Case Report

Anterior corpus callosotomy in patients with drug-resistant epilepsy: Invasive EEG findings and seizure outcomes

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ABSTRACT

Corpus callosotomy (CC) is used in patients with drug-resistant seizures who are not candidates for excisional surgery and failed neurostimulation. We examined ictal scalp and intracranial electroencephalogram (iEEG) recordings in 16 patients being evaluated for anterior CC alone or CC in combination with focal resection, to determine the role of the iEEG in predicting postoperative seizure outcomes. In our cohort, CC improved generalized atonic seizures and focal seizures with impaired awareness but did not alter outcomes for generalized tonic–clonic or tonic seizures. Invasive EEG prior to CC did not refine the prediction of postsurgical seizure outcomes in patients with inconclusive scalp EEG.

1. Introduction

Introduced by van Wagenen in 1940, corpus callosotomy (CC) is a palliative disconnection procedure for patients with drug-resistant epilepsy who are not suitable candidates for excisional surgery. Anterior callosotomy, the most commonly used modification of this procedure, involves interruption of the anterior mid-body of the corpus callosum that carries interhemispheric motor connections [1] thought to be essential for the generation of generalized atonic and tonic–clonic seizures (GTCs) [2,3]. In epilepsies with these seizure types, the successful postoperative outcomes have been consistently demonstrated. However, the treatment responses in other seizure types have not been well understood. While the previous applications of CC were largely restricted to the patients with disabling generalized seizure syndromes, such as Lennox–Gastaut syndrome (LGS) and infantile spasms, the indications have recently expanded to the patient populations with other epilepsy etiologies [3]. These include drug-resistant focal epilepsies in patients without identifiable lesions or those with multiple lesions which are not amenable for resection [4].

Postoperative seizure outcomes of CC varied significantly across patient populations and appeared to correlate with several clinical factors such as age at surgery, seizure types and presence of the abnormalities of cortical development [1,2]. Additional factors, such as the electrographic signature of patients' seizures, have been examined prior to CC [2,5]. However, the agreement on how presurgical electrographic patterns relate to seizure outcomes is lacking. The presence of anterior-dominant ictal discharges on the scalp EEG was shown to predict better seizure outcomes compared to those with posterior-dominant discharges in LGS [6]. Still, such a relationship has not been examined in other patient populations. In the present study, we examined the role of the ictal EEG findings on presurgical surface and invasive recordings in predicting postoperative seizure outcomes after CC. Furthermore, we examined the distribution of ictal discharges in the rostral–caudal dimension of the frontal grid electrodes and examined the role of preoperative invasive EEG (iEEG) in establishing lateralization of ictal onset in patients with inconclusive lateralization on non-invasive evaluation. In the treatment approach highlighted in this study, we attempted to improve upon the expected palliative effects of CC with the placement of bilateral subdural electrodes as the initial planned stage in a two-step epilepsy surgery.

2. Material and methods

2.1. Selection of patients

The present series was drawn from all retrospectively identified subjects (age 4 years and above) who received anterior CC or combined CC and resection of the epileptic focus (CC/combined) at the University of Nebraska Medical Center between October 2009 and June 2016. The CC regarded the anterior two-thirds of the corpus callosum in all patients. The patients were included if they were diagnosed with drug-resistant epilepsy, underwent comprehensive evaluation with

prolonged scalp and invasive video EEG monitoring and had clinical follow-up for more than 9 months. The patients were treated by two epileptologists and two epilepsy midlevel providers. All but one patient had magnetic resonance imaging (MRI) with a dedicated seizure protocol. Magnetoencephalography (MEG) was performed in five patients.

Patients' clinic notes, imaging reports, surgical interventions, and EEG recordings prior to CC were reviewed. The primary planned intervention in these patients was a CC. The indication for iEEG monitoring was based on the possibility of co-existing focal seizures that could not be lateralized based on the information obtained during the scalp ictal EEG recording. These indications included seizure semiology suggestive of focal onset, MEG results, MRI or ictal EEG findings showing significant asymmetry in bilateral synchronous epileptiform discharges. The patients who failed to demonstrate focal electrophysiologic lesions on iEEG underwent CC alone.

A heterogeneous approach was noted in the methodology for presurgical evaluation and iEEG intracranial EEG montages, which reflects the pattern previously reported by other epilepsy centers [7]. All surgeries were performed by a single surgeon (M. P.) and were staged similarly with the initial placement of intracranial subdural electrodes and subsequent callosotomy alone or combined callosotomy with focal resection during the same surgical admission. The CC was performed via parasagittal craniotomy that crossed the midline. Preoperative MRI was used to measure the distance corresponding to the anterior two-thirds of the CC. The midline of the corpus callosum was identified between the paired pericallosal arteries; the transection was carried out around the genu to the rostrum and body of the corpus callosum until the predetermined distance was achieved.

2.2. Seizure outcomes

The annual pre- and postoperative frequencies of five different seizure types (i.e., generalized clonic–tonic, focal with impaired awareness, generalized atonic, tonic, and generalized atypical absence) were recorded during the last ambulatory clinic visit prior to CC and during the last postoperative follow-up visit. The frequencies of other seizures, including focal aware and myoclonic were recorded but were not used for statistical analyses. Seizures were classified according to the operational classification of seizure types by the International League Against Epilepsy [8]. Patients were assigned a postoperative outcome category [5,9] that indicated the level of seizure improvement after surgery (i.e., 1 = seizure free without medications, 2 = seizure free with medications, 3 = seizure reduction more than 50% from preoperative baseline, 4 = seizure reduction less than 50%, 5 = no change, 6 = worsened) for each seizure type. In cases when the range of seizure frequency was provided instead for the exact seizure count, the mean seizure frequency was calculated. If seizures occurred in a cluster on the same day, the total count of seizures in a cluster was obtained.

An overall seizure score was assigned to each patient based on the highest (least improved) postoperative improvement category of any of their seizure types. Patients were initially categorized into three groups; i.e., improved, no change, or worsened and then dichotomized into groups consisting of patients who were improved (I), when the highest score across seizure types was less than or equal to 4 or not improved (NI) when the highest score across seizure types was equal or greater than 5. This dichotomized approach was used to assess the impact of surgery on the overall seizure density. Furthermore, these scores were used to examine the predictive value of the preoperative EEG findings and additional patient characteristics (i.e., imaging findings, type of procedure, age at seizure diagnosis, age at CC, duration of postoperative follow-up and number of seizure types in each patient) for the success of CC.

2.3. EEG recording and analysis

The EEG acquisition was performed using the XLTEC 7.1.1 video-EEG system (Natus, Oakville, ON, Canada). The scalp EEG electrodes were placed according to the 10–20 international system of electrode placement. Platinum invasive electrodes (Integra Life Sciences Corporation, Plainsboro, NJ) were placed unilaterally during craniotomy performed 3–4 days prior to CC or combined CC and focal resection. The montages for iEEG recordings were comprised of subdural grid and strip electrodes, which were chosen individually based on the information obtained from the surface EEG, imaging and other presurgical tests. The EEG recordings were reviewed for ictal patterns without knowledge of patient's clinical characteristics by two epileptologists O.T. and D.M. independently. In patients who underwent placements of frontal subdural grid electrodes, the rostral–caudal gradient of ictal discharges was determined based on a numeric score assigned to each row. The latter was calculated based on the total number of electrode columns displaying the same ictal pattern. The analysis of ictal patterns was followed by the review of video recordings to confirm ictal semiology.

2.4. Statistical analysis

Statistical analysis was performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC). Descriptive statistics (i.e., annual pre- and post-operative frequencies) were calculated for the entire study population. Patients who did not have a specific seizure type either before or after CC were assigned corresponding missing values. Patients who exhibited a seizure type in one period but not the other were assigned a value of zero for the period without activity.

The postoperative seizure improvement categories 1–5 were assigned as noted above and a sign test was run for each seizure type except for atypical absence (small sample size) with a null hypothesis value of 5 (i.e., no change) to determine improvement after surgery. A sign test was also used on the overall seizure score to determine if there was an overall significant change in density of seizures postoperatively. In addition, a difference score was created to indicate the change in the number of medications taken after surgery (relative to that prior to surgery), and a sign test was carried out to see if there was a significant change. Following the assignment of the overall seizure scores as improved or unimproved, Fisher's exact tests were performed to determine if improvement was associated with surgery type (CC vs. combined CC), MRI findings (normal vs. abnormal), or particular ictal patterns on preoperative iEEG. In addition, the differences between the I and NI groups were assessed using Wilcoxon two-sample exact test for age at epilepsy diagnosis, age at surgery, duration of postoperative follow-up, and number of seizure types.

3. Results

3.1. Participant demographic and clinical characteristics

Clinical records from 21 pediatric and adult patients with CC and combined CC/focal resection were reviewed. Two patients were excluded from the study: one patient expired on day 11 following CC due to the acute respiratory failure caused by laryngomalacia and possible vocal cord paralysis, and the other patient relocated and was lost to follow-up. Three additional patients did not have invasive preoperative monitoring and were also excluded. Sixteen patients met the inclusion criteria (11 male, 5 females; Table 1). The mean age of participants was 26.1 years (range 4–53); there were 7 children and 9 adults. The mean age at epilepsy diagnosis was 4.9 years (range 0.2–19), while the mean age at CC was 24.8 years (range 3–51). The patients' diagnoses prior to CC were established on the basis of the clinical features, and scalp EEG data included drug-resistant bifrontal epilepsy (6), encephalopathic generalized epilepsy (4), multifocal epilepsy (3), LGS (2), and drug-resistant focal epilepsy (1) (Table 1).

All but one patient had various degrees of cognitive disability. Formal neuropsychological assessment prior to CC was available only in 31% (5) of patients. The results revealed the presence of moderate and mild cognitive impairment in three and two patients, respectively. The

Table 1
Patient demographic and clinical characteristics.

ID#	Preoperative epilepsy diagnosis	Additional comorbidities	MRI findings	Age at diagnosis, years	Age at surgery, years
1	Multifocal epilepsy		Polymicrogyria	10	42
2	Multifocal epilepsy	Down syndrome	Normal	0.75	6
3	Encephalopathic generalized epilepsy		Bilateral frontal cortical dysplasia	1.5	11
4	Drug-resistant focal epilepsy	Sturge–Weber s-m, hemorrhagic stroke	Left hemispheric angiomatosis	0.2	3
5	Drug-resistant bifrontal epilepsy	Autism	Normal	1	13
6	Drug-resistant bifrontal epilepsy		Normal	19	27
7	Refractory bifrontal epilepsy	Oligodendroglioma resection, stroke	Encephalomalacia, left frontal parietal	4	43
8	Symptomatic generalized epilepsy	Static encephalopathy	Generalized cerebral volume loss	12	44
9	Symptomatic generalized epilepsy	Static encephalopathy	Mild diffuse cerebral atrophy	6	21
10	Multifocal epilepsy	Tuberous sclerosis	Multifocal cerebral hemispheric tubers and subependymal nodules	0.5	14
11	Symptomatic generalized epilepsy		Signal void, subcortical white matter and right inferolateral parietal occipital region	8	13
12	Refractory bifrontal epilepsy		Normal	7	14
13	Refractory bifrontal epilepsy	Static encephalopathy	Vascular malformation, suprasellar region	2	17
14	Lennox–Gastaut s-m		Normal	1	10
15	Lennox–Gastaut s-m		Not performed	1	28
16	Refractory bifrontal epilepsy		Normal	4	11

other seven patients had severe cognitive impairment with minimal or absent verbal ability per assessment of their neurologist. Four patients had no available assessment of their cognitive function.

Additional central nervous system co-morbidities were present in 44% (7) of patients (Table 1). Abnormal findings on the cranial MRI were present in 56% (9) of all participants while MRIs were normal in 38% (6) of participants and data was unavailable in one patient (Table 1). All patients but one were treated with vagal nerve stimulation (VNS) prior to CC and all patients were receiving 2–5 (median 5) anti-seizure drugs at the time of surgery.

3.2. Postoperative seizure outcomes

Fifty percent of the patients underwent CC alone while the remaining half of the patients had additional excision of an epileptiform foci or disconnection during the same craniotomy (Table 2). The indication for CC was drug-resistant epilepsy with generalized tonic, atonic, GTCs or atypical absence seizures leading to falls and injuries. The other indications included bilateral or bisynchronous ictal discharges on EEG with no localizing findings on brain imaging (patients 6 and 13).

The combined procedure of CC and resection of an epileptiform focus was performed in seven patients (Table 2). The indications for this procedure were drug-resistant focal seizures expected to be palliated following the resection of ictal foci identified in regions of cortical dysplasia (patients 2 and 3), cortical angiomatosis (patient 4), encephalomalacia from the previous tumor resection (patient 7) and tuberous sclerosis (patient 10). Patients 8 and 12 underwent CC and left and right frontal lobectomy, respectively, based on the findings of the ictal focus on iEEG.

Following the procedure, patients were seen in the clinic on average for 15.5 months (range 9–28 months). The mean annual counts of GTCs, focal seizures with impaired awareness (FIAs), generalized atonic, tonic, and atypical absence seizures prior to CC were 20 ($n = 6$), 5884 ($n = 7$), 2395 ($n = 7$), 207 ($n = 4$), and 1940 ($n = 2$), respectively. Following the surgery, the mean seizure counts of GTCs and FIAs decreased by 30% and 21%, respectively. The frequency of generalized atonic, tonic, and atypical absence seizures reduced by 65%, 55% and 100%. Patients 4 and 10 also had frequent preoperative focal motor and myoclonic seizures related to cerebral angiomatosis and tuberous sclerosis respectively. The latter resolved but the former remained unchanged after CC (Table 2).

Table 2
Seizure characteristics after corpus callosotomy.

ID#	Type of surgical procedure	Postoperative seizure category						Duration of follow-up, mon	Reduction in number of ASDs	Cumulative seizure score
		GTC	FIAs	Atonic	Tonic	Atyp absence	Other			
1	CC				3			17	−1	I
2	CC, right frontal lobectomy, right parietal lobe resection			3				18	0	I
3	CC, right frontal lobectomy	5	5					25	0	NI
4	CC, left frontal lobectomy		4				5	11	2	NI
5	CC			3				14	0	I
6	CC	2	3					9	0	I
7	CC, left frontal lobectomy, left temporal lesionectomy		3					9	1	I
8	CC, left frontal lobectomy				2			21	0	I
9	CC				5			18	−1	NI
10	CC, left frontal lobectomy				2		2	14	0	I
11	CC, disconnection of bifrontal adhesions				2	2		13	0	I
12	CC, right frontal lobectomy	2	3					14	1	I
13	CC	2	3					17	0	I
14	CC	5		2	5			10	−1	NI
15	CC	6		2		2		28	0	NI
16	CC			2	2			11	0	I

GTC, generalized tonic–clonic; FIA, focal with impaired awareness; I, improved; NI, not improved; ASD, anti-seizure drugs.
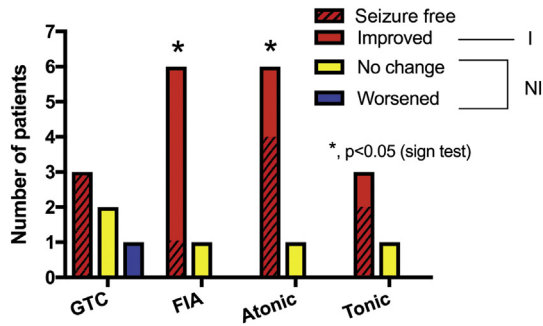
Fig. 1. Postoperative seizure status after corpus callosotomy. I, improved; NI, no improvement. GTC, generalized clonic–tonic; FIA, focal seizures with impaired awareness.

To account for large inter-subject variabilities in seizure frequency, further analysis was performed using postoperative seizure categories assigned based on the change in seizure density from individual preoperative baselines for each seizure type (Table 2). Using this approach, we revealed that 11 out of 16 patients (69%) achieved an improved overall seizure status after the surgery ($p = 0.003$; Fig. 1). This improvement was significant for the generalized atonic and FIAs types ($p = 0.003$, post-hoc tests) but not for the GTCs or generalized tonic seizures ($p = 0.63$ and $p = 0.25$, respectively; Fig. 1). Specifically, 86% and 71% of patients with generalized atonic and FIAs respectively achieved postoperative seizure categories 1–3 (i.e., at least 50% reduction of seizure density from preoperative baseline) (Table 2). Furthermore, 50% and 75% of patients with GTCs and FIAs respectively achieved similar favorable seizure categories. Two patients with generalized atypical absence (patient 11 and 15) and one patient with myoclonic seizures (patient 10) achieved postoperative category 2, (i.e., complete resolution of seizures), while one patient with focal unaware seizures (patient 4) did not improve (category 5). Overall, when tonic, atonic and focal myoclonic seizures leading to falls were considered collectively, eight patients had an improvement while three had no change. Further analysis was not performed for generalized atypical absence and other types given the small sample size. Patients who improved after surgery tended to have fewer seizure types (median = 1) relative to patients who did not improve after CC (median = 2); however, this difference only approached significance ($p = 0.05$). Interestingly, there was no change in use of anti-seizure drugs after CC ($p = 1.0$; Table 2).

The analyses of additional clinical characteristics, including preoperative MRI findings or type of surgery, revealed no association between these variables and overall improvement after surgery defined as postoperative seizure categories 1–4 ($p = 0.60$ and $p = 1.0$, respectively).

Patients who improved after CC tended to be older at the time of surgery (mean age 29.8 years) relative to patients who did not improve (mean age 13.6 years), however, this difference approached significance ($p = 0.05$). There was no significant difference in the median age at epilepsy diagnosis or duration of follow-up between the patients who improved and those who did not improve after CC.

3.3. Patient complications

There were no deaths in the cohort of patients who met the inclusion criteria. One patient developed a subdural abscess that required drainage. Two patients required treatment in an acute rehabilitation facility for focal weakness after the surgery. One patient developed gait instability, which necessitated treatment in an inpatient rehabilitation facility. Five patients had varying degrees of transient postoperative dysphagia. One required placement of a temporary gastric feeding tube. Five patients had a mild degree of deconditioning and speech difficulties, which improved with outpatient physical, occupational, and speech therapies.

3.4. Ictal EEG characteristics

The data obtained during the analysis of surface EEG recordings was inconclusive to lateralize ictal onset in 10 out of 16 patients (63%). The ictal patterns of these patients on the scalp EEG were characterized by multifocal, generalized or bilateral synchronous spike–wave discharges (SWD) which were frontally-predominant (Table 3). The patterns in the remaining five patients (31%) were focal SWD. The scalp EEGs for 6% of the patients were not available.

The intracranial electrode montages for all participants included right or left frontal grid arrays (64 contacts; 8×8 array or 32 contacts; 4×8 array) combined with various combinations of ipsi- or contralateral frontal strip electrodes as well as parietal, temporal, or interhemispheric strip or grid electrodes (Table 3). In all but one patient the electrodes were placed bilaterally (Table 3). There were 4–8 contacts in the strip electrodes, 32–64 contacts (4×8 or 8×8 arrays) in parietal grids, and 20 contacts (4×5 array) in temporal grids. The interhemispheric grid arrays were comprised of 16 (4×4), 20 (4×5), or 32 (4×8) contacts.

The ictal onset patterns on iEEG recordings were characterized by SWD in 13 patients (81%) or by electrodecremental response with superimposed fast activity (DSF) in 7 patients (44%) (Fig. 2A–B). Four patients (25%) had a combination of these patterns. The SWD and DSF were recorded during seizures of multiples types, including FIA, generalized tonic, atonic and atypical absence events with no apparent

Table 3
Preoperative ictal EEG findings and intracranial electrode montages.

ID#	Preoperative ictal EEG findings		Intracranial EEG montages	
	Surface	Intracranial	Left hemisphere	Right hemisphere
1	Left temporal SWD	SWD, DSF (bilateral fronto-temporal)	FG, PS × 2; IHS × 4, TS × 2	FS × 2; PS × 4; IHS × 4, TS × 2
2	Left frontal and right centro-parietal SWD	SWD, DSF (right frontal and right parietal)	FS × 2, PS × 1; IHS × 3	FG; PG; IHS × 3
3	Right frontal SWD	SWD, DSF (right frontal)	FS × 2; PS × 1; IHG	FG; IHG
4	No ictal	SWD (left frontal)	FG, PG, IHS × 4	
5	Generalized SWD	SWD (bifrontal, right > left)	FS × 3; IHS × 2	FG; TG; IHS × 3
6	Multifocal and bifrontal SWD	SWD (bifrontal)	FS × 3; IHS × 2	FG; IHS × 3
7	Left fronto-central SWD	DSF (left frontal)	FG; TG; sub TS × 3, IHS × 5	
8	Generalized SWD	SWD (left frontal)	FS × 2; PS × 1; IHS × 4	FS × 2; PS × 1; IHS × 4
9	Left frontal SWD	DSF (left frontal)	FG; IHS × 3	FS × 3; IHS × 2
10	Bifrontal synchronous SWD	SWD (left frontal)	FG; TG; IHG	FS × 2; PS × 1; IHG
11	Bifrontal synchronous SWD	DSF (bifrontal)	FS × 4; IHG; IHS × 1	FG; FS × 1; IHG; IHS × 1
12	Bifrontal synchronous SWD	SWD (right frontal)	FS × 5; IHS × 3	FG; LFS × 4, IHS × 4
13	Generalized SWD	SWD (left frontal)	FG; IHS × 4	FS × 3; PS × 3; IHS × 4
14	Bifrontal synchronous SWD (left > right)	SWD (bifrontal)	FS × 3; IHS × 2	FS × 4; IHS × 3
15	Generalized, frontally predominant SWD	SWD (bifrontal)	FS × 2; PS × 4; IHS × 4	FG; PG; IHS × 4
16	Generalized SWD	SWD, DSF (bifrontal)	FS × 3; IHS × 2	FS × 4; IHS × 3

SWD, spike–wave discharges; DSF, electrodecremental response with superimposed fast activity; FG, frontal grid; TG, temporal grid; PG, parietal grid; FS, frontal strips; TS, temporal strips; PS, parietal strips; IHS, interhemispheric strips.
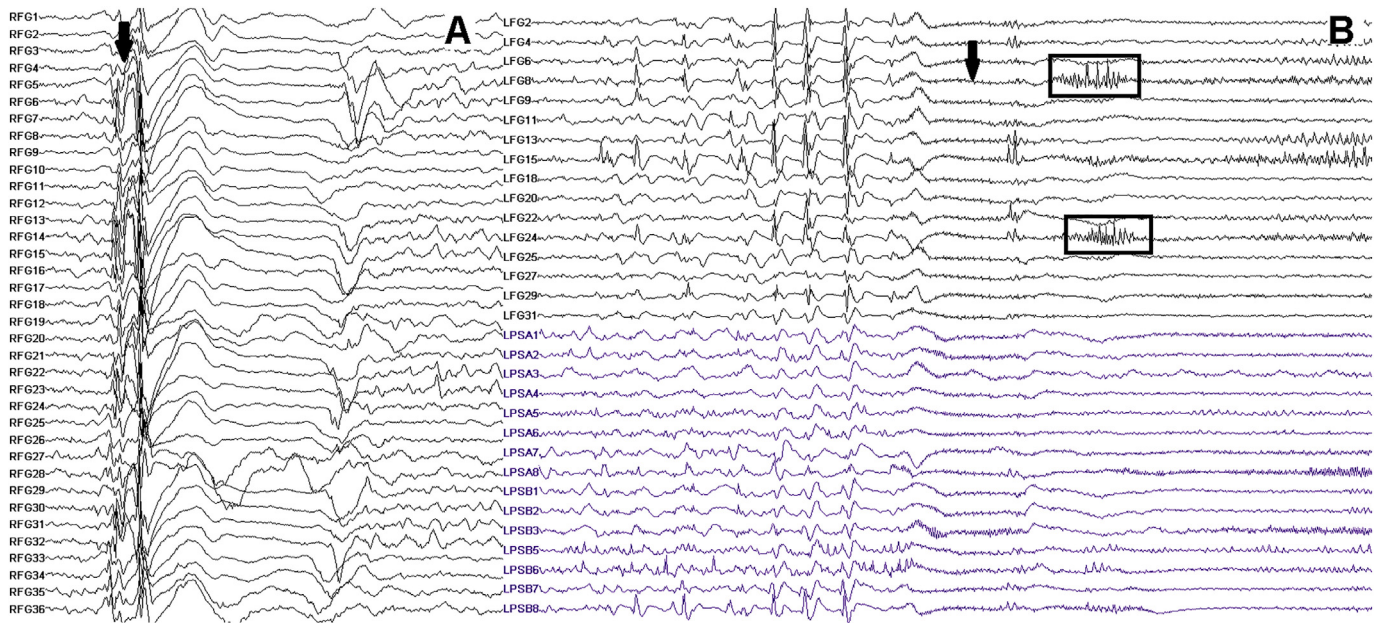
Fig. 2. (A–B). Representative ictal tracings on intracranial EEGs prior to CC. A: Spike and wave discharges (SWD, arrow) in the right frontal grid (RFG) electrodes 1–36. B: Electrodecremental response with superimposed fast activity (DSF, arrow) in left frontal grid (LFG) electrodes 8 and 24 (boxes). Low and high frequency filter settings 1 and 100 Hz, respectively; sensitivity 100 μV/mm.

predilection to the specific seizure type. Furthermore, there was no association between the presence of a specific ictal pattern and the overall postoperative seizure improvement ($p = 1.0$). The distribution of total counts of ictal SWD or DSF patterns identified in the frontal grid electrodes of all patients was devoid of any rostral–caudal gradient (Fig. 3 A-B).

While lateralization of ictal onset on scalp EEG was inconclusive in the majority of patients (63%), it was ultimately achieved in 75% of all patients upon completion of both scalp and iEEG monitoring. Furthermore, the collective findings from the scalp and subdural recordings were sufficient to localize ictal onset in 7 patients (44%) who were then treated with combined CC and resection of focal electrophysiologic foci. With the exception of two patients (patients 3 and 4), all patients treated with combined surgical approach (patients 2, 7, 8, 10, 12) have improved after the surgery (Table 2).

4. Discussion

This retrospective case series has provided the description of the preoperative intracranial EEG patterns and seizure outcomes in a consecutive cohort of adult and pediatric patients undergoing anterior CC or a combined CC and resective surgery. While the iEEG findings in a similar surgical protocol were previously demonstrated in a cohort of children with drug-resistant epilepsy [10], to our knowledge no published literature has documented similar results in adult patients.

4.1. Surgical outcomes for different seizure types

Consistent with previous reports, anterior CC alone and in combination with resective surgery significantly reduced overall seizure frequency in 75% of patients in our population [11–16]. Specifically, we found that 85% of patients with generalized atonic seizures from the present cohort had at least 50% reduction in these seizures after the surgery. Remarkably, 4 out of 7 patients became free from these seizures. These findings are in line with previous reports demonstrating a comparable degree of postoperative improvement in 70–80% of adult or pediatric patients with atonic seizures [4,9,12,17]. Interestingly, while several studies have combined atonic and tonic seizures into a single category of "drop attacks" [18,19], the proportion of patients with

favorable seizure outcomes was similar across the studies recounting "drop attacks" and atonic seizures alone [12,18,20,21]. The decrease in frequency of atonic seizures following the anterior CC was also demonstrated by Kagawa et al. [22]. The authors proposed that surgery disrupted anterior ictogenic pathways responsible for the propagation of atonic seizures. The relief of drop seizures was also achieved with selective posterior callosotomy, which spared the anterior connections, as reported by Paglioli et al. [23]. Contrary to other studies, we found no significant decrease in generalized tonic seizures after CC. Nonetheless, CC leads to a decrease in tonic seizures from an individual baseline in three out of four patients.

We demonstrated that callosal section alone or in combination with targeted resection significantly reduced the frequency of FIAs in 71% of patients which is in line with other reports [9,12,13]. The improvement of FIAs in patients with discrete unilateral lesions was thought to be due to the abolition of bihemispheric ictal spread from the discrete seizure focus which was not possible in the settings of bilateral hemispheric dysfunction [24]. We did not observe any difference in the overall seizure outcomes in patients who had nonlesional MRI in relation to those who had abnormalities on the imaging; however, this association was not assessed for the FIAs alone due to the small sample size. Although GTCs are commonly alleviated by CC [9,15,17,25], we did not observe any significant improvement in the frequency of these seizures in our cohort. Despite that, CC leads to reduction in GTCs from the individual baselines in half of patients with these disabling seizures. The lack of the significant reduction of GTCs in the entire cohort was likely due to the small sample size.

4.2. Impact of surgery type and clinical characteristics on seizure outcomes

Given that the number of patients with individual seizure types was small, further analysis of other determinants of surgical outcomes was carried out using overall seizure scores for each patient. We found that overall improvement in postoperative seizures status had no association with the type of surgery. The lack of differences in seizure outcomes between CC alone and combined CC was noted by Silverberg et al. who retrospectively examined 26 adolescent and adults with CC [7]. In contrast to our approach, the authors employed staged callosotomy and subsequent focal resection during separate surgical
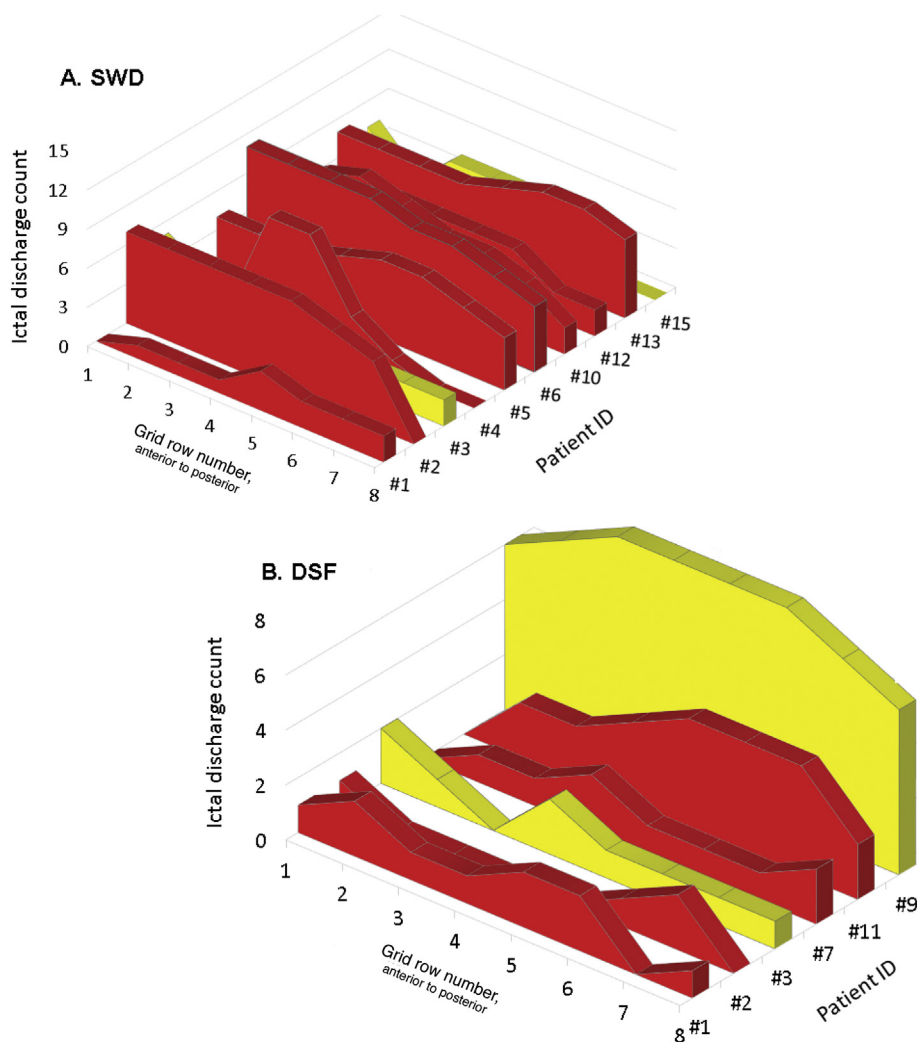
Fig. 3. (A–B). Anteroposterior distribution of the ictal discharge count on the frontal grid electrodes. Spike and wave discharges (SWD; A) or electrodecremental response with superimposed fast activity (DSF; B) in patients with improved seizure control (red) or with no improvement (yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

admissions [7]. The expectations from the combined CC in our patients was the reduction of frequency of both generalized and focal seizures anticipated to be achieved following a single craniotomy procedure. The resection of "dominant" epileptogenic focus to palliate seizure frequency and reduce medication burden in a population of patients with similar clinical characteristics has been reported by Qualmann et al. [26]. Moreover, these authors did not perform simultaneous CC. Given the lack of an additional benefit from a combined CC and focal resection in our study and that performed by Silverberg and co-authors, at the present stage, the CC alone should be considered in these patients.

The patients who improved after the surgery tended to be older at the time of surgery and had fewer seizure types relative to those who did not improve. This difference only approached significance. The reliance on parent and caregiver reports of seizure frequency with potential for recall bias should be respected while interpreting these results [27]. Consistent with previous reports, the age at epilepsy diagnosis or duration of postoperative follow-up did not appear to predict improvement after CC [28]. Furthermore, we found no significant decrease in usage of anti-seizure drugs after CC as reported by other authors [17,21]. It is not clear whether the number of anti-seizure drugs after CC would decrease if the duration of postoperative observation is extended beyond the time reported in this study (i.e., average 15.5 months).

4.3. Contribution of ictal iEEG patterns

In our study, which involved iEEG recordings from different intracranial locations, two identified preoperative ictal patterns (i.e., SWD and DSF) did not appear to correlate with specific ictal semiology. Furthermore, we found that there was no association between the presence of either pattern on iEEG and improvement in seizure density after CC. While the findings from iEEG in this cohort allowed ictal lateralization in 39% of patients and led to combined CC, no additional benefit was derived from this approach. Taken collectively, ictal patterns on intracranial electrodes placed prior to CC do not predict the seizure status after CC.

Since the anterior CC is thought to interrupt interhemispheric propagation of seizures starting in the rostral regions of the frontal lobe, we further explored whether the cumulative burden of ictal discharges at particular rostral–caudal dimension predicts seizure outcome. In the recordings from the frontal grid array, the appearance of either SWD or DSF did not follow any appreciable anteroposterior gradient in either improved patients or in those with no improvement. The visual determination of the gradient of ictal discharges on iEEG in the present study creates a limitation. It is unclear if existing objective methods used in the analysis of the specific gradients (e.g., high frequency oscillations) could be applied to other patterns [29,30].

4.4. Limitations

Despite our best attempt to classify patients according to their epilepsy syndrome, it proved to be difficult given the retrospective design of the study. Therefore, several patients were classified as encephalopathic generalized epilepsy without further defining their epilepsy pathology. Inherent to the challenges of studies in patients with drug-resistant epilepsy, the introduction of new anti-seizure drugs in the postoperative period, which can affect outcomes, makes the understanding of the effects of surgery less clear. However, we did not observe the overall quantitative changes in the number of anti-seizure drugs after CC. Furthermore, no measures were performed on neurocognitive outcomes which constitute a limitation in drawing conclusions from these clinical observations.

5. Conclusions

From the present data, we conclude that multistage surgical approaches that involve intracranial EEG recordings prior to CC improves the success of seizure lateralization but does not refine the prediction of postsurgical seizure outcomes in patients with inconclusive scalp EEG. Furthermore, the absence of the organized gradient of seizure discharges in the recordings from frontal grid electrodes suggests that anatomical distribution of these patterns within the frontal cortex has no association with outcomes after CC. As an effective treatment for generalized atonic seizures and focal seizures with impaired awareness, CC should be considered in patients with generalized and multifocal drug-resistant epilepsies. Further data are required before surgical consideration is indicated for patients with other seizure types. In the current series of patients, the benefits of performing combined iEEG in patients considered for CC were not apparent; and therefore further studies involving larger cohorts of patients are needed.

Disclosure of conflicts of interest

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Ethical statement

The work described herein has been conducted in accordance with the Code of Ethics of the World Medical Association. The study was approved by the institutional review board of the University of Nebraska Medical Center.

References

[1] Asadi-Pooya AA, Malekmohamadi Z, Kamgarpour A, Rakei SM, Taghipour M, Ashjazadeh N, et al. Corpus callosotomy is a valuable therapeutic option for patients with Lennox-Gastaut syndrome and medically refractory seizures. Epilepsy Behav 2013;29:285–8.

[2] Asadi-Pooya AA, Sharan A, Nei M, Sperling MR. Corpus callosotomy. Epilepsy Behav 2008;13:271–8.

[3] Wong TT, Kwan SY, Chang KP, Hsiu-Mei W, Yang TF, Chen YS, et al. Corpus callosotomy in children. Childs Nerv Syst 2006;22:999–1011.

[4] Gates JR, Rosenfeld WE, Maxwell RE, Lyons RE. Response of multiple seizure types to corpus callosum section. Epilepsia 1987;28:28–34.

[5] Kwan SY, Wong TT, Chang KP, Yang TF, Lee YC, Guo WY, et al. Seizure outcomes after anterior callosotomy in patients with posterior-dominant and with anterior-dominant epileptiform discharges. Childs Nerv Syst 2001;17:71–5.

[6] Kwan SY, Wong TT, Chang KP, Chi CS, Yang TF, Lee YC, et al. Seizure outcome after corpus callosotomy: the Taiwan experience. Childs Nerv Syst 2000;16:87–92.

[7] Silverberg A, Parker-Menzer K, Devinsky O, Doyle W, Carlson C. Bilateral intracranial electroencephalographic monitoring immediately following corpus callosotomy. Epilepsia 2010;51:2203–6.

[8] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017; 58:522–30.

[9] Reutens DC, Bye AM, Hopkins IJ, Danks A, Somerville E, Walsh J, et al. Corpus callosotomy for intractable epilepsy: seizure outcome and prognostic factors. Epilepsia 1993;34:904–9.

[10] Lin JS, Lew SM, Marcuccilli CJ, Mueller WM, Matthews AE, Koop JI, et al. Corpus callosotomy in multistage epilepsy surgery in the pediatric population. J Neurosurg Pediatr 2011;7:189–200.

[11] Passamonti C, Zamponi N, Foschi N, Trignani R, Luzi M, Cesaroni E, et al. Long-term seizure and behavioral outcomes after corpus callosotomy. Epilepsy Behav 2014;41: 23–9.

[12] Nordgren RE, Reeves AG, Viguera AC, Roberts DW. Corpus callosotomy for intractable seizures in the pediatric age group. Arch Neurol 1991;48:364–72.

[13] Oguni H, Olivier A, Andermann F, Comair J. Anterior callosotomy in the treatment of medically intractable epilepsies: a study of 43 patients with a mean follow-up of 39 months. Ann Neurol 1991;30:357–64.

[14] Turanli G, Yalnizoglu D, Genc-Acikgoz D, Akalan N, Topcu M. Outcome and long term follow-up after corpus callosotomy in childhood onset intractable epilepsy. Childs Nerv Syst 2006;22:1322–7.

[15] Andersen B, Rogvi-Hansen B, Kruse-Larsen C, Dam M. Corpus callosotomy: seizure and psychosocial outcome. A 39-month follow-up of 20 patients. Epilepsy Res 1996;23:77–85.

[16] Rayport M, Ferguson SM, Corrie WS. Outcomes and indications of corpus callosum section for intractable seizure control. Appl Neurophysiol 1983;46:47–51.

[17] Graham D, Tisdall MM, Gill D. Corpus callosotomy outcomes in pediatric patients: A systematic review. Epilepsia 2016;57:1053–68.

[18] Maehara T, Shimizu H. Surgical outcome of corpus callosotomy in patients with drop attacks. Epilepsia 2001;42:67–71.

[19] Hanson RR, Risinger M, Maxwell R. The ictal EEG as a predictive factor for outcome following corpus callosum section in adults. Epilepsy Res 2002;49:89–97.

[20] Sunaga S, Shimizu H, Sugano H. Long-term follow-up of seizure outcomes after corpus callosotomy. Seizure 2009;18:124–8.

[21] Park MS, Nakagawa E, Schoenberg MR, Benbadis SR, Vale FL. Outcome of corpus callosotomy in adults. Epilepsy Behav 2013;28:181–4.

[22] Kagawa K, Iida K, Hashizume A, Katagiri M, Baba S, Kurisu K, et al. Magnetoencephalography using gradient magnetic field topography (GMFT) can predict successful anterior corpus callosotomy in patients with drop attacks. Clin Neurophysiol 2016; 127:221–9.

[23] Paglioli E, Martins WA, Azambuja N, Portuguez M, Frigeri TM, Pinos L, et al. Selective posterior callosotomy for drop attacks: A new approach sparing prefrontal connectivity. Neurology 2016;87:1968–74.

[24] Spencer SS, Spencer MD, Williamson PD, Sass K, Novelly RA, Mattson RH. Corpus callosotomy for epilepsy. I. Seizure effects. Neurology 1988;38:19.

[25] Hader W, Bezchlibnyk I, Pillay N, Wiebe S. Corpus callosotomy, risks and benefits: a systematic review of the evidence. Epilepsy Curr 2012;12:S:400.

[26] Qualmann KJ, Spaeth CG, Myers MF, Horn PS, Holland K, Mangano FT, et al. Pediatric epilepsy surgery: the prognostic value of central nervous system comorbidities in patients and their families. J Child Neurol 2017;32:467–74.

[27] Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, et al. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 2011;52(Suppl. 7): 2–26.

[28] Papo I, Quattrini A, Ortenzi A, Paggi A, Rychlicki F, Provinciali L, et al. Predictive factors of callosotomy in drug-resistant epileptic patients with a long follow-up. J Neurosurg Sci 1997;41:31–6.

[29] Bartolomei F, Chauvel P, Wendling F. Epileptogenicity of brain structures in human temporal lobe epilepsy: a quantified study from intracerebral EEG. Brain 2008; 131:1818–30.

[30] Nariai H, Nagasawa T, Juhasz C, Sood S, Chugani HT, Asano E. Statistical mapping of ictal high-frequency oscillations in epileptic spasms. Epilepsia 2011;52:63–74.