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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:

- **Impact of modified Atkins diet on stress biomarkers in adult patients with drug-resistant epilepsy**
- **Assessment of Social Cognitive Function in Idiopathic Generalized Epilepsies and Nonlesional Temporal Lobe Epilepsy**
- **Identification of Epileptogenic Brain Pathologies Through Interictal High-Frequency Oscillations, Spikes, and Connectivity Profiles**
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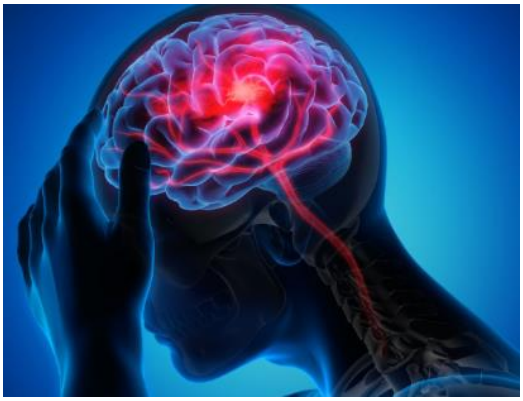
Impact of modified Atkins diet on stress biomarkers in adult patients with drug-resistant epilepsy

INTRODUCTION

Drug-resistant epilepsy (DRE) is a global health issue, proving challenging to manage even with numerous antiepileptic drugs (AED) available.[1] The Modified Atkins Diet (MAD) is used alongside medication for drug-resistant epilepsy, mostly in children. Limited evidence exists for DRE in adults.[2] Concerns have arisen regarding adherence to the diet, particularly among adult patients. Following the diet involves a substantial commitment, including meticulous nutritional calculations and meal preparation, which can be challenging. Additionally, the strict dietary regimen may induce mental stress, a known seizure trigger for many epilepsy patients.[1] So, this study aimed to assess the effects of a 12-week MAD on stress biomarkers in adult patients with drug-resistant epilepsy.



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Free cortisol index(FCI) considerably lowered after 12 weeks on modified Atkins diet (MAD). The decline in FCI could be a result of decreased stress, but it could also be a result of increased cortisol-binding globulin (CBG).

METHODS

This prospective study was conducted among 49 adult patients with drug-resistant epilepsy. These individuals were placed on MAD with specific dietary parameters of 5% carbohydrates, 70% fat, and 25% protein. Inclusion criteria were age over 16 years, prior use of at least three anti-seizure medications, a body mass index greater than 18.5 kg/m², and a history of at least three measurable seizures per month. Adherence to the MAD was confirmed through ketosis measurements in urine and blood. Patients recorded urine ketosis at home twice daily, and blood ketosis was assessed during hospital stays after 4 and 12 weeks. Reference data were collected from a group of patients who had not started the MAD, following a typical Norwegian diet. Blood samples were collected at baseline and after 3 months for both the MAD and reference groups. Stress biomarkers, including cortisol and cortisol-binding globulin (CBG), were measured and analyzed in serum. Additionally, markers for epinephrine, norepinephrine, and dopamine were assessed. The study examined changes based on gender and anti-seizure medications and explored correlations between these stress biomarkers and seizure frequency, weight loss, and thyroid function using linear regression analysis.

RESULTS

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The reference group had a higher number of patients with intellectual disability compared to the MAD group. In the diet group, there was a significant increase in cortisol-binding globulin (CBG) levels and a decrease in the free cortisol index (FCI). However, there were no significant changes observed in cortisol, metanephrine, or normetanephrine levels. Furthermore, no significant association was found between the difference in FCI and thyroid-stimulating hormone (TSH) levels. In the reference group, there were no significant changes in any of the stress biomarkers. Linear regression analysis revealed no significant associations between FCI, metanephrine, or normetanephrine levels and seizure frequency at baseline or after 12 weeks on the diet. It's worth noting that all patients were using anti-seizure medications (ASMs), often in combination. Some patients used both enzyme-inducing ASMs (EIASMs) and non-enzyme-inducing ASMs (NEIASMs), but this didn't result in significant differences between the groups (Table 1). At the beginning of the study, the mean body weight for the patients using the MAD was 79.0 kg (with a range from 51.6 to 138.8 kg). After 12 weeks on the MAD, there was a significant reduction in weight to an average of 74.6 kg (ranging from 46.7 to 126.3 kg). However, no significant association was observed between weight loss and FCI or weight loss and CBG.

Table 1: Mean stress biomarker values at baseline and 12 weeks on MAD, divided by the kind of ASM being used (enzyme-inducing ASMs (EIASMs) and nonenzyme-inducing ASMs (NEIASMs)).

MEAN	Baseline	12weeks	% change	P-value
Cortisol (ref ≥16 years 130–600nmol/L)				
EIASMs (n=11) Mean (95% CI)	415.1 (384.4–445.8)	504.6 (408.8–600.4)	21.6	0.06
NEIASMs (n=38) Mean (95% CI)	438.1 (400.2–475.9)	398.9 (359.2–438.6)	−8.9	0.08
CBG (ref ≥18 years 750–1600nmol/L)				
EIASMs (n=11) Mean (95% CI)	1269.0 (1135.4–1402.6)	1557.5 (1385.3–1729.6)	22.7	<0.01
NEIASMs (n=38) Mean (95% CI)	1085.1 (1034.4–1135.8)	1190.0 (1143.6–1236.5)	9.7	<0.001
FCI (ref <0,54)				
EIASMs (n=11) Mean (95% CI)	0.33 (0.30–0.37)	0.33 (0.27–0.38)	0	0.7
NEIASMs (n=38) Mean (95% CI)	0.41 (0.37–0.44)	0.34 (0.30–0.37)	−17.0	<0.01
Metanephrine (ref <0.34 nmol/L)				
EIASMs (n=11) Mean (95% CI)	0.16 (0.12–0.20)	0.18 (0.13–0.22)	12.5	0.2
NEIASMs (n=37) Mean (95% CI)	0.19 (0.16–0.22)	0.18 (0.15–0.20)	−5.3	0.2
Normetanephrine (ref<1.2 nmol/L)				
EIASMs (n=11) Mean (95% CI)	0.48 (0.29–0.68)	0.43 (0.32–0.54)	−10.5	0.8
NEIASMs (n=37) Mean (95% CI)	0.52 (0.44–0.60)	0.49 (0.41–0.56)	−5.8	0.3
Metoksythyramine (ref ≥3 år<0.11nmol/L)				
EIASMs (n=11) Mean (95% CI)	<0.08	<0.08	0	
NEIASMs (n=37) Mean (95% CI)	<0.08	<0.08	0	

DISCUSSION

This study involving 49 drug-resistant epilepsy patients treated with MAD for 12 weeks, significant changes were observed in stress biomarkers. There was a noteworthy decrease in FCI, which is likely attributed to the notable increase in CBG levels. Importantly, the total cortisol levels remained unchanged throughout the study period.[2] FCI is recognized as an

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indicator of active cortisol effects in humans and is associated with stress. An elevation in FCI is often seen as a stress signal. Furthermore, cortisol is known to raise brain excitability, and there's a documented link between increased cortisol levels and the occurrence of seizures.[3] The decrease in FCI and the increase in CBG could potentially be attributed to reduced insulin resistance after 12 weeks on MAD. This notion is supported by the previously observed reduction in body weight.[4] However, Weight loss showed no significant correlations with CBG or FCI.

CONCLUSION

The findings showed, a significant decrease in the free cortisol index (FCI) after 12 weeks of MAD, which was not seen in the reference patient group. This reduction could be attributed to metabolic changes induced by the diet, potentially resulting in elevated cortisol-binding globulin (CBG) levels over the 12-week treatment period. However, it remains unclear whether this signifies a reduction in stress or is simply indicative of metabolic alterations in these patients.

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Assessment of Social Cognitive Function in Idiopathic Generalized Epilepsies and Nonlesional Temporal Lobe Epilepsy

INTRODUCTION

Social cognition(SC), a higher-level cognitive domain, encompasses the ability to recognize and understand interpersonal relationships. It plays a crucial role in guiding social behavior.[1] It is the process of perceiving and understanding the thoughts, emotions, and behaviors of others to respond appropriately. It encompasses various aspects like theory of mind, emotion recognition, empathy, prosody perception, and body language interpretation. Deficiencies in

Pathophysiological changes, potentially induced by seizures, may also play a significant role in the development of Social cognition deficits.

social cognition are seen in various neurological and psychiatric disorders. While research on social cognition in epilepsy is still emerging, studies have shown impairments in emotion recognition and theory of mind in people with temporal lobe epilepsy (TLE) and extratemporal lobe epilepsy (extra-TLE), impacting their quality of life.[2] So, this study aimed to determine the extent of social cognition impairments in both generalized and focal epilepsies without apparent brain lesions. It also sought to investigate the connection between seizures and these impairments.

METHODS

This was an observational cross-sectional study, involving 48 adults with either idiopathic generalized epilepsy (IGE) or temporal lobe epilepsy without brain lesions (cryptoTLE), alongside 24 healthy controls. Detailed medical and neurological examinations were conducted for all patients to establish their diagnoses based on criteria from the International League Against Epilepsy (ILAE), considering seizure symptoms, EEG findings, and MRI results. Data was collected during neurological visits, encompassing information such as age at seizure onset, duration of epilepsy, seizure characteristics, demographic details, and the presence of comorbid conditions. To be eligible, participants had to be at least 18 years old, have completed at least 5 years of schooling, possess average abstract reasoning skills (Raven's Colored Progressive Matrices score greater than 17.5), demonstrate verbal comprehension (Token Test score greater than 26.25), and show no signs of autism spectrum disorders in their clinical history. Healthy controls were selected from hospital staff and visitors, free from neurological and psychiatric issues, and matched to the patients in terms of age (within ±5 years), years of schooling (within ±3 years), and gender distribution. Both patients and controls underwent a comprehensive neuropsychological assessment, which included tests like the Faux Pas Tests (FPT), Social Situation Test (SST), Moral/Conventional Distinction Test (MCDT), and Empathy Questionnaire (EQ). These evaluations focused on aspects of social cognition, including theory of mind (ToM), recognition of social behaviors, understanding of moral and conventional rules, and empathy. The clinical work-up also covered information on age at seizure onset, epilepsy duration, seizure characteristics, demographics, and comorbid conditions. To assess individual performance, z-scores from the FPT, RBSS, SMCR, and EQ were compared with percentiles derived from the controls' z-scores.

RESULTS

Based on normative data, a significant portion of patients demonstrated average performance on the attentive matrices (AM) (93.8%) and Corsi block span (CBS) (81.3%), indicating good attention and working memory. However, a notable percentage of patients exhibited impairments on the trail making test A (TMTA) (18.7%) and trail making test B (TMTB) (14.6%). The SC tests were completed by all of the patients and controls. The mean test results are summarised in Table 1. Conversely, patients displayed more frequent deficits in memory, lexical-semantic retrieval, and constructive praxis, with varying percentages ranging from 8.5% to 37.5%. Both IGE and cryptoTLE patients showed similar frequencies of equivalent scores. Compared to controls, individuals with cryptoTLE or IGE achieved comparable scores on questions without faux pas (no-FP exclusion), demonstrating their ability to distinguish real

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from non-existent faux pas. However, these patients had significant difficulties in understanding real faux pas on the FPT and comprehending others' intentions and mental states. In the Social Situation Test (SST), a significant group influence was observed, particularly in recognizing normative behaviors, with minor differences in recognizing violations and appreciating the severity of violations. Compared to controls, cryptoTLE individuals had deficits in recognizing normative behaviors and a slight tendency to recognize violations and appreciate their severity. IGE patients showed mild impairments in recognizing normative behaviors. Furthermore, the patients with IGE performed better than those with cryptoTLE in recognizing violations and appreciating their severity. In the Empathy Questionnaire (EQ) and Moral/Conventional Distinction Test (MCDT), the controls and individuals with IGE or cryptoTLE displayed similar scores. The percentages of patients and controls with varying levels of performance in recognizing moral and conventional rule violations were similar. In the EQ, performance levels were also comparable. In cryptoTLE individuals, comprehension scores correlated with seizure frequency and age, while in IGE patients, recognition of moral rule transgression severity correlated with age, and recognition of normative behavior correlated with years of schooling. Analyses of cryptoTLE and healthy controls (HC), as well as IGE and HC, demonstrated consistent patterns. In both cases, specific comprehension scores had significant effects, allowing for the correct classification of patients and controls. No variables had predictive value in the analysis of cryptoTLE and IGE.

Table 1- Scores for social cognition in healthy controls, those with cryptogenic temporal lobe epilepsy, and people with idiopathic generalised epilepsies.

	HC	Patients subgroups		All participants
		IGE	C-TLE	
Faux Pas Test				
Exclusion of nonfaux pas	9.62 ± 1.10	9.45 ± 1.82	9.54 ± 1.35	9.54 ± 1.43
Recognition on faux pas	9.46 ± 0.72	8.12 ± 1.92	7.87 ± 2.38	8.18 ± 2.00
First question	9.5±0.59	7.58 ± 2.10	7.37 ± 2.63	7.84 ± 2.20
Second question	9.12 ± 1.07	6.67 ± 1.93	6.46 ± 2.60	7.17 ± 2.28
Third question	8.67 ± 1.43	6.02 ± 2.10	4.75 ± 2.54	6.20 ± 2.51
Third question	9.00 ± 1.02	6.75 ± 1.96	6.29 ± 2.44	7.06 ± 2.22
Total comprehension	36.29 ± 3.57	27.16 ± 6.88	24.79 ± 8.77	29.41 ± 8.32
Social Situation Test				
Normative behaviors	14.08 ± 1.14	13.08 ± 1.77	11.96 ± 3.73	13.06 ± 2.57
Violations	23.20 ± 2.67	23.00 ± 2.32	21.29 ± 3.34	22.57 ± 2.92
Severity of violations	52.33 ± 10.36	50.96 ± 9.71	45.37 ± 10.53	49.90 ± 10.84
Moral/Conventional Distinction Test				
Recognition of moral rules	6±0	5.95 ± 0.20	5.96 ± 0.20	5.97 ± 0.17
Recognition of the severity of disregard of moral rules	52.50 ± 6.76	50.96 ± 10.64	53.83 ± 6.49	52.26 ± 8.19
Recognition of moral rules in the absence of expressed norms	11.29 ± 1.65	11.17 ± 1.93	11.58 ± 1.28	11.24 ± 1.71
Recognition of conventional rules	5.79 ± 0.41	5.66 ± 0.56	5.75 ± 0.53	5.70 ± 0.52
Recognition of the severity of disregard of conventional rules	40.37 ± 10.34	34.42 ± 15.17	41.21 ± 12.28	39.10 ± 12.94
Recognition of conventional rules in the absence of expressed norms	9.91 ± 2.68	9.00 ± 3.59	10.10 ± 2.72	9.49 ± 3.14
Empathy Questionnaire	46.04 ± 12.77	47 04 ± 10.45	47.37 ± 8.94	46.82 ± 10.70

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DISCUSSION

The current study showed that temporal lobe epilepsy without brain lesions (cryptoTLE) is associated with a higher degree of deficits in social cognition (SC) domains when compared to idiopathic generalized epilepsy (IGE), although impaired theory of mind (ToM) is a common characteristic in both conditions.[1] Ziaei M study showed that individuals with frontal or temporal lobe epilepsy face challenges in various aspects of social cognition compared to non-clinical controls. Notably, the impact was more pronounced in theory of mind than in emotion recognition for those in the temporal lobe epilepsy group.[3]

CONCLUSION

CryptoTLE is associated with a higher degree of deficits in social cognition (SC) domains when compared to IGE, although impaired theory of mind (ToM) is a common characteristic in both conditions. While it is established that brain lesions in significant areas can contribute to SC impairment, this study indicates that pathophysiological changes, potentially induced by seizures, may also play a significant role in the development of SC deficits.

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Identification of Epileptogenic Brain Pathologies Through Interictal High-Frequency Oscillations, Spikes, and Connectivity Profiles

INTRODUCTION

Predictive model offers excellent potential to determine the nature of the lesion, which could be valuable in guiding epilepsy surgery and patient counseling.

Modern neuroimaging has significantly enhanced our ability to detect potential epileptogenic lesions. However, it's important to note that not all visible lesions are necessarily epileptogenic, and standard MRI scans may not always identify all epileptogenic lesions.[1] High-frequency oscillations (HFOs) offer promise as a biomarker for pinpointing epileptogenic brain areas during neurosurgery. However, solely relying on HFO occurrence rates makes it challenging to distinguish between physiological and pathological HFOs, potentially reducing their specificity in identifying

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epileptic regions. Recent research reveals a substantial spatiotemporal connection between HFOs and interictal epileptiform spikes, showing a stronger link to epileptogenic regions compared to spikes or HFOs on their own. This suggests an improved biomarker for epileptogenicity.[2] This study assessed spikes and high-frequency oscillations (HFOs) in patients with different pathological substrates using stereo-electroencephalography (SEEG).

METHODS

In a retrospective study, 33 patients with drug-resistant epilepsy who had undergone Stereo-electroencephalography (SEEG) and subsequent surgery were analyzed. The study focused on specific histopathological findings, including focal cortical dysplasia (FCD), hippocampal sclerosis (HS), neoplasms (NG), and non-specific tissue (NT), among patients who achieved seizure free (Engel I) one-year post-surgery. Resting-state SEEG recordings were examined to identify differences in electrophysiological patterns such as spikes, high-frequency oscillations (HFOs), and functional connectivity across these histopathological groups. Inclusion criteria involved surgery outcomes categorized as Engel I at Year 1 post-surgery, availability of seizure-free SEEG recordings during a resting state, precise electrode placement data, and histopathological confirmation of FCD, HS, NG, or NT. Depth electrodes were implanted, and the study analyzed seizure-free postoperative outcomes for 15 cases of FCD, 8 cases of HS, 6 cases of NT, and 4 cases of NG. Interictal spikes and HFOs were automatically detected within channels overlapping with the seizure onset zone. Functional connectivity measures were computed for adjacent electrode pairs, and differences between pathologies were evaluated by using Wilcoxon signed-rank tests with Bonferroni corrections and Cliff delta as an effect size measure.

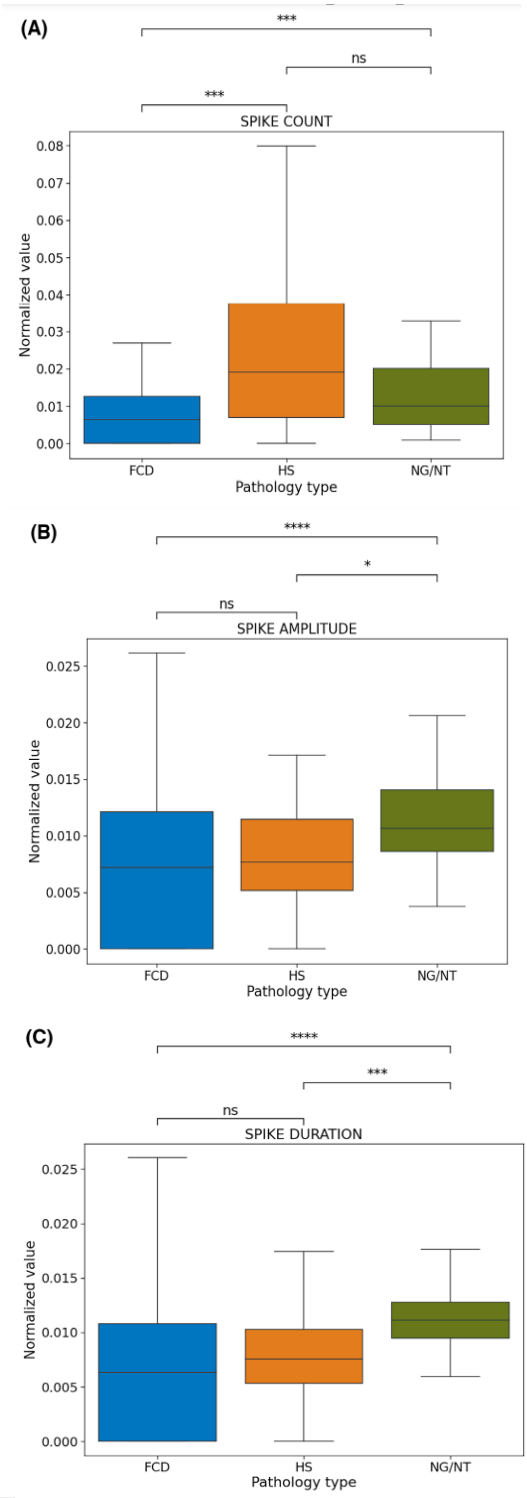

Figure 1. Variations in interictal spike attributes, including count (A), amplitude (B), and duration (C), were compared among focal cortical dysplasia (FCD), hippocampal sclerosis (HS) and nonspecific gliosis/normal tissue (NG/NT).

RESULTS

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In a study of 33 patients who underwent resective brain surgery for epilepsy and achieved Engel I postoperative outcomes, histopathological findings included focal cortical dysplasia (FCD), hippocampal sclerosis (HS), neoplasms (NG), and non-specific tissue (NT). Higher spike rates were observed in HS, followed by NG/NT and FCD (Figure 1), with significant differences between HS and FCD and between HS and NG/NT. The duration and amplitude of spikes were highest in NG/NT, followed by HS and FCD, with significant differences between NG/NT and HS FCD. Ripple rates were higher in both NG/NT and HS compared to FCD. Regarding functional connectivity, higher connectivity was observed in FCD compared to HS in the spike band. In the ripple band, Relative entropy (REN)values were higher in HS compared to FCD, and phase consistency was higher in NG/NT compared to HS. Using predictive models, accuracy and F-scores varied, with better performance in the group with conclusive MRI results compared to the inconclusive MRI group.

DISCUSSION

The current study identified that there were significant differences between pathologies, particularly in HFO rates, spikes, and their characteristics, with the highest values observed in hippocampal sclerosis (HS). Functional connectivity measures showed the lowest values in HS.[1] In adults with drug-resistant focal epilepsy need surgery, the most frequent diagnosis was hippocampal sclerosis (36.4%) while in children, focal cortical dysplasia was the top diagnosis. Overall, common categories included tumors (23.6%, mainly ganglioglioma) and malformations of cortical development (19.8%).[3] Lee DA et al. results indicate that patients with temporal lobe epilepsy who have hippocampal sclerosis (HS) tend to have a less connected functional brain network compared to those without HS.[4]

CONCLUSION

Significant differences were identified between pathologies, particularly in high-frequency oscillations (HFO) rates, spikes, and their characteristics, with the highest values observed in hippocampal sclerosis (HS). Functional connectivity measures showed the lowest values in HS. The study established a predictive model based on electrophysiological profiles to determine the nature of the lesion, which could be valuable in guiding epilepsy surgery and patient counseling. It also highlighted varying levels of epileptogenicity among different pathologies, suggesting distinct epileptogenic mechanisms within these tissues.

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Case Report on Surgical Management of Epilepsy in a Patient with Bilateral Periventricular Nodular Heterotopia

INTRODUCTION

Surgical intervention can be an effective approach for seizure control in specific cases of Bilateral periventricular nodular heterotopia.

Periventricular nodular heterotopia (PNH) is a brain malformation caused by disrupted neuronal migration. It features clusters of abnormal tissue shaped like nodules, separated by myelin layers. These nodules can be inside or near the ventricles, varying in size, shape and position .[1] PNH typically lead to medically-intractable epilepsy. The exact contribution of PNHs to seizure generation and best treatment remain topics of debate. Surgical interventions for PNH-related epilepsy have shown diverse outcomes .[2] This article outlines a clinical case of a patient with bilateral periventricular heterotopia.

CASE PRESENTATION

This case study describes a 17-year-old patient who began experiencing seizures at the age of 13. Initially, the seizures involved brief loss of consciousness and freezing with maintained posture. At the age of 15, the patient had their first generalized clonic-tonic seizure during sleep, leading to hospitalization. An electroencephalogram (EEG) revealed sharp-slow wave complexes in the left occipital region, and a brain MRI showed heterotopia of the gray matter of the left hemisphere and nodules of the lateral ventricles. Treatment began with valproic acid 500 mg twice daily and later included topiramate, but the seizures persisted. Carbamazepine was added, which helped reduce seizure frequency, allowing the discontinuation of topiramate. The patient's seizures included stopping activity, head-turning to the right, hand automatisms, and swallowing movements, lasting up to 2 minutes once every 10-14 days. Due to ongoing seizures and structural brain abnormalities, surgical treatment was recommended. In preparation, the patient continued valproic acid 500 mg and carbamazepine 400 mg twice daily. Extensive brain imaging revealed bilateral subependymal nodular heterotopy, predominantly on the left side at the level of the temporal and occipital horns of the lateral ventricles (Figure 1), as well as a subcortical heterotopy in the right cerebellar hemisphere (Figure 2). Prolonged video-EEG monitoring

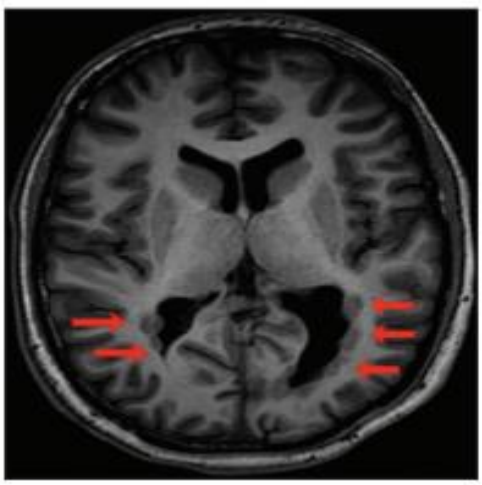

Figure 1. Epilepsy 3T magnetic resonance imaging of the brain showing bilateral subependymal nodular heterotopia at the level of temporal and occipital horns of the lateral ventricles.

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showed epileptiform activity during wakefulness and sleep, primarily in the left temporal and parietal regions. During observation, a focal motor seizure was recorded, starting during sleep and progressing to orofacial and faciobrachial clonic movements. Invasive video-EEG with depth electrodes was then used, recording numerous focal motor seizures, some evolving into bilateral tonic-clonic seizures. Surgical evaluation revealed an extensive epileptogenic zone in the left temporal, parietal, and occipital lobes, involving heterotopic and neocortical regions. Functional MRI indicated right-hemisphere dominance for speech. The patient underwent posterior quadrant disconnection (PQD) surgery to isolate the epileptogenic zone of the left temporal, parietal, and occipital lobes. Postoperatively, the patient displayed mild speech impairments of the amnestic aphasia type and general mental status fluctuations, including reduced attention and right-sided homonymous hemianopsia. Six months' post-surgery, the patient remained seizure-free while still taking anticonvulsants.

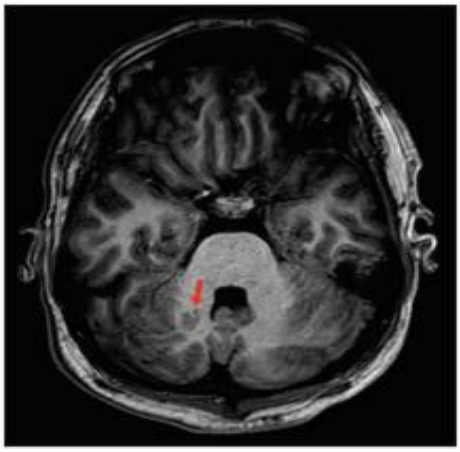

Figure 2. Epilepsy 3T magnetic resonance imaging showing focal subcortical heterotopia of the right cerebellar hemisphere.

DISCUSSION

In the current study, an electroencephalogram (EEG) revealed abnormal activity in the left occipital region, and a brain MRI showed gray matter heterotopia and ventricular nodules in the left hemisphere. Although the heterotopias are typically found on both sides and cover a significant area, surgical intervention in specific cases can prove to be an effective approach for seizure control.[1] Brain MRI is the key diagnostic tool for detecting periventricular gray matter accumulations.[3] When medications fail to control epileptic seizures, surgery becomes a necessary option. One surgical intervention choice involves stereotactic destruction of small heterotopic nodes.[4] Deeply located epileptogenic PNHs are well-suited for stereotactic ablative techniques, allowing the simultaneous ablation of multiple areas and achieving relatively positive seizure outcomes.[5]

CONCLUSION

Bilateral periventricular nodular heterotopia (PNH) is an uncommon genetic disorder often associated with drug-resistant epileptic seizures. Although the heterotopias are typically found on both sides and cover a significant area, surgical intervention in specific cases can prove to be an effective approach for seizure control.

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