EPILEPSY

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Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "EPILEPSY Newsletter'' which contains latest and interesting news in the field of Neuropsychiatry.

This issue contains:

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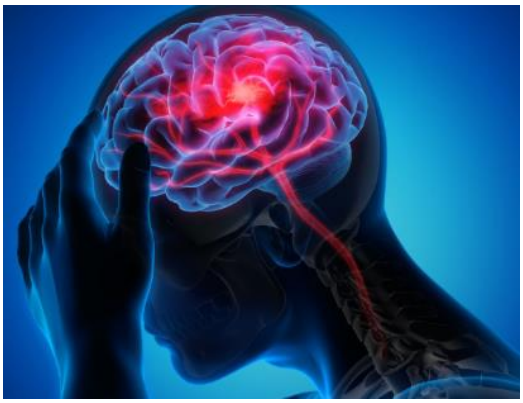
Headache Presents as a Common Aura in Individuals with Generalized Seizures

INTRODUCTION



SEIZURES

Individuals who had earlier seizure start were more likely to have headaches as an aura. Headache was the most frequent aura in individuals with generalised seizures.

Headaches are commonly linked with epilepsy, presenting as a typical characteristic in multiple childhood epilepsy syndromes and can also manifest in adult epilepsy patients before, during, or after seizures.[1] Moreover, headaches can be the sole symptom of an epileptic seizure, termed ictal epileptic headache. However, this condition is exceptionally uncommon, presenting challenges in confirming epileptiform discharges during a brief headache episode and assessing the response to intravenous antiseizure medication.[2] Aura in epilepsy was typically associated with focal seizures that have localizing significance. Nonetheless, multiple studies indicated that individuals with generalized seizures also encounter diverse types of auras, including headaches. In cases of ictal epileptic headache, recurrent generalized spike-wave discharges were frequently observed on electroencephalograms (EEGs), indicated a strong correlation between headaches and generalized seizures.[3] However, there was a lack of adequate research on the frequency and features of headaches as an aura in individuals experiencing generalized seizures. This study aimed to investigate the prevalence and attributes of headaches as an aura in patients with generalized seizures.

METHODS

A 14-year retrospective analysis was conducted on 102 patients diagnosed with generalized seizures. Epileptic seizure classifications were determined based on clinical symptoms, Magnetic resonance imaging (MRI) findings, and EEG results, with the presence of generalized epileptiform discharge deemed crucial for diagnosis. Clinical aspects examined included gender, age at seizure onset, seizure types, presence of aura, and aura types. A comparison of clinical features between patients with and without headaches as an aura was performed using student's t-test for continuous variables and chi-squared test or fisher's exact test for categorical variables.

RESULTS

Out of the 102 patients, 44 were males and 58 were females. The average age of seizure onset was 22.2 years, ranging from 6 to 94 years. The most common seizure types were absence seizures in eight patients, myoclonic seizures in 54 patients, and generalized tonic-clonic

seizures in 40 patients. Auras were reported in 45 patients (44.1%), with 11 patients experiencing at least two types. Headache was the most prevalent aura, affecting 26 patients, followed by dizziness (17 patients), palpitations (four patients), cephalic sensations (four patients), nausea (three patients), and visual symptoms (two patients). There were no gender or seizure type differences between patients with and without headache as an aura. However, patients with headache as an aura had a significantly younger age of seizure onset compared to those without (14.8 years vs. 24.7 years, p=0.003). Patients experiencing headache as an aura had seizure onset before their early twenties, while those without headache had a more varied age distribution of seizure onset (Figure 1). The age of seizure onset did not differ between patients with other types of auras and those without (21.6 years vs. 22.5 years, p=0.78).

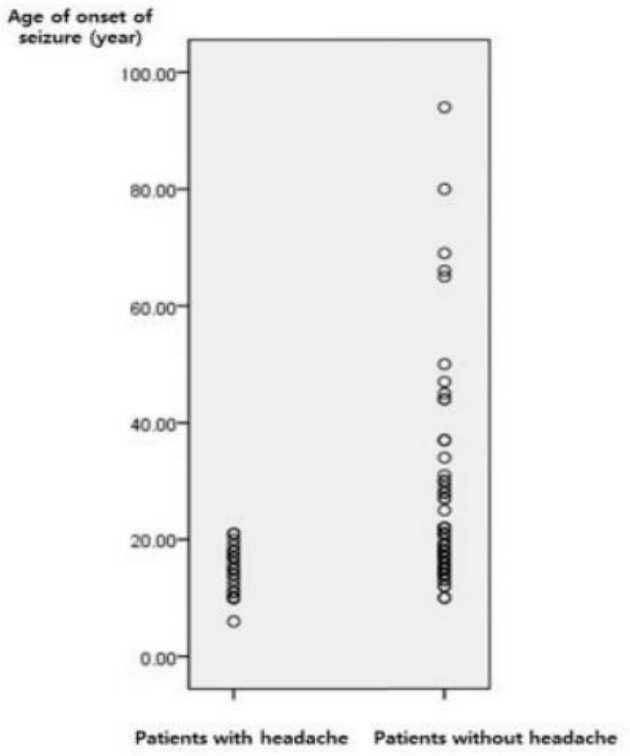


Fig 1. Age of Onset of seizures in patients with headache and patients without headache

DISCUSSION

The study's findings indicated that headache was the predominant aura in individuals with generalized seizures, with those experiencing an earlier onset of seizures being more prone to experiencing headache as an aura. Ludvigsson et al. revealed that migraine was linked to a fourfold higher likelihood of developing epilepsy, primarily attributed to migraine with aura. Migraine without aura, however, did not elevate the risk of epilepsy.[4]

CONCLUSION

Headache emerged as the predominant aura among individuals with generalized seizures, particularly in those who had an earlier onset of seizures.

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Analysis of the factors associated with potential autoimmune causes in individuals with drug resistant epilepsy

INTRODUCTION

Autoimmune epilepsy is not always ruled out by the absence of antibodies to neuronal antigens. Autoimmune epilepsy is more common in people with a history of SE.

Approximately 65 million people worldwide are impacted by epilepsy, with nearly 80% residing in developing nations. However, a significant number of epilepsy patients experience drug-resistant epilepsy (DRE), affecting approximately 30–40% of individuals with epilepsy.[1] In recent years, there has been a growing number of studies focusing on drug-resistant epilepsy with immunological or inflammatory origins. The International League Against Epilepsy (ILAE) has acknowledged autoimmune epilepsy as a distinct condition. It was estimated that 14–20% of drug-resistant epilepsy cases are autoimmune, with disruptions in both cellular and humoral immune responses playing a significant role. Research suggested that anywhere from 14% to 20% of drug-resistant epilepsy cases stem from autoimmune factors. Autoimmune epilepsy commonly presented as new-onset refractory status epilepticus (NORSE). Additionally, an untreated and chronic autoimmune process can lead to recurrent focal status epilepticus.[2] The objective of this study was to evaluate disorders of both humoral and cellular immune responses and their influence on the progression of the disease, as well as identifying factors indicative of an autoimmune origin. The study aimed to examine these factors and explore any associations with a history of status epilepticus.

METHODS

A prospective study was carried out involving 30 patients diagnosed with drug-resistant epilepsy. This study included individuals showing no correlation between changes observed in neuroimaging and the occurrence of epileptic seizures. Patients were divided into two groups based on their history of experiencing status epilepticus. Detailed information regarding patients' medical backgrounds, standard blood laboratory tests, levels of albumin and immunoglobulin (IgG), neuropsychological assessments, electroencephalography (EEG) tests, general cerebrospinal fluid (CSF) examinations, tests for the presence of oligoclonal bands, determination of IgG index, MRZ-reaction (MRZR), chitotriosidase activity, and detection of anti-herpes simplex virus type 1 (anti-HSV-1) antibodies and neural autoantibodies were collected and analyzed. Each patient underwent magnetic resonance imaging (MRI) of the head with intravenous contrast administration using the epileptic protocol.

RESULTS

Out of the 14 patients, three experienced multiple episodes of status epilepticus, with two patients encountering two episodes and one patient encountering three. For two patients, status epilepticus was the initial symptom of their condition. The types of status epilepticus observed

included nine patients with focal onset to bilateral tonic-clonic seizures, one with focal motor to bilateral tonic seizures, two with focal motor onset, two with focal non-motor onset, and one with focal onset myoclonic seizures. Additionally, one patient experienced status epilepticus during pregnancy after 35 years of illness. Table 1 displayed the characteristics of patients with a history of SE as well as those without a history, together with statistical data. Statistical analysis revealed significant differences in the age at which the first seizure occurred and in the duration of illness up to the study period. Furthermore, a statistically significant difference was noted in the level of chitotriosidase in the cerebrospinal fluid and the occurrence of epileptic seizures during sleep, which were more prevalent in the group with status epilepticus(SE). Focal onset impaired awareness seizures were present in 27 patients (90%), with temporal morphology in 10 (33%) and frontal in 11 (37%). Focal to bilateral tonic-clonic seizures were observed in 25 patients (83%), while myoclonic seizures occurred in four patients (13.3%). Three patients reported polymorphic seizures, and one patient had facial dyskinesia. Depending on the type of seizure, statistical significance was found in the frequency of seizures during sleep, the level of lactic acid in the blood serum, and the presence of neuropsychiatric changes. In 10 patients (36%), seizures occurred more than once per day, with the majority having a history of status epilepticus (eight patients, 80%). There was no correlation between the frequency of epileptic seizures and the number of current and past antiepileptic drugs used. However, a statistical difference was confirmed in the number of antiepileptic drugs used in the past compared to the present. None of the patients tested positive for antibodies against neuronal surface antigens or oligoclonal bands in the cerebrospinal fluid.

Student's t-test	SE	N	Average	Standard deviation	t	p-value
Age	.00	16	35.25	11.416	.274	.786
	1.00	14	34.21	8.894		
New-onset seizures	.00	16	15.1875	7.42266	3.575	.001
	1.00	14	6.7086	5.18461		
Duration of the disease	.00	16	20.06	8.797	-2.399	.023
	1.00	14	27.43	7.891		
Chitotriosidase in serum (mmol/ml/h)	.00	14	46.429	33.5896	.896	.379
	1.00	14	35.614	30.2185		
Chitotriosidase in CSF (mmol/ml/h)	.00	16	2.687500	1.8198443	2.240	.033
	1.00	14	1.440000	1.0807120		
APE 2 score	.00	16	3.00	1.155	-.768	.449
	1.00	14	3.36	1.393		

Table 1. Characteristics that differentiate patients with and without a history of SE
SE – status epilepticus, CSF – cerebrospinal fluids, APE 2 – antibody prevalence in epilepsy and encephalopathy

DISCUSSION

The study evaluated the patient group based on their history of status epilepticus as a potential indicator of autoimmune epilepsy. However, none of the patients tested positive for antibodies

against neuronal surface antigens. A recent study found that the APE score had limited sensitivity for patients with epilepsy lasting ≥12 months.[3] In present analysis, the average duration of the disease in the group with a history of status epilepticus was 27.43 years (± 7.89), whereas in those without a history of status epilepticus, it was 20.06 years (± 8.80). Therefore, the prolonged course of the disease in our patients could contribute to the absence of neural antibodies. Additionally, the limited number of patients included in the study may also be a contributing factor. Regarding the MRZR and the presence of herpes type 1 (HSV-1) antibodies, the index was positive in two patients. A positive index indicates the production of specific antibodies in the central nervous system and local infection. Hottenrott et al. indicated a high prevalence of positive MRZR in multiple sclerosis (MS), particularly in patients with primary-progressive multiple sclerosis (PPM) and those with relapsing-remitting multiple sclerosis (RRMS).[4] This observation implied that it could serve as an indicator pointing towards an autoimmune origin of epilepsy, particularly after ruling out other potential diseases.

CONCLUSION

Identifying antibodies against neuronal antigens remains a challenging and resource-intensive test. Additionally, a negative outcome does not definitively eliminate the potential for autoimmune epilepsy, as indicated by the APE2 scale. Ongoing efforts are focused on establishing diagnostic criteria for autoimmune epilepsy and creating new assessment tools to screen individuals with drug-resistant epilepsy. A patient's history of status epilepticus was among the factors indicating a diagnosis of autoimmune epilepsy. The author anticipated that the next phase in managing drug-resistant epilepsy with an unknown etiology will involve devising a novel therapeutic approach following the identification of autoimmune mechanisms.

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Comparison of scalp EEG and SEEG seizure onset patterns in patients diagnosed with drug-resistant focal epilepsy with negative MRI results

INTRODUCTION

Scalp electroencephalography (EEG) is commonly used to evaluate epilepsy patients, but it lacks precise spatial localization. Other non-invasive methods like positron emission tomography (PET), Single-photon emission computed tomography (SPECT),

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Scalp SOP does not correlate with surgical outcome in patients with MRI-negative focal epilepsies, however it may indicate the SEEG SOP and some aetiology (focal cortical dysplasia). In situations when the EEG and clinical onset occur simultaneously, the scalp surface area potential (SOP) coincides with the SEEG SOP; in other circumstances, the scalp SOP represents the spread of the SEEG discharge.

Magnetoencephalography (MEG), source modelling and Functional magnetic resonance imaging (fMRI) are used but don't directly measure seizure activity or pinpoint seizure onset zones accurately. In drug-resistant epilepsy patients eligible for surgery, invasive monitoring was often necessary.[1] Scalp EEG has limited abilities for localising and diagnosing. On the other hand, local field potentials produced and propagated by seizure-causing brain regions can be directly recorded by intracerebral electrodes. Thus, the great spatial resolution and more accurate detection of spatially confined discharges were offered by the Stereoelectroencephalography (SEEG). Nevertheless, in contrast to non-invasive whole-brain electrophysiological techniques like electro-magnetic source imaging, the quantity and location of implanted electrodes restrict SEEG's capacity to identify the epileptogenic zone (EZ). In order to maximise EZ localization using scalp EEG in a particular patient, it was therefore critical to combine the benefits of both methods and look for connections between the electrical activity recorded on the scalp during seizures and on the SEEG**.** The scalp and SEEG seizure onset pattern (SOP) received more attention in the past decades. Few studies, largely focusing on cases of temporal lobe epilepsy, have looked at the connections between them, though. A study evaluated these connections in individuals with MRI-visible lesion and showed that the SEEG SOP, the depth of the EZ site, and the underlying lesion could all be inferred from the scalp SOP.[2] Researchers examined the relationships between the scalp and SEEG SOPs in the current study since patients with negative MRIs have been shown to be more challenging candidates for epilepsy surgery. Furthermore, this study sought to determine the underlying causes to occurrences of inconsistency between the SEEG SOP and the scalp.

METHODS

A retrospective review was conducted on 41 patients with normal brain MRI results who underwent video-EEG followed by SEEG. All patients underwent a comprehensive pre-surgical evaluation, including medical history review, neurological examination, brain MRI, cerebral positron emission tomography, and scalp video-EEG recording. Patients with at least one typical spontaneous seizure captured on both scalp EEG and SEEG were included. The study categorized five types of SOPs on scalp EEG and eight types on SEEG. Patients were categorized into ten subgroups based on the location of their EZ: mesio-temporal, lateral temporal, mesio-lateral temporal, temporal plus, bitemporal, frontal, frontal plus, operculo-insular, parietal, and occipital plus. Each patient's EZ was further classified as either deep (involving the mesial part of the brain hemispheres, orbitofrontal region, and insula) or superficial (other locations or a combination of both deep and superficial EZ). For patients who underwent resective surgery, neuropathological diagnoses were reported following the International League Against Epilepsy classifications. Surgical outcomes were regularly assessed during post-operative follow-up and rated according to the Engel classification. The Engel score from the last available follow-up was utilized for statistical analyses. The study investigated the impact of various clinical variables on scalp EEG SOPs.

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RESULTS

The associations between matched scalp and SEEG SOPs are illustrated in Figure 1. Only 68% of rhythmic sinusoidal activity (RSA) and 40% of repetitive epileptiform discharges (RED) on scalp were linked with SEEG SOPs that included a low-voltage fast activity (LVFA). Additionally, scalp RSA and RED were associated with nearly all types of SEEG SOPs. Overall, scalp SOPs did not show a significant association with SEEG SOPs (p=0.161). The most common scalp SOPs were rhythmic sinusoidal activity (56.8%), repetitive epileptiform discharges (22.7%), paroxysmal fast activity (15.9%), and attenuation (4.5%). Paroxysmal fast activity on scalp EEG was consistently observed without delay from clinical onset and correlated with the presence of low-voltage fast activity in SEEG (sensitivity=22.6%, specificity=100%). The primary factor contributing to the discrepancy between scalp and SEEG SOPs was the delay between clinical and scalp EEG onset. A correlation between scalp and SEEG SOPs was observed when the scalp onset coincided with the clinical onset (p=0.026). A significant delay between clinical and scalp discharge onset was noted in 25% of patients, consistently featuring rhythmic sinusoidal activity on scalp, corresponding to a similar discharge morphology on SEEG. The presence of repetitive epileptiform discharges on scalp was associated with an underlying focal cortical dysplasia (sensitivity=30%, specificity= 90%). There was no significant association between scalp SOPs and the location of the epileptogenic zone (deep or superficial), or surgical outcome.

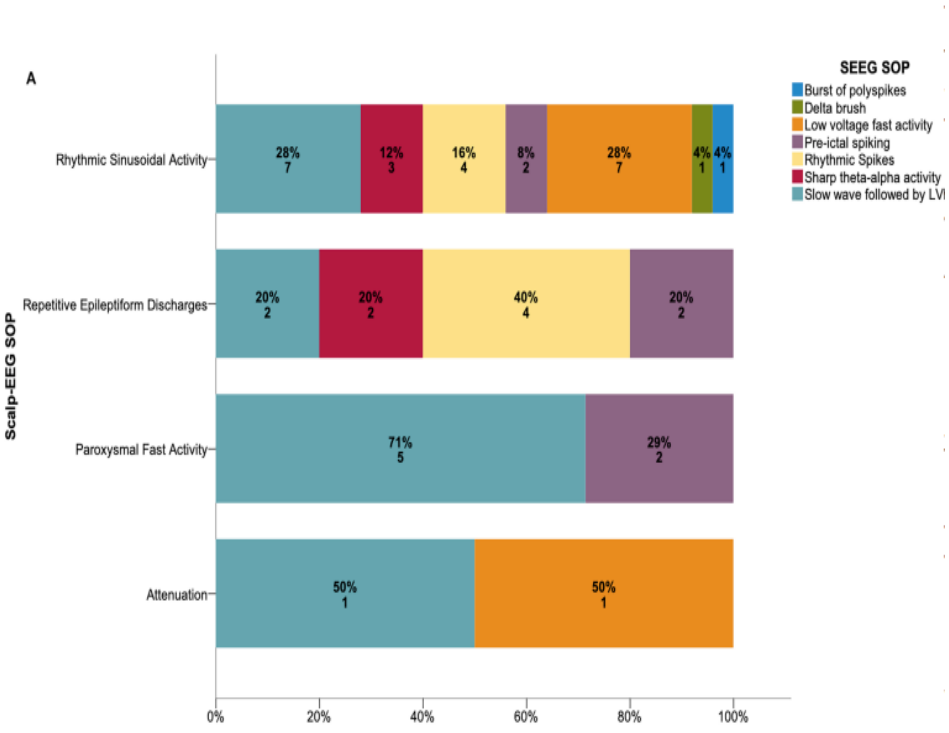

Figure 1. Histogram illustrating the overall SEEG SOP repartition in accordance with the scalp EEG SOP

DISCUSSION

In this study, scalp SOPs did not significantly correlate with the patients' surgical eligibility or outcome, in contrast to SEEG. In temporal lobe epilepsy, similar results have been described.[3] One of the study's drawbacks was that scalp EEG and SEEG recordings were made independently. The scalp SOP that would have been recorded simultaneously during SEEG monitoring would not have been the same as the one recorded during video-EEG monitoring due to a certain amount of intra-individual variability in electrical seizure organisation.

Nonetheless, a prior investigation has demonstrated that scalp SOPs do not differ significantly between simultaneous scalp-SEEG and scalp-EEG recordings in the same subject.[4]

CONCLUSION

Low frequency RSA was the most common scalp SOP observed in patients with focal MRI-negative epilepsy. There was a strong correlation between scalp and SEEG SOPs when there was no significant delay between clinical and scalp EEG onset. However, in approximately 25% of patients, RSA appears on the scalp several seconds after clinical onset, indicating the evolution and/or propagation of the SEEG discharge at that time. REDs on the scalp may suggest an underlying focal cortical dysplasia (FCD), even in patients with negative MRI results. These findings could assist clinicians in managing the challenging group of patients with negative MRI results and may serve as the basis for future studies on ictal electrical source imaging with improved methodologies.

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Case report on epilepsy in a patient with Gitelman syndrome caused by a homozygous deletion in the SLC12A3 gene

INTRODUCTION

Neurologists should be aware of the possibility of GS when uncommon seizures are the major clinical presentation, even though GS is often first seen in nephrology, endocrinology, and other medical fields.

Gitelman syndrome (GS), also known as familial hypokalemia-hypomagnesemia, is a condition affecting the tubules characterized by low potassium levels, metabolic alkalosis, reduced magnesium, and low calcium excretion. It is quite common, with a prevalence estimated at approximately 1 to 10 per 40,000 individuals, possibly higher in Asia. GS is considered one of the most common inherited tubulopathies, primarily caused by mutations in both copies of the SLC12A3 gene, which encodes the sodium-chloride transporter (NCC) located on the apical membrane of cells in the distal convoluted tubule.[1] Studies indicated that the occurrence of epilepsy related to GS was relatively rare, approximately around 0.8%. Prior accounts of GS-related epilepsy have been limited, lacking detailed descriptions of patients' epilepsy symptoms, and frequently

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employing simplistic diagnostic and treatment methods.[2] In this case study, the authors described a patient with GS who has experienced epileptic seizures since birth, showing particularly pronounced epilepsy symptoms. Additionally, this patient demonstrated a notably positive short-term outlook. The purpose of this report was to enhance comprehension of GS and clarify the connection between epilepsy and this rare genetic condition.

CASE PRESENTATION

A 21-year-old woman visited the Neurology Department's outpatient clinic due to recurring limb convulsions and associated consciousness disturbances persisting for over two decades. These seizure-like episodes began in infancy, featuring symptoms like hand clenching, eye rolling, teeth clenching, and profuse sweating, occurring 2-3 times annually while awake. Over time, the episodes progressed to include symptoms like blurred vision, cold extremities, trembling hands, and loss of limb control, often accompanied by severe vomiting about 6-8 times yearly, exclusively during wakefulness. Seizures were triggered by sudden fright, more frequent in winter and spring, and concentrated between 3:00 PM and 6:00 PM. Previous medication trials with oxcarbazepine and levetiracetam resulted in adverse effects or insufficient control. In 2023, treatment with lacosamide effectively stopped seizure episodes. The patient exhibited developmental delays compared to her twin sister, including delayed crawling, walking, lower academic performance, and discontinuation of education after ninth grade. At age 3, she experienced a fall leading to unconsciousness for half an hour. Family history revealed a maternal aunt with epilepsy. Lab tests consistently showed low potassium and magnesium levels. The right parietal and left occipital lobes of the hippocampus high-resolution magnetic resonance imaging (MRI) had sporadic Flair hyperintensity (Figure 1). During sleep, intermittent epileptiform discharges were seen in the right parietal, posterior temporal, and midline areas of the video electroencephalogram (EEG). Genetic testing revealed a homozygous deletion in the SLC12A3 gene associated with GS, inherited from both parents who each carried a heterozygous deletion in the same gene. This genetic variant was classified as pathogenic according to ACMG standards, confirming the diagnosis of GS with associated electrolyte disorders, prolonged QT interval, diarrhoea, and developmental delay.

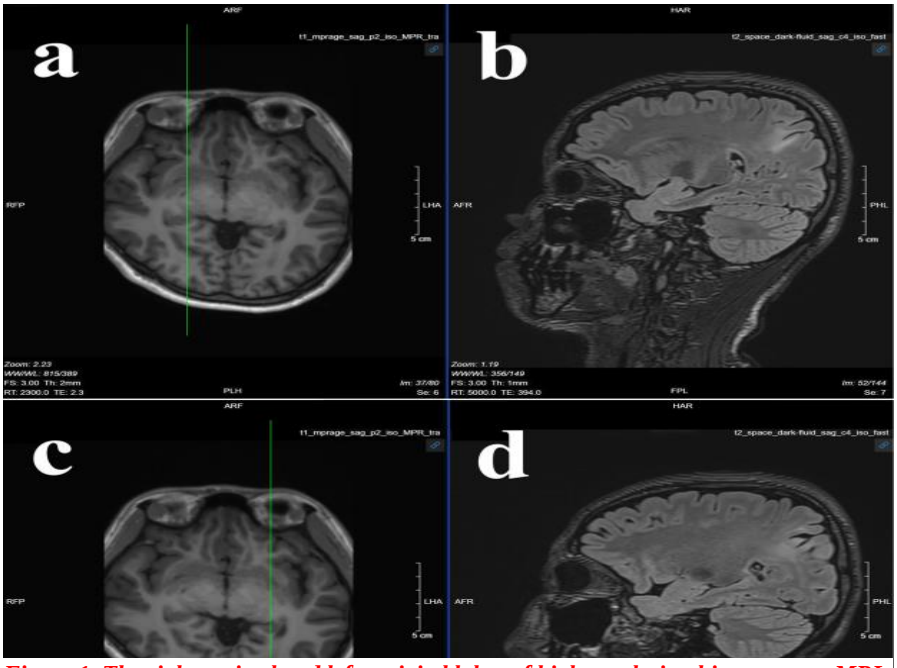

Figure 1. The right parietal and left occipital lobes of high-resolution hippocampus MRI images have patchy Flair hyperintensity, indicating the necessity for a contrast-enhanced cranial plain CT scan. Plain MRI scans of both hippocampi did not reveal any obvious abnormalities. A) image transversely. b) Patchy Flair hyperintensity in the right parietal lobe on a sagittal scan. C) Image transverse. D) Patchy Flair hyperintensity in the left occipital lobe in the sagittal picture

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DISCUSSION

This case study contributes to the documentation of a homozygous deletion in exons 4–6 of the SLC12A3 gene, highlighting the varied and complex clinical manifestations of GS within a familial context. Furthermore, it broadened the understanding of GS by showcasing a patient whose primary symptom was epilepsy.[2] GS arises from inactivating mutations in both alleles of the SLC12A3 gene, which encoded the thiazide-sensitive sodium-chloride cotransporter (NCC) found in the apical membrane of cells that line the distal convoluted tubule.[1] Diagnostic tests for GS commonly showed specific characteristics including low potassium levels, metabolic alkalosis, reduced magnesium levels, low urinary calcium excretion, and often normal or lower-than-average blood pressure readings.[3] Muhammad et al. conducted a thorough analysis of 122 cases of GS documented in 100 articles. They compiled a table outlining the various clinical symptoms, complications, diagnostic methods, and treatments observed in GS patients. The study found that commonly reported symptoms included fatigue, muscle spasms, vomiting (accounting for 6% of cases), as well as polyuria and epilepsy (each present in 0.8% of cases).[4]

CONCLUSION

The documentation of homozygous exon 4–6 deletion in the SLC12A3 gene was expanded by this case report. Insight for future study was provided by highlighting the complexity and diversity of GS clinical manifestations in a family setting. This case report highlighted a patient whose major presenting symptom was epilepsy, hence broadening the scope of clinical symptoms associated with GS. Neurologists should be aware of the possibility of GS when uncommon seizures were the major clinical presentation, even though GS was often first seen in nephrology, endocrinology, and other medical specialties.

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