Pediatric Neurology 95 (2019) 79–83

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Analysis for the Association Between Corpus Callosum Thickness and Corpus Callosotomy Outcomes for Patients With Epileptic Spasms or Tonic Spasms

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ARTICLE INFO

Article history:
Received 12 October 2018
Accepted 21 January 2019
Available online 30 January 2019

Keywords:
Intractable epilepsy
Corpus callosotomy
Corpus callosum
Thickness
Seizure outcome
Epilepsy surgery

ABSTRACT

Background: This retrospective study is designed to determine whether the thickness of the corpus callosum can predict corpus callosotomy outcome in pediatric patients with epileptic or tonic spasms.
Methods: We retrospectively studied 25 patients (18 boys) with intractable childhood-onset epileptic or tonic spasms who underwent corpus callosotomy between March 2008 and January 2017. Seizure outcomes were classified as favorable (class I and II of Engel's outcome classification) or unfavorable (class III and IV of Engel's outcome classification) at 12 months postoperatively. We measured the corpus callosum area on the midline and maximum cerebral area on the para-midline in sagittal magnetic resonance images just before surgery. We statistically analyzed the associations between surgical outcomes and corpus callosum area, corpus callosum area/maximum cerebral area (corpus callosum/cerebrum ratio), or age at magnetic resonance imaging just before surgery, using univariate and multivariate logistic regression analyses.
Results: Age at surgery ranged from six to 237 months (mean: 119). Main seizure types were epileptic spasms in 17 patients and tonic spasms in eight. Favorable outcomes occurred in 10 (40%) patients and unfavorable outcomes in 15 (60%). Both corpus callosum area and corpus callosum/cerebrum ratio did not show significant associations with the outcomes in the univariate and multivariate analyses. The 95% confidence intervals of corpus callosum/cerebrum ratio strongly overlapped between the favorable and unfavorable outcome groups.
Conclusions: Our data failed to support that corpus callosum thickness on the sagittal image is associated with corpus callosotomy outcomes in pediatric patients with epileptic spasms or tonic spasms.

Introduction

Corpus callosotomy is a palliative treatment for patients with intractable epilepsy who are not candidates for resective surgery.[1] Corpus callosotomy is considered to be effective because the corpus callosum (CC) is the most important pathway for the spread of epileptic activity between the hemispheres. Erickson et al. described the mechanism of epileptic discharges spreading through the CC in a monkey model in 1940.[2] Van Wagenen and Herren published a case series of 10 patients with tumors in their CC. The investigators found that as the tumors grew, generalized

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Declaration of interest: None.
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https://doi.org/10.1016/j.pediatrneurol.2019.01.012
0887-8994/

seizure activities were lateralized to one hemisphere. Van Wagenen and Herren were the first to perform corpus callosotomy in humans and thereby proved the effectiveness of the procedure for severe generalized seizures.[3]

It has been reported that corpus callosotomy is particularly effective for suppressing drop attacks, including a few cases of epileptic spasms,[4-8] and the procedure has been adapted for pediatric patients with epileptic spasms in Japan. Recently, Baba et al. reported 56 Japanese pediatric patients who underwent corpus callosotomy for epileptic spasms.[9] A seizure-free outcome was achieved in 18 patients (32.1%), with excellent outcome (more than 80% reduction in seizure frequency) in 15 of 56 (26.8%).

It is important to identify clinical factors in pediatric patients because the control of seizures can positively influence development.[10] In previous studies of patients who underwent corpus callosotomy, good prognostic factors included the absence of image abnormalities, normal development at the time of surgery, no background etiology, and total callosotomy.[1,6,11-13] Developmental delay before the onset of epilepsy was associated with the outcomes of epileptic spasms in patients with West syndrome.[9] It has been suggested that the thickness of the CC is associated with the effectiveness of corpus callosotomy. However, to date, only one study has investigated the association in a group of 15 patients, including 10 adults, with generalized tonic-clonic, tonic, and atonic seizures.[14] Here, we examined the associations between the effectiveness of corpus callosotomy and the thickness of the CC in pediatric patients with epileptic spasms or tonic spasms.

Patients and Methods

This study was approved by the ethics board of the Seirei Hamamatsu General Hospital. We retrospectively studied 32 patients who met the following criteria: (1) underwent corpus callosotomy between March 2008 and January 2017 at the Seirei Hamamatsu General Hospital, (2) were less than 20 years old at the time of the surgery, (3) had epileptic spasms or tonic spasms as the main seizure type. We excluded seven patients who had follow-up periods of less than 12 months or who had received additional resection surgery or undergone implantation of a vagus nerve stimulator (VNS) within 12 months after the surgery. We reviewed the clinical profiles of the remaining 25 patients (18 boys, seven girls), including their age at epilepsy onset, at magnetic resonance imaging (MRI), and at corpus callosotomy; etiologies; seizure types; presence of drop attacks (sudden falls with the seizures); frequencies of the main seizure; development (developmental or intellectual quotients) at the time of surgery; numbers of administered antiepileptic drugs; the patient's history of adrenocorticotropic hormone therapy or VNS implantation; MRI findings; operation types (total or anterior corpus callosotomy); and seizure outcomes from the medical records. Seizure outcomes were classified into favorable (class I [seizure free] or II [greater than 90% reduction] of Engel's outcome classification of 2001 International League Against Epilepsy (ILAE) recommendation) and unfavorable (class III [worthwhile reduction, but less than 90%] or IV [no worthwhile reduction] of Engel's outcome classification of 2001 ILAE recommendation)[15] at 12 months after surgery.

MRI and measurements of the CC cross-sectional area

MRI was performed according to our epilepsy protocol in two different 3.0-T scanners (Discovery MR-750 and 750W and SIGNA Pioneer, GE, Milwaukee, WI, USA). The field of view was 200 to 240 mm, and the matrices were between 224 $\times$ 224 and 320 $\times$ 320. The protocol included axial fluid-attenuated inversion recovery (slice thickness: 4.0 mm, interslice gap: 1.0 mm, repetition time: 9000 ms, echo time: 90 ms, inversion time: 2469 ms) and coronal 3D fluid-attenuated inversion recovery (1/-0.5/5000/135/1600) and sagittal T1-weighted (conventional protocol; 5.0/2.0/500/8/-), axial 3D T1-weighted (1.4/-0.7/8.5/3.2/450), axial T2-weighted (5.0/2.0/4025/95/-), and axial 3D T2-weighted (1.4/-0.7/2500/90/-) sequences.

Cross-sectional areas of the cerebrum and CC were measured in sagittal views with conventional or 3D T1-weighted sequences. The maximum cross-sectional area of the CC was measured at the midline slice (Fig 1A). The maximum cross-sectional area of the cerebrum was measured one or two slices away from the midline, at the slice that showed the largest area among all sagittal views in each patient (Fig 1B). For these measurements, we used the Aquarius iNtuition image processing software for MRI (version 4; TeraRecon, Foster City, CA, USA).

Furthermore, to consider the head size of each patient, we additionally defined the “CC/cerebrum ratio” as follows:

$$CC/cerebrum\ ratio = the\ maximum\ cross - sectional\ area\ of\ the\ CC/the\ maximum\ cross - sectional\ area\ of\ the\ cerebrum.$$

CC/cerebrum ratio was calculated for each patient and used for the statistical analyses.

Statistical analyses

We statistically analyzed the associations between the clinical profiles and surgical outcomes using Fisher's exact test, Welch t test, and Spearman's rank correlation coefficient.

We analyzed the association between seizure outcomes (favorable/unfavorable) and the CC area or CC/cerebrum ratio. We also assessed the age at MRI, which potentially affected the CC area as a covariate. We analyzed 95% confidential intervals of the CC/cerebrum ratio among the favorable and unfavorable outcome groups. We conducted univariate and multivariate logistic regression analyses and used JMP 12.0 (SAS institute Japan Ltd., Tokyo) for all analyses. We considered $P < 0.05$ as statistically significant.

Results

Patients and clinical information

Clinical information for each outcome group is described in Table 1. Favorable outcomes occurred in 10 patients (classes I and II of Engel's outcome classification of 2001 ILAE recommendation, five patients in each) and unfavorable outcomes occurred in 15 patients (classes III and IV of Engel's outcome classification of 2001 ILAE recommendation, 10 and five patients, respectively). Age at epilepsy onset ranged from one to 144 months (mean: 33.2 months). Age at surgery ranged from six to 237 months (mean: 119 months). An etiology of the epilepsy was identified in 11 patients. The classifications of epilepsy types or syndromes were as follows: combined generalized and focal epilepsy in eight patients, focal epilepsy in three patients, generalized epilepsy in two patients, Lennox-Gastaut syndrome in four patients, West syndrome in seven patients, and early myoclonic encephalopathy in one patient. The number of administered antiepileptic drugs ranged from one to 11 (mean: 6). Adrenocorticotropic hormone (ACTH) treatment and VNS implantation were performed in 11 and five patients, respectively. Severely delayed development (development or intelligence quotient less than 30) occurred in 19 patients, and moderate or mild delayed development was seen in six patients. MRI detected abnormalities in 13 patients (unilateral: three patients, bilateral: 10 patients). The main seizure types were epileptic spasms

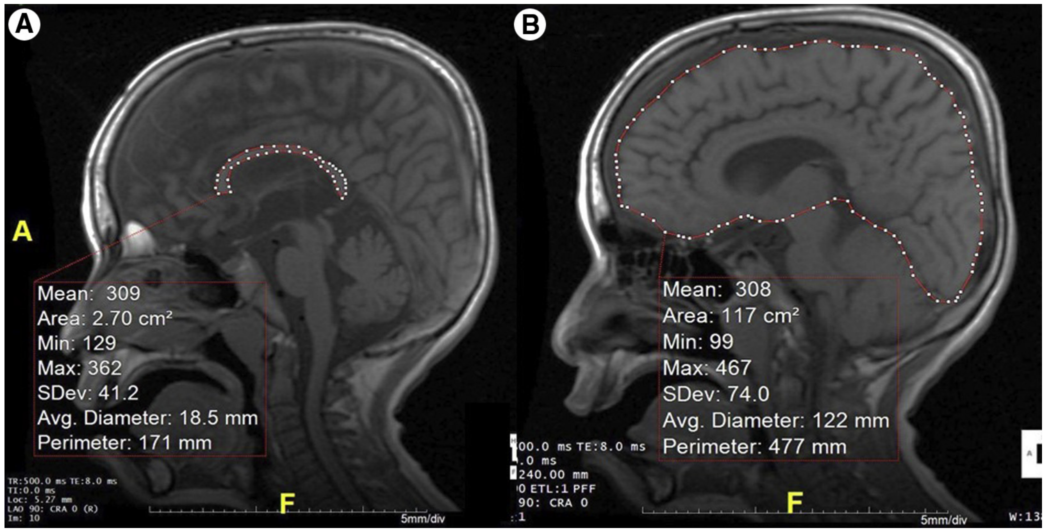

FIGURE 1. Examples of measurements of the corpus callosum (CC)/cerebrum ratio. We measured the cross-sectional area of the CC with the maximum size on the midline sagittal slice (A) and the maximum cross-sectional area of the cerebrum on the adjacent sagittal slice (B) in T1-weighted magnetic resonance images. We calculated A/B in each patient as an index of the thickness of the CC. The color version of this figure is available in the online edition.

in 17 patients and tonic spasms in eight patients. Thirteen patients experienced falls during their seizures (drop attacks). Main seizures occurred hourly in 13 patients, daily in nine patients, and weekly in three patients. The procedures were total corpus callosotomy in 19 patients and anterior 2/3 or 4/5 callosotomy in six patients. The details are described in the Supplementary Table.

Cross-sectional area of the corpus callosum and CC/cerebrum ratio

Age at MRI ranged from six to 234 months (mean: 116 months). The cross-sectional area of the CC ranged from 0.755 to 6.26 cm^2 (mean: 3.46 cm^2), and the cross-sectional area of the cerebrum ranged from 46.1 to 117 cm^2 (mean: 90.1 cm^2). The CC/

TABLE 1.
Clinical Information in Each Outcome Group

	Favorable Outcome (Engel I-II)	Unfavorable Outcome (Engel III-IV)	*P* value
Numbers of patients	10	15	
Gender			0.118
Male	9	9	
Female	1	6	
Age at onset (mo): mean (range)	36.3 (1-132)	31.1 (1-144)	0.777
Age at surgery (mo): mean (range)	103 (6-237)	129 (34-237)	0.429
Epilepsy duration (mo): mean (range)	67 (5-232)	97.8 (27-219)	0.282
Etiologies			0.183
Known	6	5	
Unknown	4	10	
Numbers of AEDs: mean (range)	5.2 (1-9)	6.7 (3-11)	0.09
ACTH therapy	2	9	0.058
VNS implantation	1	4	0.313
Main Seizure types			0.274
Epileptic spasms	8	9	
Tonic spasms	2	6	
Drop attacks	4	9	0.284
Frequency of main seizures			0.758
Hourly	5	8	
Daily	5	4	
Weekly	0	3	
MRI findings			0.455
None	4	8	
Unilateral	1	2	
Bilateral	5	5	
Development			0.455
Mild to moderate delay	3	3	
Severe delay	7	12	
Operation type			0.455
Total callosotomy	7	12	
Anterior callosotomy	3	3	

Abbreviations:
ACTH = Adrenocorticotropic hormone
AEDs = Antiepileptic drugs
MRI = Magnetic resonance imaging
VNS = Vagus nerve stimulator
For the statistical analyses, we used Fisher's exact test, Welch *t* test, and Spearman rank correlation coefficient analysis, appropriately.

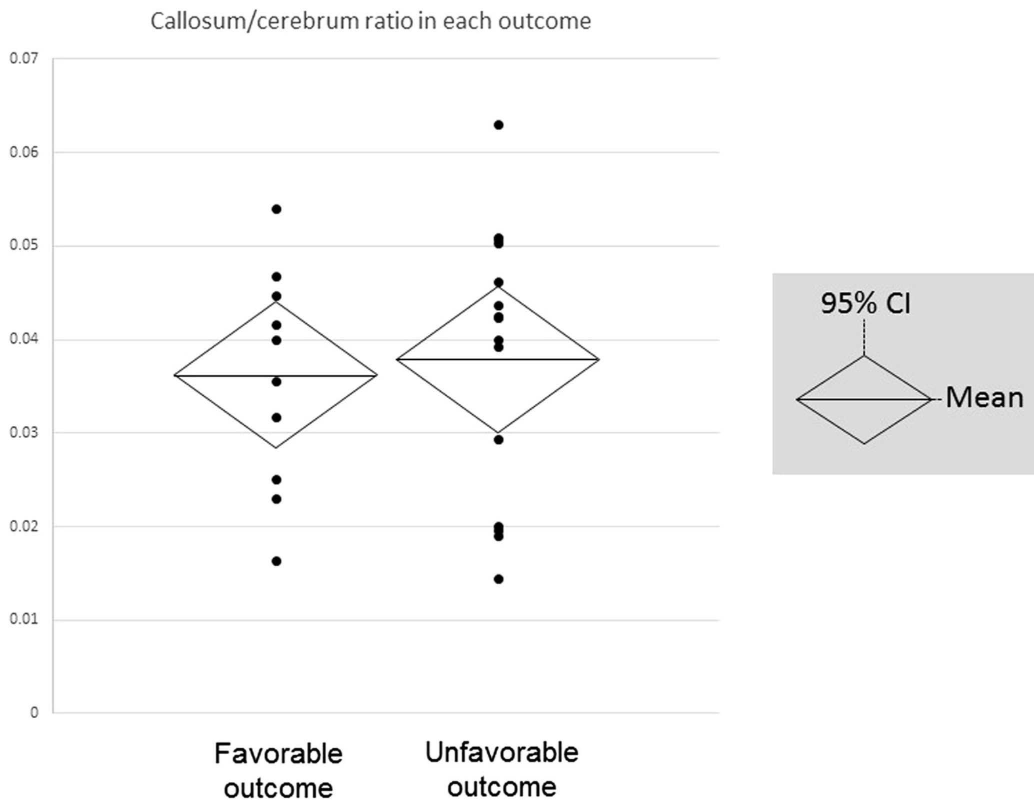

FIGURE 2. Plots of the corpus callosum (CC)/cerebrum ratio in each outcome group. The CC/cerebrum ratio was not significantly associated with surgical outcomes of corpus callosotomy ($P = 0.68$, univariate logistic regression analysis). The 95% confidence intervals of the CC/cerebrum ratio strongly overlapped between the favorable (0.0286-0.0432) and unfavorable (0.0308-0.0454) outcome groups.

cerebrum ratio ranged from 0.0143 to 0.0631 (mean: 0.0372). The plot of CC/cerebrum ratios for the favorable and unfavorable outcome groups are shown in Fig 2. The means and standard errors were 0.0359 ± 0.00373 in the favorable and 0.0381 ± 0.00372 in the unfavorable outcome groups. The 95% confidence intervals in the groups ranged between 0.0286 and 0.0432 in the favorable and 0.0308 and 0.0454 in the unfavorable outcome groups.

Statistical results

None of the clinical information was significantly associated with corpus callosotomy outcome (Table 1). Neither the CC/cerebrum ratio nor any covariates were significantly associated with surgical outcomes of corpus callosotomy in the univariate or multivariate analysis (Table 2).

Discussion

From the present study, the CC/cerebrum ratio showed similar distributions between the favorable and unfavorable outcome groups. The statistical analyses did not show significant associations between the CC/cerebrum ratio and the corpus callosotomy outcomes. Thin appearance of the CC on the midline sagittal MRI slice did not indicate excluding corpus callosotomy in patients with spasms.

Since Van Wagenen and Herren first reported the procedure of corpus callosotomy in 1940,[3] it has been widely used to treat patients with medically intractable epilepsy with drop attacks who are not eligible for focal resection.[1] This procedure is also effective for epileptic spasms in West syndrome.[9] This method achieved a seizure-free outcome in 42.9% of patients and more than 80% reduction of seizure frequency in 23.2% of patients with epileptic spasms, whereas it was less effective for tonic seizures. The clinical

TABLE 2.
The Associations Between Outcomes of Corpus Callosotomy, Corpus Callosom Area, Callosum/Cerebrum Ratio, and Age at MRI Scanning

	Estimate	Standard Error	The Likelihood Ratio Chi-square	*P* Value
Univariate analysis				
Corpus callosum area	-6.37×10^{-2}	0.272	5.48×10^{-2}	0.82
Callosum/cerebrum ratio	−13.10	31.65	0.17	0.68
Age at MRI scanning	4.52×10^{-3}	5.47×10^{-3}	0.70	0.40
Multivariate analysis				
Corpus callosum area	0.502	0.786	0.42	0.52
Callosum/cerebrum ratio	−54.6	88.30	0.40	0.54
Age at MRI scanning	-5.58×10^{-3}	6.38×10^{-3}	0.80	0.38

Abbreviation:
MRI = Magnetic resonance imaging
We used univariate/multivariate logistic regression analysis.

profiles associated with postoperative seizure remission that have been previously reported include absence of image abnormalities, normal development at surgery, no background etiology, and total callosotomy.[1,6,11-13] Developmental delay before onset of epilepsy was associated with seizure remission in patients with epileptic spasms in West syndrome.[9] In our study, the records were insufficient to consider developmental delay before the onset of epilepsy, and none of the other factors had any association with the surgical outcome in pediatric patients mainly presenting with epileptic spasms or tonic spasms. The outcomes were relatively worse (seizure free in 20% of patients) than those reported by Baba et al. (42.9%).[9] The reason for the worse outcome might be that our study included patients with tonic spasms.

As for the morphological analysis of the CC for the association with the outcomes of corpus callosotomy, Mamelak et al. reported that the cross-sectional area of the CC did not differ between the outcome groups after corpus callosotomy. That study included 15 patients with generalized tonic-clonic, tonic, and atonic seizures, consisting of 10 adults and five pediatric patients.[14] Our study is the first to assess only pediatric patients with spasms and revealed no association between the thickness of the CC and corpus callosotomy outcomes. These findings suggest that even in pediatric patients with spasms with a thin CC, callosotomy can have a positive impact on seizure remission.

It is hypothesized that the CC promotes bilateral synchrony or interhemispheric recruitment of epileptic activity in patients with severe epileptogenesis in both hemispheres.[16,17] However, some previous studies have indicated that the thickness of the CC is not important for these interhemispheric recruitments. Patients with idiopathic generalized epilepsy have a thinner CC than do normal controls, although they show bilaterally synchronous epileptic discharges.[18] In a study using advanced MRI, the fractional anisotropy in white matter including the CC decreased in patients with generalized epilepsy.[19] The CC may promote bilateral epileptic activities regardless of thickness or fiber density. Corpus callosotomy may disrupt the malfunction of the CC even in cases involving thin morphology.

In conclusion, the cross-sectional area of the CC relative to that of the cerebrum does not correlate with the outcomes of callosotomy in pediatric patients with epileptic spasms or tonic spasms. Regardless of the thickness of the CC, corpus callosotomy can be an appropriate treatment for these patients. This study has some limitations. The patient data were obtained from a single center. The follow-up period was short in some patients. We used the CC area and CC/cerebrum ratio, a relatively simple method, for the measurement of CC. A fractional anisotropy or volumetric study may find a difference in the white matter fibers or volumes between favorable and unfavorable outcome groups. Developmental or other factors that might be associated with the outcomes could be included in the statistical analyses if a larger number of patients are recruited.

Acknowledgment

We are grateful to T. Yamamoto for managing the patient data.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2019.01.012.

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