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CASE REPORT **OPEN ACCESS**

PEDIATRIC EPILEPSY SURGERY IN A DRUG-RESISTANT EPILEPSY PATIENT AGGRAVATED BY SARS-COV-2: A CASE REPORT

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ABSTRACT

Introduction: Epilepsy is a manageable neurological disorder, but about one-third of cases are classified as drug-resistant epilepsy (DRE). DRE in pediatrics is more complex and may lead to cognitive function impairment, while surgery can offer seizure control in cases of focal DRE.
Case: A 10-year-old male presented with a four-year history of recurrent seizures, thought to be caused by a left temporal cerebral cyst diagnosed five years earlier. During episodes, he experienced body stiffness, bilateral eye twitching, and drooling, with intact consciousness. After SARS-CoV-2 exposure, seizures became more frequent despite antiepileptic treatment, leading to partial resection of the left temporal lobe nine months later. Two years post epileptic surgery, he has become drug-responsive and achieved seizure control with symptomatic relief through medication.
Discussion: Epilepsy is common in children, and DRE should be considered in cases of intractable epilepsy. Various factors can cause DRE, and in this patient, SARS-CoV-2 is thought to aggravate seizures by binding to ACE2 receptors in the central nervous system. This neural interaction may trigger reactive astrogliosis and neuroinflammation, disrupting the balance between glutamate and GABA levels. However, epilepsy surgery has been effective in improving the quality of life.
Conclusion: Epilepsy surgery, either resective or non-resective surgery, is still rarely performed in Indonesia, while the management of DRE may require surgery. Although complete seizure freedom is not guaranteed, surgery can often convert DRE into a drug-responsive condition.

Keywords: children, drug-resistant epilepsy, epilepsy surgery

Introduction

Epilepsy is a chronic neurological illness that accounts for a considerable portion of the global disease burden. It is characterized by recurrent unprovoked seizures or episodes of unusual behavior with impaired vegetative, cognitive, or mental functions due to abnormal brain activity and excessive neuronal discharges in the gray matter of the cerebral cortex.[1] As a result, the clinical manifestations of epilepsy will depend on the site of origin, duration, and distribution of these discharges. Epilepsy can be treated with antiepileptic drugs (AEDs), either as monotherapy or in combination with two or more drugs. In some cases, seizures can be controlled, while others may require lifelong treatment to maintain seizure control. On the other hand, 30% of cases involve various factors that cause failure to control epilepsy, known as “intractable” or “refractory” epilepsy, where seizures do not respond well to medications or other complicating factors that make treatment difficult.[2] Intractable epilepsy that persists and is unlikely to be controlled with further manipulation of AED therapy is classified as drug-resistant epilepsy (DRE).[3]

The International League Against Epilepsy (ILAE) defines DRE as the persistence of seizures despite adequate trials of two tolerated, appropriately chosen, and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. The ILAE defines seizure freedom as freedom from all types of seizures for 12 months or three times the pre-intervention inter-seizure interval, whichever is longer.[4] In children, 5% experience a seizure by the age of 20, and among the 50 million people with epilepsy, 30% experience DRE. DRE in pediatric cases is more complex than in adults, primarily due to diverse etiologies and the remarkable capabilities of neuroplasticity in children. The consequences of longstanding DRE can diminish cognitive function, education, and employment opportunities and increase the child's mortality.[5]

Epilepsy is classified by onset into generalized, focal, or unknown. Focal onset starts in one hemisphere and is divided into aware and impaired awareness types.[2] DRE in pediatric focal epilepsy can be treated with surgery, with the possibility of achieving seizure freedom. Alternatively, less invasive options, which serve as adjunctive treatments beneficial for seizure reduction, are available for those who are unsuitable for surgery.[5] This case report aims to describe intractable epilepsy, specifically DRE, in children that can achieve seizure control through epilepsy surgery, which is still rarely performed in Indonesia.

Case Report

A 10-year-old male patient presented with a history of recurrent seizures for the past four years, worsening in the past year. The seizures included bilateral eye twitching, more prominent in the right eye, body stiffness, clenched hands, and drooling. During seizures, the patient's consciousness remained intact, allowing him to follow commands and walk. The seizures lasted less than a minute, with increasing frequency from seven times a month to almost every day. Before a seizure, the patient's mouth would become stiff, and saliva would drip. After the seizure, the drooling stopped, and the patient could resume activities, but he would feel drowsy.

The patient reported that his condition worsened after being exposed to SARS-CoV-2. Before the first exposure to SARS-CoV-2, the patient was diagnosed with epilepsy at the age of 6 and was prescribed Keppra (levetiracetam) 6 mL twice daily, as he was allergic to carbamazepine. The patient was seizure-free for 1.5 years before experiencing a deterioration that occurred 4 days after being infected with SARS-CoV-2. The patient also reported a fear of hospitalization due to SARS-CoV-2, anxiety, and sleep disturbance. The epilepsy was thought to be caused by a left temporal cerebral cyst that had been diagnosed 5 years earlier. As an antiepileptic medication, a ventriculoperitoneal shunt was placed through the left temporal lobe, along with levetiracetam and valproic acid (Figure 1). The patient remained seizure-free for 6.5 months until a second exposure to SARS-CoV-2, during which the patient's father was infected. However, the patient's PCR test came back negative.

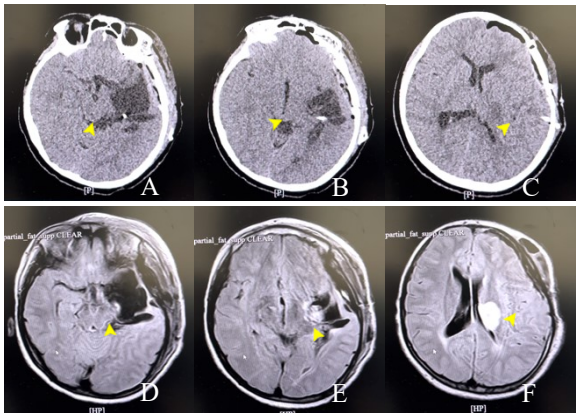

Figure 1. CT Scan head without IV contrast (A-C) and MRI head without IV contrast (D-F) showed that a ventriculoperitoneal shunt was placed through the left temporal region, with the tip located in the subarachnoid space of the left temporal region (yellow arrowhead)

AEDs were no longer able to control the seizures, and after several follow-up examinations and considerations, epilepsy surgery was performed 9 months later. The patient was vigilant, with a normal level of consciousness deemed suitable for surgery, and underwent a left parietotemporal craniotomy followed by partial resection of the left temporal lobe. Histopathological examination showed gliosis tissue with findings of reactive glial cells, regions of clustered cells suggestive of ependymal cells, and congested, dilated blood vessels.

A brain MRI without IV contrast demonstrated acute infarction involving the periventricular area of the left lateral ventricle, left thalamus, left basal ganglia, posterior horn of the internal capsule, and posterior aspect of the left external capsule. After the left parietotemporal craniotomy, there was a subacute epidural hematoma approximately 1 cm thick on the left frontotemporal region, compressing the left frontal and temporal lobes, a subacute epidural hematoma approximately 0.35 cm thick with pneumocephalus on the left frontotemporal region, and a midline shift to the right of approximately 0.25 cm. After the partial resection of the left temporal lobe, there was a parenchymal defect with perifocal gliosis on the left temporal lobe, which was the lateral aspect of the cystic mass. The cystic mass measured approximately 4.2 x 5.75 x 4.2 cm in the left temporal lobe, compressing the temporal horn of the left lateral ventricle (Figure 2).

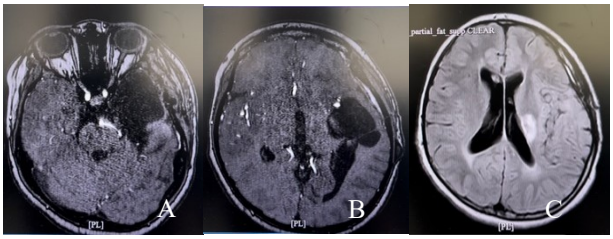

Figure 2. The MRI of the head performed without intravenous contrast revealed the presence of an arachnoid cyst located in the left temporal region, which is clearly visible on the axial T1-weighted images (A, B). Additionally, there is evidence of a parenchymal defect in the left temporal lobe accompanied by perifocal gliosis, as demonstrated on the T2-weighted fluid-attenuated inversion recovery (FLAIR) sequences (C)

After the surgery, the patient no longer experienced seizures, although it was not yet possible to discontinue the medication. The seizure control was maintained using a combination of Keppra (7.5 cc in the morning and 10 cc in the evening) and Zonegran (125 mg in the morning and 100 mg in the evening). Postoperative EEG results revealed intermittent slowing in the left temporal region and intermittent generalized slowing; notably, no epileptogenic waves were detected, indicating an absence of active seizure activity. Despite these positive neurological changes, the patient continued to experience right-sided hemiparesis, which had first appeared two weeks before the surgery.

Over seven months following the operation, the patient's right-sided hemiparesis gradually showed signs of progressive improvement, suggesting recovery of motor function. A brain MRI conducted nine months after surgery demonstrated a reduction in the size of the arachnoid cyst, which measured approximately 4.1 x 5.55 x 2.95 cm, as well as a decrease in the size of the ventricular system. Despite these improvements, a midline shift to the left side of the brain was still observed, indicating some ongoing structural displacement. This imaging provided significant insight into the patient's anatomical changes during recovery and the partial resolution of brain abnormalities.

A follow-up EEG examination revealed only intermittent generalized slowing with no epileptogenic waves, which marked an improvement compared to the earlier EEG findings. These electrophysiological changes suggest that the patient's brain condition progressively stabilized after the surgery. Unfortunately, preoperative MRI and EEG data were unavailable for this patient, limiting the ability to make detailed comparisons of imaging and electrophysiological parameters before and after the surgical intervention (Figure 3). The clinical and diagnostic findings indicate positive postoperative progress in seizure control and neurological recovery.

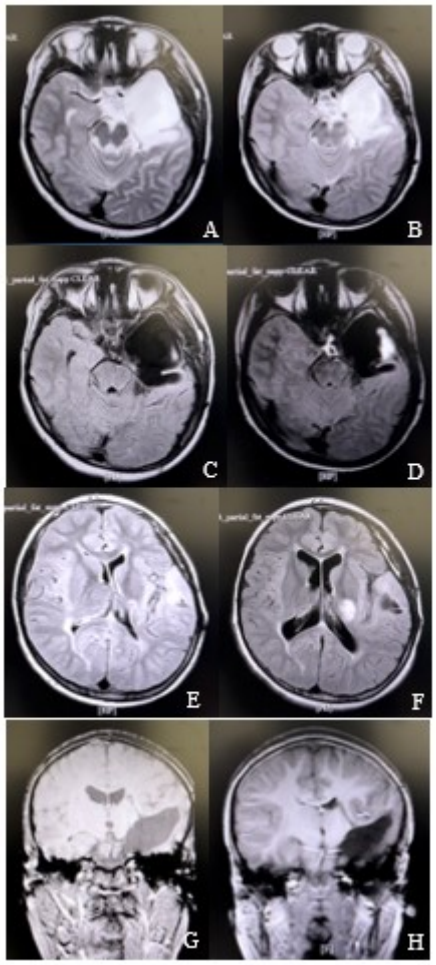

Figure 3. Postoperative (3 days) MRI head without IV contrast in axial T2 (A), T2-weighted FLAIR (C), and sagittal T1 (E) views. Follow-up (9 months) MRI head without IV contrast in axial T2 (B), T2-weighted FLAIR (D), and sagittal T1 (F) views showed a reduction in arachnoid cyst and ventricular system. Compared to the previous MRI, the size of the cystic parenchymal defect appeared slightly reduced (A-D), the ventricular system appeared smaller (E-H), and a midline shift to the left was observed (E, F)

Since the first exposure to SARS-CoV-2, the patient experienced cognitive decline, making it difficult for him to keep up with elementary school lessons. The patient also developed precocious puberty and testosterone hormone disorders, which improved with hormonal injections every 3 months.

Discussion

Epilepsy is one of the most common chronic neurological disorders and has a higher morbidity rate among pediatric diseases. One-third of epileptic patients have problems managing seizures, which can severely affect their quality of life, primarily due to pharmacoresistance to AEDs (antiepileptic drugs).[6,7] As seen in this patient, the failure to control seizures with two or more adequate AEDs is termed drug-resistant epilepsy (DRE).[6]

Several hypotheses exist regarding DRE, including the "drug transporter hypothesis," "altered target hypothesis," "gene variant hypothesis," "missing target hypothesis," and "remodeling of neural networks."[7] The drug transporter hypothesis is the most intensively investigated, suggesting that there is an overexpression of efflux drug transporters on the apical surface of cerebral capillary endothelial cells in the epileptogenic zone, such as P-glycoprotein, BCRP, MRPs, and other ABC transporters. These multidrug-resistant transporters expel the drugs from the cell, preventing them from reaching the site of action and leading to resistance. The altered target hypothesis suggests that modifications in the target cellular regions, whether ion channels or receptors, lead to resistance at the target site of AEDs. The gene variant hypothesis suggests that variations in genes regulating the pharmacokinetics or pharmacodynamics of the drugs cause resistance to AEDs. The missing target hypothesis posits that AEDs do not target the pathogenic processes, leading to auto-inflammation. Meanwhile, the remodeling of the neural networks hypothesis suggests that seizure-induced neuromodulation can trigger the remodeling of neuronal networks as compensation for the antiseizure system, which hinders AEDs from reaching the target site.[3,7]

In this patient, there was a worsening of epilepsy following exposure to SARS-CoV-2. Several studies have reported new-onset seizures or worsening epilepsy due to SARS-CoV-2's contribution to epileptogenesis.[8,9] SARS-CoV-2 can infect human host cells through angiotensin-converting enzyme 2 (ACE2) receptors, which are found in the lower respiratory tract and cells of multiple organs, including the brain.[10] Additionally, SARS-CoV-2 can directly enter the brain through the olfactory tract without the assistance of ACE2 receptors, infecting sensory or motor neurons and traveling into the central nervous system. This neural pathway can trigger reactive astrogliosis and activate microglia, leading to the release of pro-inflammatory cytokines (TNFα, IL1B, IL-6), prostaglandin E2, nitric oxide, and free radicals, resulting in a sizeable inflammatory cascade. Pro-inflammatory cytokines can cause blood-brain barrier (BBB) impairment, neurotransmitter imbalances where glutamate and aspartate levels increase while GABA levels decrease, and disruptions in ion channel functions. These cytokines can also trigger calcium entry into neurons through NMDA and AMPA receptors, increasing neuronal hyper-excitability, seizures, and cell death.[11]

However, some studies have also found that seizure worsening in patients with epilepsy during SARS-CoV-2 infection is due to anxiety, depression, increased stress, and sleep disturbances, all of which can increase cortical excitability.[8,12,13] Stress has been associated with elevated brain inflammation.[14] After confirming the infection, the patient reported a fear of hospitalization due to SARS-CoV-2. Sleep disruption can cause neuroinflammation and worsen neurodegeneration in the epileptic brain. Episodes of seizures can activate peripheral and brain-resident immune cells to release pro-inflammatory mediators as danger signals, such as cytokines, prostaglandins, and complement factors, which then trigger a vicious cycle of neuroinflammation. During this inflammatory process, monocyte infiltration into the brain and activation of astrocytes or microglia produce more pro-inflammatory cytokines, leading to neurodegeneration. Sleep disruption can act as a secondary inflammatory factor that aggravates neuronal loss, thereby increasing seizure frequency and the progression of epilepsy.[15] Consequently, whether SARS-CoV-2 directly or indirectly causes microglia activation and reactive astrogliosis, it may contribute to intractable epilepsy, potentially leading to drug-resistant epilepsy (DRE) in this patient.

Management of DRE

In the management of DRE, some patients require epilepsy surgery as the most effective therapeutic modality for drug-resistant focal epilepsy, which may lead to seizure freedom and improvement in quality of life.[6] The first step in managing DRE is to rule out pseudo resistance in epilepsy, such as misdiagnosis (for example, psychogenic nonepileptic seizure [PNES]), incorrect classification, lack of medication adherence, inadequate choice of drugs or dosage, inappropriate assessment of response, inadequate lifestyle, or associated psychiatric and medical conditions.[16]

Some underlying diagnoses, such as cortical dysplasia, polymicrogyria, hypothalamic hamartoma, tuberous sclerosis complex, hemispheric syndrome, Rasmussen syndrome, and Sturge-Weber syndrome, are conditions that are appropriate for early surgical referral.[5] Although early surgery shows benefits, it is recommended only for cases with identifiable epileptogenic regions and DRE, given the surgical risks. Epilepsy surgery may also affect cognitive and behavioral functions. Still, the effects are often unpredictable, difficult to quantify, typically rare and minor (such as wound infection or pseudo meningocele), and therefore generally considered safe. Surgery can improve developmental outcomes because a longer duration of epilepsy negatively affects multiple domains, quality of life, and postoperative seizure freedom.[6] If localization is indeterminate, several potential options exist for identifying regions associated with seizures, such as high-resolution imaging, single-photon emission computed tomography (SPECT), and magnetoencephalography.[5]

Several surgical choices can be used depending on the seizure type, the location of the epileptogenic zone, and the presence or absence of detectable abnormalities on brain imaging. In general, epilepsy surgery can be classified into resective and non-resective procedures, where complete resection has a higher probability of seizure freedom but also carries risks of postoperative impairments. Therefore, a risk assessment of the surgery tailored to each patient is necessary. The most common systems used to classify surgical outcomes are the ILAE classification system (Table 1) and the Engel classification system (Table 2).[2]

Table 1. ILAE Outcome Scale Classification System[2]

Class	Outcome
Class 1	Completely seizure-free, no auras
Class 2	Only auras, no other seizures
Class 3	1 to 3 seizure days per year, with/without auras
Class 4	4 seizure days per year to a 50% reduction of baseline seizure days with/without auras
Class 5	Less than 50% reduction of baseline seizure days, with/without auras
Class 6	More than 100% increase of baseline seizure days, with/without auras

Table 2. Engel Outcome Scale Classification System[2]

Class	Outcome
Class I: Free of disabling seizures	
IA	Completely seizure-free since surgery
IB	Non-disabling simple partial seizures only since surgery
IC	Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
ID	Generalized convulsions with antiepileptic drug withdrawal only
Class II: Rare disabling seizures ("almost seizure-free")	
IIA	Initially free of disabling seizures, but has rare seizures now
IIB	Rare disabling seizures since surgery
IIC	More than rare disabling after surgery, but rare seizures for at least 2 years
IID	Nocturnal seizures only
Class III: Worthwhile improvement	
IIIA	Worthwhile seizure reduction
IIIB	Prolonged seizure-free intervals amounting to greater than half the follow-up period but not less than 2 years
Class IV: No worthwhile improvement	
IVA	Significant seizure reduction
IVB	No appreciable change
IVC	Seizure worse

Before referring to surgery, presurgical evaluations, known as phase 1 evaluation, are required. In this phase, the investigation aims to determine the location of the epileptogenic zone and assess the risk of potential postoperative deficits. This uses high-resolution MRI, video scalp electroencephalography (EEG), and detailed neuropsychological assessments.[17,18] The patient may be referred directly to surgery if the results are conclusive. However, if the results regarding the location of the epileptogenic zone are ambiguous, an additional phase 1 evaluation may be necessary. Advanced structural imaging techniques on MRI can be used to detect epileptogenic lesions. For accurate delineation of the irritative zone, interictal high-resolution EEG (HD-EEG), interictal EEG-functional MRI (EEG-fMRI), interictal magnetoencephalography (MEG), interictal magnetic source imaging (MSI), and interictal electrical source imaging (ESI) can be used. Interictal 18F-fluoro-deoxyglucose (FDG) positron emission tomography (PET) may be used to detect the location of the functional deficit zone. Ictal single-photon emission CT (SPECT), ictal HD-EEG, and ictal ESI may be employed to detect the ictal onset zone.[18,19]

Functional MRI (fMRI) and tractography of the pyramidal tract can be used to predict the risk of postoperative motor deficits. For predicting postoperative memory decline, fMRI and the Wada test are helpful. Visual field tests and tractography of Meyer's loop can be used to assess the risk of postoperative visual field defects. FMRI, MEG, and the Wada test help predict postoperative language function deficits.[18]

In cases where the epileptogenic zone cannot be localized or there is a lack of certainty from non-invasive techniques, a phase 2 evaluation with intracranial EEG (IEEG) may be performed. Extraoperative IEEG can be done with open craniotomy (CEEG), where a combination of depth electrodes and subdural electrodes is placed after the craniotomy. Stereotactic intracerebral electroencephalography (SEEG) involves placing multi-contact depth electrodes through a drill or burr hole. Hybrid extraoperative EEG (HEEG) combines CEEG and SEEG. Epidural IEEG uses epidural peg electrodes to record from several cortical areas. Foramen ovale IEEG involves using multi-contact electrodes along the long axis of the hippocampus.[18]

Respective Surgical Options

Respective surgery aims to remove the epileptogenic zone as completely as possible so that the patient no longer requires drug treatment. Seizure freedom has been reported in many case series, clinical trials, and systematic reviews. However, despite advances in surgical techniques, 30-40% of patients still experience seizures after resective surgery, while

55-70% of patients who had temporal lobe resection and 30-50% of patients who had extratemporal resection achieve seizure freedom. The reasons for these unfavorable outcomes are complex. They may include incomplete resection, incomplete interruption of the complex network, rekindling of the epileptogenic circuit, or the presence of a widespread neuronal network.[7]

In managing temporal lobe epilepsy (TLE), the earliest procedure used was anterior temporal lobectomy (ATL).[2] In ATL, the surgeon targets the lateral middle and inferior temporal gyri, removing 3.5 to 4 cm in the language-dominant hemisphere and up to 6 cm on the non-dominant side to the vein of the Labbe region.[5] The temporal lobe is a vital location for memory functions, so a significant risk of this procedure is memory impairment. A previous meta-analysis found that 44% of patients undergoing dominant hemisphere ATL experienced memory decline on neuropsychological verbal memory tests, compared to 20% for those who underwent nondominant hemisphere ATL.[20] Additionally, neurovascular structures at risk during ATL include white matter tracts such as optic radiations, the inferior longitudinal fasciculus, and the uncinate fasciculus; white matter when approaching the insula via the Transylvanian or transopercular route, such as the arcuate fasciculus, extreme capsule, and external capsule; the lenticulostriate branches and anterior choroidal artery, which can cause unilateral hemiparesis; and vascular structures in the deep brain stem on the medial side, where vascular injury can result in neurological damage.[2] Aphasia may also occur if extensive resection is performed in the dominant hemisphere.[5]

In 1984, Spencer introduced anteromedial temporal resection (AMTR), a surgical technique that preserves the lateral temporal cortex while effectively treating TLE, thereby minimizing the significant memory impairment often caused by ATL. Therefore, AMTR has become the more commonly preferred surgical procedure worldwide.[2]

Extratemporal resections are procedures used to treat seizures outside the temporal lobe, such as lesions in the occipital, frontal, or parietal lobes. In children, extratemporal lobe epilepsy is more common than mesial temporal lobe epilepsy. Underlying neurological conditions for extratemporal epilepsy commonly include cortical dysplasia, arteriovenous malformation, prior stroke, and Rasmussen encephalitis. Focal cortical dysplasia is also a common etiology in pediatric multilobar epilepsy. However, relapse after neocortical resective surgery is more common than after mesial temporal surgical resection. Additionally, resection of the lateral occipital lobe can increase the risk of vision impairment.[5]

In cases of generalized or multifocal tonic, atonic, or myoclonic seizures or Lennox-Gastaut syndrome, corpus callosotomy can be performed with options for anterior partial and complete callosotomy resection. This surgery aims to disrupt the contralateral propagation of epileptic activity. Still, care must be taken with the motor cortex, the cingulum (which accounts for neuropsychiatric injury), distal segments of the anterior cerebral arteries (ACA), venous sinuses, and deep cerebral veins. The primary concern with corpus callosotomy is disconnection syndrome, especially with complete callosal resection.[5] The acute form of disconnection syndrome can cause severe decreases in spontaneous speech, paresis of the nondominant leg, incontinence, severe dysphagia leading to aspiration pneumonia, or severe loss of activity requiring tube feeding or intravenous total parenteral nutrition. The chronic form can result in hemispatial neglect, nondominant hand agraphia, dichotic listening suppression, alien hand syndrome, or tachistoscopic visual suppression.[21] Recent approaches have developed, including laser interstitial thermal therapy (LITT) and endoscopic techniques for pediatric patients, which help prevent exposure to critical neurovascular structures.[5]

Medication usage is an essential parameter in evaluating surgical outcomes. The majority of patients continue AEDs for the first 6-24 months to prevent seizure recurrence, with some eventually being able to reduce or withdraw medication. However, among seizure-free post-surgery patients, only 45% can withdraw AEDs, while the rest still require AEDs to maintain seizure control. Therefore, epilepsy surgery is not always "curative" but can help convert a drug-resistant condition to a drug-responsive one. This indicates that pathological tissue is responsible for pharmacoresistance, known as the drug-resistant epileptogenic zone (DREZ), and its removal can lead to drug responsiveness. The DREZ may be located in several foci of the epileptogenic zone, with a size equal to or smaller than the epileptogenic zone.[7]

To achieve seizure control post-surgery, the patient used Keppra and Zonegran. Keppra (levetiracetam) is a second-generation antiepileptic drug (AED) approved for adults and children older than 1 month, with better tolerability and efficacy than other AEDs.[22] The primary mechanism of action of levetiracetam is to modulate synaptic vesicle protein 2A (SV2A). SV2A is a transmembrane protein found in nearly all synaptic terminals.[23] SV2A plays a role in both the exocytosis and endocytosis processes. During exocytosis, the SV2A protein serves as a target for residual calcium, and during endocytosis, it regulates the calcium-sensor synaptotagmin protein in the vesicle. Additionally, SV2A facilitates vesicular priming, helping vesicles reach a release-competent state, and regulates the size of the readily releasable

pool (RRP). Levetiracetam works by blocking the effects of SV2A during vesicular priming, ultimately reducing the size of the RRP, decreasing neurotransmitter release, and inhibiting synaptic transmission.[24] Levetiracetam also has other targets, such as Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid (AMPA), adenosine, noradrenaline, and serotonin receptors, contributing to its role in pain modulation, anti-inflammatory effects, neuroprotection, and antioxidant properties. It is also involved in the gamma-aminobutyric acid (GABA) system, calcium homeostasis, and regulation of intracellular pH, all of which contribute to its antiepileptic mechanisms.[24] Therefore, levetiracetam can provide seizure control as monotherapy (50%) or in combination therapy (84%) in the pediatric population.[25]

Zonegran (zonisamide) is a broad-spectrum AED that effectively manages focal and generalized onset seizures. Zonisamide primarily works by blocking sodium channels, reducing repetitive neuron firing, and blocking calcium channels to prevent the spread of abnormal electrical activity. It enhances GABA distribution from the hippocampus, suppresses neuronal hypersynchronization, and weakly inhibits carbonic anhydrase. In addition to its antiepileptic properties, zonisamide is a neuroprotective agent.[26,27] Zonisamide inhibits monoamine oxidase B (MAO-B), making it helpful in treating Parkinson's disease.[26] It is commonly used as an add-on therapy for intractable epilepsy in adults and children.[27] Aslan et al. (2022) also found that zonisamide is an effective and reliable option as an add-on therapy for managing pediatric intractable epilepsy.[28]

Non-respective Surgical Options

For patients who are unsuitable for seizure focus removal, such as those with multifocal seizures or an epileptogenic zone overlapping with the functional cortex, non-respective surgical options can be more beneficial.[2] These options include neuromodulation-based interventions and brain stimulation therapies, such as vagus nerve stimulation, responsive neurostimulation therapy, and transcranial magnetic stimulation therapy.

Vagus nerve stimulation (VNS) is a therapeutic approach that stimulates the vagus nerve, either manually or electrically. It is helpful for drug-resistant epilepsy (DRE), depression, and even chronic heart failure. VNS consists of an implanted pulse generator placed below the collarbone, a lead wire with two platinum electrodes wrapped around the left vagus nerve, a subcutaneous tunnel, a programming wand, and a hand-held magnet. The vagus nerve is an essential autonomic nervous system component, regulating metabolic homeostasis. The antiepileptic effect of VNS is produced by stimulating its afferent nerve endings, which enter the medulla at the nucleus tractus solitarii (NTS) and innervate the locus coeruleus (LC) nucleus. This increases the release of noradrenaline for an extended period (80 minutes), enhances blood flow, and raises the level of GABA in the cerebrospinal fluid. Therefore, VNS can be used as adjunctive therapy for patients with DRE to reduce seizure frequency and improve quality of life.[3,5]

Responsive neurostimulation (RNS) consists of intracranial leads that detect seizures and an implanted neurostimulator that responds with electrical stimulation to stop the seizures. RNS can be used as an additional treatment under certain conditions, such as resistance to two or more AEDs, having two or more seizures per month for three consecutive months, and having no more than two epileptogenic foci.[3]

Transcranial magnetic stimulation (TMS) therapy is a procedure that stimulates the brain's motor cortex. TMS generates a short-duration current (100-400 μs) that passes through a coil, creating a varying magnetic field (1.5-2 T) and subsequently producing an electrical field (200 V/m) that stimulates or depolarizes the neurons of the cortex. TMS can suppress epileptic discharges and modify neuronal activity, such as altering the excitability of neurons and the function of ion channels, as well as modifying synaptic transmission and communication between neurons. TMS can also be an option for presurgical functional mapping of key eloquent regions, helping to create a safer pathway during surgical resection.[5]

Other non-pharmacological treatments include metabolic therapy and complementary therapies. Metabolic therapy involves dietary approaches, such as the classic ketogenic diet (CKD), the modified Atkins diet (MAD), and a triheptanoin-based diet (anaplerotic diet). Complementary therapies include biofeedback therapy, where the patient learns to regulate physiological functions of the body under voluntary control, and music therapy, where listening to Mozart's music has been shown to help control epileptiform discharges.[3]

Histopathology: 'Gliosis Only'

One-third of temporal lobe resections have found hippocampal sclerosis (HS) as the underlying etiology of drug-resistant epilepsy (DRE). Specifically, 52.5% of patients with onset before the age of 43 had HS, while only 18.4% of those with later onset exhibited this pathology. HS is predominantly found in young adults undergoing temporal lobe resection, compared to adults or older people. Punia et al. (2019) found that no patients aged 60 years or above had HS; half had gliosis or remote infarcts, and 21% had cavernoma or a tumor. HS is characterized by neuronal cell loss and varying degrees of gliosis.[29] According to the ILAE classification, HS can be divided into three distinct groups, with Type 1 being the most common

(approximately 60-80% of all TLE-HS cases). In ILAE HS Type 1, the cornu ammonis 1 (CA1) segment is the most severely affected, with over 80% cell loss. However, significant neuronal cell loss can also be found in the pyramidal neurons of CA2 (30-50%), CA3 (30-90%), CA4 (40-90%), and granule cell loss in the dentate gyrus (50-60%). In ILAE HS Type 2, neuronal cell loss and gliosis predominantly occur in CA1. Still, the damage is often not detectable by visual inspection, while other segments show mild cell loss (<20% in CA2, <20% in CA3, and <25% in CA4 of principal cells). In ILAE HS Type 3, the predominant neuronal cell loss and gliosis occur in CA4 (50%) and the dentate gyrus (35%), while other segments are moderately affected (<20% in CA1, <25% in CA2, and <30% in CA3). Types 2 and 3 are rare variants, accounting for 5-10% and 4-7.4% of all TLE surgical cases.[30]

In addition to these three types, there is also a variant called "no hippocampal sclerosis" or "gliosis only," referred to as "no-HS." In 20% of TLE cases, only reactive gliosis is found in histopathology, without significant neuronal cell loss.[30] The neuropathological hallmark of no-HS is extensive cellular astrogliosis and the absence of segmental neurodegeneration, as opposed to the fibrillary scar-type astrogliosis typically found in HS. No-HS is also considered a pre-HS stage in TLE patients. In no-HS, inflammation is known as innate inflammatory gliosis only (I2GO), characterized by a neuropathological pattern dominated by cellular gliosis. The release of inflammatory cytokines and the loss of homeostatic functions can provoke alterations in neuronal synapses, supported by the neurotoxic effects of reactive astrocytes in the hippocampus. This distinct inflammatory nature of the disease makes it less curable by surgery. Consequently, no-HS patients are less likely to achieve seizure freedom and often exhibit diffuse cognitive impairment before surgery (Table 3).[31]

Table 3. Summary of the Differences between HS and "Gliosis Only"

	Hippocampal sclerosis	**Innate inflammatory 'gliosis only'**
Age onset	Early adolescence	Late adolescence
Seizure-free outcome	Favorable seizure outcome	Unfavorable seizure outcome
MRI	More likely unilateral	More likely bilateral
Histology	Fibrillary astrogliosis, neuronal loss	Cellular astrogliosis, absence of neuronal loss
Transcriptome	Sclerosis marker	Inflammatory marker

There is also a variant called granule cell dispersion (GCD) as a result of Reelin deficiency in the dentate gyrus, which is associated with more significant cell loss in the hilus and generally occurs in cases with a longer epilepsy duration or when epilepsy surgery is performed at an older age.[30]

Arachnoid Cyst Association with Epilepsy

Approximately half of focal epilepsies that begin in childhood have an unknown cause, while the other half are due to a known underlying cause. The majority of known causes of pediatric epilepsy are structural, either due to abnormal brain development or acquired factors. In this patient, the structural cause is an arachnoid cyst (AC), which may be associated with the patient's epilepsy.[32] ACs, or intracranial arachnoid cysts (IACs), are fluid-filled cysts encased in arachnoidal cells that contain cerebrospinal fluid (CSF).[33,34] ACs typically do not communicate with the ventricular system, are often found incidentally, and can occur at any age, with the majority (75%) occurring in children. Arachnoid cysts are the brain's most common cystic congenital abnormality, with a male predominance (male-to-female ratio: 2:1).[33] Most cases requiring surgery occur in the pediatric population, which has led to growing hypotheses and evidence for a genetic etiology.[35] ACs can form by splitting the arachnoid membrane at the margin of the cyst, leading to an abnormal collection of cerebrospinal fluid (CSF) occurring anywhere along the neuroaxis from the head to the spine. Some hypotheses suggest the presence of an osmotic gradient, a ball-and-valve mechanism, or internal fluid production. Although the arachnoidal cells are normal, they can alter CSF flow and compliance, contributing to symptomatic cysts.[34]

ACs are generally asymptomatic, but in some patients, they can become symptomatic and require neurosurgical intervention. Symptoms may include headaches or signs of increased intracranial pressure, local mass effects, hydrocephalus, seizures, or even cyst rupture, which can cause subdural hemorrhage or hygromas. Depending on the affected anatomy and neural structures, the local mass effect can lead to focal neurological deficits.[33] Seizures and hydrocephalus are most commonly associated with temporal ACs, which in some cases can also cause decreased visuospatial orientation, dizziness, imbalance, and impairment of higher cognitive functions such as memory.[36] If there are signs of localized seizures, hydrocephalus, or neurological deficits in a patient with a symptomatic arachnoid cyst, surgery may be necessary. Additionally, a ventriculoperitoneal shunt can be performed to prevent neurological decline caused by compressive cysts.[37]

In some cases, IACs also have endocrine manifestations such as growth hormone deficiency, hypothalamic dysfunction, or even precocious puberty.[38] As seen in this patient, he experienced precocious puberty at the age

of 10, which the patient's IAC likely caused. The average onset of puberty is 11-12 years in boys and 10-11 years in girls. The majority of precocious puberty cases are caused by central precocious puberty (CPP), where there is premature activation of the hypothalamic-pituitary-gonadal (HPG) axis, leading to pulsatile secretion of gonadotropin-releasing hormone (GnRH). Activation of the HPG axis is marked by testicular enlargement, increased penile length, pubic hair growth, and voice changes in boys, as well as breast enlargement, pubic hair growth, and menstruation in girls.[39]

In girls, CPP is often idiopathic (ICPP) as the cause is not detected. Meanwhile, one-third of CPP cases in boys are caused by organic brain lesions such as arachnoid cysts, hypothalamic hamartoma, and hydrocephalus.[39] Organic CPP is 3.5 times more common in boys than in girls.[40] When these organic brain lesions have an anatomical connection and exert mechanical pressure on the anterior hypothalamus, they can trigger the secretion of GnRH and increase neuroendocrine activity in GnRH neurons.[41]

GnRH analogs (GnRH-a) are widely used and highly effective in treating CPP. GnRH-a can induce sustained desensitization of the GnRH receptor and act as a GnRH agonist, reducing circulating gonadotropins, gonadal steroids, and gonadal peptides, thereby successfully inhibiting the progression of pubertal changes.[42] Through a similar mechanism, a hormonal injection every 3 months in this patient acts as negative feedback to suppress sex hormones, with follow-up laboratory results showing a reduction in testosterone levels.

Conclusion

Epilepsy is a chronic neurological disorder, with drug-resistant epilepsy (DRE) affecting one-third of patients. Managing DRE can be particularly challenging in pediatric cases, where various factors contribute to pharmacoresistance. It is crucial to evaluate potential causes of intractable epilepsy, such as genetic variants, underlying neuroinflammatory processes, or structural abnormalities like arachnoid cysts, which may further complicate treatment. This case report highlights the role of epilepsy surgery, such as partial resection of the left temporal lobe, which offers seizure control and significantly improves the patient's quality of life. While not all patients who undergo epilepsy surgery will achieve complete seizure freedom, the procedure can often convert a drug-resistant condition into a drug-responsive one. This is supported by histopathological findings like gliosis, where the inflammation associated with reactive gliosis makes the condition less amenable to surgical intervention.

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