Corpus callosotomy for treatment of drug-resistant epilepsy: a review of 16 pediatric cases in northern Vietnam

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OBJECTIVE The aim of this study was to evaluate postoperative seizure outcome in children with drug-resistant epilepsy not eligible for focal resection who underwent corpus callosotomy.

METHODS The study included 16 patients undergoing corpus callosotomy between September 2015 and May 2018. Seizure semiology and frequency, psychomotor status, and video electroencephalography and imaging findings were evaluated for all patients.

RESULTS Of the 16 patients who underwent callosotomy during the study period, 11 underwent complete callosotomy and 5 underwent anterior only. Seizure improvement greater than 75% was achieved in 37.5% of patients, and another 50% of patients had seizure improvement of 50%–75%. No sustained neurological deficits were observed in these patients. There were no significant complications. Duration of postoperative follow-up ranged from 12 to 44 months.

CONCLUSIONS Corpus callosotomy is an effective treatment for selected patients with drug-resistant epilepsy not eligible for focal resection in resource-limited settings. Fostering and developing international epilepsy surgery centers should remain a high priority for the neurosurgical community at large.

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KEYWORDS drug-resistant epilepsy; corpus callosotomy; postoperative seizure outcomes

MEDICALLY refractory epilepsy (MRE) is an epidemiologically significant disease with a global burden and high economic cost to both patients and caregivers.^{4,15} Resective surgery is a well-established procedure for treatment of drug-resistant epilepsy, particularly in the presence of a focal epileptogenic lesion. However, in cases of nonlesional epilepsy or cases in which there are multiple lesions scattered across both hemispheres, the surgical approach requires significant preinvestigation and often invasive monitoring. In limited-resource settings in which invasive localization of seizure focus and palliative neuromodulation are not feasible, such cases have often remained untreated. In these circumstances, corpus callosotomy is a viable treatment option to reduce the burden of seizures and thus improve quality of life and ease of care.

Whereas there is a robust body of literature regarding the surgical treatment of epilepsy in high-income settings,

there are very limited data regarding its application in low- and middle-income countries. Based on this, the purpose of the current study was to report the early experience of performing corpus callosotomy at a single high-volume neurosurgical center in Hanoi, Vietnam. In so doing, we seek to show the safety of developing an epilepsy program in a middle-income country and demonstrate the utility of this surgical approach in reducing burden of disease in such settings.

Methods

Patient Selection

Approval was obtained from the University of Alabama at Birmingham and Vietnam National Cancer Hospital ethical review boards. A retrospective chart review was performed in children under the age of 18 years in whom

ABBREVIATIONS AEDs = antiepileptic drugs; Denver-II = Denver Developmental Screening Test, 2nd edition; MRE = medically refractory epilepsy; VEEG = video electroencephalography.

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a corpus callosotomy procedure was done during the period 2015–2018. Patients were identified from the National Cancer Hospital and National Hospital of Pediatrics, Hanoi, Vietnam. All surgeries were performed at the National Cancer Hospital. Follow-up information was available for all 16 patients. Patients were chosen for callosotomy based on the following criteria: 1) drug-resistant epilepsy despite trials of appropriately chosen antiepileptic drugs (AEDs) for at least 1 year; 2) seizures were frequent and disabling in character, such as causing traumatic falls; and 3) brain imaging findings were either normal or revealed abnormalities that were bilateral or not amenable for focal resection.

Preoperative Evaluation

Patients were evaluated preoperatively with multiple diagnostic modalities, including MRI, video electroencephalography (VEEG), and PET to exclude resectable foci. Information regarding seizure type, frequency, and age at onset of epilepsy was obtained from medical records. Clinical description of seizures and prolonged VEEG monitoring reports for each patient were also reviewed. Additionally, all patients underwent a Denver Developmental Screening Test, 2nd edition (Denver-II), to assess the degree of developmental delay.

Subspecialty Mentorship

The first author underwent complete neurosurgical training in Vietnam, which provided excellent volume and technical training, but did not include surgical management of epilepsy. In an effort to add this skill set to his practice, a collegial partnership was established with the senior author who had completed neurosurgical training in the US, with inclusion of a pediatric neurosurgical fellowship that provided expertise in epilepsy surgery. In 2015, an initial visit was made to the National Cancer Hospital to explore how a sustainable epilepsy program could be developed in northern Vietnam. Given the first author's extensive experience in the resection of intraventricular tumors it was decided that corpus callosotomy would be an ideal initial technique to teach. This was therefore the focus of the first visit, with particular emphasis on surgical indications and patient selection. Two surgical cases were performed during this visit with both the first and senior authors working together. Following this visit the primary author traveled to the senior author's institution in the US for a 3-month observership, during which time he was exposed to all aspects of the epilepsy program. On his return to Vietnam the collegial partnership continued in the form of telecollaboration for discussion of surgical candidates and patient selection. The details of this partnership have been previously published and are discussed at length elsewhere.¹⁴ All surgical procedures in this case series, other than the first 2, were performed independently by the first author and his surgical team at the National Cancer Hospital. We present here the details of the patients selected for intervention and their outcomes in this initial case series.

Operative Technique

The anterior corpus callosotomies were performed ac-

cording to previously published techniques. In brief, the patient is positioned supine, with his or her head turned parallel to the floor. A U-shaped skin incision is made, with the scalp flap elevated laterally in order to maintain adequate vascular supply. A square-shaped craniotomy is created, extending medially across the sagittal suture and proceeding laterally approximately 5 cm, with the anterior two-thirds of the opening anterior to the coronal suture and one-third behind it. A U-shaped dural incision is made with the flap elevated medially to protect the superior sagittal sinus. Minimal retraction of the ipsilateral cerebral hemisphere is necessary given the positioning of the head. Careful microneurosurgical techniques are used to dissect the interhemispheric fissure, with care taken to preserve venous structures where possible. Once the body of the corpus callosum is exposed and the anterior cerebral arteries are identified and protected, then a combination of bipolar electrocautery and suction aspiration are used to perform the callosotomy and separate the two cerebral hemispheres, stopping either after disconnection of the anterior two-thirds or separation of the entirety of the corpus callosum, depending on the preoperative indications. Following this, adequate hemostasis is obtained and the dura mater is closed in watertight fashion with layered closure of the scalp incision. Postoperatively the patient is observed overnight in the intensive care unit with normotension and adequate pain control. Following this the patient is transferred to a lower-acuity unit and mobilized as able.

Postoperative Analysis

Postoperatively, the character and frequency of seizures were compared to preoperative information. Reduction in daily seizure frequency was categorized into 1 of 4 groupings: Less than 50% improvement, 50%–75% improvement, more than 75% improvement, and seizure freedom. Each patient was followed for at least 12 months before being included in the study. Records were reviewed for perioperative or long-term complications following surgical intervention.

Results

Demographics

A total of 16 patients underwent callosotomy between September 2015 and May 2018. Fifteen of the patients were male. The average age at onset of epilepsy was 12 ± 11.4 months (range 3–48 months) with an average age at time of surgery of 63.8 ± 37.1 months (range 36–180 months). Epilepsy in all patients had been unsuccessfully managed with at least 3 AEDs at the time of surgery, with an average of 7.5 prior AEDs per patient. The mean frequency of seizures per day was 6.2. Atonic seizures were present in 11 (68.75%) of the 16 patients, tonic seizures were primarily present in 2 (12.5%), generalized tonic-clonic in 1 (6.25%), and multiple seizure types were present in 2 (12.5%) (Table 1).

Preoperative Workup

All patients underwent VEEG evaluation, which demonstrated bilateral spike-and-wave complexes that were

TABLE 1. Summary of 16 patients who underwent corpus callosotomy during the study period—with demographic, preoperative workup, and final surgical outcomes

Case No.	Age at Surgery (mos)	Age at Epilepsy Onset (mos)	Seizure Semiology	MRI Findings	Initial Procedure	Length of Hospitalization (days)		No. of Prior AEDs	Postop Seizure Outcome	Length of Follow-Up (mos)
1	48	5	Atonic	Normal	Complete	5	5	4	Improvement by 50–75%	44
2	96	5	Atonic	Normal	Anterior 2/3*	5	5	3	Seizure freedom	43
3	48	3	Atonic	Normal	Anterior 2/3*	6	6	3	Improvement by 50–75%	43
4	84	5	Generalized tonic-clonic	Normal	Complete	7	7	6	Improvement by <50%	42
5	48	5	Atonic	Normal	Anterior 2/3*	5	5	4	Improvement by 50–75%	42
6	36	17	Atonic	Normal	Complete	6	6	5	Improvement by 50–75%	42
7	48	10	Multiple	Bilat cortical encephalomalacia	Complete	5	5	6	Improvement by >75%	42
8	180	12	Tonic	Bilat cortical malformation	Anterior 2/3	6	6	4	Improvement by 50–75%	42
9	36	5	Atonic	Normal	Complete	8	8	3	Improvement by 50–75%	41
10	48	25	Multiple	Bilat cortical encephalomalacia	Complete	9	9	5	Improvement by >75%	41
11	96	48	Atonic	Nonspecific white matter changes	Anterior 2/3	6	6	6	Improvement by >75%	38
12	72	6	Atonic	Normal	Complete	7	7	5	Improvement by >75%	32
13	36	13	Atonic	Bilat cortical encephalomalacia	Complete	5	5	6	Improvement by <50%	32
14	36	7	Atonic	Normal	Complete	6	6	5	Improvement by 50–75%	30
15	60	4	Tonic	Bilat cortical malformation	Complete	8	8	3	Improvement by 50–75%	25
16	48	8	Atonic	Normal	Complete	7	7	6	Improvement by >75%	12

* Patient returned for completion of callosotomy during study period due to persistent seizures.

symmetrical in 15 cases and predominantly unilateral in 1. MRI was completed in all patients, with abnormal findings present in 6 patients. Three patients had bilateral cortical encephalomalacia, secondary to prior intraparenchymal hemorrhage in 1 and viral encephalitis in 2 others. Bilateral cortical malformations were seen in 2 patients and nonspecific white matter changes were found in 1. The remaining 10 MR images were without abnormality. PET imaging was done for 10 patients and demonstrated bilateral multilobar hypometabolism in 5 (50%), multifocal hypometabolism in 1 (10%), and no abnormalities in 4 (40%). All patients underwent pre- and postoperative Denver-II assessment, which demonstrated that 3 patients (18.7%) had mild delay, 7 (43.8%) had moderate delay, and 6 (37.5%) had severe delay before surgery. Postoperatively the distributions were similar, with 3 (18.7%) having mild delay, 8 (50%) having moderate delay, and 5 (31.25%) having severe delay.

Operative Intervention and Outcomes

A total of 11 patients underwent a complete callosotomy at first procedure, and the remaining 5 initially underwent anterior callosotomy. During the follow-up period, 3 patients returned for completion of their callosotomy due to persistent seizures. The average operating time was 120 ± 20.4 minutes. All hospital stays were between 7 and 10 days postoperatively. All patients were followed in clinic after discharge from the hospital; the average follow-up time was 20.2 ± 8.3 months (range 12–44 months). One patient obtained complete seizure freedom after callosotomy, with another 5 having greater than 75% reduction in their daily seizure frequency. Eight others obtained between 50% and 75% reduction in daily seizure frequency, and 2 patients had less than 50% improvement. There were 3 cases of postoperative fever, which resolved spontaneously. There were no infections, CSF leakage, postoperative hydrocephalus, or other complications. There were no patients lost to follow-up.

Discussion

The Global Obstacle of MRE

In a recent metanalysis by Vaughan et al.,¹⁵ the global prevalence of epilepsy was estimated to be 690 per 100,000 person-years. Additionally, there were an estimated 1.3 million new cases of surgically treatable epilepsy each year, with more than 400,000 of these being found in the Western Pacific region, which includes Vietnam. In the same study, the regions with the highest burden of estimated surgically amenable epilepsy were comprised primarily of low- and middle-income countries where access to neurosurgical care is most limited. Given that the surgical management of MRE has been shown to be financially efficacious in both adult¹³ and pediatric¹⁶ populations, the development of the needed infrastructure to provide these surgical services in resource-constrained settings should be a priority of the neurosurgical community.

An apparent obstacle to the provision of surgical intervention for MRE is the significant resources and expertise that are required beyond the level of the individual surgical provider. As such the task can appear daunting.

Specifically, the training and provision of adequate electrophysiological equipment and technologists, epileptology support, diagnostic imaging capabilities, and the multidisciplinary cohesion necessary to develop and implement complex treatment plans are difficult to achieve with limited resources. Despite these obstacles there is probably a large cohort of patients who could benefit from straightforward lesionectomies and disconnection procedures such as callosotomy. Such techniques typically have a more well-defined anatomical stopping point that allows for their use even in the absence of more complex diagnostic and monitoring capabilities.

Our Experience With Callosotomy

We present here the initial results of the adoption of epilepsy surgery techniques at a large neurosurgical center in Hanoi, Vietnam. The details and growth of the partnership between our two centers has been described previously.¹⁴ In our series 16 patients received a surgical intervention, with half obtaining at least 75% improvement in their seizure frequency, and nearly all (15 [93.7%] of 16) reducing their seizures by at least 50%. An analogous series by Kwan et al. in Taiwan demonstrated significant improvement in seizure burden ranging from 58.6% to 82.1% of patients, depending on preoperative seizure semiology.⁸ Another series by Fandiño-Franky et al. reported the outcomes of 97 patients undergoing callosotomy in Cartagena, Colombia, in which approximately 66% of patients obtained seizure freedom or were left with minimally disabling seizures.²

The literature from high-income settings is summarized in a meta-analysis by Graham et al.³ of 12 pediatric studies indicating that meaningful seizure reduction was achieved in 88.2% of patients undergoing complete callosotomy and 58.6% of patients undergoing anterior callosotomy only. Notably, these authors also found that the incidence of disconnection syndrome was much higher in those cases undergoing complete callosotomy (12.5%) in comparison to anterior only (0%).³ Additional series by Luat et al.⁹ and Jalilian et al.⁵ demonstrated meaningful seizure reduction in high-income settings ranging from approximately 50% to 91%.

The outcomes of our own series were compatible with the above-reported results as well as others¹² that reflect both high- and low-income settings. It is notable that there were no cases of disconnection syndrome diagnosed postoperatively; however, this is most likely explained by the fact that most patients who were considered candidates for complete callosotomy were significantly debilitated, with either a moderate or severe delay according to the Denver-II assessment.

Strategies for Moving Forward

Our series currently represents the only study of epilepsy surgery outcomes based in Vietnam. As such, the data we present here represent a significant evolution in the neurosurgical sophistication and capability in the region. Indeed, Vietnam has a relatively large and well-experienced neurosurgical workforce⁶ that provides significant familiarity with surgical approaches via the corpus cal-

losum. As a result, the technique was able to be adopted as an epilepsy intervention with minimal additional surgical mentorship. This perhaps dispels an unfounded concern that teaching complex surgical techniques during a short-term visit is neither safe nor achievable. Our experience suggests that the opposite is true: apart from the first 2 cases, all procedures were performed independently by the first author and without surgical assistance from foreign collaborators. Once the Vietnamese colleagues became facile with the surgical technique the majority of the mentorship occurred in the form of telecollaboration to facilitate appropriate patient selection. Thus, the relationship was not confined to a short-term surgical trip, but rather the visits are highlights in the broader long-term collaboration. It is important to note that in any one trip even the most ambitious visiting surgeon is only able to complete a finite number of procedures. In contrast, by focusing one's efforts on education and collaboration the number of patients treated is increased exponentially. The success of this paradigm highlights the feasibility and sustainability of such subspecialty training models and transcontinental neurosurgical partnerships. Similar feasibility is reported by Kuzniecky et al. regarding multidisciplinary and longitudinal epilepsy surgical education provided to neurosurgical partners in Panama.⁷

All neurosurgeons are aware of the significant burden that comes with operating on another human being and making decisions on their behalf intraoperatively. The complexities related to this require significant insight and consideration of the patient's individual values. Although cross-cultural surgical education is challenging, we would propose that cross-cultural surgical decision-making is far more complex and arduous. Thus, beyond the logistical benefits of closer care such as lower cost and shorter travel distance, the patients are undeniably better served by the availability of a same-culture neurosurgeon.

Last, the outcomes of our surgical experience indicate that with proper patient selection, a highly effective surgical epilepsy practice is possible, even in the absence of more costly investigative technologies. The data by Vaughan et al. would suggest that full-scale epilepsy centers should be a priority for resources, but the sheer volume of the global burden also indicates that thousands of patients could have their lives improved with lesionectomy and palliative disconnection alone.¹⁵ Thus, whereas a full-scale epilepsy center will take time and local financial investment to establish,^{1,10,17} many people can and should receive the care that they need with little more than the status quo for available treatments.¹¹

Conclusions

The initial results of epilepsy surgery in northern Vietnam are very favorable. The outcomes attest to the well-established surgical skill of the Vietnamese neurosurgeons and the growth of the specialty as a whole in the region. Strategic collaborations focused on building and educating local partners with long-term goals in mind are an ideal use of time and resources for visiting neurosurgeons. Although epilepsy surgery requires a complex network of expertise and infrastructure, there are many patients who could re-

ceive benefit with the resources currently available. Fostering and developing international epilepsy surgery centers should remain a high priority for the neurosurgical community at large.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Duc Lien, Tuan, Vu Hung. Acquisition of data: Duc Lien, Tuan, Vu Hung. Analysis and interpretation of data: Lepard. Drafting the article: Lepard. Critically revising the article: Rocque. Reviewed submitted version of manuscript: Rocque. Study supervision: Rocque.

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