

Behavioral Improvements following Lesion Resection for Pediatric Epilepsy: Pediatric Psychosurgery?

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Established Facts

- Surgery for lesional epilepsy is well accepted and has a high rate of seizure reduction or freedom.
- Epilepsy can be associated with behavioral changes, either due to the underlying lesion or repetitive overstimulation of the epileptogenic circuits.

Novel Insights

- In children with epileptic lesions who experience a concomitant decline in behavior, surgical resection may offer both seizure reduction as well as behavioral improvements.
- In lesional epilepsy patients with previously diagnosed psychiatric disorders such as autism or ADHD, resection of lesions and decreased seizure burden may improve behavioral symptoms of these disorders.

Keywords

Behavior symptoms · Pediatric brain lesion · Pediatric epilepsy

Abstract

Introduction: Resection of brain lesions associated with refractory epilepsy to achieve seizure control is well accepted. However, concurrent behavioral effects of these lesions such as changes in mood, personality, and cognition

and the effects of surgery on behavior have not been well characterized. We describe 5 such children with epileptogenic lesions and significant behavioral abnormalities which improved after surgery. **Case Descriptions:** Five children (ages 3–14 years) with major behavioral abnormalities and lesional epilepsy were identified and treated at our center. Behavioral problems included academic impairment, impulsivity, self-injurious behavior, and decreased social interaction with

diagnoses of ADHD, oppositional defiant disorder, and autism. Pre-operative neuropsychiatric testing was performed in 4/5 patients and revealed low-average cognitive and intellectual abilities for their age, attentional difficulties, and poor memory. Lesions were located in the temporal (2 gangliogliomas, 1 JPA, 1 cavernoma) and parietal (1 DNET) lobes. Gross total resection was achieved in all cases. At mean 1-year follow-up, seizure freedom (Engel 1a in 3 patients, Engel 1c in 2 patients) and significant behavioral improvements (academic performance, attention, socialization, and aggression) were achieved in all. Two patients manifested violence pre-operatively; one had extreme behavior with violence toward teachers and peers despite low seizure burden. Since surgery, his behavior has normalized. **Conclusion:** We identified 5 patients with severe behavioral disorders in the setting of lesional epilepsy, all of whom demonstrated improvement after surgery. The degree of behavioral abnormality was disproportionate to epilepsy severity, suggesting a more complicated mechanism by which lesional epilepsy impacts behavior. We propose a novel paradigm in which lesionectomy may offer behavioral benefit even when seizures are not refractory. Thus, behavioral improvement may be an important novel goal for neurosurgical resection in children with epileptic brain lesions.

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Introduction

Seizures are a common manifestation of pediatric brain lesions, occurring on presentation in 10–15% of children with brain tumors [1]. Tumor histology and location are strongly linked to seizure activity. Typically, slow growing tumors such as gangliogliomas, dysembryoplastic neuroepithelial tumors, and oligodendrogliomas located in the frontal, temporal, or parietal lobes have the highest risk of causing seizures [2]. Psychiatric symptoms have also been linked to brain lesions, which most commonly include personality changes, emotional dysregulation, social impairment, inattention, executive function deficits, and aggression [3, 4]. Eighty percent of tumor patients experiencing these symptoms have a frontal or limbic tumor etiology, suggesting a connection between affective abnormalities and lesion location [3]. These cognitive-behavioral changes can have far-reaching effects on a patient's functioning at home and at school [5]. Furthermore, the long-term implications of such changes on psychosocial development are concerning.

Behavioral abnormalities are seldom considered when deciding treatment options for patients with epileptic brain lesions despite lesion location contributing to both behavioral symptoms and seizures. When these lesions are radiographically stable, they are initially treated medically with anti-seizure medications (ASMs) to reduce seizure burden [6, 7]. Surgical resection is currently reserved for refractory cases when at least two trials of ASMs fail to provide seizure control, are not well tolerated, or when the lesion demonstrates growth [8]. Resection for epilepsy provides excellent seizure control, particularly when an underlying lesion is present [9], and can additionally improve cognition, quality of life, and psychosocial function [10]. In a few reported cases of extreme behavior dysregulation, excision of the lesion resulted in dramatic recovery [11–14]. Thus, factors beyond seizure control may be important to consider when deciding the best management strategy for each patient.

In this series, we report the cases of 5 patients presenting with lesional epilepsy associated with debilitating behavioral abnormalities that began around the time of seizure onset. They were initially medically managed but failed to achieve seizure freedom. Following lesion resection, all patients reported seizure freedom and drastic improvement in behavioral problems.

Case Descriptions

Case 1

A 10-year-old, right-handed female presented with daily, cluster seizures characterized by inattention, oral automatisms, and tonic posturing of the arms that began around age 3 (Table 1, patient characteristics). At that time, she also experienced psychomotor regression and was diagnosed with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Her neurological exam was normal. MRI of the brain demonstrated a 5.3 cm enhancement of the right temporal lobe with concomitant T2-hyperintense mesial temporal sclerosis and a small right hippocampus. She was placed in special education and had progressive decline in academic performance. She exhibited self-injurious behavior (head banging and self-biting), sensory deficits, pica, and reduced social skills (Table 2, behavioral descriptions). Speech regressed from short sentences to single word utterances. EEG identified bilateral temporal, parietal, and frontal epileptiform discharges suggestive of multifocal seizures. Zonisamide and valproic acid were able to control her seizures; she was weaned off her ASMs 3 years after onset and remained seizure free for 2 years thereafter. During this period, her speech, motor skills, and coordination improved. She then relapsed with daily seizures and behavioral challenges, although repeat MRI showed a stable lesion. Due to this reason, resection of the right mesial temporal lesion and amygdalo-hippocampectomy were performed, and gross total resection (GTR) was achieved. Pathology revealed WHO grade 1 ganglioglioma (BRAF V600E mutation), cortical dysplasia, and ILAE (International League Against Epilepsy) type 1 hippocampal

Table 1. Summary of patient demographics, clinical findings, surgery, and seizure outcomes for all 5 patients

Clinical summary												
case	age at presentation, age at surgery	comorbidities	seizure semiology	seizure frequency	pre-surgical ASMs	post-surgical ASMs	lesion location (hemisphere)	maximum dimension, cm	extent of resection	pathology	follow-up (months)	Engel outcome
1	3, 9	ASD, ADHD	Oral automatisms, tonic arm and head movements, staring spells	Daily, cluster	Zonisamide Valproic acid	Lamotrigine	Temporal (R)	5.3	GTR	Ganglioglioma, WHO 1 (BRAV V600E), cortical dysplasia, hippocampal sclerosis (ILAE type 1)	13	1a
2	14, 14	ASD	Sensory event preceding seizures, loss of consciousness, unresponsive episodes of disorientation/poor memory, dizziness	3–4 times/week	Levetiracetam	Levetiracetam	Temporal (R)	2.7	NTR then GTR	Pilocytic astrocytoma, WHO 1 (BRAV V600E)	14	1c
3	10, 12	ASD, ADD, ODD	GTC seizures, staring spells with impaired awareness +/- dizziness	3–4 times/week	Levetiracetam Oxcarbazepine	Oxcarbazepine Clonazepam	Temporal (R)	1.4	GTR	Cavernous malformation	24	1c
4	7, 8	ADHD, impulse control disorder	Body stiffness with mild shaking, loss of consciousness, unresponsive, occasional urinary incontinence, both daytime and nocturnal episodes triggered by fatigue	4 times/week	Eslicarbazepine Zonisamide	Eslicarbazepine Zonisamide	Temporal (L)	6.1	GTR	Ganglioglioma, WHO 1 (BRAV p.V503_R506), focal cortical dysplasia, hippocampal sclerosis (ILAE type 3)	7	1a
5	11, 11	ADHD, ODD, disruptive mood dysregulation disorder	GTC	Sporadically (7 times total at time of surgery)	Oxcarbazepine	Oxcarbazepine	Parietal (L)	2.6	GTR	DNET, WHO 1	8	1a

ASD, autism spectrum disorder; ADHD, attention-deficit hyperactivity disorder; ADD, attention-deficit disorder; ODD, oppositional defiant disorder; GTR, gross total resection; NTR, near total resection; DNET, dysembryoplastic neuroepithelial tumor.

Table 2. Summary of parent-reported behavioral characteristics before surgery and behavioral outcomes after surgery at last follow-up

Behavioral characteristics before and after surgery		
case	pre-surgery behavioral characteristics	post-surgery behavioral outcome
1	Regression in behavior, speech, and language. Developed self-injurious behavior (head banging, biting), hyperactivity, impulsivity, sensory problems, social interaction deficits, fixation, repetitive behaviors, pica, echolalia	Improvement in impulsivity, academic performance, and speech and language abilities. Cessation of self-injurious behavior
2	Delay in progression of speech, language, and social/emotional communication skills. Difficulty in academics	Improvement in personality (now less withdrawn/more outgoing)
3	Significant decline in academic performance. Developed severe depression, anxiety, self-injurious behavior (wrist cutting), impulsivity, fixations/automatisms, and suicidal ideation	Improvement in academic performance. Cessation of self-injurious behavior, impulsivity, and suicidal ideation. Ongoing significant anxiety and depression
4	Significant decline in academic performance. Developed aggression (only at school), impulsivity, hyperactivity, ADHD, poor memory, self-mutilation, suicidal ideation	Improvement in academic performance, behavior, impulsivity, hyperactivity, and aggression. Cessation of self-injurious behavior and suicidal ideation
5	Developed aggression, emotionality, social interaction deficits, oppositional, defiant, decreased attention	Improvement in academic performance, aggression, impulsivity, less opposition/defiance, self-control, social relationships

sclerosis. Lamotrigine was prescribed post-operatively. At the 13-month follow-up, she remained seizure free. Her parents described dramatic improvement in impulsivity and cessation of self-injurious behavior. They also reported that she was more affectionate, social, inquisitive, creative, and less hyperactive. Although she remains in special education, she has been more attentive and able to retain more information at school since surgery.

Case 1 had both pre- and post-operative neuropsychological testing completed (Table 3). Overall, the patient was better able to tolerate performing the battery of tests post-operatively. Comparing results on the Behavior Assessment System for Children-3 (BASC-3) Parent Report Scale, she had notable improvements in her behavioral symptoms index, attention, functional communication, and depression scores after surgery. Hyperactivity and atypicality scores decreased but remained clinically significant.

Case 2

A 15-year-old, right-handed male presented with a 1-year history of focal impaired awareness seizures 3-4 times per week. The patient was diagnosed with ASD at age 3 with deficits in speech, language, social/emotional communication, requiring placement in special education. His mother noted staring spells for 4 years prior to presentation but did not seek medical attention. His neurological exam was normal. MRI showed a heterogeneous, cystic, and solid, 2.6 cm enhancing medial right temporal lobe mass. EEG revealed right temporal slowing. The patient was prescribed levetiracetam which reduced seizure frequency but did not provide seizure freedom. Repeat MRI 2 months later demonstrated growth of the cystic component. The patient thus underwent lesion resection; however, post-operative MRI revealed a small residual lesion in the collateral sulcus. He returned for repeat surgery 2 days later and GTR was achieved. Pathology revealed a WHO grade 1 pilocytic astrocytoma (BRAF V600E mutation). He reported 1 or 2 seizures immediately after surgery, but he was otherwise seizure free at the

14-month follow-up, remaining on levetiracetam. Comparison of pre- and post-operative neuropsychological testing was largely stable across behavioral domains (Table 3). However, his parents have noticed tremendous academic improvement, successfully completing 10th grade in special education. Despite his pre-existing ASD diagnosis, he is more social and less withdrawn, more verbal, expressive, and interactive following surgery.

Case 3

A 15-year-old, right-handed male presented with recurrent seizures characterized by staring spells with impaired awareness occurring 3-4 times per week and two generalized tonic-clonic (GTC) seizures since seizure onset around age 10. The patient was developmentally normal and in the gifted program at school. His academic performance declined (performing at a second-grade level despite being the age of a sixth grader) for 6 months before his first witnessed seizure. He transitioned to home-school and became irritable, self-injurious, and suicidal. He was subsequently diagnosed with ASD, attention-deficit disorder, and oppositional defiant disorder. Neuropsychological testing revealed clinically significant deficits across several behavioral domains (Table 3). His neurological exam was normal. MRI of the brain demonstrated right middle temporal gyrus cavernous malformation and developmental venous anomaly. EEG recorded focal seizures from the right frontotemporal region spreading to the left hemisphere. Despite administration of levetiracetam and oxcarbazepine, the patient continued to have refractory subclinical seizures. He underwent resection of the right temporal lesion. Post-operative MRI showed GTR. The patient had rare seizures immediately following surgery but was seizure free at the 2-year follow-up on oxcarbazepine and clonazepam. He had significant improvement in his academic and social performance, although he has ongoing psychiatric problems requiring therapy and escitalopram. He no longer engages in self-injurious behavior and shows no signs of suicidal ideation.

Table 3. Neuropsychological assessment: Behavior Assessment System for Children-3 (BASC-3) Parent Rating Scale

Behavioral domain	Case 1		Case 2		Case 3	Case 4	Case 5
	pre-operative T-score, %ile (description)	post-operative T-score, %ile (description)	pre-operative T-score, %ile (description)	post-operative T-score, %ile (description)	pre-operative T-score, %ile (description)	pre-operative T-score, %ile (description)	
Externalizing problems	67, 94% (AR)	54, 73% (NR)*	44, 31% (NR)	43, 16% (NR)	66, 92% (AR)	102, 99% (CS)	NA
Internalizing problems	56, 78% (NR)	54, 70% (NR)	50, 61% (NR)	55, 79% (NR)	69, 95% (AR)	85, 99% (CS)	NA
Behavioral symptoms index	81, 99% (CS)	67, 83% (AR)*	57, 81% (NR)	54, 76% (NR)	70, 95% (CS)	90, 99% (CS)	NA
Adaptive skills	44, 25% (NR)	45, 28% (NR)	39, 14% (AR)	32, 5% (AR)	40, 17% (NR)	50, 47% (NR)	NA
Hyperactivity	91, 99% (CS)	71, 96% (CS)	49, 60% (NR)	44, 32% (NR)	61, 87% (AR)	83, 99% (CS)	NA
Aggression	48, 55% (NR)	44, 34% (NR)	44, 35% (NR)	42, 2% (NR)	65, 92% (AR)	111, 99% (CS)	NA
Conduct problems	55, 77% (NR)	46, 36% (NR)	39, 3% (NR)	44, 31% (NR)	70, 95% (CS)	90, 99% (CS)	NA
Anxiety	49, 55% (NR)	49, 55% (NR)	58, 80% (NR)	62, 88% (AR) ^a	59, 83% (AR)	84, 99% (CS)	NA
Depression	61, 87% (AR)	52, 66% (NR)*	45, 38% (NR)	49, 63% (NR)	93, 99% (CS)	84, 99% (CS)	NA
Somatization	56, 75% (NR)	58, 81% (NR)	48, 54% (NR)	54, 74% (NR)	48, 54% (NR)	69, 94% (AR)	NA
Atypicality	105, 99% (CS)	83, 99% (CS)	54, 78% (NR)	51, 72% (NR)	72, 95% (CS)	85, 99% (CS)	NA
Withdrawal	71, 95% (CS)	71, 95% (CS)	90, 99% (CS)	49, 94% (NR)*	43, 25% (NR)	49, 60% (NR)	NA
Attention problems	64, 90% (AR)	56, 75% (NR)*	52, 63% (NR)	64, 91% (AR) ^a	63, 89% (AR)	58, 78% (NR)	NA
Adaptability	49, 45% (NR)	58, 75% (NR)	46, 33% (NR)	38, 14% (AR) ^a	40, 18% (AR)	36, 8% (AR)	NA
Social skills	48, 38% (NR)	54, 59% (NR)	39, 15% (AR)	32, 6% (AR)	50, 46% (NR)	63, 92% (NR)	NA
Leadership	54, 63% (NR)	36, 10% (AR) ^a	32, 4% (AR)	29, 2% (CS) ^a	48, 43% (NR)	56, 71% (NR)	NA
Activities of daily living	38, 12% (AR)	38, 12% (AR)	50, 45% (NR)	46, 34% (NR)	30, 4% (CS)	37, 10% (AR)	NA
Functional communication	34, 7% (AR)	42, 18% (NR)*	34, 8% (AR)	27, 2% (CS) ^a	40, 18% (AR)	57, 75% (NR)	NA

Cases 1 and 2 were the only patients who had pre- and post-operative neuropsychological assessments completed at the time of reporting. Cases 3 and 4 had pre-operative testing only and case 5 had no testing performed. The table above contains parent-reported scoring of various behavioral domains via the Behavior Assessment for Children-3 (BASC-3). NR, normal range; AR, at risk; CS, clinically significant. *Improvement. ^aDecline.

Case 4

An 8-year-old, right-handed male presented with a 1-year history of nocturnal focal seizures occurring 4 times per week and daytime seizures once per week. His seizures were characterized by unresponsiveness, drooling, body stiffness, and occasional urinary incontinence. Around the time of seizure onset, he began to exhibit aggression, inattention, and hyperactivity. Because of these symptoms, he was required to transition to home-school and was diagnosed with ADHD and impulse control disorder. He developed suicidal ideation and self-mutilation (e.g., cutting his wrists), resulting in multiple psychiatric admissions. Neuropsychological testing revealed clinically significant deficits across several behavioral domains (Table 3). His neurological examination was normal. MRI showed infiltrative, cortical-subcortical expansile left temporal mass with small regions of internal nodular enhancement, left mesial temporal sclerosis with T2 hyperintensity, and an enlarged left hippocampus. EEG recorded focal seizures with left temporal onset characterized by rhythmic, high-amplitude spikes. He was placed on eslicarbazepine and zonisamide but remained refractory. The patient underwent

resection of the lesion and amygdalohippocampectomy, and GTR was achieved. Pathology revealed WHO 1 ganglioglioma (BRAF p. V504_R506 duplication) with focal cortical dysplasia, abnormal radial lamination, hippocampal sclerosis with CA4 neuronal loss and gliosis (ILAE type 3). He was seizure free at the 7-month follow-up on continued eslicarbazepine and zonisamide. His parents noted significant improvements in impulsivity, hyperactivity, attention, communication, and resolution of suicidal ideation. He returned to school where he has shown academic improvement and no aggression to teachers or other children.

Case 5

A 12-year-old, right-handed male presented with unprovoked GTC seizures lasting <2 min which have occurred four times at the time of presentation and began at age 11. He was previously diagnosed with ADHD at age 5, ODD at age 6, and disruptive mood regulation disorder at age 9. He was described as defiant and physically aggressive with his teachers, parents, and peers. He has had several psychiatric hospitalizations due to threatening homicidal behavior and aggressive behavior. He

frequently ran away from home, destroyed household objects, and punched holes in walls. Due to the severity of his behavioral issues, his parents sought to admit him to specialized residential facilities. These behavioral issues were maintained after seizure onset. His neurological exam was normal. MRI showed a nonenhancing mildly expansile T2 hyperintense, cortically based lesion in the left parietal lobe (Fig. 1). EEG did not record seizures but revealed left posterior slowing and diffuse generalized slowing with bifrontal sharp wave activity suggestive of diffuse cortical dysfunction. His seizures were controlled with oxcarbazepine for a period but subsequently had 3 more GTC seizures (total of 7 seizures at the time of surgery). During the period in which his seizures were controlled, his behavioral symptoms persisted. Thus, early resection was considered rather than another trial of ASMs, in part to improve his behavioral symptoms, although he did not meet the formal indications for surgery. The lesion was easily accessible for resection, and GTR was achieved. Pathology revealed a dysembryoplastic neuroepithelial tumor. At 8-month follow-up, he was seizure free on oxcarbazepine. Although no formal neuropsychological testing was performed, his mother noticed significant improvements in his behavior. She reported that he was less oppositional and has been compliant with medication. He no longer has episodes of running from home and shows no aggression to family members. She is no longer seeking a psychiatric shelter/residential facility for him. He also returned to school where he has shown significant academic improvement. Teachers have reported no problems with attention, hyperactivity, or aggression to other students.

Discussion

Here, we describe 5 patients who had epileptogenic lesions with concurrent behavioral symptoms who all underwent lesion resection and achieved seizure freedom. However, the most notable result was their dramatic behavioral improvement which was beyond our expectations and warranted reporting. Patients 1–4 met the formal criteria for epilepsy surgery due to medically refractory epilepsy or tumor growth. Patient 5 only had one trial of oxcarbazepine which offered some seizure control but did not provide relief of his behavioral symptoms. He was recommended for early surgery, in part, due to the severity of his behavioral symptoms. Our series suggests that surgery should be offered, in specific cases, before tumor progression or determination of refractory seizures as it can provide a dramatic rescue of behavioral decline, including return from home-schooling to general education, cessation of destructive/violent behavior, and improved social behavior. For these patients, behavioral improvement was arguably as important as seizure control for overall outcome due to the disruptive nature of these changes. This may have been particularly critical for the 3 patients who reported self-injurious behaviors and suicidality which resolved after surgery.

Personality changes like aggression, disinhibition, difficulty with emotional control, and social deficits have been documented with tumors involving the frontal lobe and limbic system [3, 15]. Mood dysregulation such as increased anxiety, depression, and social withdrawal have also been reported with brain tumors more generally [16]. However, behavioral symptoms may arise due to the lesions or due to the psychosocial stressors surrounding a tumor diagnosis, making it difficult to elucidate a clear relationship. In our cases, behavioral changes were noted by caregivers and either coincided with or occurred earlier than seizure onset before the lesions were identified. The behavioral changes significantly improved or normalized after resection. Similar patterns of increased aggression pre-diagnosis that improved after surgery have been noted in patients with temporal, parietal, frontal, and cerebellar tumors, suggesting an association between lesions and behavioral changes [11, 14, 17]. Furthermore, Simpson et al. [15] found that the presence of epileptic seizures in patients with brain tumors was associated with higher degrees of behavioral symptoms. Conversely, other reports have highlighted cases of increased anger, sadness, and disgust occurring only after surgery [18]. Findings in suicidality for brain tumor patients who undergo treatment have also been mixed [19]. There is overall no consensus regarding what effect resection of brain tumors has on behavioral outcomes. Interestingly, many of the cases that reported post-surgical behavioral improvement also noted a pre-surgical decline whereas those that reported post-surgical decline noted no pre-surgical symptoms [3]. Further investigation is needed to understand the mechanisms by which resection can lead to varying behavioral outcomes.

Behavior is thought to arise from communication between regions like the frontal cortex, striatum, and thalamus (cortico-striato-thalamic circuit) which putatively control decision-making, reward evaluation, affect regulation, and cognition [20]. The limbic system contributes to learning, memory, and emotional response – specifically fear, anxiety, and aggression [21]. These circuits have been implicated in a variety of psychiatric disorders [20]. Studies of seizure patients with elevated aggression have found decreased volume and hypometabolism in the regions mentioned [22, 23]. Behavioral abnormalities in epilepsy are well described and may include cognitive regression, poor IQ, difficulty with attention, memory dysfunction, and mood dysregulation [24] – many of which were observed in our patients whose lesions involved epileptogenic circuits. Interestingly, our patients demonstrated no clear correlation between seizure burden and severity of behavioral symptoms, but they all showed behavioral improvement after resection of the lesion. While resection can

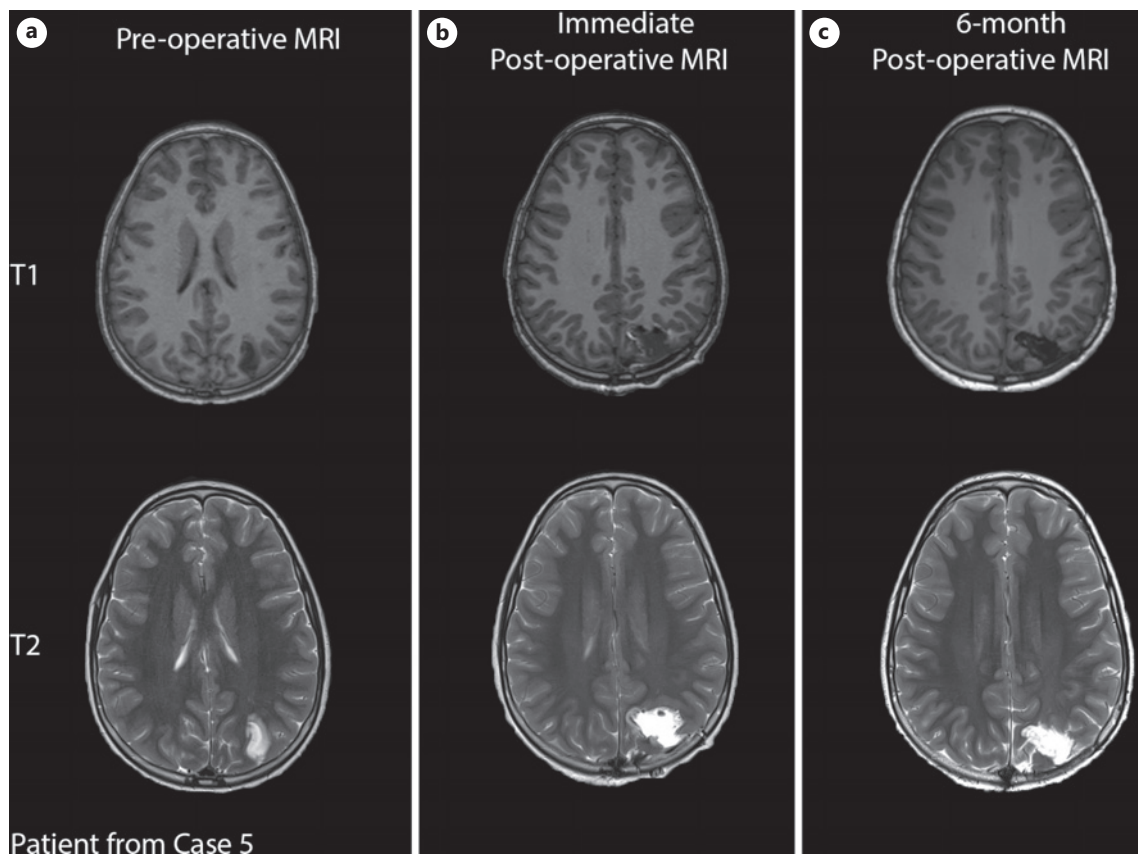


Fig. 1. Case 5 T1 and T2 MRI images. **a** Pre-operative MRI T1/T2, demonstrating mildly expansile T2 hyperintense lesion in the left parietal lobe. **b** Immediate post-operative MRI T1/T2, demonstrating expected post-surgical changes. **c** 6-Month post-operative MRI T1/T2, demonstrating expected post-surgical changes after GTR of lesion. Imaging for case 5 was chosen for this representative figure as this patient had the worst behavioral symptoms.

offer therapeutic benefit for both seizures and behavioral symptoms, seizure outcome is currently the dominant metric used to assess the indications and efficacy of epilepsy surgery pre- and post-operatively. Our experience suggests that behavioral metrics should be given more weight when considering resection for epileptogenic lesions. We suggest a paradigm shift in which surgery is considered for patients with predominantly behavioral issues rather than only for refractory seizures or tumor progression.

Beyond driving behavioral symptoms, epileptogenic lesions may be associated with psychiatric disease; however, this relationship is understudied and sporadically reported in the literature. Only a few case reports have described ASD associated with epileptogenic tumors, specifically in the cerebellum [25, 26] and mesial temporal lobe [27–29]. Two of the cases with temporal tumors saw major improvements in ASD symptoms [27, 28], and the last case demonstrated full clinical recovery from ASD, after surgery

[29]. The latter patient was a 3-year-old boy who had ASD and developed a mesial temporal lobe ganglioglioma with seizures [29]. After resection and complete seizure freedom, psychology follow-up showed increased sociability, decreased hyperactivity and aggression, improved eye contact, and decreased stereotyped behavior. Based on quantitative metrics, the clinicians determined that the patient had fully recovered from ASD. Notably, all of our patients were diagnosed with ASD, ADHD, or other psychiatric disorders either before or, in one case, after their lesions were identified. They all saw post-surgical improvements in sociability, attention, and aggression which are characteristic deficits in these disorders [30]. Given these promising initial reports, early surgery represents a possible mode of treatment for behavioral disorders in this specific subset of patients. By treating the underlying pathology in brain regions involved with behavior, the symptomatic dimensions of these comorbid behavioral disorders may also

improve to the point of remission. Moving forward, it will be important to establish the relationship between brain lesions and psychiatric disorders. Furthermore, given the controversial history of psychosurgery [31], we must also rigorously and methodically characterize the effects of resection on behavioral outcomes.

Limitations

We are aware that this case series is limited, as neuropsychological testing was not available for most patients in either the pre- or post-operative periods, making objective comparisons of behavioral improvement challenging. Formal neuropsychological testing can be challenging to obtain for patients due to personal, availability, and time constraints. However, we felt it was important to qualitatively report this phenomenology, so we highlighted the most salient examples of behavioral symptoms in our patients. In order to circumvent this issue in the future, we may collect validated parent-reported behavioral assessments that can be completed within the span of a clinical visit. Another limitation is that we do not have epidemiological data for this phenomenon as there are currently no formal criteria to define this patient population. More stringent criteria will be needed to include cases of subtle behavioral changes associated with epileptogenic lesions to understand the extent to which this phenomenon occurs and how often it improves after resection. Continued efforts at our center are aimed at bridging these challenges.

Conclusion

The present series describes 5 patients with lesional epilepsy who presented with significant behavioral abnormalities which significantly improved or resolved after resection of the lesion. Removal of epileptogenic lesions for medically refractory epilepsy is well accepted and has demonstrated high rates of seizure reduction or freedom. Although our understanding of the anatomy and neural circuitry involved in psychiatric symptoms in these epileptic lesions is limited, several reports, including our own, have documented dramatic behavioral improvements with

surgical intervention. We therefore propose a novel paradigm in which lesion resection is considered for patients with epileptogenic lesions and severe psychiatric or behavioral symptoms coinciding with seizure onset even in the absence of debilitating seizure burden.

Statement of Ethics

This study protocol was reviewed and approved by the Baylor College of Medicine Institutional Review Board, approval number H-51678. Written informed consent was obtained from the parents for publication of the details of their children's medical cases presented in this series and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Huy Dang drafted the work, acquired the data, approved the final version, and agreed to be accountable for the work. Abdul Basit Khan and Nisha Gadgil helped with data acquisition, revision for intellectual content, approved the final version, and agreed to be accountable for the work. Himanshu Sharma contributed to the intellectual content, approved the final version, and agreed to be accountable for the work. Cristina Tradafir and Fatema Malbari helped with conception and design of the study, revision for intellectual content, approved the final version, and agreed to be accountable for the work. Howard Weiner helped with conception and design of the study, revision for intellectual content, approved the final version, and is the corresponding author.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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