EPILEPSY

Vol.3|Issue 18|2024

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 Sleep Disorders in Epilepsy Patients**
- **Utility and efficacy of dynamic contrast-enhanced magnetic resonance imaging in identifying Blood–Brain Barrier Dysfunction in Epilepsy patients**
- **Efficacy of surgical treatment in children with drug-refractory infantile epileptic spasms syndrome**
- **Case Report on developmental epileptic encephalopathy with spike-wave activation in sleep treated with iECoG-guided surgical resection**

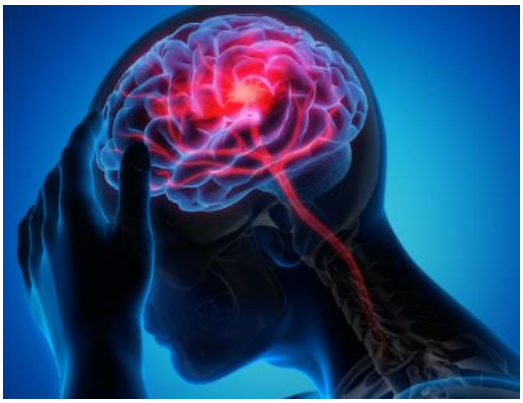
Should you require any specific article or medical information, please feel free to contact us at medicalservices@microlabs.in
Looking forward to your valuable feedback

Best Regards,
Medical Team, Micro Labs Limited

EPILEPSY
Vol.3|Issue 18|2024

Assessment of Sleep Disorders in Epilepsy Patients

INTRODUCTION



EPILEPSY

The quality of life of patients may be considerably impacted by the existence of psychiatric comorbidities, which have a complex interaction with sleep disorders and epilepsy.

Insomnia is frequently observed in individuals with epilepsy, with a prevalence reaching up to 50%. Sleep disturbances are about twice as prevalent in people with epilepsy compared to healthy individuals, with nearly one-third of epilepsy patients reporting such issues. Increased cortical excitability during non-rapid eye movement (NREM) stage 2 sleep is believed to contribute to the occurrence of seizures in this stage, while desynchronization during rapid eye movement (REM) sleep is considered to have an antiepileptic effect. Sleep deprivation is a known trigger for epileptic seizures, which can also occur during sleep. Around 20% of epileptic seizures take place during sleep, with this rate rising to 60% in cases of frontal lobe epilepsy.[1] Seizure frequency and severity, along with the side effects of antiepileptic drugs (AEDs), can alter sleep patterns and reduce sleep quality.[2] The bidirectional relationship between epilepsy and sleep can contribute to co-occurring psychiatric conditions, such as depression and anxiety, which are more prevalent in people with epilepsy.[3] Identifying and managing sleep disorders, depression, and anxiety in individuals with epilepsy is crucial. Proper treatment of these coexisting conditions can greatly enhance quality of life and help in better controlling epileptic seizures.

METHODS

A case-control study was carried out, involving patients aged 18 years or older who had been diagnosed with epilepsy, followed up in an epilepsy outpatient clinic for at least two years, and consistently attended their follow-up appointments. The study included 100 epilepsy patients without psychiatric or systemic conditions that could cause sleep disturbances, along with 50 healthy controls matched to them. The following patients were excluded: those with severe mental retardation; those with primary neurological diseases, such as tumors, ischemia, demyelinating lesions, prior intracranial operations, or other neurodegenerative diseases causing seizures; patients with known psychiatric disorders and antidepressant use who were being monitored by the psychiatry department; and those who presented with single or provoked seizures. Participants completed various assessments, including the Epworth Sleepiness Scale, STOP-Bang questionnaire for obstructive sleep apnea (OSAS), REM

EPILEPSY
Vol.3|Issue 18|2024

Behavior Disorder-Hong Kong Questionnaire, Swiss Narcolepsy Scale, Restless Legs Syndrome (RLS) Diagnostic Form, Beck Depression Inventory, and Beck Anxiety Inventory.

RESULTS

The prevalence of sleep disorders in the epilepsy and control groups were summarized in Table 1. Increased daytime sleepiness, assessed using the Epworth Sleepiness Scale, was observed in 30% of epilepsy patients, with half of these individuals experiencing seizures within the past 6 months. The risk of OSAS was notably higher in epilepsy patients, particularly in those with left temporal lobe epilepsy, males, and older individuals (p=0.02). RLS was more prevalent among epilepsy patients, with a higher risk seen in females (p=0.04). Insomnia affected 33% of the epilepsy group, but no significant association was found between insomnia and factors such as age, gender, or the number of anti-seizure medications. Moderate to severe depression was present in 45% of epilepsy patients, significantly exceeding the rate in the general population (p=0.03). Additionally, anxiety was identified in 50% of patients (p<0.01).

Table 1. Sleep disorders in the epilepsy and control groups

	Epilepsy patients (n=100)	Control (n=50)	p value
ESS	30	7	p<0.01
Insomnia	33	15	p=0.7
STOP-Bang Survey			
High risk	15	4	p<0.01
Medium risk	4	4	p<0.01
Low risk	81	44	p<0.01
Restless Leg Diagnosis Form	20	5	p<0.01
RBDQ-HK	12	1	p=0.01
Swiss Narcolepsy Scale	15	1	p=0.01
Beck Depression Scale			
Minimal	29	19	p>0.01
Mild	31	8	p<0.01
Moderate	14	-	p<0.01
Beck Anxiety Scale			
Minimal	20	15	p>0.01
Mild	21	5	p<0.01
Moderate	29	3	p<0.01

ESS: Epworth Sleepiness Scale, RBDQ-HK: REM Behavioral Disorder-Hong Kong Questionnaire, REM Sleep Behavior Disorder Questionnaire

DISCUSSION

In epilepsy patients, complaints of increased daytime sleepiness are common and are often subjective. Reports indicated that the prevalence of increased daytime sleepiness in this population ranges from 10% to 47.5%.[4] In the current study, epilepsy patients with a high risk of OSAS exhibited significantly higher anxiety scores (p=0.02). This aligns with existing study where one study found that anxiety related to seizures was more pronounced in individuals with both epilepsy and OSAS, potentially leading to elevated Beck Anxiety Scale scores.[5]

CONCLUSION

EPILEPSY
Vol.3|Issue 18|2024

The relationship between sleep disorders, psychiatric comorbidities, and epilepsy is intricate, with these conditions often having a profound impact on patients' quality of life. To better comprehend this complex interaction, further comparative studies involving more homogenous patient groups are essential.

REFERENCE

1. Bostan S, Algın Dİ. Evaluation of Sleep Disorders in Patients with Epilepsy: A Case-control Study. Evaluation. 2024 Dec;30(4):120-6.
2. Lehner J, Frueh JS, Datta AN. Sleep quality and architecture in Idiopathic generalized epilepsy: A systematic review and meta-analysis. Sleep Med Rev. 2022 Oct;65:101689.
3. Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. Nat Sci Sleep. 2017 May 19;9:151-161.
4. Giorelli AS et al. Excessive daytime sleepiness in patients with epilepsy: a subjective evaluation. Epilepsy Behav. 2011 Aug;21(4):449-52.
5. Brandt C, Mula M. Anxiety disorders in people with epilepsy. Epilepsy Behav. 2016 Jun;59:87-91.

Utility and efficacy of dynamic contrast-enhanced magnetic resonance imaging in identifying Blood–Brain Barrier Dysfunction in Epilepsy patients

INTRODUCTION

DCE-MRI can be used as a valuable tool for pre-operative evaluations for detecting and potentially localizing the seizure-onset zone.

Blood-brain barrier dysfunction (BBBD) has been detected in individuals with several neurological conditions, including epilepsy.[1] The effect of BBBD on neural activity remains unclear, but research in rodents has demonstrated that BBB disruption or the exposure of brain cells to serum proteins, such as albumin, triggers the activation of the pro-inflammatory transforming growth factor β (TGFβ) signaling pathway in astrocytes.[2] These cascading effects ultimately result in dysfunction of the local neural network, leading to spontaneous seizures, and are thought to contribute to resistance to antiepileptic drugs. In recent years, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has become the preferred method for assessing the extent and location of BBBD in humans. A recent advancement in this field is the implementation of the Veksler linear model, which enables the detection of slower and more subtle BBB leakage, measured approximately 6–20 minutes after contrast injection. A recent study involving people with epilepsy (PWE) utilized pre- and post-contrast-enhanced MRI to quantify BBBD, suggesting a connection with the suspected seizure-onset zone.[3] The current study aimed to thoroughly evaluate the effectiveness of DCE-MRI in identifying brain areas with BBBD in PWE.

METHODS

EPILEPSY
Vol.3|Issue 18|2024

This multi-center prospective study involved scanning 50 patients with drug-resistant epilepsy (DRE) and 58 healthy control participants from four specialized epilepsy centers worldwide using DCE-MRI. Healthy participants were included if they were aged 18–90 years, had no known history of neurological, neurosurgical, or psychiatric disorders, and had normal kidney function. Epilepsy patients were included if they met the following criteria: (1) age 18–90 years; (2) a clinical diagnosis of epilepsy based on the International League Against Epilepsy (ILAE) 2017 classification; (3) regular laboratory and clinical follow-ups; (4) at least one electroencephalogram (EEG) interpreted by an epileptologist; and (5) classification as DRE, meaning they continued to experience seizures despite adequate treatment with two or more anti-seizure medications. All participants underwent MRI scans using a 3T MRI machine. The presence and extent of BBBD were assessed and compared between the epilepsy patients and the healthy control group.

RESULTS

In the study, PWE showed significantly greater brain volume and a higher number of brain regions with BBBD compared to healthy controls ($p<10^{-7}$). No significant differences in total brain volume with BBBD were found between patients with focal seizures and those with generalized epilepsy, although the affected regions varied. Additionally, there was no difference in overall brain volume with BBBD between epilepsy patients with MRI-visible lesions and those without lesions. BBBD

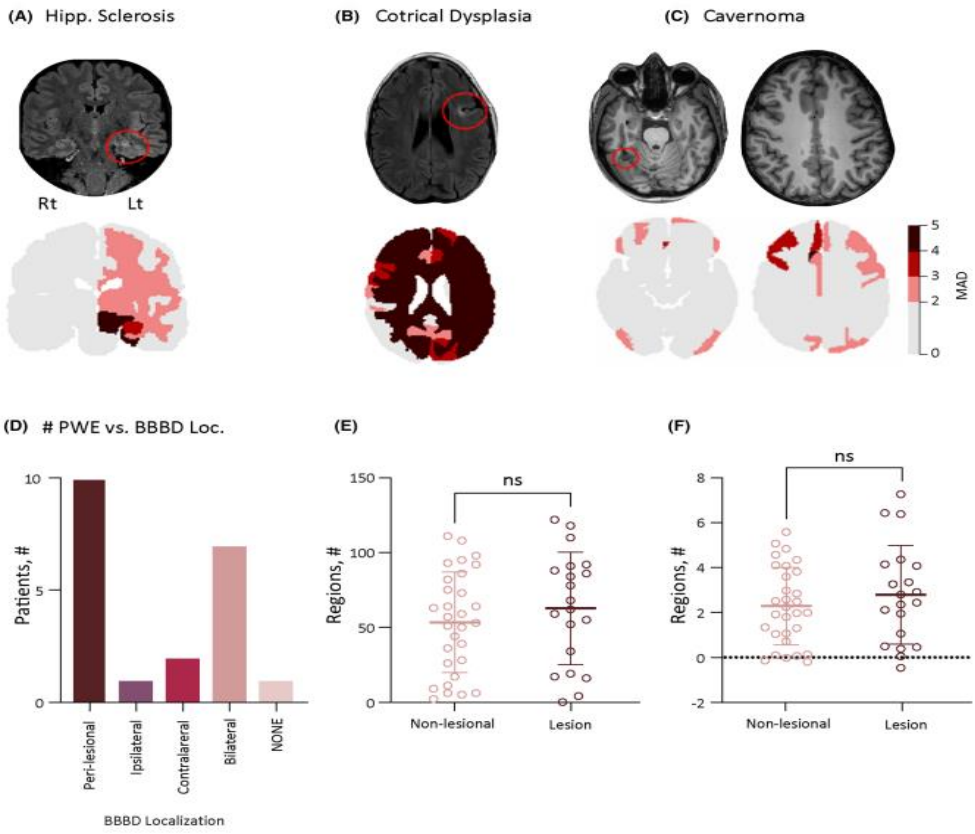


Figure 1. BBBD in individuals with "lesional MRI": (A) A person aged 35 years with left hippocampal sclerosis B) A person aged 33 years with left frontal cortical dysplasia (C) A 20 years old woman with a right occipital cavernoma. Anatomical images of the lesion (red circle) are displayed in the upper row. Regional analysis of BBB leakage is shown in the lower row (D) Region(s) with the highest BBBD with respect to the lesion site (p=0.49) (E) The number of brain areas in individuals with and without MRI-positive lesions that have BBBD (MAD >2) (F) Mean ASD for patients with and without a lesion detected by MRI (p=0.41)

was observed in brain areas thought to be associated with seizure onset in 82% of patients (n=39) and was commonly found in or near the suspected epileptogenic lesion, or within the same hemisphere (n=10) (Figure 1).

DISCUSSION

This study provides evidence of interictal BBBD in patients with DRE. The findings of this study are based on previous imaging research conducted in canine epilepsy models and align with results observed in rodent models.[4] While BBBD has been observed in previous DCE-MRI studies across various neurological conditions, its effects on disease onset and progression are still unclear. Earlier studies shown that patients with transient ischemic attacks or minor strokes, who experience BBB compromise, face an increased risk of recurrent strokes.[5] The study findings validate the effectiveness of DCE-MRI in evaluating BBBD, consistent with previously reported results.[6]

CONCLUSION

The quantitative analysis of the extent and distribution of BBBD in PWE has revealed a high prevalence of compromised BBB integrity. These results support the use of DCE-MRI as a valuable tool for detecting and potentially localizing the seizure-onset zone during pre-surgical evaluations. Larger studies are needed to explore the role of BBB imaging in diagnosing, predicting outcomes, assessing drug responsiveness, and determining surgical success in PWE.

REFERENCE

1. Serlin Y et al. Anatomy and physiology of the blood-brain barrier. Semin Cell Dev Biol. 2015 Feb;38:2-6.
2. Heinemann U et al. Blood-brain barrier dysfunction, TGFβ signaling, and astrocyte dysfunction in epilepsy. Glia. 2012 Aug;60(8):1251-7.
3. Cafri N et al. Imaging blood-brain barrier dysfunction in drug-resistant epilepsy: A multi-center feasibility study. Epilepsia. 2024 Nov 6.39503526.
4. Hanael E et al. Blood-brain barrier dysfunction in canine epileptic seizures detected by dynamic contrast-enhanced magnetic resonance imaging. Epilepsia. 2019 May;60(5):1005-1016.
5. Serlin Y et al. Blood-Brain Barrier Leakage: A New Biomarker in Transient Ischemic Attacks. Stroke. 2019 May;50(5):1266-1269.
6. Reiter JT et al. Evidence for interictal blood-brain barrier dysfunction in people with epilepsy. Epilepsia. 2024 May;65(5):1462-1474.

EPILEPSY
Vol.3|Issue 18|2024

Efficacy of surgical treatment in children with drug-refractory infantile epileptic spasms syndrome

INTRODUCTION

Surgery is a crucial treatment option for patients with drug-resistant IESS caused by structural factors, such as congenital or early acquired cortical lesions.

Infantile epileptic spasms syndrome (IESS) is a developmental epileptic encephalopathy that usually affects children between 3 months and 2 years of age. The incidence of IESS is estimated at 2–5 cases per 10,000 live births, with a slightly higher prevalence in males.[1] This condition is defined by a combination of epileptic spasms (ES), hypsarrhythmia on scalp electroencephalography (EEG), and developmental delay or regression. According to the 2017 classification by the International League Against Epilepsy (ILAE), ES are categorized into focal, generalized, and unknown-onset types.[2] ES with a focal onset in IESS often suggest the presence of focal epileptogenic foci. Infants with ES may also experience focal seizures. These cases are frequently resistant to medication and should be quickly considered for surgical evaluation. Surgical treatment can result in seizure remission and improvements in neurocognitive function; however, there are limited case reports on the effectiveness of surgery and the factors that influence the prognosis of children with epileptic encephalopathy.[3] So, this study was conducted to evaluate the effectiveness of surgical treatment in children with drug-resistant IESS and investigate the factors that impact post-surgical outcomes.

METHODS

In this retrospective study, the clinical data of 30 children (18 males and 12 females) with ES who underwent surgery at the Epilepsy Center of Shenzhen Children's Hospital from June 2018 to June 2020 were analyzed. The inclusion criteria were: (1) a diagnosis of IESS based on the ILAE Classification 2017; (2) meeting the criteria for drug-resistant epilepsy; (3) age at onset between 1 month and 3 years; and (4) regular follow-up for at least one year after epilepsy surgery at Shenzhen Children's Hospital. Post-surgical outcomes were assessed using the Engel Epilepsy Surgery Outcome Scale. Scalp electroencephalography and developmental quotients were measured both before and after surgery. Univariate and exact logistic regression analyses were performed to identify factors influencing postoperative outcomes.

RESULTS

Of the 30 patients who underwent surgical resection, 22 (73.3%) achieved Engel class I–II outcomes. Additionally, motor and cognitive functions improved in 14 patients (46.7%). Development in 12 patients (40%) remained at the same level as before surgery. The median number of antiepileptic drugs used preoperatively was 5.27 (range 2–10), which decreased to 1.90 (range 0–4) at the final follow-up. Factors such as seizure duration, etiology, positive PET-MRI findings, type of surgery, and lesion location were significantly associated with

EPILEPSY
Vol.3|Issue 18|2024

postoperative outcomes (P<0.05). Positive PET/MRI results and lesion location were independently predictive of postoperative endpoints (Table 1 and 2). Permanent motor or language impairments were rare, with only two cases of hydrocephalus and one case of hemiplegia reported.

Table 1. Results of the conditional exact test (α=0.05)

Factor	Test	Statistics	Exact P-value	Mild P-value
Joint	Conditional score	20.5741	<0.0001	<0.0001
	Conditional probability	0.000015	<0.0001	<0.0001
PET-MRI	Conditional score	12.4096	0.0060	0.0030
	Conditional probability	0.00589	0.0060	0.0030
Lesion location	Conditional score	19.0909	0.003	0.0002
	Conditional probability	0.000334	0.003	0.0002
Mild P-value: P-value adjusted for discrete distribution.				

Table 2. Exact parameter and OR estimates (α=0.05)

Factor	Point estimation	OR value	95%CI	P-value
PET-MRI	−3.7186	0.024	(<0.001–0.527)	0.0119
Lesion location	−1.9639*	0.140*	(0.000–0.378)	0.0003
***median-unbiased estimator**				

DISCUSSION

This study examined postoperative outcomes in 30 children with IESS and drug-resistant epilepsy. This study results showed that seizures were successfully controlled in 22 patients (73.3%) following surgery. This outcome aligns with previous study, which reported seizure-free rates ranging from 50% to 70% after surgery for infantile epilepsy.[4] In this study, the length of the disease course was identified as a key factor influencing postoperative outcomes. Among the 13 patients who had surgery within one year of onset, 12 (92.3%) achieved favorable results. A previous report showed a similar trend, with an 87.9% success rate when the time from the first seizure to surgery was less than 36 months, and a decrease to 64.7% when the interval exceeded 50 months.[5]

CONCLUSION

Surgery is a crucial treatment option for patients with drug-resistant IESS caused by structural factors, such as congenital or early acquired cortical lesions. Early preoperative evaluation and identification of the EZ are vital, and a thorough etiological assessment should be performed for all patients with IESS or drug-resistant epilepsy. Careful planning of the extent of resection or disconnection is necessary to prevent seizure recurrence and optimize the brain's potential for plasticity. To ensure surgical safety, an appropriate approach should be chosen to control seizures and improve the prognosis for children with IESS.

REFERENCE

1. Kelley SA, Knupp KG. Infantile Spasms-Have We Made Progress? Curr Neurol Neurosci Rep. 2018 Apr 19;18(5):27.
2. Fisher RS et al. Operational classification of seizure types by the International LeagueAgainst Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):522-530.

EPILEPSY
Vol.3|Issue 18|2024

3. Cao X et al. Surgical outcomes of drug-refractory infantile epileptic spasms syndrome and related prognostic factors: a retrospective study. Acta Epileptologica. 2024 Dec;6(1):36.
4. Kwon HE et al. Surgical treatment of pediatric focal cortical dysplasia: Clinical spectrum and surgical outcome. Neurology. 2016 Aug 30;87(9):945-51.
5. Chipaux M et al. Refractory spasms of focal onset-A potentially curable disease that should lead to rapid surgical evaluation. Seizure. 2017 Oct;51:163-170.

Case Report on developmental epileptic encephalopathy with spike-wave activation in sleep treated with iECoG-guided surgical resection

INTRODUCTION

Although surgical management of DEE-SWAS is not common, in certain cases with a focused onset, surgical intervention can result in the complete remission of EEG abnormalities. The extent of resection in DEE-SWAS may be guided by iECoG.

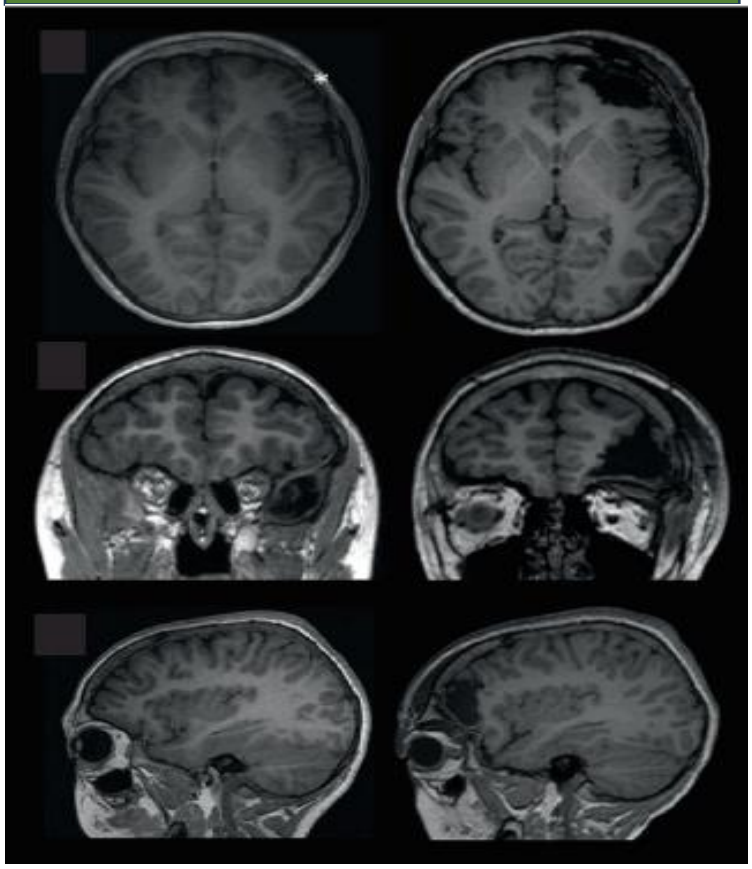
Developmental epileptic encephalopathy with spike-wave activation in sleep (DEE-SWAS) is a rare and not well-understood epileptic disorder marked by spike-wave discharges occurring during sleep, often linked to neurodevelopmental regression or stagnation.[1] DEE-SWAS is linked to a variety of causes, including genetic and structural abnormalities. Treatment guidelines have mostly been derived from retrospective studies. These studies of patients who underwent resective surgery for DEE-SWAS generally report positive outcomes in terms of seizure control, resolution of electroencephalogram (EEG) abnormalities, and improvements in cognitive and language functions.[2] In a retrospective case series, 51% of patients with DEE-SWAS showed focal electrographic activity, while 49% had identifiable structural abnormalities on neuroimaging.[3] The current study describes an 11-year-old boy with medically resistant focal DEE-SWAS who underwent iECoG-guided surgical resection via the orbit which aims to highlight the clinical, imaging, and electrographic features of focal DEE-SWAS that can be treated surgically and also demonstrating the potential benefits of using iECoG in such cases.

CASE PRESENTATION

A 11-year-old left-handed boy with a history of Attention-deficit/hyperactivity disorder (ADHD) and focal epilepsy presented with cognitive decline. His medical history was otherwise unremarkable except for ADHD diagnosed at age 6, when he had two focal seizures involving awakening from sleep, staring, jaw clenching, hypermotor limb movements, and vomiting. These seizures were brief and self-resolving. At baseline, he attended school but struggled with multi-step instructions, slow progress, and difficulty answering questions. A routine EEG showed left frontal spike-wave discharges and slowing. He was initially treated for focal epilepsy with oxcarbazepine (OXC). However, as his attention worsened and school performance declined, an ambulatory EEG on OXC showed a spike-wave index (SWI) over

80% during sleep, leading to a diagnosis of DEE-SWAS. Between ages 7 and 10, neuropsychological testing revealed a decline in multiple cognitive areas, particularly verbal comprehension and fluid reasoning, which dropped from the low average to extremely low range. On the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V), his verbal comprehension index fell from 86 to 68. Structural MRI showed subtle abnormal folding in the anterior left frontal lobe, raising concerns about cortical malformation. Magnetoencephalography (MEG) detected numerous epileptiform abnormalities in the left frontopolar region. Stereoelectroencephalography (sEEG) revealed a single cluster of spike discharges localized to the left frontal convexity, most notably in the pars orbitalis and middle frontal gyrus, with fields extending to the anterior and posterior orbitofrontal gyri and anterior insula. These findings were consistent with the MRI and MEG results. Functional MRI (fMRI) confirmed left-sided language function in the left inferior frontal gyrus, close to the focus of SWAS. Surgical resection was considered the best option to address his neurological decline. Post-operative MRI showed resection extending slightly beyond the MEG-identified spike abnormalities (Figure 1). One month after surgery, the patient's mother reported no new language deficits and noted improvement in his preoperative word-finding difficulties. At two and a half months, he had no new neurological deficits, and his cognitive and language functions were more age appropriate. Parents observed clearer expression compared to before the surgery. Repeat ambulatory EEGs at 2- and 8-months post-surgery, while the patient was on lamotrigine and levetiracetam (the latter discontinued after 6 months), showed complete resolution of SWAS and no epileptiform discharges in any sleep stage or while awake. He remained stable across cognitive domains, including memory, fine motor skills, verbal retrieval, and word reading. His mother reported improved executive function in daily activities.

Table 1. Pre- and post-operative non-contrast TI-weighted MRI (left and right columns, respectively) showing extent or resection in axial (top), coronal (middle), and sagittal (bottom) planes.



DISCUSSION

In patients with both DEE-SWAS and clinical seizures, resective surgeries can lead to the resolution of both DEE-SWAS and seizures.[4] A meta-analysis by van den Munckhof et al. revealed that surgery for DEE-SWAS led to clinical improvement in 90% of cases and cognitive improvement in 80%. Additionally, these improvements were sustained in 93% of cases with available follow-up data. These outcomes were more favorable than those seen in patients treated with anti-seizure medications, benzodiazepines, and steroids.[5]

CONCLUSION

Although DEE-SWAS is not usually treated with surgery, surgical intervention can result in the complete resolution of EEG abnormalities in certain cases with focal onset. While there is a lack of extensive studies on its impact on cognitive decline, case reports suggest that surgery can lead to positive outcomes and should be considered in specific situations. Additionally, iECoG may be a valuable tool in determining the appropriate extent of resection for DEE-SWAS.

REFERENCE

1. Freibauer AE et al. The genetic landscape of developmental and epileptic encephalopathy with spike-and-wave activation in sleep. Seizure. 2023 Aug;110:119-125.
2. Baumgartner ME et al. Transorbital intraoperative electrocorticography-guided surgical resection for medically refractory developmental epileptic encephalopathy with spike-wave activation in sleep. Epilepsy Behav Rep. 2024 Sep 23;28:100712.
3. Van Hirtum-Das M et al. Children with ESES: variability in the syndrome. Epilepsy Res. 2006 Aug;70 Suppl 1:S248-58.
4. Loddenkemper T et al. Epilepsy surgery in children with electrical status epilepticus in sleep. Neurosurgery. 2009 Feb;64(2):328-37.
5. van den Munckhof B et al. Treatment of electrical status epilepticus in sleep: A pooled analysis of 575 cases. Epilepsia. 2015 Nov;56(11):1738-46.