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Epilepsy Surgery in Tuberous Sclerosis: An Overview of Neurosurgical Concerns in a Low-Income Country

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Background and importance: Oftentimes, patients with early-onset seizures fail to respond well to initial medication. Mental retardation and early onset seizures are linked. There is growing evidence that early seizure control may adversely affect the development of cognitive skills and social behaviour in children with Tuberous sclerosis complex. According to recent studies, despite the challenges associated with epilepsy surgery planning for TSC patients, a substantial number of patients (>60%) can be seizure-free if the right clinical candidates are selected and evaluated.

Materials and methods: Using revised diagnostic criteria, we report the series of 10 patients diagnosed with TSC between 2014 and 2021. A referral was made to the department of pediatric neurosurgery at Shiraz University of medical sciences. Besides a thorough history and physical examination, a comprehensive neuropsychological assessment was conducted along with a high resolution (HR) EEG, seizure recording, and long-term video EEG. A neuropsychological test was performed at 6 months, 12 months, and 24 months after surgery. An MRI was also performed at 3 months. Seizure progression was classified according to the Engel classification at each time point.

Results: At the time of seizure onset, age ranged from 0.1 to 13 years, with the median age being 0.8 years. On average, each surgical candidate had epileptogenic foci located on their right side (in the temporal region of 3 patients, the frontal region of 4 patients, and the parieto-occipital region of 3 patients). A follow-up of 12-60 months revealed three patients reaching Engel class 1. The seizure frequency of the remaining 7 patients improved significantly by at least 50% during the first year of follow-up.

Conclusion: There have been several series published in the last few decades documenting good seizure results following epilepsy surgery in TSC. Over the past several decades, the perspective has changed, and different studies demonstrate that even if several tubers are present in the same area of the brain, the epileptogenic zone and one or two tubers almost always overlap, and this is especially true when partial seizures are present. TSC patients with DRE, multiple seizure types with early onset, multiple cortical tubers, and more than one epileptogenicity should consider epilepsy surgery as there is still no empirical evidence that these patients will have poor outcomes.

Keywords: Epilepsy surgery; Tuberous sclerosis; Drug resistant.

Abbreviations: TSC: Tuberculous Sclerosis Complex; DRE: Drug Refractory Epilepsy; EEG: Video-Electroencephalographic; Aeds: Anti-Epileptic Drugs; CNS: Central Nervous System; SGCA: Subependymal Giant Cell Astrocytomas; MRI: Magnetic Resonance Imaging.

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Introduction

A healthy individual with tuberous sclerosis complex (TSC) may develop a drug refractory epilepsy (DRE) as a result of cortical tubers. Childhood mental retardation has been linked to early seizure onset, an increased seizure burden, and early seizure control by any means [1]. Even though we have gained increasing knowledge about the genotype-phenotype relationship and about the basic mechanisms at the molecular level on which epilepsy is focused, we still face a problem in predicting seizure outcomes early on in epilepsy [2]. Oftentimes, patients with early-onset seizures do not respond well to initial medication and are left with an intractable condition. In video-electroencephalographic (EEG) recordings, the precipitation of epileptic spasms has been shown to precede focal signs. Traditional anti-epileptic drugs (AEDs) tend to be relatively frustrating as far as medical treatment is concerned. Further complicating this doom scenario is the fact that cortical tubers have a multifocal origin and a non-static behavior, as well as a propensity to become epileptogenic with age, presumably related to gradual maturation of cortical networks [3]. A growing body of evidence indicates that early seizure control may have an adverse effect on cognitive development and social adjustment of patients with Tuberous sclerosis complex. While the major factors affecting the long-term cognitive and behavioral outcome are the number and topography of the cortical lesions, there is a growing body of evidence suggesting the impact of early seizure control on long-term cognitive and behavioral outcomes [4]. As far as the neurosurgical aspect of tuberous sclerosis is concerned, this report examines the available literature and highlights the rationale behind performing a neurosurgical procedure to cease the medically refractory epileptic syndromes resulting from tuberous sclerosis.

It is estimated that one in 6,000 live births is affected by tuberous sclerosis complex. The condition is ranked third among neurocutaneous syndromes [5]. Mutations in either TSC1 or TSC2 cause the disease. TSC1 is located on chromosome 9q34 and encodes for hamartin. TSC2 is found on chromosome 16p13 and encodes for tuberin. Clinically and pathologically, both types of genetic conditions are often characterized by similar characteristics [6]. TSC is a multisystem disease that affects most organs of the body, including the central nervous system (CNS) as well as other organ systems with particular patterns of presentation and behavior in each of these areas. The clinical and pathological features of cerebral lesions are more pronounced and require additional neurosurgical treatment. Subependymal giant cell astrocytomas (SGCA) are the second leading cause of death among TSC patients, only outnumbered by renal disease [7]. These benign (WHO Grade I) intraventricular tumors almost always go hand in hand with TSC. They rarely occur sporadically. Patients with TSC are at increased risk of developing SEGA, a slow-growing tumor that arises from the lateral surface of the ependymal tissue adjacent to the foramen of Monro and projects into their lateral ventricles [8]. Asymptomatic tumors may result in hydrocephalus, which includes one or both sides of the lateral ventricle, when foraminal obstruction occurs. There is some evidence that mTOR inhibitors, including everolimus, can prevent or reverse SEGA growth, despite the fact that resection was the only treatment for tumor growth or hydrocephalus [9]. Astrocytomas with subependymal giant cells may also hemorrhage, resulting in acute neurological decline and the need for neurological surgery.

These types of tumors are usually benign glial tumors that develop around the nucleus caudatus, as well as the Monro foramen, and originate in the caudate-thalamic groove, causing obstructive hydrocephalus in most cases. Despite their slow growth and given their location, they are characterized by high mortality (around 50%) for bleeding, acute hydrocephalus, or intratumoral cystization [10]. In recent studies, it has been shown that, despite the difficulties associated with epilepsy surgery planning for TSC populations, a substantial percentage of patients (>60%) can become seizure-free with the right selection and evaluation of clinical candidates. Therefore, it is of great significance to identify predictors of seizure-free/unfavorable seizure outcomes prior to epilepsy surgery candidates [11]. It is a challenge to plan epilepsy surgery in a majority of TSC patients since they typically have multiple cortical tubers rather than just a single lesion, the common occurrence of multiple seizure types, and the presence of multifocal scalp EEG epileptiform activity. The EEG findings on scalp and MRI were concordant and localized, particularly interictal (but not ictal) focalizations, as well as concordant and localized findings on EEG and MRI. However, these results are not universally accepted [12].

In this study, our center describes how it has confronted a long road of seizures surgery for TSC patients.

Materials and methods

The Shiraz Comprehensive Epilepsy Surgery Programme in Shiraz, Iran, handled the preoperative work-up of 10 consecutive patients diagnosed with TSC between 2014 and 2021 according to the revised diagnostic criteria. The patients were referred to the department of paediatric neurosurgery at Shiraz University of medical sciences (Shiraz, Iran) for a preoperative evaluation. Comprehensive neuropsychological assessment was conducted in addition to a thorough history and physical examination, high resolution (HR) EEG, seizure recording, and long-term video EEG. All in all, electrode positions according to the 10-20 system were planned for video EEG. Registration of at least two seizures from each seizure type was required for continuation of the pre-surgical programme. Neurological testing was conducted at 3, 6, and 12 months and at the end of the follow-up period (latest trip to the outpatient clinic). Following surgery, an MRI was performed at 3 months and neuropsychological tests were performed at 6 months, 12 months, and 24 months. We used the Engel classification for assessing seizure outcome following surgery.

Results

A summary of demographic and pre-surgical illness characteristics of the 10 patients with TSC is summarized in (Table 1).

Observations on seizure semiotics

A median age of 0.8 years was observed at seizure onset, ranging from 0.1 to 13 years. Three patients presented with infantile spasms, five presented with complex partial seizures, two presented with secondary generalised tonic-clonic seizures. Seven patients suffered seizures daily, one patient suffered seizures weekly, and two patients had seizures less frequently.

The surgical intervention

Each surgical candidate had an epileptogenic foci located in

their right hemisphere (in the temporal region in 3 patients, the frontal region in 4 patients, and the parieto-occipital region in 3 patients). There were multiple tubers present in the temporal lobes of all four patients with temporal lobe epilepsy.

The series included 3 temporal lobectomies, 3 posterior temporal resections, 2 parieto-occipital tuberectomies, and 2 right-sided frontal corticectomies. In all of the patients studied, histopathological findings indicated a disorder of cortical lamination, which was corroborated by ballooning cells within the surrounding white matter, which is consistent with the diagnosis of tuberous sclerosis. One patient had a giant cell astrocytoma as well, which was partially exposed through a trans-callosal corridor.

The Engel's classification

The Engel class 1 was reached in 3 patients after follow-up (12-60 months). Following two years of seizure-free living, all of the three seizure-free patients have completely stopped taking their medication. There was fabulous improvement at the end of follow-up in all 7 other patients whose seizure frequency improved by >50% in the first 12 months.

During the first 12 months following surgical intervention, the parents of our patients noticed both a positive change of development and behavior. The most common postoperative complication involved transient short-term memory deficits in two patients.

Table 1: Detailed preoperative demographics for 10 consecutive patients with TSC and DRE.

Age (yrs)	Age at seizure onset (mo)	Seizure type	Seizure frequency	Inter-ictal EEG	Number of tubers
9		Infantile spasm	Weekly	Frontal	6
0.6	1	Complex partial	Daily	Frontal	4
1	4	Complex partial	Daily	Frontal	5
1.1	11	Secondary GTC	Daily	Parietal-occipital	9
5.4	33	Complex partial	Monthly	Temporal	3
5	7	Infantile spasm	Daily	Temporal	6
13	12	Secondary GTC	Daily	Frontal	8
1.6	4	Infantile spasm	Monthly	Parietal-occipital	5
3	2	Complex partial	Daily	Temporal	7
5	8	Complex partial	Daily	Parietal-occipital	11

Discussion

There have been several series published within the last few decades reporting good seizure outcomes following epilepsy surgery in TSC [1,4-6]. Among the patients in our series (30% Engel class 1), seizure outcome is comparable to other reports [4-6,13]. However, we were initially concerned that our relatively small sample size would undermine the study.

Oftentimes when there is a history of bilateral epileptogenic zones or when it is presumed that a progressive epileptic encephalopathy may occur, epilepsy surgery is not considered. As mental retardation is frequently associated with diffuse cerebral dysfunction, it is often regarded as a contraindication for epilepsy surgery [7,8,14]. For these reasons, along with the fact that - more often

than not - tubers are not always clearly delineated and may lie within the eloquent cortex, epilepsy surgery has long been unavailable to patients with TSC suffering from DRE. The perspective has changed over the past few decades, and different studies have demonstrated that after all, even if several tubers is coexisting in the same brain, the epileptogenic zone and one or two tubers almost always coincide, and even more so when partial seizures are experienced [15]. Hence, even a small number of tubers is not a hindrance to good seizure outcomes even if one or two tubers can't be resected. Emergence of new foci is often feared as a potential cause of epilepsy. It stands to reason that even with these factors, very few data support the epilepsy-prone tuber's hypothesis, instead, consistent electroencephalographic patterns are observed over time [14,15]. Historically it has been proven that patients with concordant semiology, EEG, and MRI findings are more likely to have a favorable surgical outcome [16]. Due to the fact that only a few patients with an epileptogenic zone suffer a favorable outcome, it is worthwhile to identify the area in patients with a primary epileptogenic zone. Despite the fact that follow-up time varies greatly between studies, many of them demonstrate that the tubers that remain do not develop epilepsy after the main epileptogenic region and associated tubers are removed [10,14,16]. After resection of a primary focus, there may be an opportunity to suppress the secondary foci or eliminate them following resection, which our study corroborated. We believe that epilepsy surgery should be considered for all TSC patients with DRE, multiple seizure types with early onset, multiple cortical tubers, and more than one epileptogenicity should undergo this surgery as the assumption of poor outcomes is not (yet) empirically supported [16]. There is too little data to make any conclusive statements from our series of patients; however, spikes of activity in other regions bordering the resection and incomplete resection of the tuberal regions (or parts the roof) appear to be associated with recurrent seizures. With the proposed technique of multistage surgery, epilepsy surgery has proven very effective when multiple epileptogenic tubers are identified in distant brain regions. In the context of severe epilepsy (e.g. during a critical period of neurodevelopment), the prospect of seizure recurrence must be weighed against the prospect of relief from severe epilepsy (temporarily). Psychometric follow-up indicated neither a catch-up nor a decay in the behavior of three subjects in our series, despite parents' assessment that development and behavior had improved.

Conclusion

To conclude, it can be stated that every patient with a TSC and drug-resistant epilepsy should consider the possibility of surgical removal. In spite of the fact that seizure freedom is an intangible goal for patients with severe intellectual disabilities, the possibility of dramatic seizure reduction makes surgery a compelling option if the comprehensive investigation is consistent with the seizure theory. The use of multimodal non-invasive techniques is very worthwhile and necessary in patients with complex medical problems without clear characterization of the epileptogenic tuber.

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