VNS has a poor effect on late-onset LGS, as observed in this case, which showed obvious improvement after surgery, suggesting the effectiveness and necessity of early surgery for patients with late-onset LGS with definite focal lesions (15, 18).

For 1 year after the RFTC, not only were the patient's seizures well controlled, but his cognition improved and the EEG spikes "calmed down" gradually for 2 years. Such changes were first mentioned in 1979 (19). These observations not only suggest that electroclinical changes in late-onset LGS are the result of secondary alterations in brain networks (20), but also confirm the efficacy of RFTC. However, his seizure recurred and he eventually underwent left occipital resection and has been seizure free until now. This indicated the limited efficacy and scope of RFTC compared to craniotomy in lesion damage and pathological network disconnection in some cases with accurate lesion targets, which may be the main reason explaining the low rate of seizure-free cases with RFTC (21). However, the improvement of clinical outcomes after RFTC may further suggest the correct location of epileptic foci and good prognosis after craniotomy, as in this case. Nevertheless, RFTC is superior in some small foci that can be located precisely and destroyed completely but are inaccessible by surgery, and has the advantages of less damage to brain function, fewer complications, and faster postoperative recovery (22, 23).

In summary, LGS, with onset after 8 years of age known as late-onset LGS, may be caused by focal lesions. Individualized follow-up is necessary. Late-onset LGS and classical LGS have some differences in terms of clinical manifestation, cognitive changes, prognosis, and treatment. MRI is important in determining the etiology of late-onset LGS and is useful for early treatment. Comparing to craniotomy, RFTC is limited and less effective in lesion damage. However, clinical improvement after RFTC would support the appropriate identification of seizure onset zone location indicated by SEEG results and therefore help with surgical plan for cortical resection.

PATIENT PERSPECTIVE

We spent a lot of money and time in the treatment of our son's disease before the second evaluation. After the RFTC, our son's seizures were miraculously controlled and he could go to school again. This was beyond our expectations.

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

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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CASE REPORT
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Seizures and Consciousness Disorder Secondary to Intracranial Hypotension After Spinal Surgery: A Case Report and Literature Review

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Rationale: Cerebrospinal fluid (CSF) leakage is a common condition after spinal surgery and is also the most common cause of intracranial hypotension. Intracranial hypotension (IH) is typically characterized by an orthostatic headache with associated nausea, vomiting, tinnitus, vertigo, hypoacusis, neck stiffness, and photophobia. There have been limited case reports describing surgery-associated IH presenting with seizures and disorder of consciousness. Due to the atypia of symptoms, these clinical manifestations are usually ignored or even misdiagnosed. As a result, clinicians face a significant challenge in detecting IH early and understanding its various clinical presentations. Meanwhile, we summarize the cases of IH presenting as seizures in recent years, including its clinical characteristics and effective treatment, which will be very helpful for the early diagnosis of IH.

Patient concerns: A 72-year-old Chinese male patient developed status epilepticus, a disorder of consciousness, and quadriplegia when he finished spinal surgery, although he had no previous seizures or any seizure risk factors.

Diagnosis: After MRI and CT examination, subdural hygromas were found under both sides of the skull, and combined with the clinical manifestations of the patient, intracranial hypotension due to cerebrospinal fluid leakage was diagnosed.

Interventions: In the early stage, we carried out strict perioperative critical care for the patient. Trendelenburg position was conducted to relieve intracranial hypotension. The dural repair surgery was performed after the diagnosis of CSF leakage.

Outcomes: Seizures in the patient were resolved. Three months after discharge, he was gradually returning to normal life.

Lessons: One possible cause of unexplained seizures and disorder of consciousness after spinal surgery is cerebrospinal fluid leakage associated with intracranial hypotension syndrome. Trendelenburg position and dural repair surgery are effective ways to relieve intracranial hypotension and associated symptoms. Better awareness of the association between IH (intracranial hypotension) and seizures may help us improve early recognition of the syndrome.

Keywords: seizure, intracranial hypotension, status epilepticus, cerebrospinal fluid leakage, spinal surgery, critical care

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INTRODUCTION

The syndrome of intracranial hypotension has been increasingly diagnosed since the introduction of magnetic resonance imaging (MRI), and its incidence is now about 5 per 1,00,000 of the population (1). Cerebrospinal fluid (CSF) leakage is the most common cause of intracranial hypotension. Defects along the dura (including tears and fistulas), leading to CSF leakage, can be congenital and traumatic in etiology (2), with surgery being the most common traumatic cause. Intracranial hypotension (IH) typically presents with a postural headache with associated nausea, vomiting, tinnitus, vertigo, hypoacusis, neck stiffness, and photophobia (2–5), while seizures and the disorder of consciousness are rare. Therefore, the disorder of consciousness and seizures after spinal surgery are of concern because they may be associated with intracranial hypotension caused by cerebrospinal fluid leakage.

ETHICS STATEMENTS

Informed written consent was obtained from the patient's son after the nature of the study had been fully explained to them. The patient's son provided informed consent for the publication of the case.

CASE PRESENTATION

A 72-year-old Chinese male patient developed seizures, disorder of consciousness, and quadriplegia when he finished spinal surgery. Due to 3 years of pain and numbness in both lower limbs, he underwent spinal surgery, including L3/4/5 posterior decompression, interbody fusion, and internal fixation, plus L2/3 left lamina decompression. His medical history was significant hypertension for about 8 years and he usually took amlodipine, an oral antihypertensive drug. Therefore, his blood pressure was well-controlled. He had no previous seizures or any seizure risk factors.

The operation went smoothly and the patient soon regained consciousness. Then, the endotracheal tube was safely removed. In the surgical resuscitation room, the patient complained of itchy skin and generalized clonic seizures, which became progressively worse, characterized by bilateral clonic movements in the upper and lower limbs. Profound tachycardia and hypertension accompanied the spell. Therefore, the patient was transferred to the intensive care unit (ICU) immediately and tracheal intubation was performed instantly. Subsequently, consciousness disturbance occurred with blood oxygen saturation declining, and the ECG (electrocardiograph) monitor displayed that there was an atrial fibrillation rhythm and it quickly developed into ventricular fibrillation. He was given timely shock defibrillation, after which sinus rhythm was regained, with Norepinephrine maintaining blood pressure. Meanwhile, the emergency blood gas analysis suggested a pH of 6.9 and a pCO_2 of 95 mmHg. For emergency seizure control, intravenous midazolam was given. In addition, an extremely high level of creatine kinase and myohemoglobin was found in his blood test, which was thought to be the result of a violent convulsion. We gave the patient rocuronium bromide, a muscle relaxant, to prevent further muscle damage.

An emergency brain CT (computerized tomography) was conducted, suggesting that the space under the inner plate of the skull was widened on both sides, which was considered a subdural effusion (**Figure 1**). No obvious signs of cerebral hemorrhage and cerebral infarction were found. After first aid, we conducted target temperature management for the patient and implemented a hypothermia strategy to maintain its core temperature between 32 and 34°C. Levetiracetam and midazolam were added to abort seizures as the disorder of consciousness and seizures persisted. Norepinephrine and dopamine were used to achieve a mean arterial pressure >65 mmHg, with a maximum of 1 μg/kg/min for norepinephrine and 15 μg/kg/min for dopamine. Blood oxygen saturation fluctuated around 85% at pure oxygen concentration due to the presence of refractory hypoxemia. On the second day of ICU admission, he was given a tracheostomy and ventilator-assisted ventilation to maintain oxygen saturation >94% and pCO_2 between 35 and 45 mmHg. Given his lack of gastrointestinal hemorrhage and intestinal dysfunction, enteral nutrition was administered within 48 h, along with insulin to keep his blood sugar at 8–10 mmol/L.

Three days after the symptom onset, the use of vasoactive agents and sedatives such as midazolam were suspended, and a significant improvement in convulsions was observed, as well as blood oxygen saturation was maintained above 94% at 35 oxygen concentration, which was an indication that respiration and epilepsy were getting better. Simultaneously, blood pressure also returned to normal, at around 140/60 mmHg, thus the use of epinephrine was interrupted. As the patient's condition stabilized, we performed an EEG for 24 h, which revealed a diffuse slow waves background with a large number of fast waves, but we did not pick up the epileptic waves. Whereas, we observed that more than 350 ml of hemorrhagic fluid could be drained from the drainage tube of the patient's waist wound every day, and he was still in a comatose state without an obvious response to pain stimuli. We reviewed the blood concentration of valproate and it was in the normal range. A CT scan of the brain was also reviewed, indicating there was mild cerebral edema and ventricular shrinkage. The existence of cerebrospinal fluid leakage was highly suspected and it was considered that the patient's consciousness disturbance and epileptic seizure might be related to it because it can lead to intracranial hypotension. We adopted a Trendelenburg position to prevent the excessive outflow of cerebrospinal fluid. Sure enough, after changing the patient's position, his disturbance of consciousness improved. Simultaneously, he was able to respond to verbal stimuli and partially follow movements. Over the next few days, his cerebrospinal fluid drainage gradually decreased to about 200 ml per day.

Abbreviations: IH, intracranial hypotension; CSF, cerebrospinal fluid; SE, status epilepticus; ECG, electrocardiograph; PH, pondus hydrogenii; PCO_2, partial pressure of carbon dioxide; MRI, magnetic resonance imaging; MR, magnetic resonance; ICU, intensive care unit; CT, computerized tomography; ICP, intracranial pressure; PRES, posterior reversible encephalopathy syndrome.

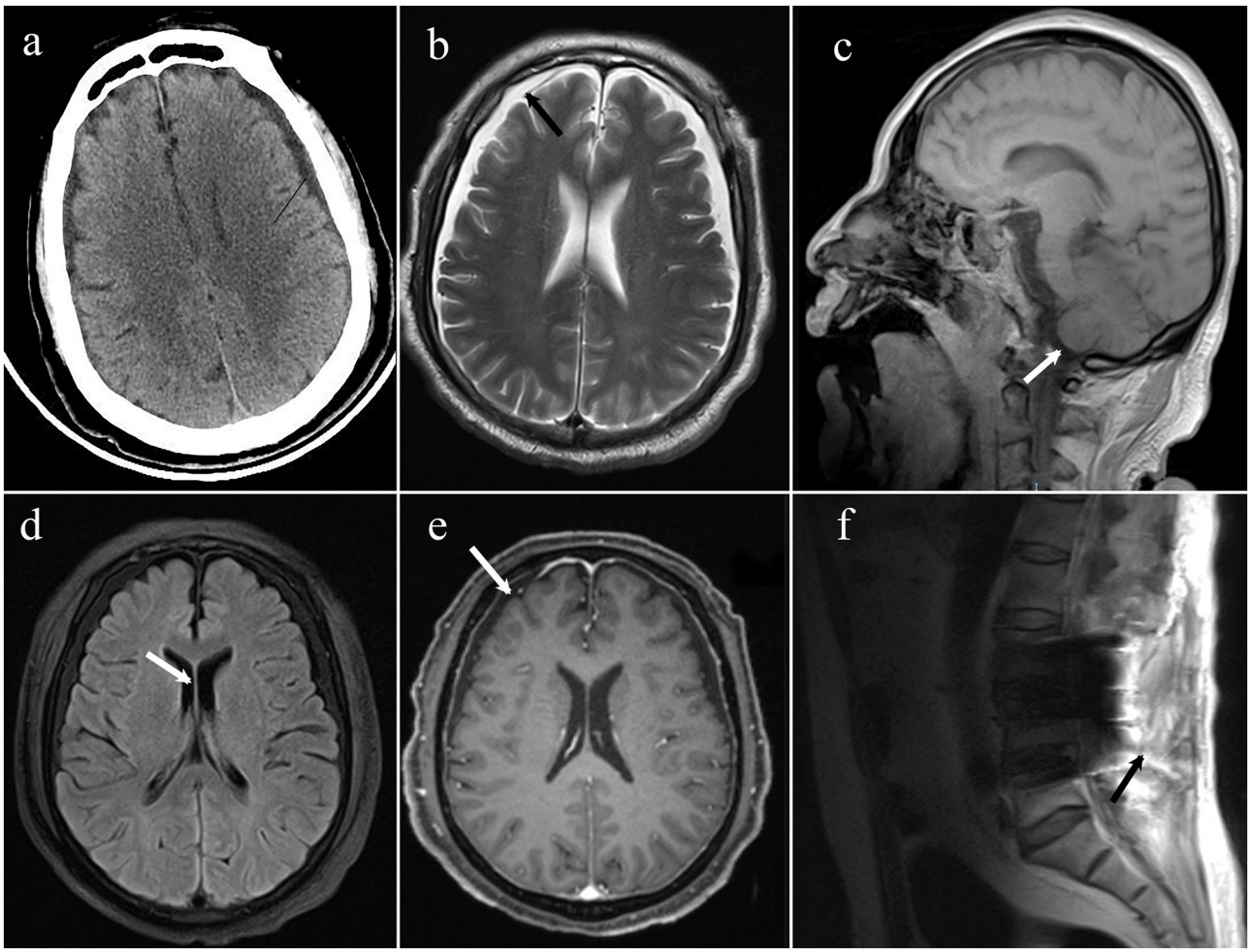

FIGURE 1 | (a) The emergency CT suggested that the space under the inner plate of the skull was widened on both sides, which was considered a subdural effusion; **(b)** axial T2 weighted MRI demonstrates bilateral subdural effusions (arrows); **(c)** sagittal T1-weighted MRI demonstrates sagging of the brain; **(d)** axial T1 weighted MRI demonstrates bilateral ventricles narrowing; **(e)** axial T1 post-gadolinium showing diffuse, mild pachymeningeal thickening, and enhancement (arrow); **(f)** MRI spine sagittal T2 sequence demonstrates a fluid collection within the posterior paraspinal soft tissue.

On day 10, the patient was successfully removed from the ventilator, so he underwent MRI and enhanced MRI of his brain and spinal cord, revealing evidence of bilateral subdural effusion and mild inferior hernia of the bilateral cerebellar tonsil, bilateral ventricles narrowing, pachymeningeal enhancement, which is consistent with intracranial hypotension. Several tiny hemorrhagic foci were also in the left cerebellar hemisphere and right temporal lobe. Spinal MRI demonstrated postoperative changes of the lumbar spine, lumbosacral fascia edema, and fluid collection between the intrathecal site and the soft tissue; however it did not identify the site of cerebrospinal fluid (CSF) leakage (**Figure 2**). These changes in the brain were indicative of typical intracranial hypotension, such as subdural effusion, mild inferior hernia of the bilateral cerebellar tonsil, ventricular narrowing, and pachymeningeal enhancement which could be caused by cerebrospinal fluid leakage.

Taking all the evidence together, we strongly suspected that he had a cerebrospinal fluid leak. Therefore, we contacted an orthopedic surgeon for dural repair and wound debridement and a drainage tube was placed in the operation area. During the operation, CSF leakage was proved to be present. Thus, intracranial hypotension due to cerebrospinal fluid leakage secondary to intraoperative dural tear was diagnosed.

After surgery, we still kept the Trendelenburg position. On the other hand, a neuro-rehabilitation doctor was brought in for muscle massage and acupuncture. Over the next few days, he gradually regained consciousness and was able to follow instructions better, accompanied by a gradual reduction of clear to bloody spinal drainage fluid. At the same time, his upper body strength was gradually recovering to level 2. The drainage tube was removed when the drainage fluid was <50 ml for more than 2 days. As the condition gradually improved, the patient's family requested that he be transferred back to the local hospital

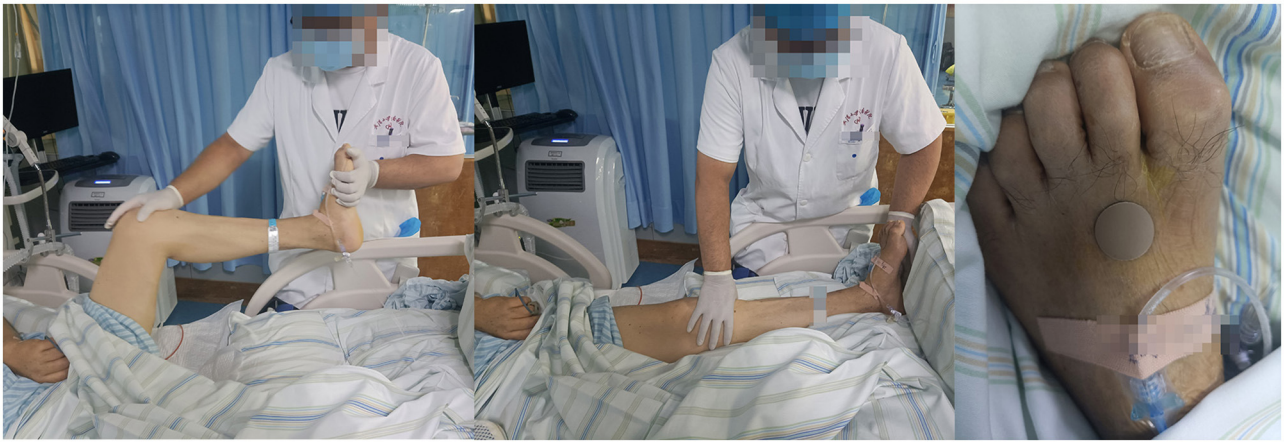

FIGURE 2 | The first two pictures show that the neuro-rehabilitation doctor is giving him muscle massages. The third picture shows the special treatment of Traditional Chinese medicine, acupoint acupuncture.

for further rehabilitation. We followed him up for 3 months. A month after discharge, with his independent diet and defecation, we learned that he had complete sensation in his limbs and level 3 strength in his lower extremities and that his trachea incision had been fully healed and closed. The only problem was the gastrointestinal disturbance, with bloating and constipation, which may be related to the neurotic disorder caused by the operation. Three months after discharge, his gastrointestinal function recovered well and he could walk about 50 m on a flat ground alone.

DISCUSSION

The syndrome of intracranial hypotension (IH) is caused by the leakage of CSF (cerebrospinal fluid) from the thecal sac within or along the spinal canal (3, 4). It is typically manifested by orthostatic headaches that may be associated with one or more of several other symptoms, including pain or stiffness of the neck, nausea, emesis, horizontal diplopia, dizziness, changes in hearing, visual blurring or visual field cuts, photophobia, interscapular pain, and occasionally face numbness or weakness or radicular upper-limb symptoms (5). Seizures caused by IH have also been observed in some rare clinical cases (6, 7). If the leakage can be arrested, it is potentially curable (3, 4, 8).

The most characteristic features of IH on intracranial MR (magnetic resonance) imaging include diffuse pachymeningeal enhancement and "brain sag" (9, 10). Sagging of the brain can cause a subdural hematoma or hygroma, kinking of the midbrain and pons toward the clivus, lessening of the distance (e.g.,) from the optic chiasm to the pituitary gland, and tension on the cranial nerves (3). Other features include dural contrast enhancement and enlargement of the pituitary gland. Homogenous contrast enhancement of the dura mater is the most sensitive sign (3).

Intracranial hypotension is usually treated with a progressive approach. Typically, headaches can be resolved with conservative management, which includes hydration and strict bed rest, allowing for relief of CSF pressure at the site of leakage and thus healing the underlying defect. Caffeine administered intravenously or orally is also effective for post-lumbar puncture IH. If a conservative approach is not effective, epidural blood patches, epidural saline infusion, and surgical correction should be considered (3, 4, 11). However, blood patches are more controversial when used for surgery-related dural leaks, although suggested to be safe in a case series because they can cause seizures and respiratory distress, or other related complications (12). Although the specific mechanism by which IH may cause seizure development and convulsive SE has not been fully elucidated, it has been proposed that IH may cause meningeal irritation or traction on cortical structures of the brain, and finally, result in seizures (6, 13). In addition, the alterations of intracranial pressure (ICP) may result in acute changes in cerebral blood flow, leading to seizure generation (14).

Intracranial hypotension presents in a variety of ways; however, reports of seizures secondary to IH are rare. We summarize the cases of IH presenting as seizures in recent years, including its clinical characteristics and effective treatment (**Table 1**). Gilmour et al. (7) describe a 71-year-old woman with chronic back pain who developed convulsive status epilepticus immediately after scoliosis surgery. MRI was consistent with IH, there was no cortical vein thrombosis, presumably due to an intraoperative dural tear causing status epilepticus, and the seizure terminated after bed rest. Lin et al. (13) describe an individual who had multiple seizures after a thoracic laminectomy and had imaging findings consistent with IH. A thoracic laminotomy was performed on this patient and a dural tear was found and repaired. Chaudhary et al. (6) describe cases of spontaneous intracranial hypotension causing focal onset seizures and impairment of awareness. Other two reports describe patients with hydrocephalus and ventriculoperitoneal shunts who had intractable epilepsy caused by overdrainage (14, 15). Delgado-López et al. (16) present a case of posterior reversible encephalopathy syndrome (PRES) following laminectomy and fixation for L4-5 lumbar stenosis and spondylolisthesis, characterized by status epilepticus, which

TABLE 1 | Summary of some reported cases of seizures secondary to intracranial hypotension (IH).

Article	Patient presentation	Seizure description	The cause of IH	Treatment
Gilmour et al. (7)	A 71-year-old woman with chronic back pain developed convulsive status epilepticus immediately after scoliosis surgery	It was characterized by bilateral clonic movements of her upper and lower extremities, with eyes open and a vertical upward tonic gaze deviation	An intraoperative dural tear secondary to elective redo-scoliosis surgery	Keep on strict bed rest
Lin et al. (13)	A 37-yr-old man with acute spinal cord compression at T9-10 because of pseudoarthritis developed generalized seizure after surgery	30 min postoperative generalized seizures lasting 15 s occurring every 10–15 min	Dural tear after laminectomy	Treated with midazolam, phenytoin, and dural tear repair
Chaudhary et al. (6)	A 60-year-old man who presented with a decreased level of consciousness developed a complex partial seizure involving left-sided facial twitching after the presentation	Focal motor-impaired awareness seizure with left-sided facial twitching	Small bilateral subdural hygromas	Treatment with a 20 cc blood patch in the lumbar spine
	A 37-year-old man who presented with a right-sided acute on chronic SDH which reaccumulated despite burr hole drainage, presenting with decreased level of consciousness	Focal impaired awareness and complex partial seizures	Chiropractic neck manipulation and trivial head trauma, potentially resulting in thoracic dural tear	A 20 cc autologous epidural blood patch was placed at the T12-L1 level
Delgado-López et al. (16)	An 82-year-old woman presented with a generalized tonic-clonic seizure after L4-5 laminectomy and decompression of the dural sac and origin of roots bilaterally	She developed transient hypotension for <1 min presented with a generalized tonic-clonic seizure that lasted 5 days	An unnoticed cerebrospinal fluid leakage secondary to surgery	Antiepileptic drugs, ventilators and other symptomatic support treatment
Pugliese et al. (17)	A 41-year-old woman presented a worsening of the headache and tonico-clonic seizures 7 days after epidural analgesia for a cesarean section	A worsening of the headache which had a gradual onset, was bilateral, pressure-like, with a postural component and tonico-clonic seizures with the left motor syndrome, mild right anisocoria, and rapid deterioration of the mental status	Inadvertent dural puncture during the epidural anesthesia	Treatment with support therapy followed by blood patch
Our report	A 72-year-old Chinese male patient developed seizures, disorder of consciousness, and quadriplegia when he finished spinal surgery	He developed itchy skin and generalized clonic seizures, characterized by bilateral clonic movements in the upper and lower limbs	Cerebrospinal fluid leakage secondary to the spinal surgery of L3/4/5 posterior decompression, interbody fusion, and internal fixation, plus L2/3 left lamina decompression	Treatment with support therapy, trendelenburg position, dural repair surgery, and traditional Chinese acupuncture and massage therapy

IH, intracranial hypotension; SDH, subdural hematomas.

is hypothesized by vasoconstriction, brain hypoperfusion, and cerebrospinal fluid. Pugliese et al. (17) report a case of a woman presenting headache and tonico-clonic seizures 7 days after epidural analgesia for a cesarean section. MRI showed alterations suggestive of the presence of intracranial hypotension (IH), as well as evidence of posterior reversible encephalopathy syndrome (PRES). They suggest that venous stagnation and hydrostatic edema, secondary to intracranial hypotension, probably played a crucial role in the pathogenesis of PRES. In our case, the patient developed seizures after spinal surgery, with imaging revealed bilateral subdural hygromas, which were thought to be related to intracranial hypotension syndrome. It is speculated that the existence of subdural hygromas may lead to the formation of hemorrhagic foci in brain, which felt to be acute, because of the pulling on the brain tissue. This may have caused the seizure due to the highly epileptogenic effect of blood. In addition, during the perioperative period, patients were given a large number of sedative drugs, such as midazolam, and whether these drugs are involved in the seizure is also a thought-provoking question.

Meanwhile, the patient did not develop typical postural headache symptoms but instead presented with a convulsive status epilepticus characterized by impaired limb movement and sensory function as well as impaired consciousness, which was also rare in previous reports. We adopted the Trendelenburg position treatment and a dural repair

surgery, which proved to be very therapeutic. Gastrointestinal dysfunction occurred during the patient's subsequent recovery, and it is reasonable to speculate that this may be related to autonomic nervous dysfunction caused by the persistent epileptic state.

CONCLUSION

Unexplained seizures and disorder of consciousness after spinal surgery may be associated with cerebrospinal fluid leakage associated with intracranial hypotension syndrome. Trendelenburg position and dural repair surgery are effective ways to relieve intracranial hypotension and associated symptoms. Better awareness of the association between IH and seizures may help us improve early recognition of the 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/s.

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

YL wrote the manuscript. HX revised the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Case Report: Cognitive Assessment Before an Amnesic Seizure in Transient Epileptic Amnesia Syndrome

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A patient with transient epileptic amnesia syndrome presented a clinically observable amnesic seizure immediately after a neuropsychological assessment. An hour and a half before the onset of the seizure, the patient progressively developed an isolated alteration of episodic memory. These data question the ictal/interictal distinction in this syndrome as well as the speed of propagation of an epileptic activity.

Keywords: epilepsy, memory, neuropsychology, transient epileptic amnesia (TEA), amnesic seizure

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INTRODUCTION

Transient epileptic amnesia (TEA) is a mesial temporal epileptic syndrome for which the diagnostic criteria, defined by Zeman et al. (1), are: (1) A history of recurrent witnessed episodes of transient amnesia; (2) Cognitive functions other than memory judged to be intact during typical episodes by a reliable witness; (3) Evidence for a diagnosis of epilepsy based on one or more of the following: (a) Epileptiform abnormalities on electroencephalography; (b) The concurrent onset of other clinical features of epilepsy (e.g., lip-smacking, olfactory hallucinations); (c) A clear-cut response to anticonvulsant therapy.

A recent general review (2), based on a substantial patient cohort, concluded that TEA is a distinctive form of late-onset limbic epilepsy. Patients have recurrent episodes of transient amnesia, typically lasting for around 30 min, often when waking, frequently occurring at intervals of around 1 month. Other symptoms can occur, such as olfactory hallucinations (43% of the patients), repetitive questioning (57%) or motor automatisms (41%) (2). During the amnesic attacks, patients remain able to carry on a conversation and act appropriately (3), which suggests the preservation of cognitive functions (other than memory) such as attention, perception, language, and executive functions. Standard interictal neuropsychological assessments (NPA), which evaluate episodic memory on a short temporality, generally show normal performance (3, 4). The majority of patients report interictal memory impairment, specifically an accelerated long-term forgetting (ALF) and autobiographical amnesia (AbA). Thirty % of the patients mention a distinctive form of emotional lability (2). Specific NPA objectify patients' subjective complaint. They evaluate the ALF with a 1 h-delayed recall (5–7), a 24 h-delayed recall (8), a 1 week (or more) delayed recall (4, 9, 10). They test AbA with semi-structured interviews (11, 12). The condition of TEA syndrome is most often of unknown etiology and has a benign prognosis.

We report here the exceptional case of a well-characterized TEA patient who presented an amnesic attack in the immediate aftermath of an NPA. We can thus detail the appearance and progression of subtle cognitive impairments 1 h and a half before the clinical seizure.

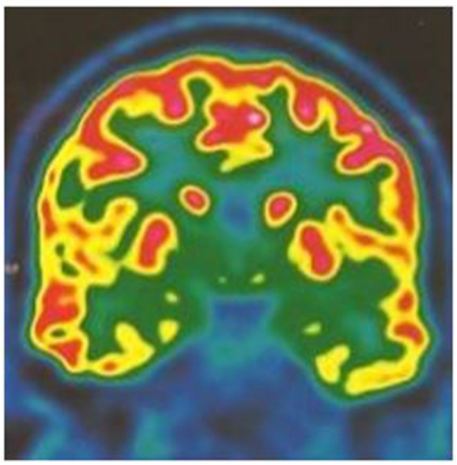

FIGURE 1 | 18 FDG PET scan coronal cut showing bilateral mesial temporal hypometabolism more pronounced on the left temporal lobe.

CASE DESCRIPTION

We report the case of a man who was 60 years old at the time of the diagnosis. He had been retired for 7 months and was house painter.

The patient came to see a neurologist for recurrent attacks:

- The first one happened four months before his retirement, during a period of overwork. While he was working, he suddenly felt disorientated, didn't know what he was doing.
- Two months later, he had a second attack when waking up. The patient describes the sensation of having a gray veil in front of his face. He felt lost, didn't know what he had to do or where he wanted to go.
- One month later, also while waking up, he had a third attack. Once again, he felt like having a gray veil in front of him and didn't know what he had to do. During the morning, while he was driving, his wife observed that he seemed haggard without any loss of contact or difficulty for driving.
- The next month, when waking up the day after Christmas, the patient felt disorientated and couldn't remember what had happened the day before.

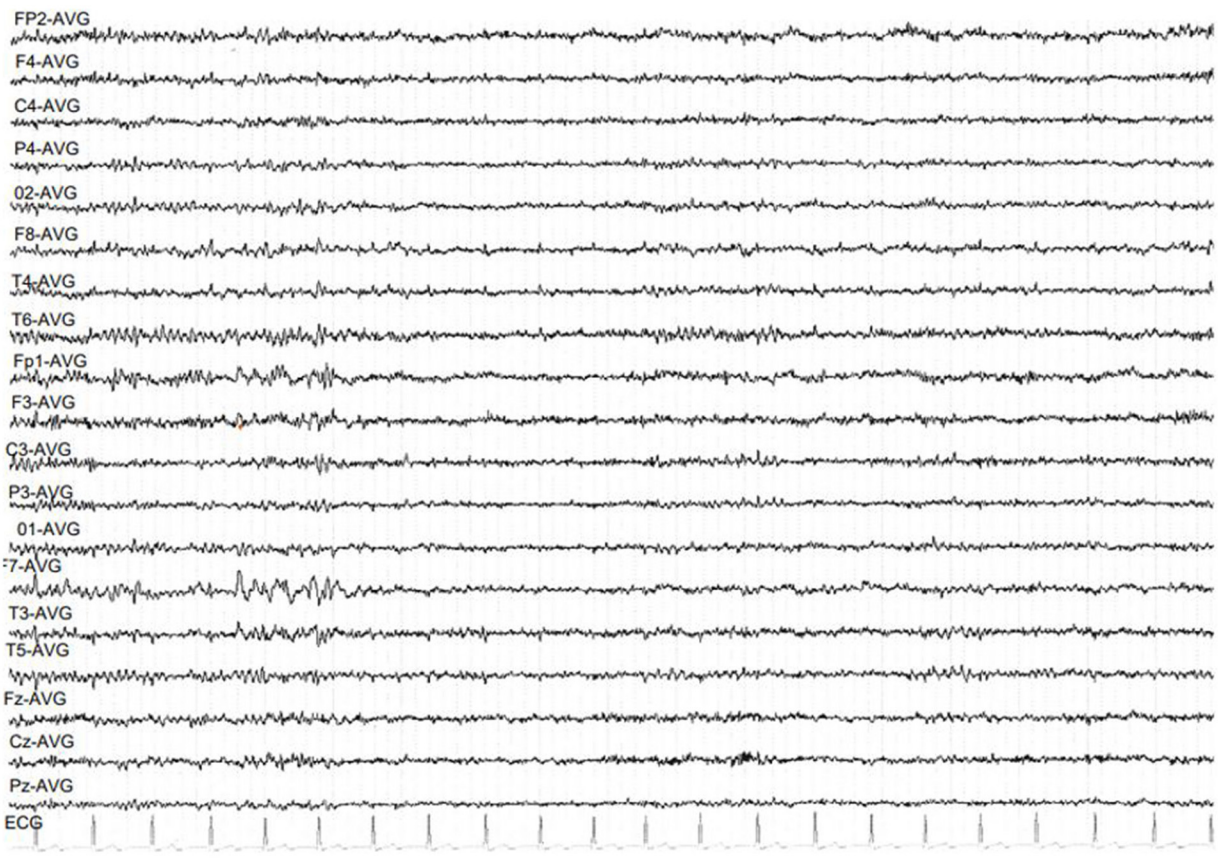

FIGURE 2 | EEG showing slow wave focus associated with spikes on the left temporal lobe.

TABLE 1 | Neuropsychological assessments.

		NPA 1	NPA 2	NPA 3	Cut off
		Score	Score	Score	
Mental status					
MMSE (13)		29/30	28/30	30/30	27
Memory					
Working memory					
Digit Span Recall (WAIS IV) (19)	Total	11/19	14/19	13/19	5
Anterograde memory					
- Verbal memory					
RL/RI-16 (15)		List A	List B	List C	
	Immediate Recall	16/16	16/16	16/16	13
	1st Free Recall	6/16	4/16**	8/16	5.16
	2nd Free Recall	6/16*	7/16	6/16*	6.42
	3rd Free Recall	8/16	3/16**	10/16	7.93
	1st Total Recall	12/16*	8/16**	12/16*	12
	2nd Total Recall	15/16	9/16**	13/16*	13
	3rd Total Recall	15/16	11/16**	14/16*	14
	Recognition	16/16	13/16*	16/16	
	20′ delayed Free Recall	9/16	6/16**	8/16*	8.16
	20′ delayed Total Recall	16/16	10/16**	15/16	14
	1 week DFR	0/16		2/16	
	1 week DTR	7/16		5/16	
	FR	0	0	0	
	Intrusions	free recall: 0 induced recall: 2	free recall: 5 induced recall: 14	free recall: 2 Induced recall: 5	
	Intrusions at 1 week	free recall: 0 induced recall: 7		free recall: 2 induced recall: 2	
Logical memory (MEM III) (14)	Immediate recall	7/19	1/19**	7/19	5
	Delayed recall	4/19*	1/19**	3/19**	5
	Recognition	22/30 C17-C25	19/30 C3-C9	15/30 ≤C2	C5
- Visual memory					
10/36 (18)	Total immediate recalls	24/30	15/30	22/30	9
	Delayed recall	9/10	3/10*	8/10	3
Face recognition (MEM III) (14)	Immediate recognition	9/19			5
	Delayed recognition	10/19			5
Rey complex figure		9/36*	7/36*	12/36*	15
Autobiographical memory					
TEMPau (12, 23)					
Episodic Score	0–17 years old	4			0
	18–30 years old	0**			1.69
	Over 30 years old	0*			0.15
	5 last years	0*			0.19
	12 last months	4			2.29
Global Score	0–17 years old	7**			9.09
	18–30 years old	7**			9.11
	Over 30 years old	9*			8.275
	5 last years	6**			7.09
	12 last months	11			9.88
Language					
Denomination (21)	DO 80	80/80	79/80	80/80	

(Continued)

TABLE 1 | Continued

		NPA 1 Score	NPA 2 Score	NPA 3 Score	Cut off
Executive functions					
GREFEX Version (20)					
Fluency	Animals (2′)	32	25	33	18
	Letter P (2′)	23	26	23	10
Stroop	Interference—Denomination (sec)	95	60	47	90
TMT	B-A (sec)	34	26	17	120
Visuoconstruction					
Rey complex figure (17)	Type	I	IV	IV	
	Score	27/36*	26/36*	30/36	29
Emotional state					
HADS (22)	Anxiety	8/21*	3/21	11/21*	8–10
	Depression	1/21	7/21	4/21	8–10

**Score below the pathological threshold or below −1.65 standard deviation; **score below −2 standard deviation.*
NPA, Neuropsychological Assessment; MMSE, Mini Mental State Examination; RL/RI-16, Rappel libre/rappel indicé à 16 items; DFR, Delayed Free Recall; DTR, Delayed Total Recall; FR, False Recognition; C, Centile; TMT, Trail Making Test; HADS, Hospital Anxiety and Depression Scale.

- A fifth episode happened 2 months later, he was shopping with his wife when he felt disorientated and didn't know what he had to do.

Three attacks appeared when the patient was waking up. During the attacks, the patient systematically had a confused look, as if he was lost, iterative questioned the people around him, but he was able to perform motor acts without error. There were no other temporal lobe epilepsy symptoms (such as olfactory hallucinations or motor automatisms) described by the patient or his wife. All these episodes lasted around 5 min with a post critical phase which could last from a few minutes to 1 h. During the post critical phase, the patient had memory impairment which seemed both retrograde—for example, after the acute phase of the first attack, he didn't remember if he had called his client the day before or not—and anterograde — his wife noted that he didn't correctly memorize information at post critical phase but she didn't notice any element of aphasia. The patient could remember that he had had a seizure because he did not feel well but he could not describe what he had done or said. Between the attacks, his wife observed some disturbance of autobiographical memory and an unusual emotionality. The patient had no more complaint.

Brain MRI, TEP-scan, video-EEG, spinal tap and NPA were performed. Clinical seizures were controlled with 100 mg lamotrigine per day.

Brain MRI was normal. PET scan showed bilateral hippocampal and parahippocampal hypometabolism (**Figure 1**) and video-EEG showed a slow wave focus associated with spikes under the left anterior and middle temporal electrodes especially during sleep (**Figure 2**). The spinal tap was normal. All known autoimmune antibodies were negative.

NEUROPSYCHOLOGICAL ASSESSMENTS

During each NPA, we evaluated the global cognitive efficiency with the MMSE (13). Anterograde verbal memory was evaluated using the logical memory from Weschler Memory Scale III (WMS—III, immediate and 30-min delayed recall, and recognition) (14) and the RL/RI-16 (immediate and 20-min delayed recall) (15). For logical memory subtest, the same two stories were presented to the patient for each NPA but we used three different lists of words to assess the RL/RI-16. These three lists are validated and considered as comparable (15, 16). Anterograde visual memory was assessed with the recall of the Rey-Osterrieth Complex Figure (17), the 10/36 spatial recall test (18) and the faces recognition test from the WMS-III. Verbal working memory was tested with the WAIS-IV digit span subtest (19). Executive functions were tested with Subtests from GREFEX battery (20). Visuoconstruction was assessed with the copy of Rey-Osterrieth Complex Figure. Language was evaluated with the DO 80 denomination test (21). Emotional state was controlled with the HADS (22). In addition, we assessed the Autobiographical memory with the TEMPau task (12, 23) during a second appointment for the first NPA. We also examined long-term consolidation with asking a 1-week delayed recall of the RL/RI-16 list of words to research an ALF. This evaluation is only a clinical observation because there are no norms for this task. We did not ask a 1-week delayed-recall for Logical Memory because of the impaired performance on 20-min delayed recall.

Three NPA were performed (summarized in **Table 1**). The tests were proposed in the same order during the three NPA (**Table 2**).

1. First NPA

The first NPA revealed a global preservation of cognitive functions on the standard evaluation, as it has been described in literature except for episodic memory. The RL/RI-16 showed an encoding impairment on the first total recall, and a slight retrieval difficulty but the middle term storage appeared normal. Delayed recall of the logical memory subtest, which requires recalling two stories presented only once, was impaired but delayed recognition remained normal. The patient said that this type of exercise had always been difficult for him. Visual memory appeared efficient except when the test required incident learning.

Furthermore, according to his complaint, the results suggest an ALF: the patient could not spontaneously recall any item of the RL/RI-16 list of words after 1 week, retrieved seven with help and proposed seven intrusions. The patient also presented an AbA. The impairment was more important for episodic memories which aligns with the literature data. We observed a U-distribution with a better performance for childhood episodic memories and for the past year (**Figure 3**). The detailed study of the profile showed that the past year episodic memories evoked by the patient concerned the last months and the last days before the evaluation. The patient could not report any episodic memory for the three interim periods (**Table 1**).

The score of Rey-Orsterrieth Complex Figure was impaired by slight disproportions and one omission but it did not constitute real visuoconstruction impairment.

Emotional state evaluation indicated anxiety manifestations.

In the end, we asked the patient to come again a year later for a new NPA.

2. Second NPA: during an acute phase

As agreed, the patient came 1 year later. He was still taking 100mg of lamotrigine per day. He only had one seizure since the first NPA. It had occurred 2 months before the second NPA, when waking up, and his wife observed the same disorientation and iterative questioning associated with some iterative deglutition movements.

During the interview, the patient was perfectly coherent and gave an informative speech. He did not mention any new complaint. He still reported an unusual emotionality and an AbA. These features did not disturb his daily functioning. There was no autonomy loss and he still managed his rental houses without difficulty. His wife agreed with this information.

The assessment revealed a preservation of global cognitive efficiency. Language, executive functions and working memory were maintained. In contrast, verbal episodic memory was significantly impaired on the RL/RI-16, more than during the first NPA: all the scores were impaired and below two standard deviations. The repetition of immediate recalls, during which the missing items are recalled by the examiner, didn't significantly improve the scores so we could notice an encoding impairment. Furthermore, the patient gave 19 intrusions. Immediate recognition was also impaired. Immediate recall of logical memory subtest was substantially impaired whereas it was normal during the first NPA. Visual episodic memory evaluation objectified an encoding difficulty and a storage impairment of visuospatial information during the 10/36 task. This time visuoconstruction was impaired by deformations and a planning trouble that was not present during the first NPA. However, the HADS did not show anxiety or depression symptoms.

We therefore observed, from this second NPA, an isolated encoding and storage impairment in verbal and visual episodic

TABLE 2 | Order of tests administration.

Order	Test	Estimated duration (minutes)
1.	MMSE	10
2.	RL/RI-16: - Immédiate recall - 1st, 2nd, and 3rd recall - Immediate recognition	25
3.	Rey-osterrieth complex figure: - Copy	3
4.	Digit span subtest (WAIS-IV)	12
5.	Rey-osterrieth complex figure: - Recall	5
6.	RL/RI-16: - 20 min delayed recall	5
7.	Logical memory - Immediate recall	10
8.	10/36: - 1st, 2nd, and 3rd recall	10
9.	TMT	5
10.	Stroop	5
11.	10/36: - Delayed recall	5
12.	Logical memory: - Delayed recall - Recognition	10
13.	Fluency	5
14.	DO 80	5
15.	HADS	10

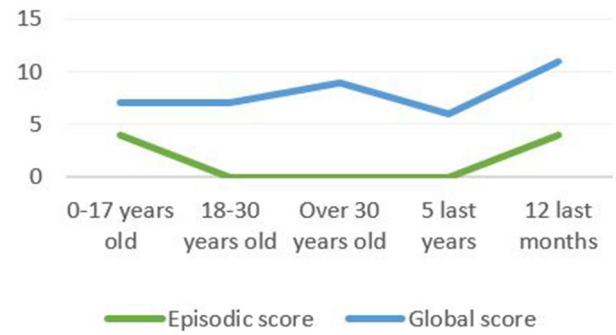

FIGURE 3 | The TEMPau shows a U-distribution with a better performance for childhood episodic memories and for the past year.

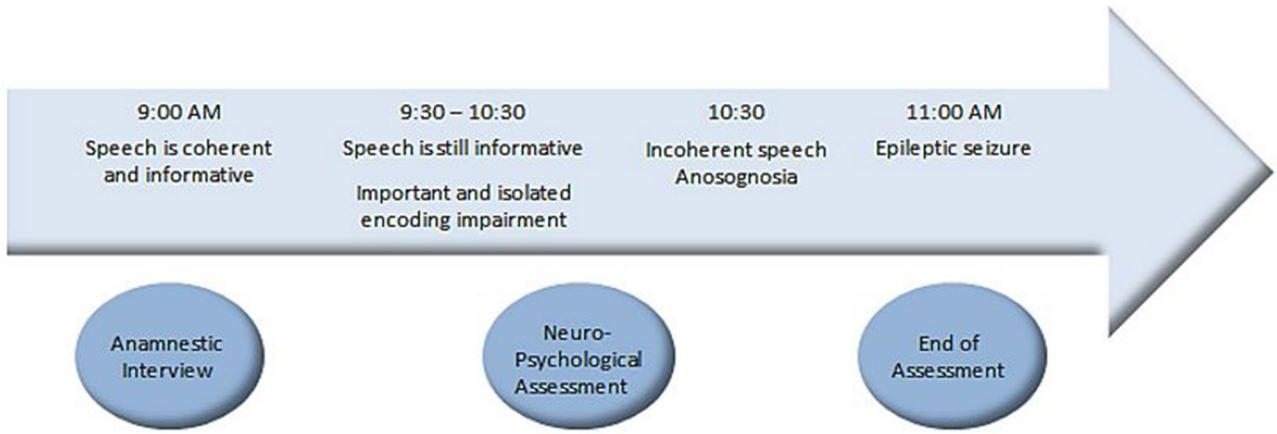

FIGURE 4 | Unfolding facts.

memory with only an associated visuoconstruction difficulty and a diminution of anxiety.

During the last part of the examination, the patient began to justify his results, saying that he had never been good for memory tasks. At the end of the tests assessment, the psychologist took some time to discuss the results. That is when the patient began to give unclear answers during the conversation. He gave repetitive justifications. When the psychologist asked questions about the daily life, he gave irrelevant responses. When the psychologist said that the NPA was complete and that he was going to call his wife, the patient had a clinically observable seizure with pallor of the face, repetitive swallowing movements, disorientation and comprehension disorder. He repeated "I don't understand what you are saying". He then repeated what the psychologist said by echolalia. The episode lasted 5 min then the patient could speak normally and said that he didn't feel well during the seizure but did not remember that he was repeating the same sentences. **Figure 4** sums up the unfolding facts.

Thus, more than an hour and a half before the observation of a clinical seizure, a significant and isolated impairment of verbal and visual episodic memory encoding and storage was measured, followed by some degree of anosognosia (patient attempted to justify the difficulties). Anxiety was reduced on the mood self-assessment questionnaire. Given the occurrence of an amnesic seizure at the end of the second NPA, the patient was asked to come back 1 month later to reassess the tests.

The appointment was set up during the afternoon, to avoid stressing the patient on awakening.

3. Third NPA

When the patient came back 1 month later, he had not had any seizure. His complaint was still the same. He remembered that he came for the NPA 2 one month before and that he had a seizure.

The third NPA revealed a preservation of global cognitive efficiency, language, executive functions and working memory. Visuoconstruction was normalized. The assessment of verbal episodic memory showed an encoding and consolidation difficulty but the 20-min delayed recall showed a normal storage. As on the first NPA, logical memory subtest showed impaired delayed recall, and the recognition was also impaired. Emotional state evaluation indicated anxiety manifestations.

An ALF was observed 1 week later: only two words of the RL/RI-16 list were spontaneously recalled and three more with the indication of the category, with four intrusions.

Overall, the third NPA showed substantially the same clinical profile than during the first NPA (**Table 1**). One year after the first evaluation, the cognitive profile was stable; the patient was still independent in daily life and managed his finances without any difficulty.

COMMENTS

This patient with TEA syndrome, characterized by amnesic episodes subjectively controlled by 100 mg lamotrigine, had a normal standard neuropsychological assessment on two occasions (NPA 1 and 3) but showed an accelerated forgetting and autobiographical memory impairment, as described in literature (2). The progressive occurrence of an encoding impairment an hour and a half before a clinical seizure requires reconsideration of the classical ictal/interictal distinction on the one hand and the speed of propagation of an epileptic discharge on the other. A clinically observable seizure is only "the tip of the iceberg". Subtle cognitive symptoms can set in within several minutes. Our observation shows that, in an apparently asymptomatic subject, there may be a reversible prolonged encoding impairment of epileptic origin. Ten cases of surface EEG recording during an amnesic seizure were reported; 8/10 cases showed bilateral temporal seizure activity, and the others had unilateral temporal seizure activity (one left sided and one right sided). Amnesia was observed as an ictal phenomenon in

six cases and as postictal in four cases (24). The precise temporal relationship between seizure onset and offset and the associated amnesia is, however, uncertain in the majority of cases of TEA (2). Epileptiform abnormalities on the EEG are rarely seen on a standard waking EEG but often on a nocturnal prolonged sleep EEG (25). Hippocampal interictal spikes recorded on S-EEG during sleep have been shown to disrupt consolidation due to transfer interference between the hippocampus and neocortex (26). It can be suggested that accelerated forgetting and impaired autobiographical memory are the consequence of insufficiently controlled epileptic activity. Some authors consider that ALF results from a consolidation and/or reconsolidation disorder and is consistent with a mesial temporal dysfunction. Encoding process remains preserved (7, 10). ALF could result from a subclinical epileptic activity, impacting the memory-related brain areas (3), which would disturb a long-term stabilization (27).

Our case report raises an important practical question: Should treatment be given to suppress observable seizures or should treatment be enhanced to reduce interictal memory impairment? Should one try to suppress the spikes seen on the sleep EEG in TEA 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

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

CB performed the neuropsychological assessment and drafted the paper. BT shared his theoretical knowledge and drafted the paper. Both authors contributed to the article and approved the submitted version.

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Conflict of Interest: BT was employed by CIC.

The remaining author declares 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: An EEG captured case of migralepsy/migraine aura-triggered seizures

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Introduction: Migraine and epilepsy are common chronic neurological disorders presenting with paroxysmal attacks of transient cerebral dysfunction, followed by subsequent return to baseline between episodes. The term "migralepsy" has been proposed to define migraine-triggered epileptic seizures classified by the ICHD-III as a complication of migraine with an aura.

Case: A 55-year-old man with a 30-year history of migraine without aura presented with a new onset left parietal pain accompanied by visual disturbances occurring up to 20 times per day. His visual distortions included kaleidoscopic vision, flashes of shadows, and a right superior quadrantanopia lasting 20 min. He described discrete 2-min episodes of scintillating scotomas in his right visual field. Ictal EEG demonstrated a left occipital onset focal aware seizure with his clinical symptoms. The patient was started on valproic Acid and has remained asymptomatic.

Discussion: The diagnostic criteria as set out by the ICHD-III for migralepsy and other syndromes with migrainous and ictal features remain confusing for practitioners as there is much overlap in clinical manifestations of these entities. EEG should be obtained when ictal features are noted among patients presenting with headache.

KEYWORDS

migralepsy, visual aura, ictal headache, homonymous hemianopsia, visual hallucinations

Introduction

Epilepsy and migraine are the most encountered chronic neurologic disorders associated with paroxysmal attacks of transient cerebral dysfunction, followed by subsequent return to baseline between episodes. Migraine and epilepsy both share a heritable component, demonstrate high rates of comorbidity, have similar underlying pathophysiological mechanisms, and overlap in symptomatology. In these conditions, we see excessive neuronal excitability characterized by visual and sensory disturbances, autonomic symptoms, and, at times, alterations in the content and level of consciousness (1–3). Although studies vary, individuals with either migraine or epilepsy are more than twice as likely to have the other disorder. The prevalence of migraine in the

epileptic population ranges between 8.4 and 23% (4) while the prevalence of epilepsy in people with migraine varies from 1 to 17% (5). The lack of published data highlights the inadequacy of the current definitions of ICHD-III about temporal and/or clinical association and overlap between migraine and epilepsy. Herein we present a case in which symptoms of the usual migraine aura developed into a focal aware seizure of occipital origin.

Case

A 55-year-old man with a known history of migraine headaches without aura, hypertension, hyperlipidemia, obesity, and newly diagnosed type 2 diabetes mellitus II was referred to the Emergency Department (ED) by his ophthalmologist. The patient had a 5-day history of visual disturbances and a severe left parietal headache. He described the quality of his headache as lancinating, continuous, and pulsatile. He described his visual distortions as having a "wavy quality" with associated kaleidoscopic patterns, flashes of shadows, and scintillating scotomas (red and green circles), occurring every 15–20 min and lasting 2 min each. His visual field was also obscured in the right hemifield, more so in his right superior quadrant.

The onset of his symptoms was associated with nausea, vomiting, and intermittent sensitivity to light. He reportedly received chiropractic manipulation hours earlier in the day prior to the onset of his symptoms. He denied sensitivity to sound or smell, or other neurologic deficits including slurred speech, double vision, focal weakness, numbness, lacrimation, painful eye movements, or nuchal rigidity. The frequency of his typical migraine headaches occurred one to two times per year.

His neurologic exam showed a right superior homonymous quadrantanopia with 20/25 visual acuity in both eyes, full ocular motility, and unremarkable funduscopy. The initial work up included computed tomographic angiography (CTA) of the head and neck, contrast-enhanced magnetic resonance imaging (MRI) of the brain and orbit with and without contrast, and blood work including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count (CBC), which were all normal. The patient was discharged from the ED with resolution of his headache and visual symptoms. He was advised to obtain an contrast enhanced MRI Orbit with and without contrast and follow up at the in ophthalmology and neurology clinics in 1 week.

He returned to the hospital 5 days later due to more frequent episodes of visual distortion. He reported that the headache was no longer prominent compared to his initial presentation a week prior and the visual field deficit had resolved. Electroencephlogram (EEG) was suggested given the unremarkable results of the previous workup and his persistent visual symptoms. An initial short-term EEG was normal. A typical event was captured during the long-term recording. Ictal EEG demonstrated a left occipital-onset focal seizure with right hemispheric involvement as it evolved (Figure 1). This correlated with the patient reporting "flashing fireworks and broken red lights mirrors" in the right eye.

He was loaded with levetiracetam 2000 mg intravenously with a daily maintenance oral dose of levetiracetam 750 mg twice daily. On this regimen, he continued to report several episodes of the visual disturbance the following next day. He was switched to valproic acid (loading dose of 2000 mg and maintenance dose of 500 mg twice daily). A repeat routine EEG the following day was normal. Upon his 2-month follow up with neurology, he reported resolution of the headaches and visual disturbances.

Discussion

The term migralepsy was first coined in 1960 by Lennox and Lennox to describe a condition wherein "ophthalmic migraine with perhaps nausea and vomiting was followed by symptoms characteristic of epilepsy" (6). The International Classification of Headache Disorders-III (ICHD-III) has refined the definition of migralepsy to denote an attack of migraine with aura attack that is complicated, by an epileptic seizure within an hour of migraine onset (7). Currently, it is better known as migraine-triggered seizure and is a rare phenomenon. Within the same family of conditions, other rare neurological disorders with migrainous and ictal components include including ictal epileptic headaches (IEH) and hemicrania epileptica. The ICHD-III refers to IEHs as secondary headache disorders to a primary epileptic condition and occurs in 3–5% of cases (8, 9). The headache can be ipsilateral or contralateral with epileptiform EEG discharges. The original diagnostic criteria for ictal epileptic hedaache as proposed by Parisi et al. also includes a prompt response to antiepileptic drugs (10). Hemicrania epileptica is recognized as an ipsilateral "ictal headache" that occurs "synchronously" with a partial seizure. To complicate matters further, there have been reports of ictal epileptic headaches that present as the sole manifestation of an epileptic event, thus making the differentiation of migraine with aura from epileptic seizures difficult (11–13).

Our case demonstrates yet another example of the complex relationship between migraine and epilepsy. Identifying the correct underlying etiology of the patient's symptoms was difficult because of the fluctuating nature of his complaints and deficits seen on neurologic exam. In this case, migraine-like symptoms appeared first followed by his visual disturbances. However, as his symptoms persisted, the visual disturbances became more prominent and were suspicious for occipital onset seizures. By ICHDIII criteria, this patient would qualify for diagnosis of migraine-triggered seizure/migralepsy because the initial migraine headaches triggered his focal aware left occipital lobe seizures. However, over the course of the patient's disease, the visual disturbances associated with his seizures became

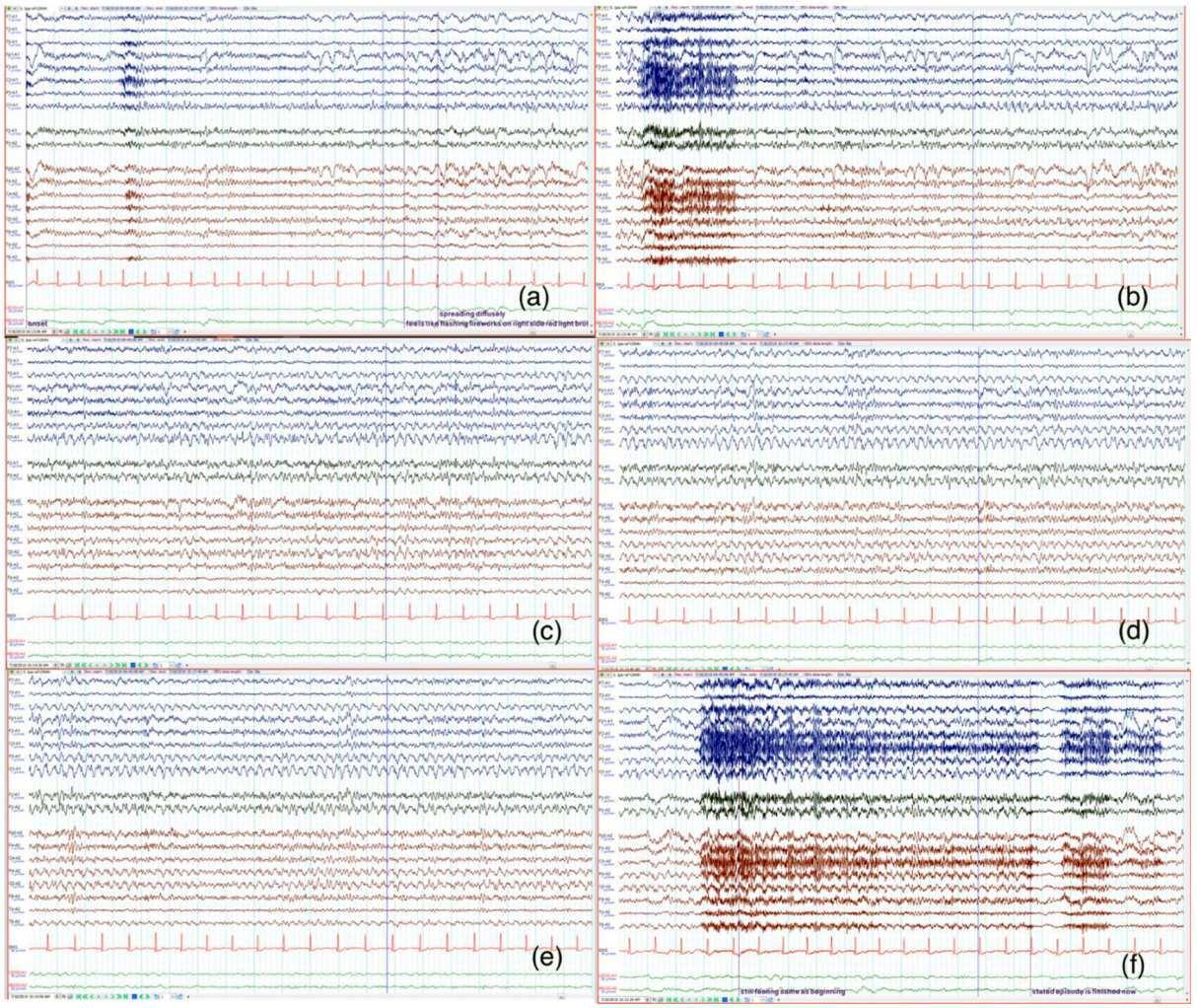

FIGURE 1
The signals from the left hemisphere is shown in blue and right hemisphere in red. Twenty sec epochs of electroencephalography (EEG) (average montage) demonstrate that the onset is from the left occipital region **(a)** with evolution and progression **(b–f)** to involve the right side. The patient's seizure correlated with the visual sensation of "flashing fireworks and broken red lights mirrors" in the patient's right visual hemifield.

the prominent feature and the headaches had resolved, thus obscuring the picture further.

Among 50 potential migralepsy cases identified in the literature, only two were found to meet ICHD criteria. Most diagnoses remaining uncertain and often questionable due to insufficient data collected at the time of diagnosis, including diagnostic EEG studies during the event (14). In the questionable cases, the description of the episode combined with EEG and brain imaging were highly suggestive of epileptic seizures particularly in the occipital lobe (15). Our patient case was fortunate because an epileptic event was documented when EEG was recorded. Notably, apart from the seizure captured on EEG, there were no focal abnormalities or interictal epileptiform discharges seen within the recording or on a follow-up EEG (obtained 2 days after initiating proper treatment) to suggest a focal predisposition to seizure in that region. To complicate differentiating the diagnosis patients with epileptic visual symptoms may show similar EEG abnormalities to those as seen in acute migraine attacks, with posterior predominant theta-delta wave activity (15). In most cases of ictal epileptic headache ictal there is a lack of a specific headache pattern with evidence of non-specific ictal EEG patterns often without corical-topographic correlations (16).

When evaluating attacks suggestive of migralepsy one must consider the characteristics of visual symptoms between migraine visual auras and occipital lobe seizures. A retrospective cohort analysis found that the visual aura was of shorter duration in epilepsy compared to migraine, with a median duration of 56 s vs. 20 min, respectively. Other factors that differentiate the quality of the visual aura in epilepsy vs. migraine

included a restriction of the visual phenomenon to a visual hemifield in epilepsy compared to migraine; and centrifugal or centripetal spread of visual symptoms (phosphenes, scotomas, etc.) occurred in migraine, but not in epilepsy. The patient described visual auras which were a combination of those typical for both migraine and epilepsy making a distinction between them a diagnostic challenge. He described a global visual kaleidoscopic pattern expected in migraine. However, the distinct flashes of shadows and scintillating scotomas described as red and green circles restricted to his right visual field of both eyes, lasting only 2 min, are more typical for epilepsy. Though there are minor differences in the quality and timing of the visual aura, an EEG was required to make a more definitive distinction. Even obtaining long-term EEG monitoring for precise diagnosis may be necessary in resolving diagnostic uncertainty (17–19). Visual auras in migraine and epilepsy are related to transient occipital lobe dysfunction which has been described in the literature as cortical spreading depression and paroxysmal depolarizing shift, respectively (19).

The therapeutic benefit of certain antiepileptic drugs (AEDs) in migraine prevention can be reasonably inferred from this shared pathogenesis with epilepsy (20, 21). The goal of management is to treat migraine and epilepsy. This can be achieved with medications including valproic acid, topiramate, or zonisamide (second line) for patients who are intolerant to topiramate (22). Our patient showed incomplete response to levetiracetam and was thus shifted to valproic acid 500 mg twice daily with complete resolution of visual symptoms and normal repeat EEG.

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

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

AH contributed to discussion and final proof reading. MP contributed to writing the case and introduction and final proof reading. NC wrote the case section. SM wrote the introduction and abstract. CA contributed to EEG discussion and proof reading. 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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New-onset refractory status epilepticus due to autoimmune encephalitis after vaccination against SARS-CoV-2: First case report

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Background: Vaccination against SARS-CoV-2 has been conducted frequently to limit the pandemic but may rarely be associated with postvaccinal autoimmune reactions or disorders.

Case presentation: We present a 35-year-old woman who developed fever, skin rash, and headache 2 days after the second SARS-CoV-2 vaccination with BNT162b2 (Pfizer/Biontech). Eight days later, she developed behavioral changes and severe recurrent seizures that led to sedation and intubation. Cerebral magnetic resonance imaging showed swelling in the (para-) hippocampal region predominantly on the left hemisphere and bilateral subcortical subinsular FLAIR hyperintensities. Cerebrospinal fluid analysis revealed a lymphocytic pleocytosis of 7 cells/μl and normal protein and immunoglobulin parameters. Common causes of encephalitis or encephalopathy such as viral infections, autoimmune encephalitis with well-characterized autoantibodies, paraneoplastic diseases, and intoxications were ruled out. We made a diagnosis of new-onset refractory status epilepticus (NORSE) due to seronegative autoimmune encephalitis. The neurological deficits improved after combined antiepileptic therapy and immunomodulatory treatment including high-dose methylprednisolone and plasma exchange.

Conclusions: Although a causal relationship cannot be established, the onset of symptoms shortly after receiving the SARS-CoV-2 vaccine suggests a potential association between the vaccination and NORSE due to antibody-negative autoimmune encephalitis. After ruling out other etiologies, early immunomodulatory treatment may be considered in such cases.

KEYWORDS

new-onset refractory epileptic state, NORSE, SARS-CoV-2 vaccination, BNT162b2, seronegative autoimmune encephalitis, postvaccinal encephalitis

Introduction

Adverse effects of SARS-CoV-2 vaccination with mRNA vaccines are rare and mostly limited to local reactions or slight systemic symptoms (1) including fatigue and headache most commonly. Generally, post-vaccination autoimmune encephalitis is rare (2, 3), but it has been reported to have an association with the adenoviral vector vaccine ChAdOx1 (Oxford-AstraZeneca) (4) as well as the mRNA vaccine (Pfizer/Biontech) for SARS-CoV-2 (3, 5).

A heterogeneous group of sporadic autoimmune encephalitis cases associated with SARS-CoV-2 infection has also been reported (6). Additionally, more and more autoimmune encephalitis cases have been linked to other viral triggers (7).

Here, we describe a case of new-onset refractory status epilepticus (NORSE) due to autoantibody-negative autoimmune encephalitis in close temporal association with the second SARS-CoV-2 vaccination dose of BNT162b2 (Pfizer/Biontech).

Case presentation

A 35-year old woman was referred to our center with recurrent focal to bilateral convulsive seizures after an episode of fever, headache, and skin rash 6 days prior. Two days before the onset of fever, she received the second dose of an mRNA-based SARS-CoV-2 vaccine (BNT162b2, Pfizer/Biontech). The first dose was well-tolerated. The patient's medical history revealed only sporadic but not recent cocaine consumption and mild SARS-CoV-2 infection a year before the vaccination.

The clinical, laboratory, and imaging findings are summarized in Table 1 and are illustrated in Figure 1. On admission, the patient presented with fever of up to 40°C, visual impairment, behavioral changes, recurrent focal to bilateral tonic-clonic seizures, reduced level of consciousness, and choreatic movements. On admission, moderately elevated TSH, normal free T3 and T4 hormone levels, and slightly elevated liver function tests possibly due to recent overuse of paracetamol were found in the blood test. Drug screening of urine was negative.

The electroencephalogram (EEG) initially showed a generalized rhythmic delta activity with superimposed multifocal interictal epileptic discharges mainly over the frontal and right-sided leads. Frequent brief electrographic seizures were also detected (Figure 2). Initial CT and MRI scans were unremarkable. The MRI on day 5 after admission revealed edema in the left mesial temporal lobe, particularly the hippocampus, which became progressive in size 10 days later. Additionally, FLAIR hyperintensive lesions in the bilateral subinsular regions were detected (Figure 3). The FDG PET showed hypermetabolism of the left amygdala and hippocampus and basal pulmonary hypoventilation. Cerebrospinal fluid (CSF) analysis revealed lymphocytic pleocytosis (7 cells/μl), normal protein, glucose, lactate, and total immunoglobulin parameters, and matched oligoclonal bands in the serum and CSF without signs of intrathecal IgG production (Table 1). The blood and CSF screening for common viral and bacterial infections and autoimmune disorders including vasculitis was negative. The diagnostic criteria for a definite autoantibody-negative autoimmune limbic encephalitis according to established criteria were fullfilled (8). However, testing for common anti-neuronal autoantibodies in serum and CSF was negative, including indirect immunofluorescence staining of mouse brain.

Due to recurrent convulsive seizures without regaining consciousness, a diagnosis of new-onset refractory status epilepticus (NORSE) was made. Levetiracetam up to 4 g/d and lacosamide up to 200 mg/d were started. Under continuous EEG monitoring, phenytoin up to 750 mg/d, midazolam up to 0.57 mg/kg/h, and ketamine up to 4 mg/kg/h were added. Phenytoin was later replaced by phenobarbital. Initially, acyclovir 3 × 10 mg/kg body weight/day and ceftriaxone were given until the CSF and serum testing for herpes viral and bacterial CNS infections turned negative. Immunomodulatory treatment with high-dose methylprednisolone (5 days of 1,000 mg/d IV) was started 2 days after hospital admission with subsequent slow tapering over 8 weeks. Because of continued seizures, plasma exchange for over 10 days starting on day 7 after the admission was performed.

Subsequently, the patient's condition rapidly improved beginning on day 12 after the admission; she regained full consciousness and had only infrequent seizures. The follow-up MRI 1 month after the hospital admission showed edema reduction in the hippocampal, amygdala, and external capsule. On discharge, she had persisting moderate mnestic deficits and infrequent seizures (2–3/month). However, after 2 months, the patient was readmitted to our hospital because of deterioration in

Abbreviations: COVID-19, coronavirus disease 2019; CSF, cerebrospinal fluid; CNS, central nervous system; EEG, electroencephalogram; ED, epileptic discharge; FDG-PET, 2-fluor-2-desoxy-D-glucose positron emission tomography; FLAIR, fluid-attenuated inversion recovery; HSV-1/2, herpes simplex virus type 1 or 2; IED, interictal epileptic discharge; MRI, magnetic resonance imaging; NORSE, new onset refractory status epilepticus; PCR, polymerase chain reaction; PD, periodic discharge with sharp morphology; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome virus 2; VZV, varicella zoster virus.

TABLE 1 (A) Symptoms and (B) therapy, (C) imaging, (D) laboratory, (E) CSF, and (F) EEG findings.

(A) Symptoms

SARS-CoV-2 vaccination	Day 0
Fever, headache, change of character, skin rash	Day 2–7
Generalized epileptic seizures	Day 7
Hyperkinetic movement disorder	Day 22
APE^2 Score	10
Neuropsychological findings	Day 42: severe neuropsychological disorder with fronto-limbic dysfunction

(B) Therapy

Therapy with acyclovir 3 × 10 mg/kg body weight/d iv	Day 8–16, until negative PCR of VZV and HSV
Therapy with ceftriaxone 2 × 2,000 mg/d	Day 8–14
Cotrimoxazol 800/160 mg	Three times a week during high doses steroid treatment
Therapy with methylprednisolone 1,000 mg/d iv	Day 10–14, followed by careful tapering
Plasmapheresis therapy	Day 15, 17, 20, 22, 24
Levetiracetam	
2 × 500 mg/d	Day 8–9
2 × 1,500 mg/d	Day 9–17
2 × 2,000 mg/d	Day 17-ongoing
Lacosamid 2 × 100 mg/d	Day 9–11
Midazolam up to 40 mg/h i.v.	Day 10–25
Phenytoin 3 × 250 mg/d	Day 11–17
Ketamin up to 300 mg/h i.v.	Day 15–21
Phenobarbital 2 × 150 mg/d	Day 17–20
Phenobarbital 2 × 200 mg/d	Day 20-ongoing
Tiprid 3 × 100 mg/d	Day 24–30
Dexmedetomidin i.v.	Day 12–34 (recurrent treatment)
Lorazepam up to 4 × 2.5 mg/d	Day 25-ongoing

(C) Imaging

CT Scan day 8 and 9:	Normal
Brain-MRI	
day 8:	– Normal MRI
day 13:	– Edematous changes in amygdala, hippocampus, and Parahippocampal gyrus predominantly left side
day 23:	– Progression of edema in amygdala on both sides, hippocampus, and parahippocampal gyrus predominantly left side, additional subcortical FLAIR hyperintensities subinsular bilaterally
day 38:	– Regression of FLAIR hyperintensities in all areas
FDG-PET day 35	No signs of metabolically active malignancies. Cerebral hypermetabolism in left amygdala and hippocampal area

(Continued)

TABLE 1 Continued

Anti-neuronal antibodies*	Negative	Negative
TSH level	10.4 mU/l	0.2–4.3 mU/l
fT3, fT4	Normal	Normal
(D) Laboratory findings	**Result**	**Normal value**
Nasopharyngeal swab or tracheobronchial fluid for SARS-CoV-2 RNA Day 8, 10, 16, 22, 29	Negative	Negative
Creatinkinase (µmol/l)	80	45–84
Leukocytecount (10^9/L)	5.76	3.9–10.2
Thrombocytecount (10^9/L)	160	150–370
Hemoglobin (g/L)	13.2	12.0–15.4
C-reactive protein (mg/L)	31.9	<5.0
(E) CSF characteristics	**Day 7**	**Normal**
CSF cellcount /µl	7	< 5
CSF Lactate (mmol/L)	2.2	1.2–2.1
Glucose (mmol/L)	4.5	2.7- 4.2
Protein (mg/L)	490	< 450
Virus PCRs in CSF	negative PCR for HSV-1/2, VZV, TBEV, Enterovirus	negative
Serologicaltesting	Negative TBEV-IgG and -IgM, antinuclear antibodies, anti-dsDNA antibodies, anti-cardiolipin and β2-glykoprotein antibodies, ANCA	negative
Oligoclonal bands**	type 4	type 1
(F) EEG findings		
Day 8:	– Generalized slowing, convusive seizure presenting on EEG with rhythmic delta activity	
Day 9:	– Generalized slowing, bifrontal interictal epileptic discharges (IEDs), polytopictriphasic potentials	
Continous EEG day 10–26:	– Periodic discharges with sharp morphology (PD), brief electrographic seizures	
Day 34:	– Polytopictriphasic potentials, no ED, slight regression of pathologies	
Day 36:	– Single ED predominately left side, no change in encephalopathy	
Day 38:	– Single ED predominately left side, no change in encephalopathy	
Day 41:	– Single ED predominately left side, no change in encephalopathy	

*Anti-neuronal autoantibody sera: GAD65, NMDA, GABAAR, GABABR, IgLON5, AMPAR 1/2, DPPX, LGI1, CASPR2, glycin-receptor, mGluR5, and mGluR1; CSF: GAD65, NDMAR, GABAAR, GABABR , IgLON5, AMPAR 1/2, DPPX, LGI1, CASPR2, glycin-receptor, mGLuR5, and mGLuR1; Neural antibody (immunoblot-IgG) sera: amphiphysin, CV2/CRMP5, Ma2/Ta (PNMA2), Ri, Yo, Hu, Recoverin, Sox1, Titin, Zic4, and DNER/Tr; CSF: amphiphysin, CV2/CRMP5, Ma2/Ta (PNMA2), Ri, Yo, Hu, Recoverin, Sox1, Titin, Zic4, and DNER/Tr.
**OCB type 1 = no oligoclonal bands in the CSF and serum, i.e., no intrathecal IgG production; OCB type 2 = oligoclonal IgG bands only in the CSF, i.e., intrathecal IgG production; OCB type 3 = oligoclonal bands in the CSF and serum with additional bands in the CSF, i.e., intrathecal IgG production; OCB type 4 = identical oligoclonal bands in the CSF and serum, i.e., no intrathecal IgG production; OCB type 5 = monoclonal IgG bands in the CSF and serum.

seizure frequency (2–3 serial seizures) and neuropsychological deficits. She again received high-dose methylprednisolone for 5 days, which led to significant reduction in seizure frequency.

Discussion and conclusions

We report the first case, to our knowledge, of NORSE due to seronegative autoimmune encephalitis 8 days after

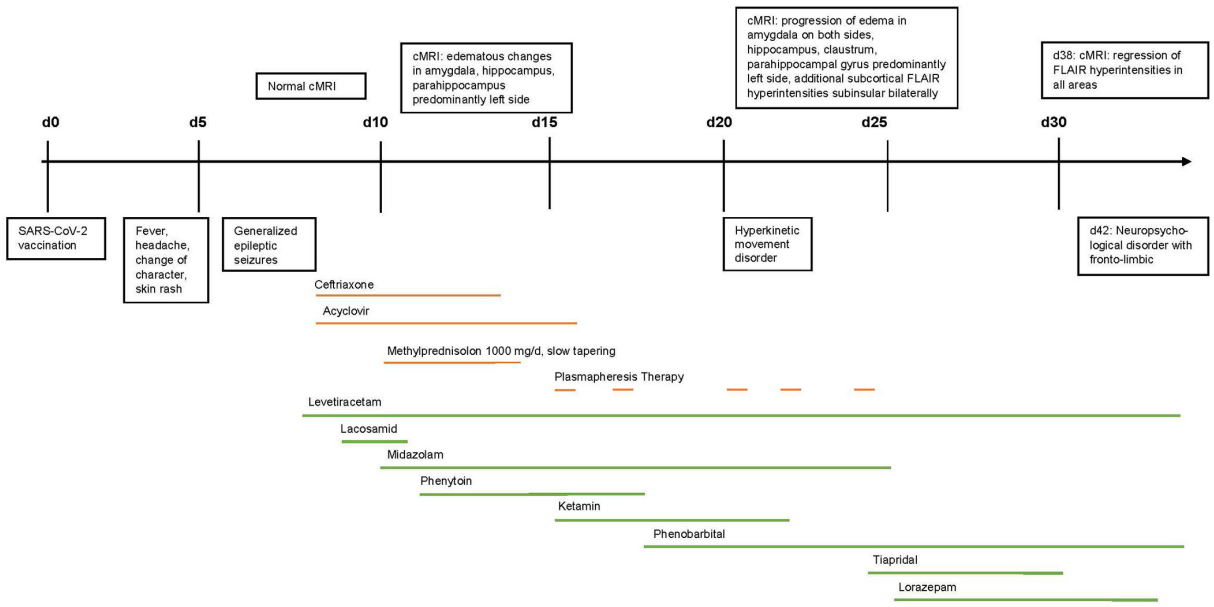

FIGURE 1
Timeline of clinical development, therapy, and MRI-findings.

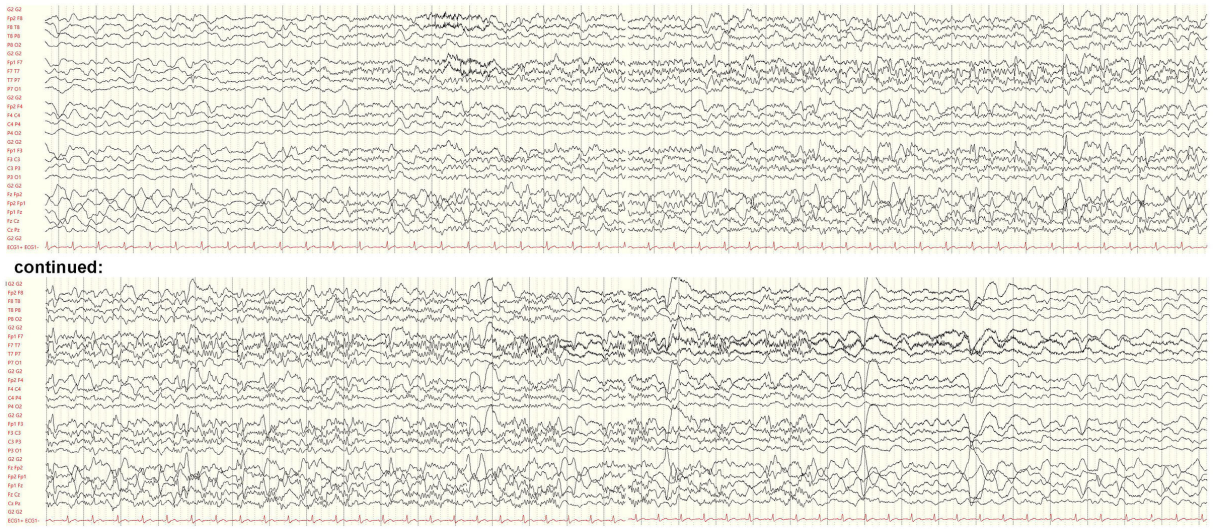

FIGURE 2
Electroencephalogram on day 8 after symptom onset showing a brief focal seizure. The seizure discharge begins with an evolving fast rhythm with onset in the left temporal leads and interspersed epileptic discharges. There is generalized background slowing following the seizure. Bipolar longitudinal montage, gain 70 μV/cm, base time 3 cm/s, high-pass filter. 53 Hz, low-pass filter 80 Hz, and notch filter 50 Hz.

vaccination with the mRNA SARS-CoV-2 vaccine. A causal relationship between vaccination and autoimmune encephalitis with NORSE is not established with certainty. Nevertheless, the onset of neurological symptoms 8 days following the vaccination suggests a potential association as well as the hyperintensities of the claustrum as a common finding in NORSE and autoimmune encephalitis (9, 10).

Given the assumed low incidence of autoimmune reactions and their favorable outcome, benefits of vaccination far outweigh the risk of side effects. Importantly, SARS-CoV-2 infection itself may trigger

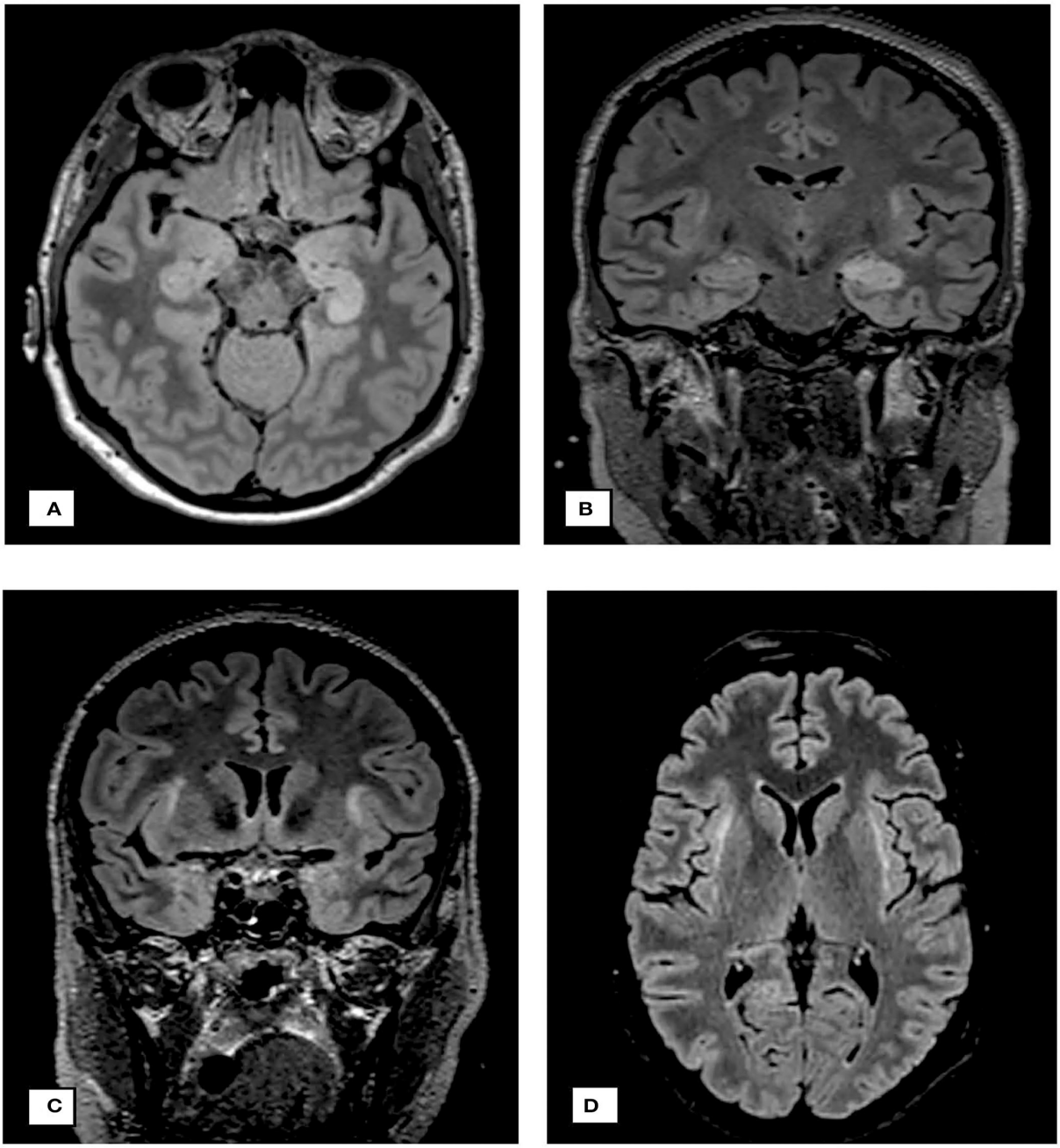

FIGURE 3
Neuroimaging findings. **(A)** cMRI on day 13: axial FLAIR sequence demonstrating edematous changes in hippocampus and parahippocampal gyrus predominantly on the left side. **(B)** cMRI on day 23: coronary FLAIR sequence demonstrating progression of edema on both sides, the hippocampus and parahippocampal gyrus, additional subcortical FLAIR hyperintensities subinsular on both sides. **(C,D)** demonstrate the claustra hyperintensities.

a heterogeneous group of autoimmune encephalitis. Hence, the observation of SARS-CoV-2 vaccine-associated NORSE does not argue against the broad use of SARS-CoV-2 vaccines.

Whether the patient's history of SARS-CoV-2 infection approximately 1 year before the encephalitis may have played a role remains unknown. Our findings should encourage clinicians to consider SARS-CoV-2

vaccination or infection as a potential trigger for autoimmune encephalitis.

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

JW collected and interpreted the clinical and radiological data and was a major contributor in the writing and revision of the manuscript. IJ collected and interpreted the clinical and laboratory data and revised the manuscript. GB interpreted the clinical findings and revised the manuscript. MG interpreted the clinical and electroencephalographic findings and revised the manuscript. All authors read and 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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Case report: Dravet syndrome, feeding difficulties and gastrostomy

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Dravet syndrome (DS) is a developmental and epileptic encephalopathy associated with variants in the voltage-gated sodium channel alpha 1 subunit (*SCN1A)* gene in around 90% of individuals. The core phenotype is well-recognized, and is characterized by seizure onset in infancy, typically with prolonged febrile seizures, followed by the emergence of multiple seizure types that are frequently drug-resistant, developmental delay, and intellectual disability. Comorbidities are common and include autism spectrum disorder, gait impairment, scoliosis, and sleep disorder. Feeding difficulties and weight loss are frequently reported by DS caregivers, and negatively impact quality of life, yet have received little attention. Here we report an adult with DS who developed reduced food and fluid intake in adolescence, resulting in weight loss and malnutrition. No underlying cause for her feeding difficulties was identified, and she subsequently required insertion of a percutaneous endoscopic gastrostomy. We review the occurrence of feeding difficulties in people with DS and discuss potential mechanisms.

KEYWORDS

Dravet syndrome, co-morbidities, SCN1A, gastrostomy (PEG), weight loss, feeding and swallowing trouble

Introduction

DS is a developmental and epileptic encephalopathy. It is associated with variants in the voltage-gated sodium channel alpha 1 subunit (*SCN1A)* gene in around 90% of individuals (1), and is one of the most common monogenic epilepsies, with an incidence of 1 per 12,200 live births (2). The core phenotype of DS is well-characterized. Symptom onset is at around 6 months, typically with recurrent, prolonged, tonic clonic, or hemiclonic seizures. The initial seizures are characteristically triggered by fever (febrile seizures), and/or vaccination (1, 3). Subsequently, multiple, afebrile seizure types emerge, that are usually resistant to treatment with antiseizure medications (1, 3). Status epilepticus is common (1), and premature mortality is estimated to affect between 10 and 20% of people (4–6), most commonly due to sudden unexplained death in epilepsy (SUDEP) or status (7). Development is initially normal, but begins to slow, plateau, or regress after seizure onset, typically from 2 years of age (1, 3). Most individuals develop moderate to severe intellectual disability (1, 3, 8).

In addition to epilepsy, developmental delay, and intellectual disability, other "comorbid" conditions are common in DS, and include autism spectrum disorder (ASD) (9–12), gait impairment (9, 10, 13–16), scoliosis (12, 16), and sleep disorder (9, 16–21).

Difficulties related to feeding, and weight loss/failure to gain weight, are frequently reported in surveys of DS caregivers (9, 12, 16, 17, 22, 23). Reported feeding difficulties include appetite disturbance (9, 12, 16, 17, 22, 23), food fads and fussy/selective eating (22), prolonged meal times (22), inability to feed independently (24), and difficulty with chewing and swallowing (9, 12, 16, 22, 24). In one of the largest surveys of comorbidities in children with DS, 99% of caregivers reported at least one concern relating to feeding, making it the most frequently reported category of concern (22). Despite this, issues related to feeding and weight loss in DS have received little attention. In our single-centre experience of caring for more than 50 adults with DS, feeding difficulties and weight loss are commonly encountered, and 20% of individuals have undergone percutaneous endoscopic gastrostomy (PEG) insertion to manage these issues (Clayton, unpublished).

Here we report an adult with DS, highlighting some of the common but under-recognized issues related to feeding and PEG insertion in this population.

Case description

Taliah was born following an uneventful pregnancy. At 2 months she had a prolonged generalized tonic clonic seizure (GTCS) 12 h after her first immunization. At 3 months, following her second immunization, she had a further prolonged GTCS. Habitual, unprovoked seizures including myoclonic jerks, unclassified unresponsive episodes (possibly absence or atypical absence seizures), and GTCS began shortly after. Seizures were drug-resistant, and she experienced several episodes of status epilepticus. Taliah's early development was normal, but after a severe and prolonged GTCS at 4 years there was developmental regression, and subsequent intellectual disability. At 10 years, Taliah was diagnosed with DS following genetic testing which identified a pathogenic stopgain variant in *SCN1A* (NM_001353948:c.G3991T:p.E1331*). Now in adulthood, she continues to have clusters of GTCS, occurring every 1–2 months. Taliah has ASD and thoracolumbar scoliosis, which was surgically corrected at 13 years.

During adolescence, Taliah's food and fluid intake began to reduce, and weight loss ensued (Figure 1). There were no clear precipitants. She had been treated with a combination of stiripentol, valproate and clobazam for 4 years prior to symptom onset, with no dose increases, or introduction of new medications, in the preceding 3 years. Assessments and investigations, including by speech and language therapy, ear nose and throat specialists, blood tests (including antiseizure drug levels and ammonia levels), and barium swallow, did not reveal a cause. Over a period of 3 years, Taliah's food intake fluctuated, with episodes lasting for weeks where she would refuse to eat or drink, and where medication compliance could be challenging. Over time, seizure-free periods which occurred between clusters of GTCS, became shorter in duration (Figure 1). The need for a PEG was discussed, but like many caregivers of children/adults with neurological disability, the decision to proceed with PEG insertion was difficult for Taliah's family (25). Overtime, weight loss and signs of malnutrition became evident, and eventually a PEG was inserted to supplement Taliah's nutrition and fluid intake, and to allow for consistent medication administration. Since undergoing the PEG insertion, Taliah's weight has increased, she has more energy and sleeps less during the day. Her overall well-being has improved, and she is more engaged, interactive, and communicative. Taliah receives all fluid, and most nutrition via the PEG, but still eats some food orally for pleasure. Mealtimes are much less stressful for her family, and medication compliance is ensured.

Discussion

The true nature and spectrum of feeding difficulties in people with DS is unknown. Caregiver-reported "loss of appetite" is one of the most common feeding difficulties described in people with DS, yet the factors that lead to reduced food intake and food refusal (observed as "loss of appetite"), are likely to be complex and multifaceted. In children with neurodisability, oropharyngeal dysfunction, dental abnormalities, gastrointestinal disorders (such as gastro-esophageal reflux and constipation), pain and behavioral factors [including those related to comorbid ASD (26)], all contribute to difficulties with feeding (27–29). Many of these issues are reported in people with DS, and may contribute to reduced food intake/food refusal, and other feeding difficulties. In addition, some of the most frequently prescribed antiseizure medications in DS, including topiramate (30), stiripentol (31), cannabidiol (32), and fenfluramine (33), are commonly associated with decreased appetite, weight loss and other gastrointestinal symptoms. Feeding difficulties may also be a consequence of the underlying disease biology of DS (Figure 2).

Despite their frequency in DS, issues related to feeding have received little attention, but are important to recognize and address, as they can have a negative impact on the quality of life for both the person with DS and their caregiver (9, 17, 22). Feeding difficulties can result in reduced food intake, leading to malnutrition and its consequences, poor medication compliance, and the risk of morbidity and mortality associated with a deterioration in seizure control. In addition, oropharyngeal dysfunction can put individuals at risk of aspiration pneumonia. We would recommend that

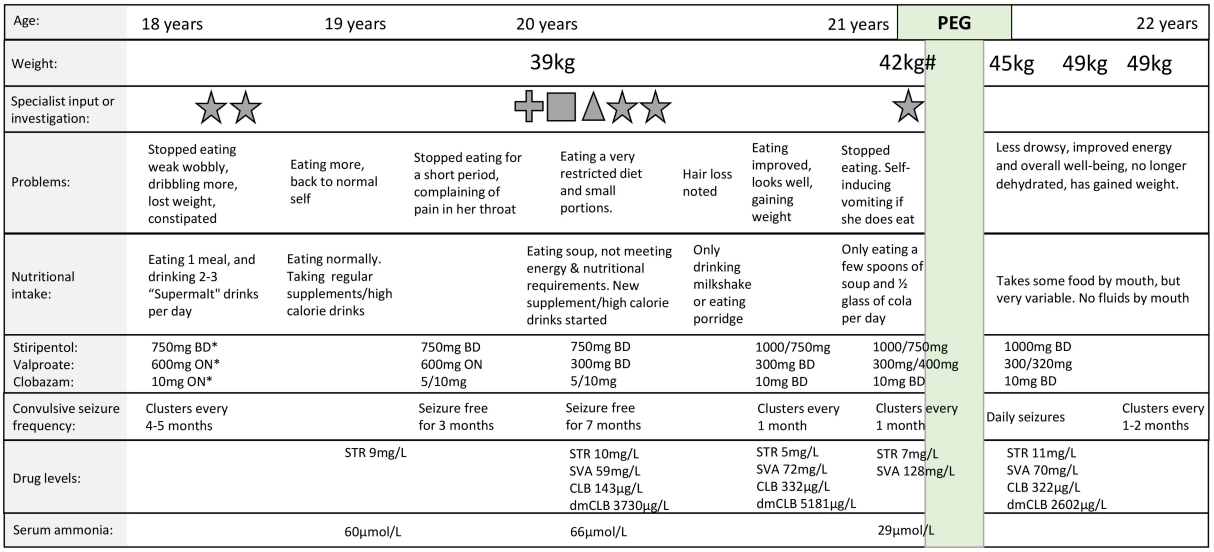

FIGURE 1
Timeline of feeding difficulties and percutaneous endoscopic gastrostomy insertion. Feeding difficulties including reduced food and fluid intake and subsequent weight loss fluctuated over 3 years prior to percutaneous endoscopic gastrostomy (PEG) insertion. # = Body mass index (BMI): 16.4 kg/m^2; * = The combination of stiripentol (STR), valproate (SVA), and clobazam (CLB) had been prescribed for 4 years prior to symptom onset at 18 years, with no dose increases, or introduction of new medications, in the preceding 3 years; star = dietician review, cross = speech and language therapy review; square = ear nose and throat specialist review; triangle = barium swallow; Green highlight = time of PEG insertion; BD = twice daily, ON = at night; drug doses separated by a forward slash (e.g., 5/10 mg) refer to a morning and evening dose; serum therapeutic drug level ranges: stiripentol 2–22 mg/L; valproate 50–100 mg/L; clobazam 30–300 µg/L; Desmethylclobazam (dmCLB) 300–3,000 µg/L; serum ammonia normal range 11–32 µg/L. Weights prior to the age of 20 were not available.

all individuals who experience feeding difficulties should be referred promptly to a dietician and speech and language therapist for formal review.

As experienced by Taliah's family, the decision to proceed with gastrostomy in children/adults with neurological disability can be difficult for caregivers (25), and it is important that adequate and appropriate information is provided to facilitate shared decision making (34). Greater awareness and understanding of feeding difficulties in DS are needed to ensure that these issues are proactively sought during clinical review, contributing factors addressed, and to facilitate earlier discussions between clinicians and caregivers around the potential need for gastrostomy. Recognition of these issues, and support from clinicians in addressing them early, should help to mitigate anxiety for caregivers around feeding, and avoid delays in intervention when necessary, minimizing the risk of malnutrition, dehydration and problems related to medication compliance.

Developmental and epileptic encephalopathies such as DS are complex conditions, often with multisystem comorbidities that extend beyond that of epilepsy. Current treatments for DS are symptomatic, predominantly aimed at controlling seizures, and do not modify underlying disease pathophysiology. Reducing seizure burden in DS has beneficial effects beyond seizure control, including improvements in cognition, language and mobility (35), but there is insufficient evidence to suggest that treatment with antiseizure medications have a direct influence on other wider disease manifestations, such as neurodevelopmental, behavioral, motor, sleep and feeding difficulties. Disease-modifying therapies, currently undergoing clinical trials, have the potential to address the full spectrum of symptoms in DS as they directly target the underlying disease pathophysiology (18). Whilst these novel therapies are undergoing development, it is important for those caring for people with DS to consider the full spectrum of comorbid conditions that occur, and ensure that all aspects of the disease are addressed where possible. Caregivers have emphasized that therapies that address the wider spectrum of comorbidities in DS (alongside seizures) will improve quality of life for people with DS and have a positive effect on family wellbeing (18).

Parent's perspective

My daughter is now 22 years old. She has had seizures for most of her life. They started when she was 2 months old, just after an immunization. She was eventually diagnosed with epilepsy at 6 months, with the doctor at the time reassuring me that she would "grow out of it." Throughout her early years she had so many seizures that we were practically living in the hospital. As she grew older her seizures never settled down. She has tried almost every antiseizure medication, and at one stage

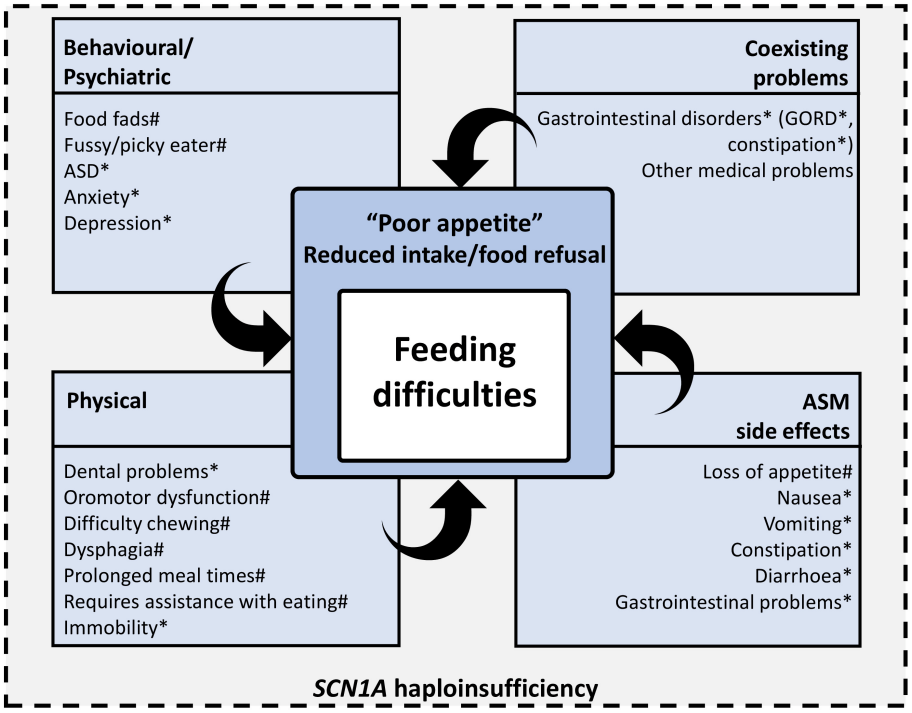

FIGURE 2
Spectrum of potential feeding difficulties in people with DS. The true spectrum of feeding difficulties in people with DS are unknown and likely reflect a combination of physical, behavioral, medication, gastrointestinal and other medical problems. These issues may directly result in feeding difficulties (i.e., dysphagia) or may lead to reduced food intake/food refusal, which is observable to caregivers and clinicians as "poor appetite." The underlying disease biology of DS (*SCN1A* haploinsufficiency) may contribute to feeding difficulties through some of these factors. # = Feeding issue reported in caregiver surveys of people with DS, * = Problems reported in people with DS that may also contribute to feeding issues.

she was taking six different types. When she was 4 years old, she had a major seizure; she stayed in hospital for weeks, and since this episode she has never been the same again.

When Taliah was 10 years old, after having numerous tests, she was eventually diagnosed with DS. I didn't know what DS was, and I found it difficult to take everything in. There was so much information, I could not fully grasp the full extent of my daughter's condition.

Over the years she was in and out of hospital. At one point she was put into an induced coma because her seizures would not stop. That was such a difficult time as I felt useless, and I was frightened that I was going to lose my daughter. The light of my life.

Since her diagnosis, things have continued to be difficult. As Taliah grew older, I noticed that she began to lose her appetite. She has never been the best eater, and would always focus on only eating certain foods, but as she grew into a young adult, she started to refuse food completely. I tried everything to get her to eat, but she wouldn't. She complained of her throat hurting and just would not consume anything, only taking a drink now and again. She was seen by numerous specialists, and had lots of tests to find out why she did not want to eat, but all of the tests were normal, and nothing seemed to help. Then, for no clear reason, she slowly started to eat again, but only soft foods like yogurt and mashed potatoes.

By this time Taliah was an adult, and I learnt from her doctors that Taliah's eating difficulties were part of her DS. I felt relieved, but worried at the same time. I had comfort knowing that this was part of her condition, but worried, as I realized that it could get worse as she grew older. It was recommended that Taliah should have a PEG fitted, so that nutrition, fluids and medication could be given by a tube directly into her stomach. The PEG, and how it would affect Taliah, was explained to me, but at the time I was concerned about Taliah having to undergo the procedure, and because she was still eating small amounts, I did not want to put her through more distress than necessary. As a parent you always want to do the best for your child, but sometimes it is difficult to figure out what the best thing is. As time went on, Taliah was doing well, I did some research and asked questions about the PEG, and my conclusion was that she was not going to have it.

Within a year she stopped eating again, this time for 3 months. My heart sank. I was watching my daughter

wither away in front of my very eyes. I didn't know what to do. Her skin changed and her hair fell out. She was starving herself again. I hated myself because I realized I had made a huge mistake. I should have gone ahead with the PEG a year ago. Now look at what I had caused. I contacted Taliah's doctors and explained what was happening, and asked if Taliah could have a PEG inserted.

The PEG procedure was promptly arranged. I was still scared about the operation, but I had to do this for Taliah, and so she had her PEG inserted. It was difficult at first as we spent almost 3 weeks in the hospital. Taliah found it difficult to accept her PEG, and she could not tolerate the required rate of feed. She had a lot of discomfort at first, and she wanted to pull it out. It was difficult to watch her being in so much pain.

Being discharged home was a relief, but also very daunting, as I now had to deal with the PEG feed on my own without the support of the nurses at the hospital. However, once we got home, I had all the equipment that I needed to use the PEG, as well as telephone numbers that I could call in case I needed support. I was so nervous at first about making mistakes, I followed all the steps and I think I did a great job!

I was supported by the PEG nurses to clean the wound and to advance and turn the PEG tube. Advancing and turning the PEG tube every week was difficult, as this was quite painful for Taliah. My first try was horrible, I was shaking, and I even cried because I hated seeing my child in pain. I didn't want to do it, but the PEG nurse reminded me how important it was to prevent the base of the tube inside the stomach from becoming stuck, which would require another operation to remove it. I had to be brave, and I did what I had to do. Overtime it got easier, and I found clever ways of turning the tube so that Taliah does not even notice what I am doing.

Having the PEG fitted for my child has been the best thing to have happened. There is no longer a worry when Taliah does not want to eat, as she has her feed every day; it has brought me peace of mind when she refuses food.

At the start of her feeds, she required a 1,000 ml bottle which took 14 h to complete, but now she only requires 500 ml which runs over 5 h. Taliah has a small rucksack which she keeps her feed and her pump in, so she can go to college and do outdoor activities easily, and feed at the same time. She is no longer dehydrated as she gets regular water flushes throughout the day. She no longer sleeps for most of the day as her body has the correct nutrients. Her hair is flowing and glossy and she is a chatter-box now!

It has been a long journey, but I can honestly say that the PEG feed has been the absolute best thing for Taliah, and a God send for our family. I would absolutely recommend anyone who needs a PEG to have one, as it really does change lives.

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

LC, SB, and SS contributed to conception and design of the case report and discussion. LC wrote the first draft of the manuscript. EW wrote the first draft of the parent perspective. All authors contributed to manuscript revision, read, and approved the submitted version.

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Permission statement

Taliah's family requested her name be used in this article.

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 novel *de novo* variant of *SCN8A* in a child with benign convulsions with mild gastroenteritis

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Benign convulsions with mild gastroenteritis (CwG) is characterized by afebrile convulsions accompanied by mild gastroenteritis, and it can be considered after central nervous system infection, hypoglycemia, electrolyte disturbance, and moderate and severe dehydration are excluded. Previous studies have suggested that genetics may be involved in CWG. Herein, we reported a novel *de novo* variant of *SCN8A* in a child with CwG. This is the first report that *SCN8A* may be associated with CwG. Our report may provides evidence for the genetic etiology of CwG and expands the phenotypic and genetic spectrum of *SCN8A*-related disorders, which previously included severe developmental and epileptic encephalopathy (DEE) phenotype, benign epilepsy phenotype, spectrum of intermediate epilepsies, and patients with cognitive and/or behavioral disturbances without epilepsy. Phenotype of CwG has a good prognosis, and it does not require long-term antiepileptic therapy. Overtreatment should be avoided clinically. However, the conclusion needs to be further defined by long-term follow-up and similar clinical reports. In spite of this, our clinical observation provides possible evidence for future studies on the relationship between *SCN8A* and CwG.

KEYWORDS

***SCN8A*, gene, benign, convulsions, gastroenteritis**

Introduction

Benign convulsions with mild gastroenteritis (CwG) was first reported by Morooka in 1982 in Japan (1), which was later repeatedly reported (2, 3). Most of the CwG cases occurs during the winter and early spring months. This clinical condition is characterized by afebrile convulsions accompanied by mild gastroenteritis in previously healthy infants. Besides, it can be considered after central nervous system infection, hypoglycemia, electrolyte disturbance, and moderate and severe dehydration are excluded, and usually has a good prognosis (4).

CwG has been more frequently described in East Asian countries, which suggests that the genetic characteristics of the host may play a role in the development of CwG (4).

In addition to this, Okumura et al. found that CwG occurred in identical twins during the course of gastroenteritis, and their convulsions occurred almost simultaneously (5). These studies suggest that CwG may be related to genetic factors. However, in recent years, several scholars have tested *SCN1A*, *SCN1B,* and *PRRT2* genes in CwG patients, but no positive results were found (6–8). Finally, in 2020, Terrone et al. found heterozygous missense mutation of *SPTAN1* gene by next generation sequencing (NGS) in a family, including a 13-year-old sister, an 8-year-old brother and their 39-year-old mother (9). The clinical observation suggests for the first time that variants in *SPTAN1* gene might be involved in the etiology of CwG. Herein, we reported a novel *de novo* variant of *SCN8A* in a child with CwG. This is the first report that *SCN8A* may be associated with CwG. Our report may provides evidence for the genetic etiology of CwG and expands the phenotypic and genetic spectrum of *SCN8A*-related disorders.

Case description

The patient was a 36 months old boy. The Chinese boy was born full term with normal birth weight. She had no history of transient hypoxia at birth. There was no family history of neurologic disorders. He developed acute gastroenteritis symptoms at 19 months, presenting with 3 times of vomiting and diarrhea (3 times daily). A day later, the boy began with 3 generalized tonic-clonic seizures (GTCS) without fever in 1 day. The duration of each convulsion was 2–3 min. Since then, phenobarbital was given (5 mg/kg, intravenous injection). However, he still had two more similar convulsions. After treatment of diazepam (0.3 mg/kg, intravenous injection), there was no further convulsion. Vomiting resolved within 2 days, while diarrhea recurred over 5 days (2–4 times a day) and then resolved. Dehydration did not occur throughout the course of the disease. In the interictal phase, the child's mental state was normal and his consciousness was clear. However, 10 days later, he developed symptoms of gastroenteritis again, including diarrhea and vomiting, and had one GTCS a day later. The duration of the convulsion was 2 min. The symptoms of the mild gastroenteritis lasted for 4 days, and the convulsions only occurred once during the course of the gastroenteritis. We did not give the child long-term antiepileptic treatment. After a long-term follow-up of 17 months, he never had another seizure. The child's motor and intellectual milestones were the same as those of normal children. Physical examination at the age of 19 months showed a height of 83 cm (50–85th centile), weight of 13.5 kg (85–97th centile) and head circumference of 47 cm (25–50th centile). His consciousness was clear. Cardiac auscultation was normal. Muscle strength and tone were normal. Knee reflex were normal and babinski signs were negative. EEG showed slow background activity during wakefulness in interictal periods, and no epileptic discharges were observed (Figure 1). Rotavirus of stool was positive. Other investigations were non-diagnostic including liver function tests, renal function, electrolytes, glucose, blood white cells, blood red cells, platelets, ammonia, creatine kinase, plasma lactate, white blood cells and red blood cells in stool, electrocardiogram, and brain MRI. Therefore, he was eventually diagnosed as suffering from CwG. Due to recurrent convulsions, the child's parents wanted to further understand the genetic causes, so we performed

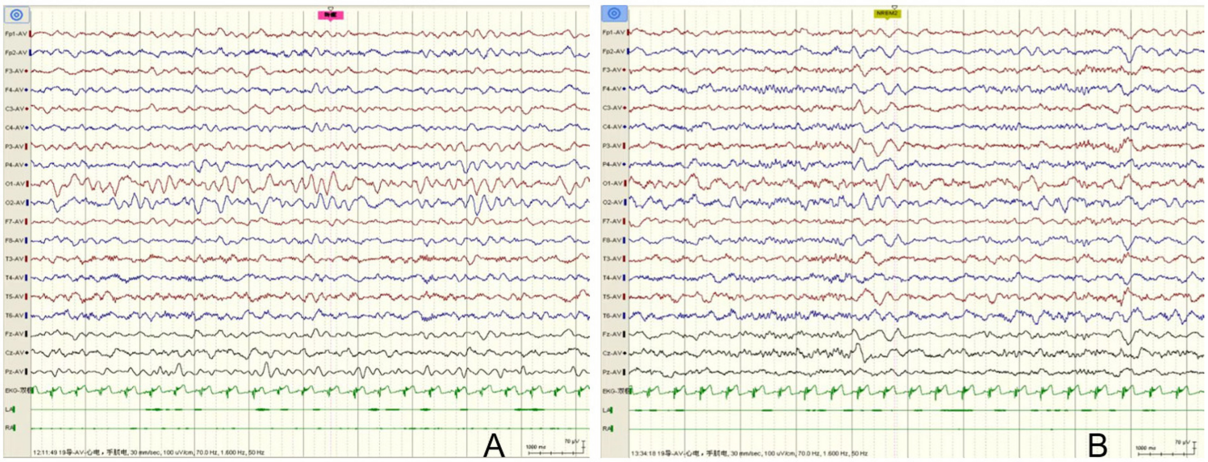

FIGURE 1
EEG of the case. **(A)** EEG showed slow background activity during wakefulness in interictal periods, and no epileptic discharges were observed. **(B)** No epileptic discharges were observed during sleep stages.

NGS on him. He was found to have a *de novo* heterozygous mutations c.5503 (exon27) C>G in *SCN8A* gene that was not detected in either parent. The variant led to protein changes p.Pro1835Ala (NM_014191.4). The variant (p.Pro1835Ala) was a *de novo* heterozygous variant (PS2), which affected highly conserved amino acid region. It was not found in the normal control population in multiple databases, such as gnomAD, ExAC, 1,000 Genomes, ESP6500 (PM2_Supporting). Various statistical methods predicted that the variation would have deleterious effects on gene products (PP3), such as SIFT (Damaging), MutationTaster (Disease_causing), FATHMM (Damaging), PROVEAN (Damaging), DANN (Damaging), CADD (Damaging) and Eigen (Damaging). In addition to this, the missense mutation of *SCN8A* gene had a high pathogenic possibility, and the Z-score was 7.64 in gnomAD database (PP2). Hence, the variant was classified as likely pathogenic in accordance with the ACMG guideline (PS2 + PM2_Supporting + PP2 + PP3).

Discussion

In our case report, the patient presented with multiple afebrile convulsions accompanied by mild gastroenteritis, and he did not present with electrolyte disturbances, dehydration, hypoglycemia, or central nervous system infection. In addition, he did not receive long-term antiepileptic medication. After a long-term follow-up of 17 months, he did not develop convulsions again, and his motor and cognitive development was normal. he has a good prognosis. In the first course of acute gastroenteritis, vomiting resolved within 2 days, while diarrhea resolved within 5 days. Ten days later, he developed symptoms of gastroenteritis again, including diarrhea and vomiting. The symptoms of the mild gastroenteritis lasted for 4 days. The convulsions only occurred during the course of the gastroenteritis. During a 10-day period, there were no symptoms of gastroenteritis or convulsions. Therefore, I think it was two episodes. Recent study has shown that children with CwG have a possibility of recurrence, with a recurrence rate of about 6.3% (10). Therefore, child of the case might suffer from recurrent CwG according to its diagnostic criteria (4, 10). However, because the interval time is too short (10-day period), it needs to be differentiated from epilepsy. The diagnosis of recurrent CwG still needs to be further defined by long-term follow-up and similar clinical reports. CwG is similar to an epileptic syndrome within benign infantile seizures in the classification set by the International League Against Epilepsy (ILAE) because of its clinical features of afebrile convulsions. However, until now, CwG has not been fully recognized as an epileptic syndrome by ILAE. Because convulsion of CwG is accompanied by mild gastroenteritis, it has been suggested that CwG might be termed as situation-related seizures (4). In conclusion, CwG is a separate disease which is different from epilepsy.

SCN8A encodes Nav1.6, which is one of four voltage-gated sodium channels expressed in the mammalian brain. Nav1.6 is found in the central and peripheral nervous system with a predominant expression in excitatory, but also in inhibitory neurons (11, 12). The first pathogenic variants in *SCN8A* have been described in an affected individual with developmental and epileptic encephalopathy (DEE) (13). In recent years, a wide clinical spectrum of neurodevelopmental phenotypes has been reported, including severe DEE phenotype, benign epilepsy phenotype, spectrum of intermediate epilepsies, generalized epilepsy, unclassifiable epilepsy and patients with cognitive and/or behavioral disturbances without epilepsy (12, 14–17). Most pathogenic variants in SCN8A are missense. Previous functional studies of selected epilepsy-associated *SCN8A* variants have revealed a gain of function (GoF) pathogenic mechanism, which cause ultimately hyperactivity of the ion channel. On the contrary, variants causing loss of function (LoF) are related with patients with cognitive and/or behavioral disturbances without epilepsy, Such as ID, ASD, myoclonus, and ataxia (14). However, this view is no longer true, a recent study showed generalized epilepsy with absence seizures was the main epilepsy phenotype of LOF variant carriers and the extent of the electrophysiological dysfunction of the GOF variants was a main determinant of the severity of the clinical phenotype in focal epilepsies including severe DEE phenotype, benign epilepsy phenotype, spectrum of intermediate epilepsies. However, a few functional studies of *SCN8A* variants in DEE were LOF (12). Our clinical observation is the first report that *SCN8A* may be associated with CwG. Our clinical observation is only a case report, which need to be supported by more case reports. Moreover, relevant functional studies will be needed to further clarify the related mechanisms. This is the limitation of our clinical observation.

In conclusion, our clinical observation suggests that variants in *SCN8A* gene might be involved in pathogenesis of CwG. Phenotype of CwG has a good prognosis. It does not require long-term antiepileptic therapy, and overtreatment should be avoided clinically. However, the conclusion needs to be further defined by long-term follow-up and similar clinical reports. In spite of this, our clinical observation provides possible evidence for future studies on the relationship between *SCN8A* and CwG.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee of Children's Hospital of Jiangxi Province. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. 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

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

Conflict of interest

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

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Case report: Successful anterior temporal lobectomy in drug-resistant temporal lobe epilepsy associated with Sotos syndrome

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The Sotos syndrome is an autosomal dominant disorder characterized by haploinsufficiency of *NSD1* gene, with some individuals affected by epilepsy and, rarely, drug-resistant seizures. A 47-years-old female patient with Sotos syndrome was diagnosed with focal-onset seizures in left temporal lobe, left-side hippocampal atrophy, and neuropsychological testing with decreased performance in several cognitive domains. Patient was treated with left-side temporal lobe resection and developed complete awake seizure control in 3-years of follow-up, with marked improvement in quality-of-life. In selected, clinically concordant patients, resective surgeries may play a significant role in improving patient's quality of life and seizure control.

KEYWORDS

Sotos syndrome, temporal lobe epilepsy, epilepsy surgery, outcome, hippocampal sclerosis

Introduction

The Sotos syndrome (OMIM #117550), previously named as cerebral gigantism, is an overgrowth syndrome (1), first described in 1964 by Sotos et al. (2). This condition is characterized by childhood overgrowth and comprises three cardinal features: childhood overgrowth (with significant macrocephaly), characteristic facial appearance (high, broad forehead, fronto-temporal hair sparsity, malar flushing, down-slanting palpebral fissures, and a pointed chin) and learning difficulties (3). Other major features may be present and include advanced bone age, poor feeding in infancy, neonatal jaundice, neonatal hypotonia, seizures, scoliosis, cardiac anomalies, renal anomalies, maternal pre-eclampsia, and joint laxity/pes planus (3).

The pathogenic haploinsufficiency of the *N*uclear receptor *S*et *D*omain containing protein 1 gene (*NSD1*) was found as major cause of Sotos syndrome (4). Mutations in *NSD1* gene or 5q35 microdeletions encompassing *NSD1* are the most common etiology (5). The condition is inherited in an autosomal dominant manner, with ~95% of individuals presenting with *de novo* pathogenic variant (6).

The presentation of seizures is common with around half of Sotos patients having at least one episode (7), with wide range of possible presentations reported in the literature. A recent cohort published by Dassi et al. (8) described the phenotype of seizures in 49 patients, with 10% showing only febrile seizures, and 90% with clear epilepsy. Among all seizure types, staring spells (both true generalized onset absence seizures and focal onset impaired awareness seizures) was the most frequent one, encompassing 67% of reported patients.

Although surgical treatment of drug-resistant seizures in one patient with Sotos syndrome was reported (9), to the best of authors' knowledge, this is the first successful surgical treatment of a genetically confirmed Sotos syndrome affected patient in the literature.

Case presentation

Patient information

A 47-years-old white female patient was referred to our institutional epilepsy clinic with a history of seizures since 2 years-old. The first epileptic event was described as sudden loss of awareness, followed by generalized clonic movements and sialorrhea with no fever or other precipitating symptom. The first antiseizure drug trial was phenobarbital. Despite correct dose and usage of antiseizure medications, the patient continued to experience seizures since 2-years old. From 20-years-old to our first clinical evaluation, the patient experienced a focal onset impaired awareness seizure, characterized by an aura of desire to cough or a feeling of dry throat and followed by staring, mouth automatisms, bimanual automatisms, and head shift to the left side, evolving to postictal state lasting about 2 min. Overall seizure time was brief, lasting around 1 min and secondary generalizations rarely happening, with only four events during lifetime. This awake seizure had a minimal frequency of two to three seizures by week, worsening frequency close to menses phase, with no history of status epilepticus. Patient's mother reported a second type of event described as agitation and frenetic rubbing of left ear with ipsilateral hand at sleeping time, with an average frequency of one to two events each week. Previous history of several antiseizure drug trials included valproate, phenytoin, lamotrigine and phenobarbital, with variable degrees of tolerance and seizure control. Current antiseizure medication was carbamazepine and clobazam, without seizure free achievement. Remarkable past medical history included no perinatal disorder, non-consanguineous parents and no history of epilepsy or seizures in the family.

Clinical findings

Patient's family reported learning disabilities and phenotypic features of Sotos syndrome (Figure 1) in clinical and imaging exams were present. The genetic testing confirmed the diagnosis showing a heterozygous mutation in exon 15 of *NSD1* gene [c.5146G>A, p.(Gly1716Arg)]. This variant was not found in The Genome Aggregation Database (gnomAD) and was classified as pathologic in Leiden Open Variation Database (LOVD) (10).

Prolonged (62 h) non-invasive video-EEG monitoring was performed on 32-channel digital EEG equipment (Ceegraph software, Bio-Logic Systems Corp., Mundelein, IL, U.S.A. and QP-110AK Nihon Kohden, Tokyo, Japan). Electrodes were placed according to the 10–20 International System, plus intermediary temporal and sphenoidal electrodes. To record ictal events, antiseizure medications were completely withdrawn. The frequency and location of interictal epileptiform discharges (IEDs) were visually assessed on 5 min EEG samples per hour, 24 h per day. This monitoring showed symmetrical and slightly disorganized base activity, with 778 bilateral interictal epileptic discharges (84.1% left anterior temporal region and 15.9% right anterior temporal region, Figure 1G) and six electroclinical seizures. Five focal onset impaired awareness motor seizures were during awake period and only one during sleep.

All seizures recorded had the ictal onset and sytomatogenic area in the left temporal lobe, and brain MRI showed left hippocampus atrophy and right hippocampus malrotation (Figure 1). Neuropsychological testing found low scores in episodic memory (verbal and non-verbal), language, speech, constructive praxis, and working memory. Quality of life was assessed using Quality of Life in Epilepsy Inventory-31 (QOLIE-31) adapted to patient's native language (11), with a pre-operative score of 45.4.

Therapeutic intervention

Left anterior temporal lobectomy was performed (En bloc resection of the 4.5 cm anterior region of temporal neocortex, piecemeal resection of uncus, amygdala and entorhinal cortex and en bloc resection of the anterior 2.5 cm of the hippocampus) by the senior epilepsy neurosurgeon (RSC). The patient was discharged from the hospital after 3 days, with no complication.

Follow-up and outcomes

During 3-years follow-up, the patient is under previous antiseizure medication dosage (carbamazepine 400 mg q8h and clobazam 20 mg q12h), with post-operative brain MRI showing complete hippocampal and temporal resection (Figure 2). Patient had no epileptic event awake, experiencing on average one nocturnal seizure each week (Engel Outcome Scale class II D).

Two awake EEG performed at 2- and 21-month after surgery showed no awake interictal epileptic discharges. Post-operative QOLIE-31 score was 63.3 (an improvement of 39.4%), and neuropsychological assessment showed no change in constructive praxis, language, speech, and verbal episodic language, and slight improvement of non-verbal episodic memory. Despite no change in verbal episodic memory, patient described subjective worsening in this cognitive domain.

Discussion

Heterogenous seizure patterns have been associated with Sotos syndrome, e.g., febrile seizures, infantile spasms, absence, tonic–clonic, and myoclonic seizures (12), occurring in 15%—50%

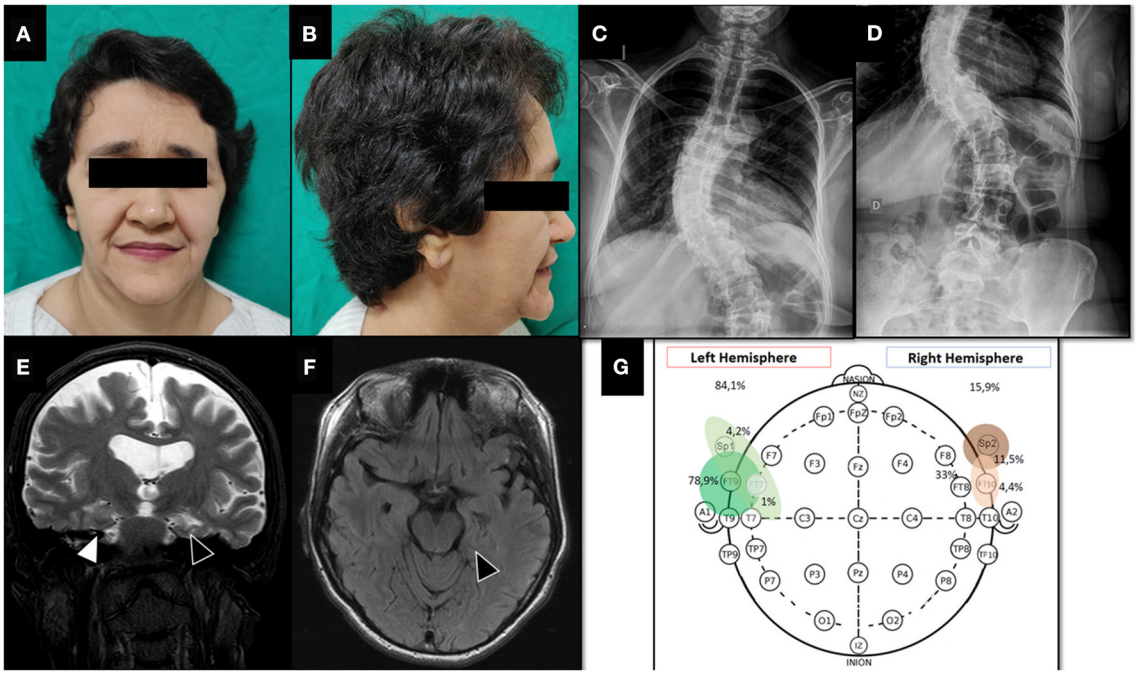

FIGURE 1
Pre-surgical evaluation. **(A, B)** Facial dysmorphic features of Sotos syndrome showing prominent forehead, pointed chin and macrodolicocephaly. **(C, D)** Plain spine radiograph shows thoraco-lumbar scoliosis. **(E)** T2-weighted coronal brain MRI showing global atrophy with marked sulcal and ventricular volume increase. Note left hippocampal malrotation/atrophy (black triangle) compared to right hippocampus (white triangle). **(F)** FLAIR-weighted axial brain MRI. Left hippocampal malrotation/atrophy with slight hyperintense signal (black triangle). **(G)** Interictal EEG monitoring showing bilateral epileptic discharges with left temporal lobe lateralization.

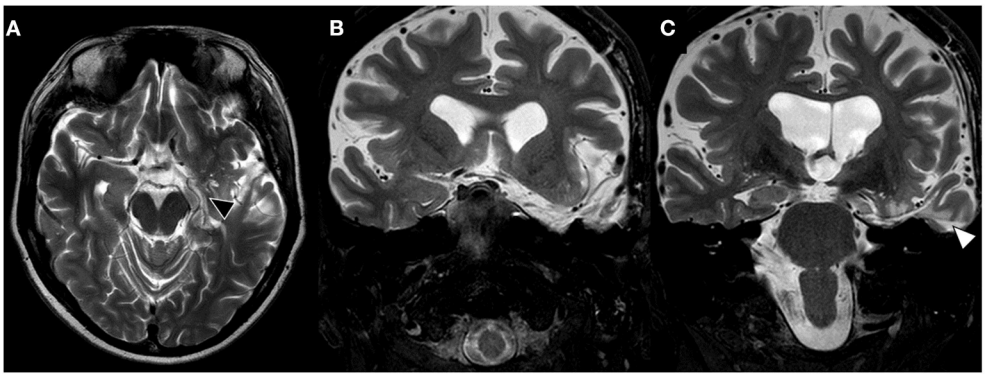

FIGURE 2
Late post-surgical brain MRI. **(A)** T2-weighted axial brain MRI shows left hippocampus resection (black triangle). **(B, C)** Coronal brain images showing complete resection of left amygdala and uncus on image **(B)** and hippocampal resection through transcortical approach (T2, white triangle).

of affected patients (3, 7) and a wide spectrum of behavioral and emotional disturbances (e.g., attention-deficit-hyperactivity disorder, aggressiveness, irritability, pyromania, social inhibition, psychosis, and autistic features) are commonly related to patients with this condition (5). Seizure-free status after one or more drug trials is the rule (12), with persistence of seizures in adulthood, i.e., drug-resistant epilepsy, an uncommon (9%) outcome (13). Around 40% of Sotos syndrome patients have a classic temporal lobe seizure (abdominal auras, automatisms with/without behavioral arrest and a temporal onset on ictal EEG), with tonic-clonic generalization developing in one third of patients (12). EEG data from big cohorts shows different characteristics, ranging from generalized, focal, or multifocal epilepsy (8). The heterogeneity in clinical behavior, genetic mutation (8) and seizure control must guide detailed evaluation by the attending clinician.

Although the goal of resective temporal lobe surgery for epilepsy treatment is to achieve seizure-free status, and with some big, published cohorts showing rates of chronic control (Engel Outcome Scale class I) ranging from 62 to 73.6% (14–16), the quality-of-life improvement impact is observed even in patients

with Engel outcome class >I (17), probably due to the multifactorial effect of seizure control in different cognitive aspects (like mood, medication use/dosage, social function, etc.).

Predictors of better outcome after epilepsy surgery include congruent electrophysiology data, lesional epilepsy, and surgical limitations to first epilepsy surgery (18). Even after recurrence of seizures, second look surgery can still be a possible therapeutic option, with reported rates of 57% of seizure free status after first surgery failure (19). The patient presented in this report continued to experience sleep seizures despite complete mesial temporal lobe resection, what may be due to partial epileptogenic zone resection. Although still presenting with nocturnal seizures, the patient and his family reported significant improvement in quality of life, enabling patient's return to unattended work.

Genetic testing is not routinely performed before surgical evaluation in most epilepsy centers and is not included in suggested presurgical list of tests of Epilepsy League Against Epilepsy (ILAE) guidelines (20, 21), with almost half of patients genetically tested after screening for epilepsy surgery (22). Genetic disorders should not preclude surgical indication for epilepsy surgery and can guide the selection of surgical candidates (23). Due to the widely diverse number of different genetic syndromes and mutations that lead to refractory epilepsy, success rates are difficult to estimate, with better outcomes reported in mutations in the mTOR pathway (23).

Our presented patient had an uncommon evolution with drug-resistant epilepsy in Sotos syndrome setting. Despite bilateral mesial temporal lobe been abnormal at investigation (left side showing sclerosis and right side malformation), the detailed investigation depicted a focal onset seizure in left medial temporal lobe due to mesial temporal sclerosis with excellent outcome after resection. Our report is the first one to describe a patient with complete awake seizure control after temporal lobe resection and the second operated patient with Sotos syndrome (9). Although both patients had Sotos syndrome, the patient reported by Bättig et al. (9) was genetically diagnosed with the syndrome after surgical procedure, had a diffuse astrocytoma in the operated temporal lobe and abundant diffuse bilateral sharp waves and polyspikes on interictal EEG, making the cases fundamentally different.

Next steps in health care include optimization of antiseizure medications, sleeping EEG to better categorize the nocturnal seizure event. During follow-up, patient stated no intention of second look surgery based on benefits achieved after first seizure and risks involved to another surgical procedure.

Conclusion

Epilepsy and, less frequently, drug-resistant seizures are features found in patients suffering from Sotos syndrome. In very selected and investigated cases, surgical resection of epileptogenic brain tissue is safe and feasible, improving patient's quality of life and promoting seizure control.

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 IRB of Federal University of São Paulo. 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

Conception and design: LF, TP, and RS. Acquisition of data: LF and TB. Analysis and interpretation of data: LF, TP, ET, HC, MG, and RS. Drafting the article: LF and TP. Reviewed submitted version of manuscript: TP and RS. Approved the final version of the manuscript on behalf of all authors: LF. 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: Functional analysis of the p.Arg507Trp variant of the *PIGT* gene supporting the moderate epilepsy phenotype of mutations in the C-terminal region

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Pathogenic germline variants in the *PIGT* gene are associated with the "multiple congenital anomalies–hypotonia-seizures syndrome 3" (MCAHS3) phenotype. So far, fifty patients have been reported, most of whom suffer from intractable epilepsy. Recently, a comprehensive analysis of a cohort of 26 patients with *PIGT* variants has broadened the phenotypical spectrum and indicated that both p.Asn527Ser and p.Val528Met are associated with a milder epilepsy phenotype and less severe outcomes. Since all reported patients are of Caucasian/Polish origin and most harbor the same variant (p.Val528Met), the ability to draw definitive conclusions regarding the genotype–phenotype correlation remains limited. We report a new case with a homozygous variant p.Arg507Trp in the *PIGT* gene, detected on clinical exome sequencing. The North African patient in question displays a predominantly neurological phenotype with global developmental delay, hypotonia, brain abnormalities, and well-controlled epileptic seizures. Homozygous and heterozygous variants in codon 507 have been reported to cause *PIGT* deficiency without biochemical confirmation. In this study, FACS analysis of knockout HEK293 cells that had been transfected with wild-type or mutant cDNA constructs demonstrated that the p.Arg507Trp variant leads to mildly reduced activity. Our result confirm the pathogenicity of this variant and strengthen recently reported evidence on the genotype–phenotype correlation of the *PIGT* variant.

KEYWORDS

***PIGT* gene, global developmental delay, epilepsy, genotype phenotype correlation, GPI transamidase**

Introduction

It is estimated that 10–20% of all membrane proteins are post-translationally modified at their C-terminus by glycosylphosphatidylinositol (GPI), a complex glycophospholipid that anchors over 150 proteins to the cell surface. The transfer of the GPI anchor to proteins is catalyzed by the GPI transamidase (GPI-TA) complex (1, 2). Phosphatidylinositol glycan anchor biosynthesis class T (*PIGT*) is a highly conserved 578-amino-acid protein. *PIGT* interacts with other components of the GPI-TA complex (PIGK, PIGS, *PIGT*, PIGU, and PGAA1) and appears to be the most important protein in the formation of this complex and the stability of the other components (3, 4). Disorders caused by germline pathogenic variants in *PareT* are referred to as multiple congenital anomalies–hypotonia-seizures syndrome 3 (MCAHS3, OMIM#615398). This syndrome is characterized by congenital hypotonia, global developmental delay (GDD) or intellectual disability (ID), and infantile-onset epilepsy with various types of epileptic EEG abnormalities (focal sharp-slow wave, focal sharp spike/polyspikes wave, and generalized polyspikes-wave complexes) (5, 6). Other congenital anomalies involving dysmorphic facial features, cerebral and cerebellar atrophy, and defects in the skeletal, ophthalmological, cardiac, and genitourinary systems are also reported (7–9).

Up to now, 50 patients with *PIGT* deficiency, most of them Caucasian, have been diagnosed with 17 pathogenic variants, including 10 missense, one non-sense, four frameshifts, and two splice sites. The largest extant genotype–phenotype study, reviewed by Bayat et al. reports on 26 patients with the p.Val528Met variant in either homozygous or compound heterozygous state and on a single patient who had the p.Asn527Ser variant (10, 11). These patients presented with moderate to severe GDD and later onset of epilepsy, and generally became seizure-free on monotherapy. Since all reported patients thus far have been of Caucasian/Polish origin and most harbor the same variant (p.Val528Met), the ability to draw definitive conclusions regarding the genotype–phenotype correlation remains limited. Here, we provide additional findings supporting this correlation by reporting a new case from North Africa, of a patient carrying the *PIGT* p.Arg507Trp variant located in the C-terminal region and associated with GDD and partially tractable epilepsy. Functional studies using *PIGT* knockout HEK293 cells showed mildly decreased activity of the GPI-TA complex, supporting the pathogenicity of the variant and providing further evidence of an association between the localization of variants in the C-terminal region and the moderate epilepsy phenotype (seizure-free or partially seizure-free on treatment).

Patient and methods

We reviewed the patient's personal history regarding progress of the pregnancy and childbirth, psychomotor milestone achievement, and neurological examinations. We also reviewed the history of epileptic seizures (type, age of onset, response to antiseizure medication), electroencephalographic data (background, epileptiform discharges, epileptic seizure if recorded), and brain imaging data, as well as the etiological assessment.

For the genetic study, DNA was isolated from peripheral blood and clinical exome sequencing was performed using the TruSight™ One Sequencing Panel. Libraries were prepared and data analysis was performed as previously described (12). The generated VCF file was annotated using the VarAft application (13). A virtual gene panel was applied using the Genetic Epilepsy Syndromes panel from Genomics England PanelApp

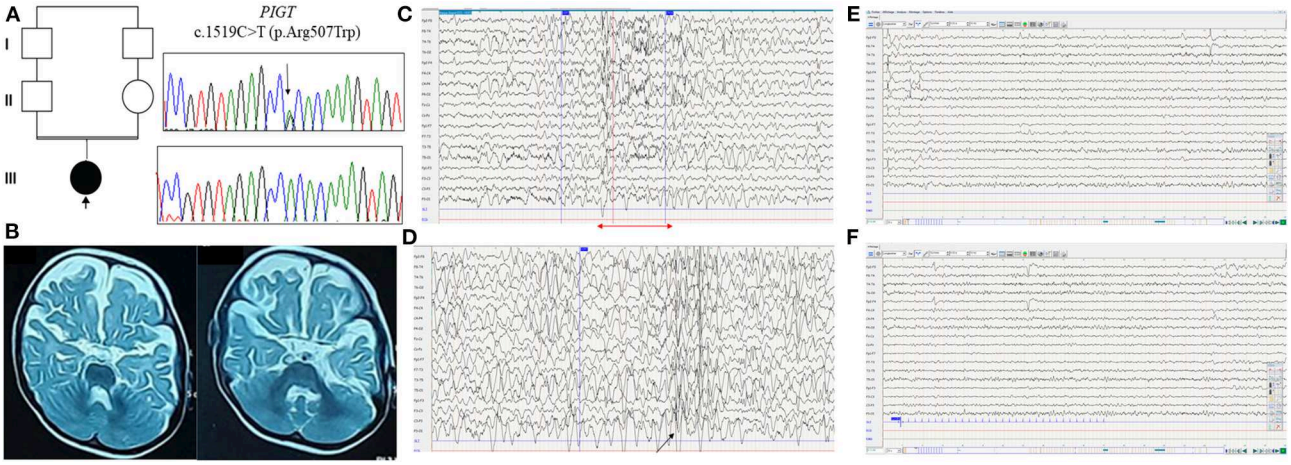

FIGURE 1
Clinical and molecular findings in the Libyan family with *PIGT* variant c.1519C>T; p.Arg507Trp. **(A)** Pedigree of the reported family with electropherograms of the identified homozygous *PIGT* variant (III.1) compared with heterozygous carrier sequences (II.1 and II.2). **(B)** Brain MRI T2-weighted axial images reveal severe atrophy of the cerebral hemispheres with slight cerebellar hypoplasia. **(C)** EEG recording, obtained when the patient was 2 years old, with the following parameters: 20 electrodes, 7 μv/mm, 0.03 s, 15, 50 Hz. The EEG shows slow spike-wave discharge followed by diffuse fast rhythms (red arrow). **(D)** Sleep EEG shows moderately organized EEG with the presence of rare spindles and diffuse spike-wave discharges (black arrow). **(E, F)** EEG showing normal background rhythm without photosensitivity.

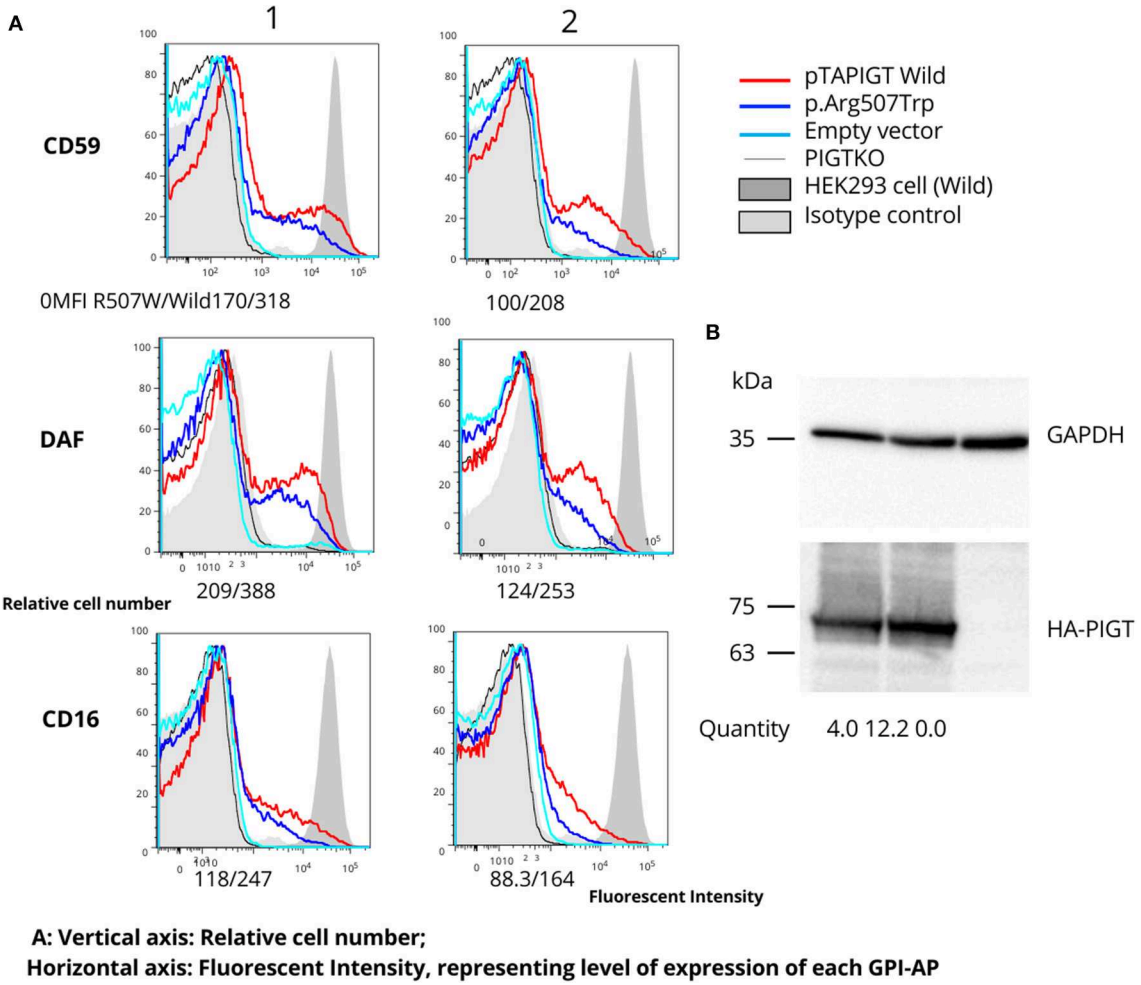

FIGURE 2
Follow-up functional studies on the p.Arg507Trp variant. **(A)** *PIGT* knockout HEK293 cells were transfected with variable amounts of p.Arg507Trp-variant *PIGT* or wild-type *PIGT* expressing plasmids driven by the weak promoter (pTA; 1: 4 ug; 2: 0.8 ug). Restoration of expression of GPI-APs (CD59, DAF, and CD16) was measured using flow cytometry. The p.Arg507Trp variant could not restore GPI-APs at a similar level to wild-type *PIGT*. The vertical axis represents the relative cell number; the horizontal axis represents fluorescent intensity, reflecting the level of expression of each GPI-AP. **(B)** Levels of expressed wild-type and p.Arg507Trp mutant HA-tagged *PIGT* in pME vector-transfected cells were analyzed by western blotting using an anti-HA antibody. After normalization to luciferase activity and GAPDH, expression of the mutant protein appeared to be similar to that of the wild-type protein.

(https://panelapp.genomicsengland.co.uk/panels/). The variant-filtering process consisted of the following four steps: (i) selection of variants localized in exons or bordering introns (±12 bp); (ii) exclusion of variants with a frequency above 1% in general populations; (iii) selection of variants predicted as pathogenic by CADD; and (iv) selection of variants predicted as pathogenic by the UMD-Predictor tool. *In-silico* pathogenicity was also evaluated using the VarCards tool (http://varcards.biols.ac.cn/). The preferentially selected variants were validated and familial co-segregation was analyzed *via* Sanger sequencing.

The study protocol was approved by the local medical ethics committee of South Tunisia (Accession number 28/2019). Written informed consent was obtained from the patient's parents.

PIGT-knockout HEK293 cells were generated and transfected, as described previously, with human wild-type or mutant *PIGT* cDNA cloned into pTA, a weak promoter (TA promoter-driven expression vector) that helps with the detection of mild partial loss of function (14). Two days later, restoration of GPI-AP (CD59, DAF, and CD16) expression was measured *via* flow cytometry. Cells were stained with PE-conjugated anti-human CD16 antibody (3G8, Biolegend) along with mouse anti-human CD59 (5H8) and mouse anti-human DAF (IA10) antibodies, followed by PE-conjugated second antibody. Levels of expressed wild-type and p.Arg507Trp mutant HA-tagged *PIGT* in pME-vector transfected cells were analyzed by western blotting using an anti-HA antibody (C29F4, Cell Signaling Tec, Danvers, MA, USA). Levels of protein expression were normalized to luciferase activity for transfection efficiencies and to expression of GAPDH for loading controls.

TABLE 1 Brief clinical overview of all individuals with *PIGT* deficiency associated with moderate seizure phenotype of variants within the C-terminal region (*PIGT*: NM_015937.6) for whom clinical information has been published.

	Group 1: Individuals with at least one variant at p.Arg507				Group 2: Individuals ($n = 25$) with either the p.Val528Met or the p.Asn527Ser variant
	p.Arg507Trp; p.Val528Met		p.Arg507Gln; p.Val528Met	p.Arg507Trp; p.Arg507Trp	Patients with compound missense/truncating ($n = 10$), biallelic missense ($n = 15$), or biallelic truncating ($n = 0$) variants
References	[(11); Family 7]		(10)	Current study	(11)
Number of patients	2		1	1	25
Geographical/ethnic origin	Russian		Polish	Libyan (North African)	8 Caucasian; 2 Caucasian/African; 1 Asian; 11 Polish; 3 Russian
	Patient 7	Patient 8	P3	Reported patient	
Age at inclusion	8 years	22 years	Born 2017	4 years	2–28 years
Febrile seizures	No	No	Yes	No	No: 7/19; Yes: 12/19
Epilepsy diagnosis	Yes	Yes	Yes	Yes	Yes: 17/25; No: 8/25
Status epilepticus	No	No	Unknown	No	No: 11; Not relevant: 2; Yes: 1; Unknown: 11
Age of seizure onset	5 months	18 months	6 months	4 months	Range: 5 months to 5.5 years
Seizure types during disease course	Myoclonic atonic epilepsy; eyelid myoclonia	Myoclonic atonic epilepsy	Focal hypomotor seizures with impaired awareness, focal to bilateral tonic–clonic seizure	Focal to bilateral tonic–clonic seizure	Atypical absences: 2; Fever-induced tonic–clonic/focal seizures: 4; Focal hypomotor, seizures with impaired awareness, FBTCS: 6; Bilateral tonic–clonic seizures: 2; Focal to bilateral tonic–clonic seizure: 4; MAE: 2; Unknown:1; Not relevant: 2
Overall antiepileptic drug response	Very good	Very good	Very good	Very good	Good (24/25, 96% seizure-free)
Degree of developmental delay	Severe	Severe	Moderate	Severe	Moderate (5/25), moderate–severe (6/25), severe (4/25), unable to ascertain (10/25)
Congenital hypotonia	Yes	Yes	Yes	Yes	24/25
Brain MRI results	10 months: Delayed myelination and enlargement of the subarachnoid spaces	15 years: Cerebellar atrophy and thinning of the corpus callosum	12 months: Decreased white matter volume, enlargement of pericerebral spaces	14 months: Atrophy of the cerebral hemispheres with slight cerebellar hypoplasia and enlargement of lateral ventricles	Delayed myelination: 7; Cerebellar atrophy: 11; Cortical atrophy: 4; Not performed: 7.

FBTCS, Focal to bilateral tonic–clonic seizure; MAE, Myoclonic atonic epilepsy.

Results

Clinical data

The proband, a Libyan girl born in 2017, was the first child of healthy consanguineous parents (Figure 1A). She was born at full term, and pregnancy and delivery were uneventful with normal menstruation. Global hypotonia and horizontal nystagmus were noted from the neonatal period. At the age of 4 months, the patient presented with multiple (two to three) daily seizures with asymmetric adduction movement of the 4 limbs and head deviation. The ictal sleep EEG showed asymmetric tonic spasm (Figure 1B). The interictal sleep EEG showed organized EEG with the presence of rare spindles and diffuse spike-wave discharges (Figure 1C). The patient presented with a global psychomotor delay with hypotonia, a severe speech delay, and walking impairment. Brain MRI, performed at age 14 months, revealed severe atrophy of the cerebral hemispheres with slight cerebellar hypoplasia and enlargement of lateral ventricles (Figure 1D). Metabolic screening was normal. She was treated with corticosteroid for 2 weeks (hydrocortisone 15 mg/kg/day) without improvement; hence, she was switched to vigabatrin (100 mg/kg/day) in association with valproate (30 mg/kg/day). Her overall antiepileptic drug response was good, but she still experienced seizures once every 2 weeks.

Based on clinical data acquired during the most recent follow-up at the age of 2 years 6 months, our patient showed severe motor and cognitive retardation: she cannot hold her head up or sit, she has no eye tracking, with wandering movements of the eyeballs, expressive language is completely absent, and she has axial hypotonia with spastic tetraparesis. She also has dysmorphic features, including a broad forehead, acquired microcephaly, deep-set eyes, epicanthus, and high-arched palate. At the most

TABLE 2 Published clinical findings in individuals harboring a severe phenotype of *PIGT* deficiency associated with missense variants.

Missense variants	c.709G>C (p.Glu237Gln)		c.547A>C (p.Thr183Pro)	c.550G>A (p.Glu184Lys)		c.1079G>T (p.Gly360Val)			c.1342C>T (p.Arg448Trp)/ c.250G>T (p.Glu84Ter)	c.1342C>T (p.Arg448Trp)/ c.918dupC (p.Val307 ArgfsTer13)	c.250G>T/ (p.Glu84Ter) c.1096G>T/ (p.Gly366 Trp)	c.1472T>A (p.Leu491His)/ 1484+2T>A	c.469T>G (p.Phe157Val)/ c.1120A>G (p.Asn374Asp)	c.514C>T (p.Arg172Cys)/ c.98delA (p.Glu33AspfsTer12)
No. families	2		1	2		3			1	1	1	1	1	1
References	(14)	(6)	(5)	(15)	(6)	(16)	(6)	(6)	(9)	(7)	(17)	(6)	(18)	(18)
Geographical/ ethnic origins (no. patients)	Afghani (1)	Bangladeshi (2)	Turkish (4)	Chinese (1)	Pakistani (1)	African (2)	Somalian (2)	- (2)	Japanese	Caucasian/ African American (2)	Japanese (1)	Danish (2)	Chinese (1)	Chinese (1)
Age of onset of epilepsy	Neonatal onset	1st day; 2 weeks	12–18 months	1 month	5 months	12 months	11–14 months	11–14 months	4 months	5 months	2 months	1st day	3 months	4 months
Seizure types during disease course	Generalized tonic–clonic	Fever-induced myoclonic and subtle focal; generalized tonic seizures	Myoclonic (2/4); generalized tonic–clonic (1/4)	Myoclonic and febrile seizure	Generalized tonic and myoclonic; focal myoclonic seizures; febrile seizures	Myoclonic, tonic, and tonic–clonic seizures that occasionally generalize	Generalized tonic–clonic and atonic seizures; myoclonic and focal seizures	Myoclonic and subtle focal seizures; febrile seizures	Myoclonic tonic with apnea that can generalize	Myoclonic, tonic, and tonic–clonic seizures that occasionally generalize	Myoclonic, tonic with apnea that can generalize	Myoclonic and febrile seizure; tonic and myoclonic with apnea; subtle focal seizures	Febrile/ afebrile seizures	Clonic afebrile seizures
Overall seizure outcome	Intractable	Intractable	Intractable	Intractable	Intractable	Intractable	Intractable (seizure-free on ketogenic diet for 1 patient)	Intractable	Intractable	Intractable	Intractable	Intractable	Intractable	Intractable
Degree of DD	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe	Severe
Premature mortality	-	1 patient deceased (6 months)	-	-	-	-	-	1 patient deceased (26 months)	-	-	-	1 patient deceased (26 months)	-	-

-, data not reported.

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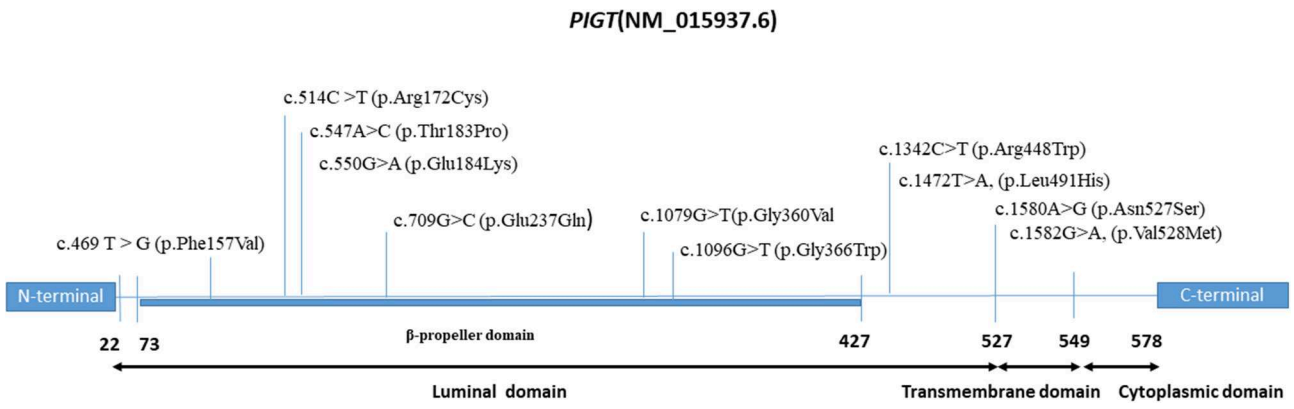

FIGURE 3
Domain map of the *PIGT* protein depicting the locations of milder and severe pathogenic variants.

recent follow-up, the patient had normal sleep EEG with normal background rhythm without photosensitivity (Figures 1E, F).

Molecular results

A total of 9,542 common single-nucleotide variants (SNVs) and indels were detected. The filtering process, as previously described, resulted in identification of 13 homozygous and 118 heterozygous variants. Based on their predicted effect on protein function and the likelihood of the autosomal recessive mode of inheritance, we evaluated the resulting variants, under the assumption that the disease gene would be more likely to cause an epileptic and/or a DD phenotype. Initially, only homozygous variants were considered and the *PIGT* variant (NM_015937.6):c.1519C>T (p.Arg507Trp) was selected as the candidate variant for the patient's phenotype. For the purpose of further investigation, we reevaluated the filtering process considering an autosomal dominant mode of inheritance; however, no relevant variants were detected. The *PIGT* variant was verified *via* Sanger sequencing, and both asymptomatic parents were found to be heterozygous (Figure 1A). The identified missense variant (rs146484791) was reported with a frequency of 0.0023% in the gnomAD database and has not been previously reported in the homozygous state. *In-silico* pathogenicity prediction using the VarCards tool showed a deleterious effect on the *PIGT* protein (damaging score 0.83), with a damaging CADD score of 35. An alternative variant, p.Arg507Gln, was found to have been reported in the heterozygous state with p.Val528Met in two patients with *PIGT* deficiency (10, 11).

Functional analysis of the *PIGT* variant

Rescue experiments using variant cDNA driven by the weak promoter pTA, performed on *PIGT*-knockout HEK293 cells, indicated that the p.Arg507Trp variant results in a mild reduction in the amounts of CD59, CD16, and DAF anchored to the cell membrane (Figure 2A). Western blot analysis showed that expression of the mutant protein was not decreased but was even higher than expression of the wild-type protein (Figure 2B).

Taking these findings together, we classified the Arg507Trp as a likely pathogenic variant in accordance with the ACMG recommendations: PM2 (variant not found in gnomAD genomes with good coverage of gnomAD genomes = 29.9; pathogenic, supporting), PM5 (alternative pathogenic variant Arg507Gln had been already reported (10, 11); pathogenic, moderate), and PS3 (well-established *in vitro* functional studies supportive of a damaging effect of the gene product; pathogenic, strong).

Discussion

Clinical exome sequencing is now used routinely as a tool to diagnose many different inborn errors of metabolism (IEMs) in patients with developmental and epileptic encephalopathy (DEE), such as congenital disorders of glycosylation. However, despite the tremendous progress that has been made in the development of both sequencing technology and bioinformatics in recent years, it should be noted that other diagnostic tests are still necessary to confirm or reject a diagnosis with certainty in cases where this approach results in the identification of genetic variants of uncertain clinical significance (VOUS). The variant p.Arg507Trp in the *PIGT* gene, identified in the homozygous state in this study, has previously been reported in a compound heterozygous state with Val528Met in two Russian patients (11). In addition, an alternative variant in the same location (Arg507Gln) has been reported in a Polish patient (10). According to ACMG classification, this variant is still classified as a VOUS, since it has not been biologically confirmed. The functional experiments performed here using mutant HEK293 cells provide evidence to support the pathogenicity of this variant; this evidence is sufficient to reclassify this variant as likely pathogenic. On the other hand, the milder decreased activity is consistent with the moderate phenotype of our patient. Here we should highlight that one of the limitations of our study is the brief period of follow-up of our patient, who is only at the age of 2 years at the time of writing. However, we were able to identify our patient's phenotype specifically as a moderate epileptic one in comparison to the majority of

PIGT-deficiency patients, who often suffer from severe drug-resistant epilepsy with convulsive status epilepticus, sometimes with neonatal–infantile onset. Together with other recent studies (10, 11), our study also serves to confirm the genotype–phenotype correlation for *PIGT* that was first described in 2019. Bayat et al. report on 24 patients harboring the p.Val528Met variant in either homozygous or compound heterozygous state and one patient with the p.Asn527Ser variant, all of whom presented with a less severe epilepsy phenotype with considerably later onset of epilepsy; there was also no premature mortality in any of these patients (11). In Table 1, we present a comparison of the clinical findings for our patient with those of previously reported patients with the p.Arg507Trp variant. All patients presenting with the p.Arg507Trp variant in either homozygous or compound heterozygous state, including our patient, have been found to exhibit GDD and became free or partially free of epileptic seizures following treatment with CBZ/VPA. Additionally, a comparison of the phenotypes of patients harboring both p.Asn527Ser and p.Val528Met variants with that of our patient revealed a similar spectrum of symptoms regarding the onset of seizures (between 4 months and 5.5 years), seizure types (focal to bilateral tonic–clonic seizures as the predominant type), degree of cognitive and developmental outcome (moderate to severe), and response to antiepileptic drugs. Therefore, we conclude that missense variants p.Asn527Ser, p.Val528Met, and p.Arg507Trp, located in the C-terminal region, are associated with an epileptic phenotype with comparatively better outcome.

The existing literature was also searched to identify all missense variants described as occurring with a severe phenotype, including severe epilepsy with frequently recurrent episodes of convulsive status epilepticus, abnormal interictal EEG, and severe drug-resistant epilepsy. In total, 10 missense variants (either in homozygous or in compound heterozygous state) were collected; these have been observed in 23 patients belonging to 14 families of various ethnicities (Table 2). Interestingly, we note that all of these variants occur in the N-terminal region of the *PIGT* protein (Figure 3). Hence, we suggest that the phenotypic variability of *PIGT* deficiency could be related to the position of the affected residue and its effect on the function or structure of the *PIGT* protein, as well as the interaction with components of the GPI-TA complex. It has been shown that *PIGT* is covalently linked to the majority of PIGK *via* a functionally important disulfide bond between *PIGT*-Cys182 and PIGK-Cys92 in the GPI-TA complex. In addition, *PIGT* and PIGS are linked to one other, and *PIGT* has an additional function in stabilizing GPI-TA by linking PIGS to GAA1 and PIGK (3, 4). In the case of the homozygous p.Thr183Pro and p.Glu184Lys variants, substitutions occur in the residue directly adjacent to Cys182, which is responsible for the *PIGT*–PIGK disulfide bond. In the p.Thr183Pro variant, the threonine is substituted by a proline, which is an inflexible residue common in very tight protein junctions (5). In the p.Glu184Lys variant, glutamate (negatively charged) is substituted by a positively charged lysine. These two substitutions could affect the biochemical environment around Cys182, possibly affecting the stability of the disulfide bond leading to loss of function in *PIGT* and the GPI-TA complex. Considering the available experimental data, a recent study has additionally suggested that the luminal part of *PIGT* (73-427 aa) consists of a β-propeller domain with a central hole that regulates the access of substrate protein C-termini to the active site of the cysteine protease PIGK (19). Therefore, missense variants located in the β-propeller domain could affect the interaction of *PIGT* with the active site of PIGK, leading to the observed severe phenotype.

Concerning variants occurring in the C-terminal region on the cytoplasmic side (p.Val528Met, p.Asn527Ser, and p.Arg507Trp), we suggest that these variants would not affect the *PIGT*-GPI-APs interaction, instead representing residual activity, which might explain the moderate phenotype. This hypothesis can be supported by the results of our rescue experiments using variant cDNA driven by the weak promoter pTA on *PIGT*-knockout HEK293 cells. Specifically, p.Arg507Trp variant did not restore the GPI-APs to a similar level as observed with wild-type *PIGT*, suggesting decreased activity of the variant. In addition, the same effect has also been demonstrated for the p.Val528Met variant, although this effect was only observed when the pTK promoter was used (14).

Our study details a new case of the p.Arg507Trp variant in the C-terminal region, associated with a moderate epileptic phenotype. This supports the previously reported genotype–phenotype correlation of *PIGT* deficiency (10, 11), which will be useful for future genetic counseling.

Data availability statement

The datasets presented in this article are not readily available because of ethical/privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The study protocol was approved by the Local Medical Ethics Committee of South of Tunisia (Accession number 28/2019). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. 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

IB conceived the study, wrote the manuscript, and analyzed and interpreted the NGS data. OJ, SMal, and FK analyzed and interpreted all clinical data. AT, AS, and AB conducted the clinical exome sequencing. YM performed the functional study. IE performed a segregation analysis. FF and AS assisted in writing the manuscript. SMas, SW, TK, and CT revised and edited the 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.

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Case report: Young-onset large vessel ischemic stroke due to hyperhomocysteinemia associated with the C677T polymorphism on *5,10-methylenetetrahydrofolate reductase* and multi-vitamin deficiency

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Hyperhomocysteinemia is an important risk factor for cerebral infarction. Herein, we report on a 30-year-old man previously diagnosed with epilepsy who presented with right hemiplegia and total aphasia. Magnetic resonance imaging showed a fronto-temporal ischemic lesion due to occlusion of the left middle cerebral artery. Clinical testing and imaging demonstrated that he had hyperhomocysteinemia induced by multiple factors including the C677T polymorphism on 5.10-methylenetetrahydrofolate reductase (*MTHFR*), and multiple vitamin deficiencies. The C677T polymorphism on *MTHFR* is closely related to hyperhomocysteinemia and folate deficiency in epileptic patients who are taking multiple anti-convulsants. Given hyperhomocysteinemia can independently cause stroke at a young age, physicians should periodically examine plasma homocysteine and serum folic acid levels in epileptic patients who are on long-term regimens of multiple anti-epileptic drugs.

KEYWORDS

hyperhomocysteinemia, 5,10-methylenetetrahydrofolate reductase, cerebral infarction, folic acid, vitamin B12, antiepileptic drug, epilepsy

Introduction

Epidemiological studies suggest that the incidence of ischemic stroke in young adults (18–50 years old) has increased substantially (1). There are a wide variety of causes for stroke in young adults such as hyperhomocysteinemia, illicit drug use, pregnancy, arterial dissections, patent foramen ovale (PFO), anti-phospholipid syndrome, malignancy, and protein S or C deficiency (1, 2). Moreover, moyamoya disease, that is one of causes of ischemic stroke in young adults, is a specific chronic cerebrovascular occlusive disease

first reported in 1957 (3). Hyperhomocysteinemia is an important risk factor for several cardiovascular diseases, including coronary artery disease, peripheral occlusive disease, stroke, and venous thrombosis (4). Increased levels of plasma homocysteine are influenced by both genetic and environmental factors. The C677T polymorphism on the *5.10-methylenetetrahydrofolate reductase (MTHFR)* gene (5, 6), which is identical to c.665C>T in *MTHFR* (NM_005957) gene, and decreased levels of vitamin B6, vitamin B12, and folic acid are associated with elevated homocysteine levels (4). We herein report on a case of young-onset cerebral infarction with hyperhomocysteinemia caused by the C677T polymorphism in the *MTHFR* gene and multiple vitamin deficiencies.

Case descriptions

At the age of 16, the patient presented with several episodes of generalized tonic-clonic seizure. He was diagnosed with epilepsy based on results of electroencephalography. Despite having started anti-epileptic drugs (AED), seizures occurred once every few months. He was prescribed a regimen of four AEDs such as valproic acid, gabapentin, topiramate, and carbamazepine. At age 28, he often encountered trouble with interpersonal relationships owing to mild developmental delay. At age 30, he expressed abnormal behaviors such as taking large amounts of medications. The day after this incident, he was admitted to our hospital due to disturbed consciousness upon his mother noticing his aberrant behavior. He had no family history of coronary artery disease, stroke, or neuropsychiatric disease. His diet was unbalanced with a predilection for eating meat and avoiding vegetables.

On admission, his blood pressure was 105/64 mmHg, heart rate was 75 beats / min, respiratory rate was 16 breaths / min and body temperature 37.4°C. Physical examination was unremarkable. On neurological examination, his consciousness was somnolence. He had total aphasia and right hemiparesis. The results of laboratory examination were as follows: white blood cell count, 9.6 × 10^9/L (reference: 3.9–9.7 × 10^9/L); hemoglobin, 15.2 g/dL (reference: 13.4–17.1 g/dL); platelet count, 315 × 10^9/L (reference: 153–346 × 10^9/L); aspartate aminotransferase, 20 IU/L (reference: 5–37 IU/L); alanine aminotransferase, 27 IU/L (reference: 6–43 IU/L); blood urea nitrogen, 8 mg/dL (reference: 9–21 mg/dL); creatine, 0.61 mg/dL (reference: 0.6–1.0 mg/dL); Na, 140 mmol/L (reference: 135–145 mmol/L); K, 3.9 mmol/L (reference: 3.5–5 mmol/L); Cl, 109 mmol/L (reference: 96–107 mmol/L); total cholesterol, 179 mg/dL (reference: 150–219 mg/dL); high-density lipoprotein (HDL) -cholesterol, 30 mg/dL (reference: 40–70 mg/dL); HbA1c, 4.9% (reference: 4.6–6.2%). Protein C and S were within normal limits. International normalized ratio (INR) was 1.28 (reference: 0.85–1.15), and d-dimer was 0.5 μg/mL (reference: 0–1). His thyroid function was within normal limits. Immunological examination for autoimmune disorders, including for anti-nuclear antibody, anti-ribonucleoprotein (RNP), anti-SSA, anti-SSB, proteinase (PR) 3-anti-neutrophil cytoplasmic antibody (ANCA), myeloperoxidase (MPO)-ANCA antibodies, and anti-cardiolipin antibodies were all negative. Plasma homocysteine level was markedly increased to 74.1 nmol/ml (reference: 3.7–13.5 nmol/ml), and methionine level was 28.1 nmol/ml (reference: 18.9–40.5 nmol/ml). Folate, vitamin B12, and pyridoxal were all below-normal ranges (folate: 1.0 ng/ml [reference: > 4 ng/ml], vitamin B12 135 pg/ml [reference: 180–914 pg/ml], pyridoxal 3.2 ng/ml [reference: 6–40 ng/ml]).

Genetic analysis was performed after written informed consent was obtained as MTHFR enzyme deficiency was suspected. Genetic analysis identified C677T polymorphism that appeared to be homozygous (Figure 1). Brain computed tomography showed a low intensity area in the region of the left middle cerebral artery (MCA) (data not shown). On diffusion weighted imaging and FLAIR of brain magnetic resonance imaging, a large high intensity area was seen in the left MCA territory (Figures 2A, B). Additionally, magnetic resonance angiography showed that the MCA was disrupted in the M1 segment (Figure 2C). Holter electrocardiogram revealed no arrhythmia or atrial fibrillation. Transesophageal echocardiography showed no thrombus in the left atrium and no right-left shunt. He was diagnosed with atherothrombotic cerebral infarction. Administration of aspirin 200 mg/day that was started upon diagnosis was decreased to 100 mg/day after 3 weeks. To treat his hyperhomocysteinemia, folic acid (15 mg/day), vitamin B1 (150 mg/day), vitamin B6 (150 mg/day), and vitamin B12 (150 mg/day) were administered. On this course of treatment, serum folic acid, vitamin B1, and vitamin B6 increased, and serum homocysteine decreased to 5.8 nmol/ml. His consciousness gradually improved to being alert and his total aphasia ameliorated to motor aphasia. Three months after admission, his condition improved to a point at which he was able to carry out activities of daily living. Therefore, he was discharged from our hospital.

After discharge, he continued a regimen of AEDs such as valproic acid, gabapentin, topiramate, and levetiracetam instead of carbamazepine. During the 3 years after discharge, he was without seizure, and electroencephalography confirmed that he had no epileptic activity. Administration of folic acid, vitamin B1, vitamin B6, and vitamin B12 was continued for hyperhomocysteinemia. His plasma homocysteine level was maintained within normal limits (5.8–10.5 nmol/ml). Two years after discharge, a brain MRI showed no new infarction (Figures 2D, E). MR angiography revealed that the occluded MCA had been recanalized, but no double lumen sign or string and pearls sign were detected (Figure 2F). For the infarct, he was treated with clopidogrel and had no recurrence of ischemia.

Discussion

We herein reported on a patient with epilepsy and developmental delay during adolescence who suffered an ischemic stroke at age 30. He was devoid of common risk factors of atherosclerosis such as hypertension, diabetes mellitus, and hyperlipidemia. Based on the results of laboratory examination, neuroimaging, and physiological function tests, his stroke was not caused by cardiogenic embolism, paradoxical embolism or vascular malformation. Hyperhomocysteinemia was the only factor associated with the large vessel occlusion.

Meta-analyses have revealed a consistent association between plasma homocysteine levels and atherosclerotic disorders (7, 8). Additionally, several studies have demonstrated that high plasma

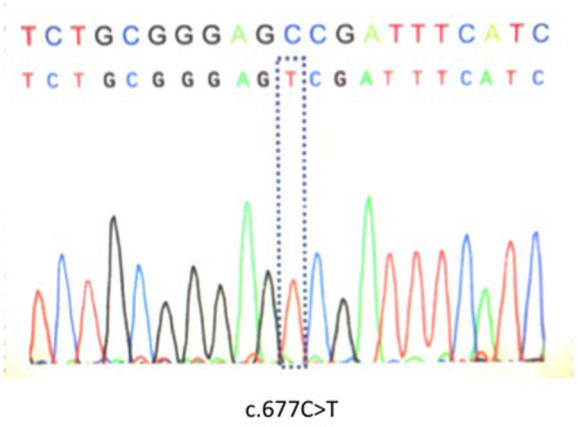

FIGURE 1
Genetic analysis identified homozygous C677T polymorphism in the *MTHFR* gene.

homocysteine levels are associated with small vessel stroke (9–11). In contrast, Tantirittisak et al. (12) reported that abnormal homocysteine levels were more pronounced in a group with large vessel stroke compared to small vessel stroke. Jeong et al. (13) showed that an increased level of plasma homocysteine was associated with internal carotid artery occlusion in patients with ischemic stroke. Taken together, these reports suggest that elevated plasma homocysteine is associated with not only small vessel but also large vessel stroke. As our patient had only hyperhomocysteinemia as a vascular risk factor, we conclude that his ischemic event was caused by a hyperhomocysteinemia independently progressed atherosclerosis leading to arterial occlusion. The exact mechanism by which increased levels of homocysteine lead to the development of atherosclerosis is still unknown. Clinical and experimental findings have shown that hyperhomocysteinemia can increase oxidative stress and change the homeostasis of the endothelium (14). At later stages of the atherosclerotic process, homocysteine increases platelet activation and aggregation and causes coagulation abnormalities, thereby promoting vascular occlusion (15). Furthermore, hyperhomocysteinemia may induce abnormal proliferation of smooth muscle cells and increase inflammatory processes that induce the development of atherosclerosis and trigger thrombosis (4).

Plasma homocysteine levels are influenced by genetic and environmental factors. Mutations in multiple genes are known to contribute to *cystathionine beta-synthase, MTHFR* and *nicotinamide N-methyltransferase (NNMT)* (5, 6, 16, 17). Cystathionine beta-synthase deficiency impairs the conversion of homocysteine to cystathionine and leads to both homocysteine and methionine accumulation (16) (Figure 3). MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate that produces methyl donor groups for the conversion of homocysteine to methionine (Figure 3). Impaired activity of the MTHFR enzyme leads to increased plasma homocysteine but not to increased plasma methionine. Our patient showed high serum homocysteine and normal methionine levels; therefore, we hypothesized that his MTHFR activity was decreased and found the C677T polymorphism in his *MTHFR* gene. As the C677T polymorphism of the *MTHFR* gene reduces the thermostability of the MTHFR enzyme, MTHFR enzyme activity under this homozygous polymorphism is 50–60% lower at 37°C compared with normal non-mutated controls (6, 18). The prevalence of the C677T polymorphism in the *MTHFR* gene is variable depending on ethnicity and nationality. For example, the percentage of the Japanese population with the homozygous mutation was reported at approximately 11% (19, 20). The A/G polymorphism NNMT (rs694539) is also known to be associated with hyperhomocysteinemia (17). NNMT is an enzyme involved in the synthesis of S-Adenosylhomocysteine (SAH); it catabolizes nicotinamide and other pyridine compounds in a reaction that uses the methyl group generated during the conversion of S-Adenosylmethionine to SAH (Figure 3) (21). In a Japanese study, there were no differences in plasma homocysteine concentration between the NNMT AA+AG and GG genotypes, suggesting that this polymorphism is not a major determinant of plasma homocysteine concentration in the Japanese men (22). However, only when together with the NNMT GG genotype and other confounding factors, such as age, folate deficiency, and/or MTHFR C677T, were they associated with an elevation of plasma homocysteine (22). In our case, unfortunately, we did not perform a NNMT gene analysis. It is possible that the patient had the NNMT GG genotype because his plasma homocysteine was elevated significantly.

As for environmental factors, sex, smoking, and low vitamin levels are associated with levels of serum homocysteine. Meta-analyses have revealed that carbamazepine, valproate sodium, and phenytoin are associated with an increase in plasma levels of homocysteine (23–25). Additionally, studies have demonstrated that these medications significantly decrease serum levels of folic acid vitamin B6 and vitamin B12 (26, 27). These vitamins play important roles in the metabolism of homocysteine (Figure 3). In our patient, the use of carbamazepine and valproate sodium may have decreased serum folate and vitamin B6 and consequently caused hyperhomocysteinemia. As a result, we changed the patient from taking carbamazepine to levetiracetam which has no effect on the levels of plasma homocysteine.

Hyperhomocysteinemia is an important risk factor for stroke due to atherosclerosis, and venous thrombosis (4). In the treatment of ischemic stroke due to atherosclerosis in patients with hyperhomocysteinemia, lowering of the homocysteine concentration through administration of folic acid and vitamin B12 is the most important therapy. Several previous studies have suggested that a lowering of homocysteinemia therapy prevented stroke recurrence (28, 29). Another previous report demonstrated that patients with hyperhomocysteinemia avoided death and altered their medical progress through the use of antihypertensive therapy and the administration of aspirin (30). These results may suggest that a combination of anti-platelet drugs and reducing homocysteine therapy is effective in preventing the progression of atherosclerosis caused by hyperhomocysteinemia. Hyperhomocysteinemia is also an important risk factor for thrombosis, both intracranially and in the

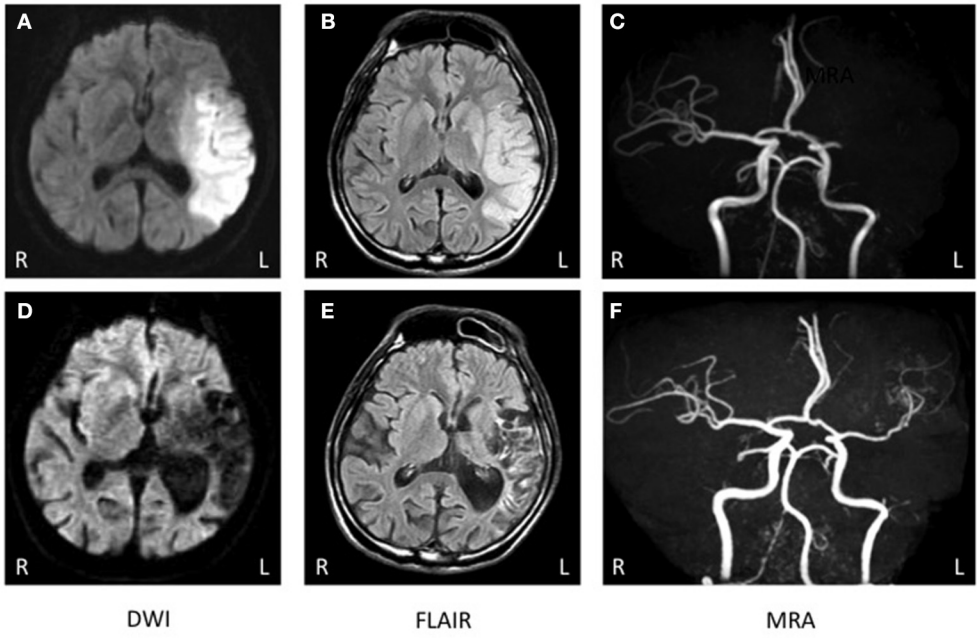

FIGURE 2
(A–C) Brain magnetic resonance imaging (MRI) at onset. **(A, B)** Brain MRI of diffusion-weighted imaging (DWI) and FLAIR exhibited a high intensity area in the left fronto-temporal region. **(C)** Brain magnetic resonance angiography (MRA) showed occlusion of the left middle cerebral artery (MCA). **(D–F)** MRI 2 years after onset. **(D, E)** Brain MRI of diffusion-weighted imaging (DWI) and FLAIR exhibited a low intensity area in the left fronto-temporal region. **(F)** Brain MRA showed that the left MCA was recanalized but there were no findings of double lumen or string and pearls signs.

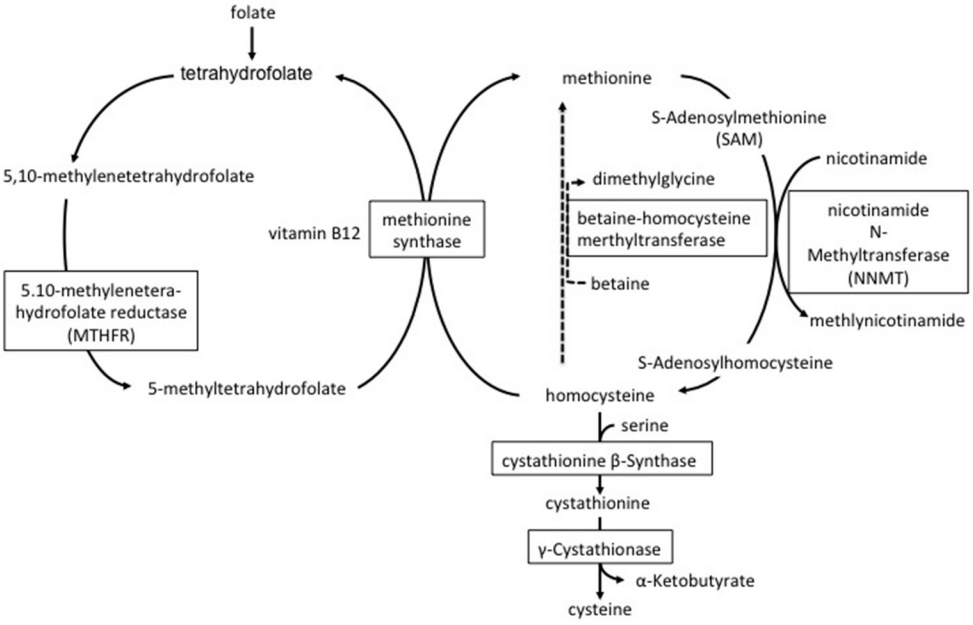

FIGURE 3
Metabolism of homocysteine.

venous return of the lower limbs (31, 32). These findings suggest that hyperhomocysteinemia increases the risk of ischemic stroke due to cerebral venous thrombosis and paradoxical embolism. A previous report shows that lowering homocysteine concentration was effective for preventing recurrent venous thrombosis (33). In the treatment of strokes due to venous thrombosis, anti-coagulant therapy is effective (34). From these viewpoints, a combination of anti-coagulant therapy and a reduction of homocysteine therapy

was effective in the prevention of strokes due to venous thrombosis caused by hyperhomocysteinemia.

In conclusion, the C677T mutation is closely related to hyperhomocysteinemia and folate deficiency in epileptic patients taking multiple anti-convulsants (27). Therefore, physicians should periodically examine plasma homocysteine and folic acid levels in epileptic patients who are on a long-term regimen of multiple AEDs. In the case of well-controlled patients, a supplement of folic acid could be prescribed to normalize plasma homocysteine levels. If patients' seizures are uncontrolled, physicians should consider using other AEDs such as lamotrigine or levetiracetam which do not affect plasma levels of homocysteine (35, 36).

Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

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

JF performed the data research and wrote the manuscript. JF and HE treated the patient. YW performed gene analysis. AF, RC, MN, and AN supported the clinical interpretation. NH and YS was critically involved in the theoretical discussion and composition of the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

NH received speaker or advisory board honoraria from Kyowa Kirin, Takeda Pharma, AbbVie, Inc, Sumitomo Pharma, Eisai, Mochida Pharma, Kissei Pharma, Ono Pharma, Teijin Pharma, Senju Pharma, EA Pharma, and Novartis Pharma K.K. He also received consulting honoraria from Mitsubishi Tanabe Pharma, Hisamitsu Pharma, and Chugai Pharma. YS received speaker honoraria from Medtronic, Boston Scientific, Otsuka Pharmaceutical, Takeda Pharmaceutical Co., Sumitomo Pharma, Novartis Pharma, MSD, FP Pharmaceutical Corporation, Kyowa Kirin, and AbbVie, 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.

Publisher's note

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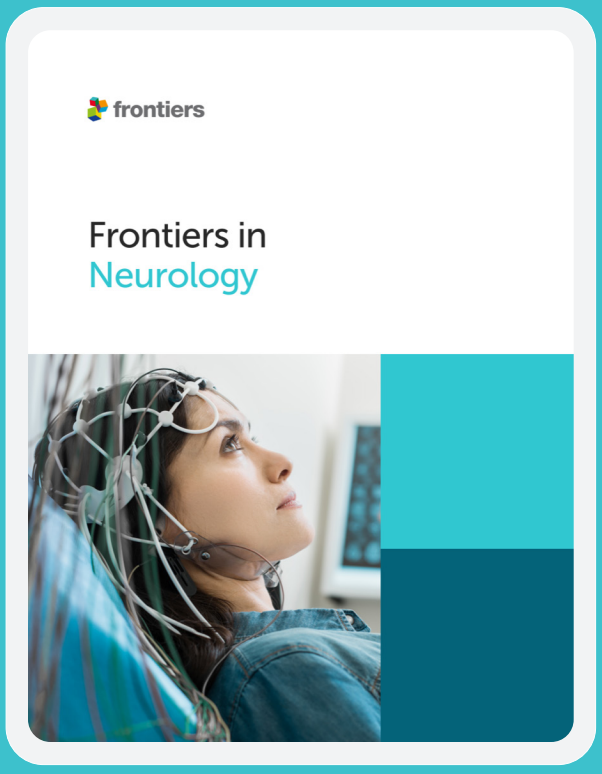

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