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:

- **Assessment of the efficacy and safety of the modified medium-chain triglyceride ketogenic diet in the treatment of drug-resistant epilepsy**
- **Efficacy and safety of resective surgery in people aged 50 years or older with drug-resistant epilepsy**
- **Localization patterns of peri-ictal Magnetic Resonance Imaging abnormalities in patients with Status Epilepticus**
- **Case Report on Alternating Hemiplegia of Childhood Initially Misdiagnosed as Hysteria**

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Assessment of the efficacy and safety of the modified medium-chain triglyceride ketogenic diet in the treatment of drug-resistant epilepsy

INTRODUCTION

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Patients with drug-resistant epilepsy can safely use the modified MCTKD with MCTs supplying 20–30% of energy, but its effectiveness has to be improved.

Ketogenic diet (KD) is a specialized nutritional regimen comprising high fat, low carbohydrates, adequate proteins, and essential nutrients. It is currently endorsed as a secure and efficacious dietary intervention for managing drug-resistant epilepsy.[1] Throughout the last century, a range of dietary approaches within the KD framework have been developed, broadly categorized into four types: classic ketogenic diet (CKD), medium-chain triglyceride ketogenic diet (MCTKD), modified Atkins diet, and low glycemic index treatment.[2] The CKD imposes strict carbohydrate limitations, making it less practical for many individuals. In the MCTKD, medium-chain triglycerides (MCTs) become the primary source for ketone production. Unlike the CKD, MCTKD doesn't necessitate caloric restriction and permits a higher carbohydrate intake of up to 20%. Studies indicate that MCTKD demonstrated similar efficacy to CKD. However, clinical observations revealed that MCTKD become poorly tolerated when MCTs contribute more than 40% of total energy, potentially leading to adverse reactions.[1] Hence, this study aimed to evaluate the effectiveness and safety of a modified MCTKD where MCTs constitute 20–30% of total energy intake, in patients diagnosed with drug-resistant epilepsy.

METHODS

A total of 123 patients ranging in age from 2.5 to 65 years were enrolled. Inclusion criteria consisted of a confirmed diagnosis of drug-resistant epilepsy, defined as the failure of adequate trials of two appropriately chosen and used anti-seizure medications (ASMs) to achieve sustained seizure freedom, an age over 2 years, and a minimum average seizure frequency of once every three months prior to enrollment. The modified MCTKD protocol in this study maintained a fat-to-carbohydrate plus protein ratio ranging from 1:1 to 2:1. Fat constituted 50–70% of total energy intake, with 20–30% derived from MCTs and 30–40% from long-chain triglycerides (LCTs), while protein contributed to 20–30% and carbohydrates to the remaining 20%. Daily monitoring of urine ketones ensured the maintenance of urine ketone levels at (++) or higher. The efficacy and safety of the diet were evaluated at 1, 3, and 6 months.

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RESULTS

Among the 123 patients, focal epilepsy was diagnosed in 69.9% (86 cases), while 4.9% (6 cases) exhibited generalized epilepsy. Furthermore, there were 9 cases (7.3%) of infantile epileptic spasms syndrome, 3 cases of Lennox-Gastaut syndrome, 2 cases of Dravet syndrome, 1 case of hypothalamic hamartoma, and 1 case of Rasmussen syndrome. The response rates at 1, 3, and 6 months following the initiation of the modified MCTKD were 49.6%, 43.1%, and 30.9%, respectively. Seizure freedom rates at 1, 3, and 6 months were 12.2%, 10.6%, and 6.5%, respectively. The retention rates at these time points were 98.4%, 65.0%, and 33.3%, respectively (Table 1). Out of the 123 patients, 26 cases (21.14%) reported side effects, including gastrointestinal symptoms such as diarrhea (4.07%), abdominal pain (3.25%), vomiting (1.63%), constipation (3.25%), and fever (0.81%). Other reported side effects included rash, hyperuricemia, allergy, iron deficiency, and fatigue, most of which resolved after dietary adjustments. Gastrointestinal symptoms were the most frequently reported adverse events. Notably, there was a significant difference in the incidence of side effects between the under-18 group (29.63%) and other age groups ($\chi 2$=4.164, P=0.041). A total of 82 patients (66.7%) discontinued treatment, citing reasons such as refusal to eat (8.1%), poor efficacy (35.0%), poor compliance (4.9%), and inability to follow-up (9.8%). Only 4 patients (3.3%) withdrew from the diet due to side effects.

Table 1. Effectiveness of the modified MCTKD and the retention rates at 1, 3 and 6 months of follow-up

		1 month			3 months			6 months		
Groups	**Cases**	**Responder rate (%)**	**Seizure freedom (%)**	**Retention rate (%)**	**Responder rate (%)**	**Seizure freedom (%)**	**Retention rate (%)**	**Responder rate (%)**	**Seizure freedom (%)**	**Retention rate (%)**
<10 years	38	17 (44.7%)	3 (7.9%)	37 (97.4%)	15 (39.5%)	3 (7.9%)	21 (55.3%)	14 (36.8%)	2 (5.3%)	14 (36.8%)
10-18 years	31	12 (38.7%)	3 (9.7%)	30 (96.8%)	13 (41.9%)	3 (9.7%)	22 (71.0%)	11 (35.5%)	2 (6.5%)	12 (38.7%)
≥18 years	54	32 (59.3%)	9 (16.7%)	54 (100.0%)	25 (46.3%)	7 (13.0%)	37 (68.5%)	13 (24.1%)	4 (7.4%)	15 (27.8%)
Total	123	61 (49.6%)	15 (12.2%)	121 (98.4%)	53 (43.1%)	13 (10.6%)	80 (65.0%)	38 (30.9%)	8 (6.5%)	41 (33.3%)
P value		0.144	0.465	0.313	0.823	0.756	0.315	0.354	1.000	0.523

DISCUSSION

The study demonstrated that the modified MCTKD, with MCTs constituting 20–30% of energy intake, exhibited favorable safety outcomes in patients with drug-resistant epilepsy. In Liu et al., children were categorized into three groups receiving diets with MCT proportions of 40–55%, 60%, and over 60%. Findings revealed that 21% of children achieved seizure freedom, 19% experienced over 90% reduction in seizures, and an additional 42% observed a reduction of 50–90% in seizurefrequency.[3] Neal and colleagues conducted the initial randomized study, comparing the efficacy of the CKD with that of the MCTKD, with MCTs accounting for 40–50% of energy intake. Their results showed responder rates of 29.6% at 3 months and 19.4% at 6 months in the MCTKD group, which were lower than those observed in the current study.[4] In Chomtho K et al. study, where MCTs provided 50% of energy, children exhibited a

responder rate similar to ours at 1 month. However, unlike the results of the current study, their effectiveness increased at 3 months.[5]

CONCLUSION

The modified MCTKD, with MCTs supplying 20–30% of energy, demonstrated good tolerability for patients with drug-resistant epilepsy. However, to improve efficacy and reduce adverse effects, further research was warranted to adjust the energy ratio of MCTKD.

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Efficacy and safety of resective surgery in people aged 50 years or older with drug-resistant epilepsy

INTRODUCTION

Surgery for epilepsy may be considered necessary for carefully chosen individuals over the age of 50.

Up to 30% of individuals with epilepsy under specialized clinic care experience drug-resistant epilepsy. Many among this group could potentially benefit from epilepsy surgery. Clinical practice guidelines stress the significance of evaluating surgery as a treatment option for those with drug-resistant epilepsy.[1] Despite its overall safety and effectiveness, epilepsy surgery was underutilized, as evidenced by research. Failure to refer patients and delays in referrals were major factors contributing to this underutilization. Additionally, misperceptions regarding the risks and eligibility for surgery among certain groups of individuals serve as significant barriers to ensuring that this crucial intervention was appropriately accessible.[2] Epilepsy was prevalent among older adults, particularly in high-income countries, where it affects nearly 1% of individuals aged 65 years and older, surpassing the prevalence among younger age groups. While epilepsy surgery was more commonly performed in children and younger adults, there was a growing body of research on epilepsy surgery in older adults. However, consensus regarding the efficacy and safety of epilepsy surgery in this demographic has yet to be reached.[1] The aim of this study was to systematically evaluate both the effectiveness and safety of resective surgery in individuals aged 50 years or older who have drug-resistant epilepsy.

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METHODS

This systematic review included studies focusing on the effectiveness and safety of epilepsy surgery in adults aged 50 years and older. Eligibility criteria encompassed studies conducted post-1990, with at least 10 participants and a follow-up period of at least 6 months. Researchers systematically searched databases such as Ovid MEDLINE, Ovid Embase, Cumulative Index to Nursing and Allied Health Literature, PsychInfo, and Web of Science Conference Proceedings Citation Index - Science for relevant publications. Included studies investigated various surgical interventions for epilepsy, including resective and nonresective procedures such as anterior temporal lobectomy, temporal or extratemporal focal resection, laser and radiofrequency ablation, and neuromodulation techniques like vagus nerve stimulation (VNS), responsive neurostimulation (RNS), or deep brain stimulation (DBS), as well as disconnection procedures like multiple subpial transections or callosotomy. The review comprised 11 case series and 14 cohort studies, totaling 1111 older adults who underwent epilepsy surgery, alongside 4111 adults younger than 50 years serving as control groups. Two reviewers independently assessed the risk of bias in each study using the MINORS (Methodological Index for Non-Randomized Studies) instrument. The primary outcome measure was freedom from disabling epileptic seizures affecting awareness throughout the follow-up period, while secondary outcomes included the occurrence of major and minor medical or neurological complications.

RESULTS

Following reconstructive surgery, the cumulative frequency of elderly people reaching Engel class I was 70.1% (95% confidence interval [CI] = 65.3–74.7; Figure 1A). Comparable results were observed among adults aged 18–49 years (70.4%, 95% CI = 66.3–74.4; Figure 1B). Among younger adults, the cumulative incidence ranged from 57.5% to 82.5%. Notably, a subgroup analysis revealed a higher incidence of favorable seizure outcomes in individuals older than 60 years, with 80.8% achieving Engel class I compared to those as young as 50 years. Meta-regression analysis further supported this finding, indicating a higher likelihood of surgical success among those older than 60 years (a 14% absolute increase). Upon examining cohort studies, no discernible difference in the incidence of seizure freedom was evident between older and younger adults (RR = 1.05, 95% CI = .97–1.14; Figure 1C, D). The pooled cumulative incidence of perioperative complications in older adults was 26.2% (95% CI = 21.3–31.7), with 7.5% (95% CI = 5.8–9.5) experiencing major complications. Notably, older adults were significantly more susceptible to experiencing any complication compared to their younger counterparts (RR = 2.8, 95% CI = 1.5–5.4).

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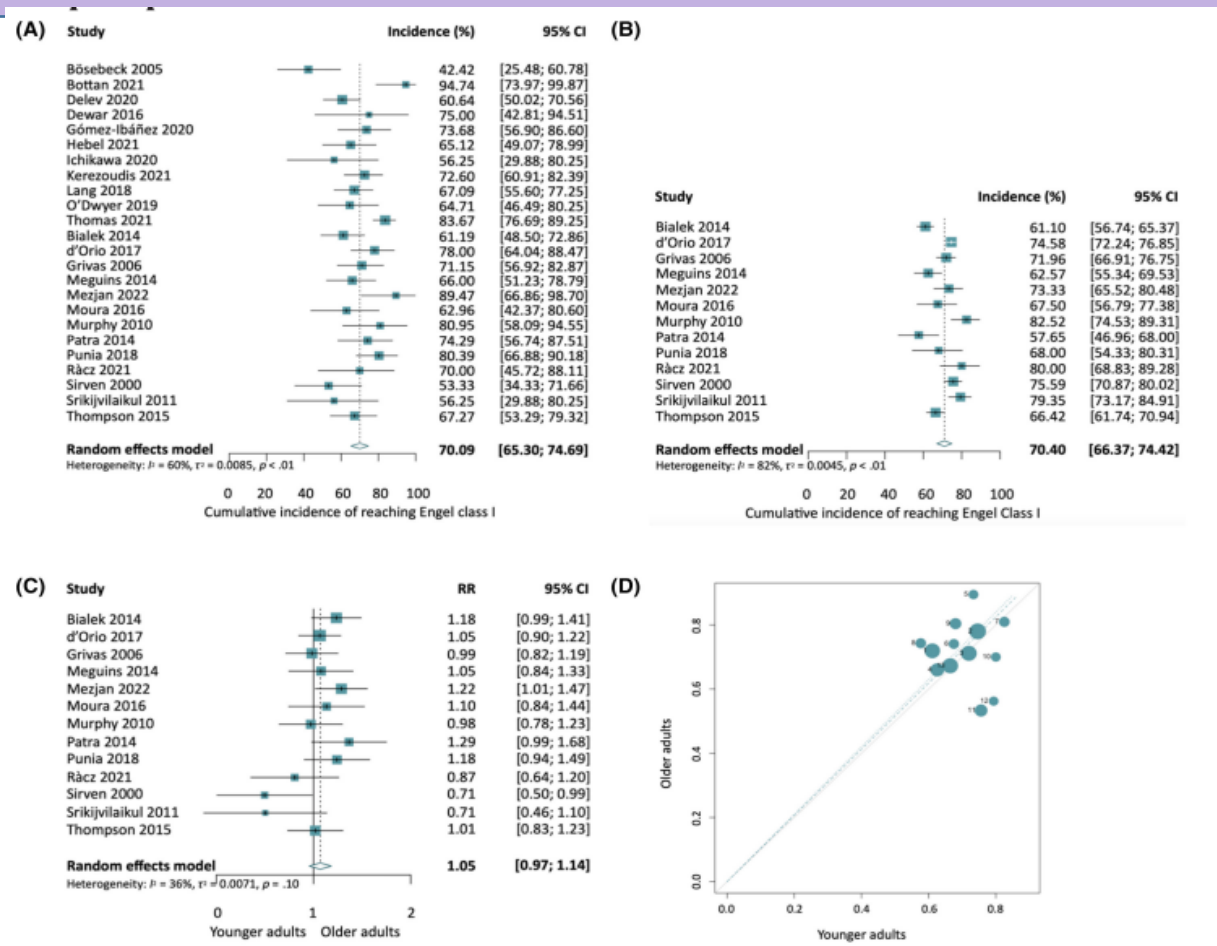

Figure 1. The combined cumulative incidence (%) of people who were younger (A) and older (B) and who achieved Engel class I following resective epilepsy surgery, together with the Forest (C) and l'Abbé (D) plots of unadjusted risk ratios (RRs). The complete line denotes the absence of influence, while the dotted lines show the estimated effect. In the l'Abbé plot, the incidence of seizure freedom in younger and older individuals was shown by the x- and y-axes, respectively. greater circles (l'Abbé plot) or squares (Forest plot) indicate studies with a greater sample size, and vice versa. Interval of confidence, or CI.

DISCUSSION

The study's findings suggested no apparent disparity in the effectiveness of epilepsy surgery between older and younger adults, with surgery proving even more successful in a subgroup of adults aged over 60 years. However, older adults faced a notably higher pooled cumulative incidence of perioperative complications following resective surgery. Lang JD et al. results underscored that epilepsy surgery, when carefully selected, can yield equal or potentially higher success rates in older patients compared to younger counterparts. Nevertheless, older patients may be at increased risk of postoperative hygroma and memory deficits, particularly following dominant temporal lobe resections.[3]

CONCLUSION

The study found no noticeable discrepancy in the effectiveness of epilepsy surgery between older and younger adults, and in fact, surgery proved to be even more successful in a subset of

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adults aged over 60 years. However, older adults experienced a significantly higher pooled cumulative incidence of perioperative complications following resective surgery.

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Localization patterns of peri-ictal Magnetic Resonance Imaging abnormalities in patients with Status Epilepticus

INTRODUCTION

Strong correlations exist between SE and diffusion-restricted MRI lesions seen in the pulvinar of the thalamus and hippocampal regions.

Status epilepticus (SE), a frequent neurological emergency, often links with peri-ictal MRI abnormalities (PMA). These abnormalities manifest during or shortly after a seizure and can resolve within days or persist, potentially causing structural alterations like hippocampal atrophy or cortical necrosis.[1] PMA were detectable across various MRI sequences, such as diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery, and perfusion techniques like arterial spin labeling (ASL) or contrast-enhanced perfusion imaging. In SE, diffusion restriction was commonly noted,[2] this can sometimes complicate distinguishing SE-related MRI alterations from those linked to other conditions like acute ischemic stroke.[3] PMA, which encompass diffusion-restricted lesions, manifest in brain regions like the cortex, hippocampus, and pulvinar of the thalamus.[1] Nevertheless, the systematic examination of the anatomical distribution of these changes has not been conducted. This study aimed to evaluate the localization patterns of PMA in patients experiencing SE.

METHODS

This case-control study, conducted at a single center involved adult participants (aged ≥18 years) exhibiting diffusion-restricted lesions on cranial MRI. Patients diagnosed with SE upon hospital discharge, who underwent MRI within the first 48 hours of onset, were prospectively recruited. A total of 201 patients were enrolled, including 51 with SE and 150 controls. Ictal EEG recordings were available for all SE patients except for 10 with generalized convulsive SE. The Salzburg EEG criteria were applied to diagnose nonconvulsive SE (NCSE). The study compared the distribution and combinations of diffusion-restricted PMA to those caused by other neurological conditions. Both the SE and control groups underwent MRI, including diffusion-weighted imaging, with SE patients imaged within 48 hours of onset.

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RESULTS

In SE, PMA most commonly occurred in the cortex (25/51, 49%), followed by the hippocampus (20/51, 39%) and pulvinar of the thalamus (10/51, 20%). In contrast, the control group showed involvement of the white matter in 53 cases out of 150, the brain in 80 instances (53%), and the basal ganglia in 33 cases (22%). Notably, the pulvinar of the thalamus was never affected in the control group, and hippocampal structures were rarely involved (7/150, 5%). The involvement of the pulvinar of the thalamus and the hippocampus exhibited high specificity for SE (100% and 95% respectively), but low sensitivi ty (pulvinar of thalamus: 20%, 95% CI=10–33; hippocampus: 39%, 95% CI=26–54). Combinations of locations affected by DWI-restricted lesions were illustrated in Figures 1 and 2 for the SE and control groups, respectively. Unique combinations observed only in the SE group included the pulvinar of thalamus + hippocampus (2/51, 4%), pulvinar of thalamus + white matter (1/51, 2%), thalamus + hippocampus (1/51, 2%), and corpus callosum + cerebellum + thalamus + hippocampus + cortex (1/51, 2%). Conversely, combinations exclusive to the control group comprised white matter + cortex (14/150, 9%), white matter + basal ganglia (10/150, 7%), white matter + basal ganglia + cortex (5/150, 3%), thalamus + basal ganglia (3/150, 2%), basal ganglia + cortex (3/150, 2%), thalamus + basal ganglia + cortex (2/150, 1%), thalamus + basal ganglia + cerebellum (1/150, .5%), and those involving white matter or the brainstem. Additionally, a negative association was observed between diffusion restriction in the hippocampus and cortical involvement (either in DWI or ASL) in the frontal, parietal, and occipital regions. No associations were found between diffusion restriction in the hippocampus and diffusion restriction or hyperperfusion in the temporal or insular cortices.

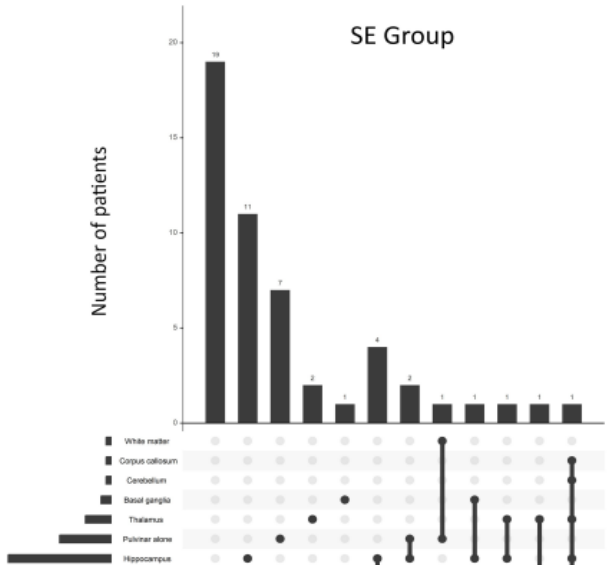

Figure 1. Combination of lesions with diffusion restriction in the status epilepticus (SE) group

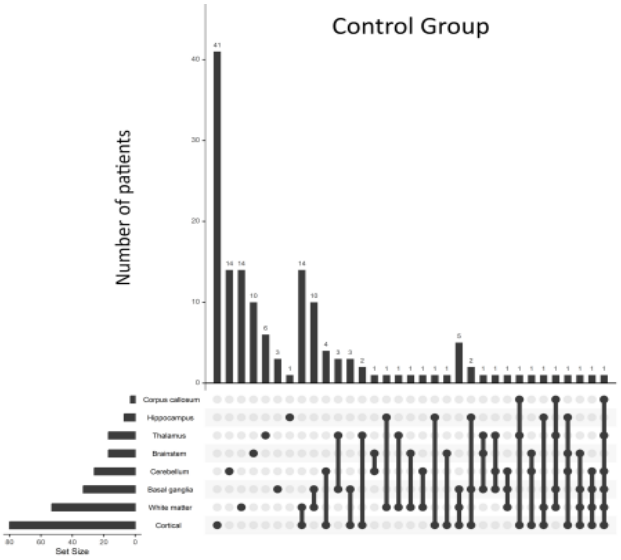

Figure 1. Diffusion-restricted lesions in combination within the control group.

DISCUSSION

The current study found a strong association between diffusion-restricted MRI lesions in the pulvinar of the thalamus and hippocampus with SE. This aligned with Rosenberg DS et al. which demonstrated that ictal changes in medial pulvinar activity were commonly seen (in 80% of patients) during temporal lobe seizures.[4] The study emphasized the pivotal role of the hippocampus in triggering SE discharges, while the thalamus appeared crucial in propagating ictal activity, indicated by their high connectivity during the pre-ictal stage. Additionally, effective connections were noted between the frontal cortex, thalamus, and hippocampus during the ictal and postictal periods.[5]

CONCLUSION

The presence of diffusion-restricted MRI lesions in the pulvinar of the thalamus and hippocampus was significantly linked to SE. These findings could aid physicians in diagnosing SE-related MRI changes promptly, particularly in situations where clinical and EEG indicators of SE were unclear.

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Case Report on Alternating Hemiplegia of Childhood Initially Misdiagnosed as Hysteria

Alternating hemiplegia of childhood (AHC) is a rare neurological disorder characterized by the onset of recurrent episodes of hemiplegia or quadriplegia during infancy. Alongside these primary symptoms, individuals with AHC often display accompanying manifestations including dystonia, autonomic dysfunction, abnormal ocular movements (such as monocular nystagmus, deconjugated gaze, ocular deviation, and up-rolling of the eyes), ataxia, chorea,

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choreoathetosis, developmental delay, and progressive cognitive impairment.[1] While most cases of AHC occur sporadically, familial occurrences have been noted, indicating an autosomal dominant inheritance pattern. The ATP1A3 gene (MIM 182350), responsible for encoding the alpha-3 catalytic subunit of the Na^+/K^+-ATPase transmembrane ion pump, is a primary genetic contributor in AHC patients. Mutations in the ATP1A3 gene have also been found in patients with other conditions, such as cerebellar ataxia, areflexia, pes cavus, optic atrophy, sensorineural hearing loss syndrome, and dystonia-12. Therefore, identifying pathogenic mutations in patients hold significant importance for diagnosis and targeted treatment approaches.[2] This report presents a case of an AHC patient harboring a known mutation c.2270T>C (p.Leu757Pro) in the ATP1A3 gene. Following treatment with funarizine, a significant reduction was observed in both the frequency and duration of hemiplegic episodes. Notably, the patient exhibited symptoms such as atypical limb weakness and episodes of suspected emotional crying and silence, differing from the typical symptomatology of AHC and resembling characteristics of epilepsy and hysteria. As a result, the patient underwent initial misdiagnoses of epilepsy and later hysteria until the age of 16.

Following a systematic strategy to localise and diagnose neurological illnesses is essential to preventing misdiagnosis and inappropriate therapies in individuals presenting with suspected symptoms. Genetic testing should also be taken into consideration as part of the diagnostic process when AHC is suspected in a patient.

CASE PRESENTATION

A 16-year-old girl arrived at the outpatient clinic because of aphasia and paroxysmal limb paralysis for the previous 15 years. During infancy, she experienced stereotyped and recurrent quadriplegia, primarily affecting her left limb, accompanied by symptoms such as sweating, pathological laughing and crying, pupil dilation, and significant increases in blood pressure. These episodes occurred every 4 to 15 days and lasted hours to three days. Although she began walking independently at age 2, her motor development was delayed, and she exhibited poor memory and learning abilities compared to her peers. Throughout childhood, she continued to experience intermittent limb weakness, speech difficulties, and dragging movements in her left lower limb during episodes. Initially, she was diagnosed with epilepsy due to the stereotypical, episodic, and repetitive nature of her symptoms. However, at age 12, she was suspected to have hysteria and did not receive specialized treatment for a decade. Upon admission to the hospital, she displayed introverted behavior and irritability, with episodes occurred during mood fluctuations or in calm circumstances. These episodes were characterized by muscle weakness, speech impairment, and dragging of the left leg while walking. Severe attacks also included an inability to walk, chest discomfort, dizziness, and profuse sweating, with blood pressure readings reaching as high as 180/120 mm Hg. Episodes lasted 1 to 3 days with fluctuating symptoms, occurring every 4 to 15 days. Medical examinations during episodes revealed bilaterally dilated pupils responsive to light, muscle strength of grade 4 with normal tone in affected limbs, and suboptimal baseline EEG rhythms with slow waves and poor symmetry. Both sides had bilateral isolated sharp waves, with the left side showing more prominence. Increased theta waves were noted in the frontal region during wakefulness (Fig. 1). Whole

exome sequencing confirmed a heterozygous p.Leu757Pro variant in exon17 of the ATP1A3 gene, a spontaneous occurrence not carried by either parent. Treatment with 10 mg of funarizine twice daily effectively prevented hemiplegic episodes when combined with 25 mg of topiramate twice daily.

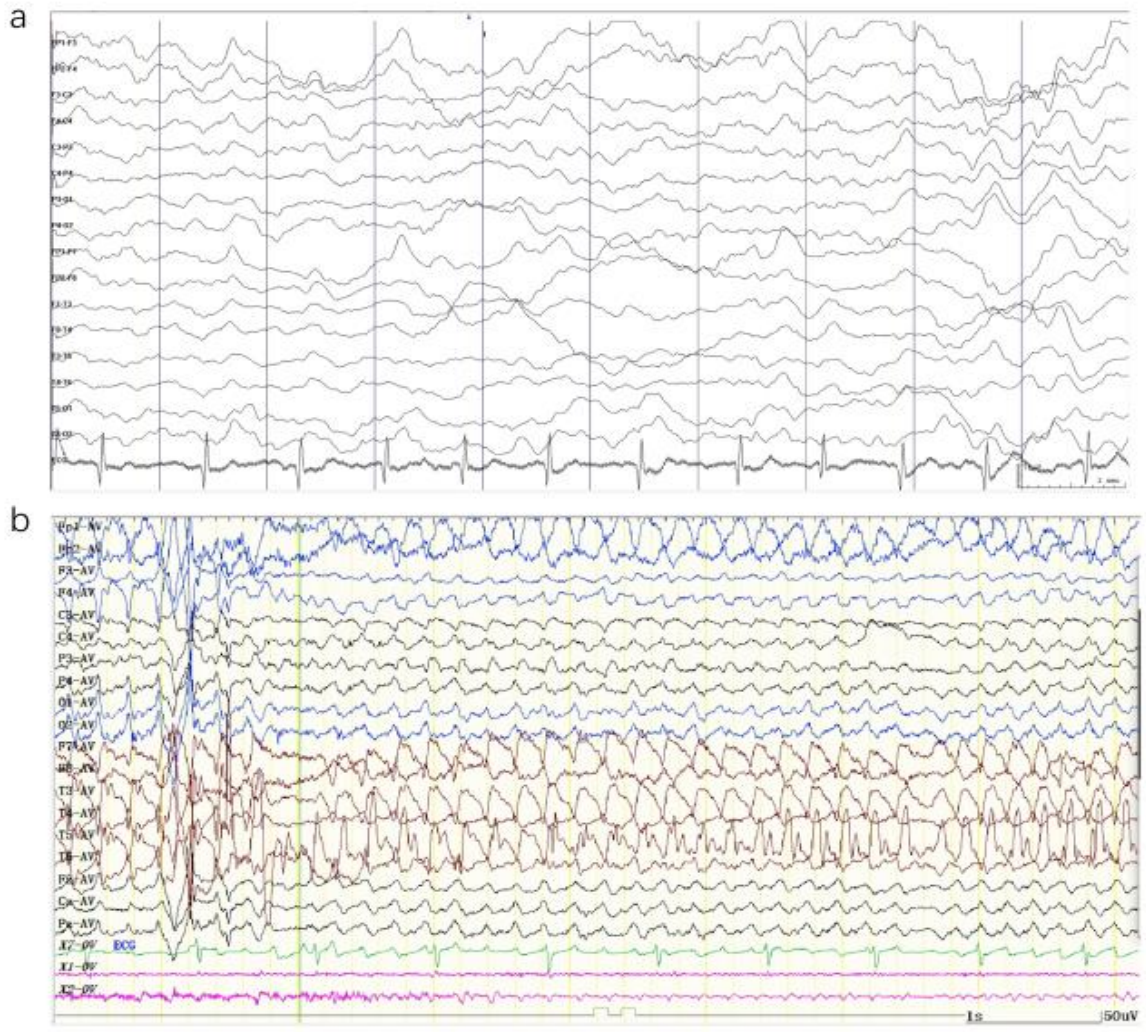

Figure 1. Patient records from their electroencephalogram (EEG). A) Fundamental rhythm with slow waves and poor symmetry was seen in the interictal EEG during the hemiplegic assault. A few isolated, sharp waves were also seen in each region of the brain, with the left side showing a larger prominence than the right. B) In the course of a hemiplegic episode assault. The frontal areas of both hemispheres exhibit an increase in theta waves during awake in borderline adolescents, but no aberrant discharge of visual events was seen.

DISCUSSION

The ATP1A3 gene was essential for sodium conjugation, regulating osmotic balance of various molecules, and controlling nerve and muscle excitability, potentially elucidating the etiology of AHC symptoms.[3] In this study, a case of an AHC girl initially misdiagnosed with hysteria, but exhibiting paroxysmal limb weakness and speech impairment. The paroxysmal symptoms in this case pose the most intriguing and challenging aspect of the diagnostic process. When investigating the underlying cause of paroxysmal muscle weakness, the diagnostic spectrum

narrows, focusing on potential etiologies within the cerebral cortex. These may include seizures, migraine, transient ischemic attacks (TIAs), paroxysmal dyskinesias, and channelopathies. Epilepsy becomes the primary diagnostic consideration due to the patient's paroxysmal, repetitive, and stereotypical symptoms. Frontal lobe epilepsy (FLE) was particularly noteworthy as it can account for the symptoms and their duration, resembling Todd's paralysis or non-convulsive status epilepticus (NCSE).[4]

CONCLUSION

Diagnosing AHC clinically presented challenges due to its complex manifestations and genetic variability among affected individuals. However, attaining a conclusive diagnosis was possible with thorough history-taking, detailed examination, and adherence to rigorous diagnostic protocols. Essential genetic testing played a pivotal role in uncovering the underlying cause, guiding clinical management, and enabling genetic counseling.

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