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Developmental outcome after corpus callosotomy for infants and young children with drug-resistant epilepsy

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ABSTRACT

Aim: To examine the developmental and seizure outcomes after corpus callosotomy (CC) in early childhood.
Methods: We retrospectively identified 106 patients who underwent CC for drug-resistant epilepsy before the age of 6 years, at the Nagasaki Medical Center, between July 2002 and July 2016. Patients' developmental outcomes were evaluated one year after CC using the Kinder Infant Development Scale.
Results: The mean preoperative developmental quotient (DQ) was 25.0 (standard deviation [SD], 20.8), and the mean difference between preoperative DQ and one-year postoperative DQ was −1.6 points (SD, 11.6). However, 42.5% of patients had a mean DQ increase of 6.5 points (SD, 6.4), one year after CC from that before surgery. Factors related to the improvement in postoperative DQ were 'low preoperative DQ', 'developmental gain 1 month postoperatively', and 'postoperative seizure-free state'. Approximately 21.7% of patients were seizure-free 1 year after CC.
Interpretation: Performing CC, in infancy and early childhood for patients with drug-resistant epilepsy and severe developmental impairment, was associated with improved development in 42.5% of patients. Remission of seizures, even if only for a short period, contributed to developmental improvement. From a developmental perspective, CC for drug-resistant epilepsy in early childhood is an effective treatment.

1. Introduction

Previous studies have reported that medically intractable epilepsies occurring during infancy and early childhood can cause severe cognitive and behavioral deficits, as infancy is a critical period for brain development [1–3]. The earlier the age at onset, the more likely patients are to have developmental delays [4–6].

For some children with drug-resistant epilepsy, surgery may provide seizure remission and result in developmental improvement [7,8]. Previous studies have reported that factors affecting development after resective surgery for epilepsy include the underlying etiology, the preoperative developmental level, age at onset, age at surgery, duration of epilepsy, and postoperative seizure outcomes [9–12].

Corpus callosotomy (CC) is a palliative surgery performed in patients with drug-resistant epilepsy who are not eligible for resective surgery. This procedure has been used to prevent epileptic discharges from spreading from one hemisphere to the other, and minimize the frequency and severity of seizures [13]; however, recent studies have shown that CC could prevent the bilateral synchrony of epileptic discharges, while also reducing epileptogenic susceptibility [14–17]. Although the seizure-free rate after CC is not high compared to resective surgery, CC is reportedly effective for the treatment of drop attacks, secondary generalized tonic-clonic seizures, atypical absence seizures, and epileptic spasms [13,17–19].

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Several studies have also reported CC-mediated improvements in cognitive function and behavioral deficits; however, the results vary among reports, due to differences in age at surgery and the period between onset and CC [17,20–22]. Therefore, the effect and impacts of CC in infancy and early childhood are still unclear.

In this study, we retrospectively analyzed the determinants for the developmental and seizure outcomes, in patients who received CC during infancy and early childhood.

2. Material and methods

This study was approved by the Ethics Review Committee of the National Hospital Organization Nagasaki Medical Center (approval number 2019017). Informed consent was obtained from the guardians of patients; an opt-out model was used based on an announcement about the study on the hospital's bulletin board and website.

2.1. Participants

Out of 224 patients who underwent CC for drug-resistant epilepsy at the National Hospital Organization Nagasaki Medical Center between July 2002 and July 2016, 121 children with age less than six years were included. Patients who underwent other epilepsy surgeries prior to CC and those with a follow-up period of less than 1 year were excluded. A total of 106 patients were included in the final analysis.

2.2. Preoperative evaluation

All patients underwent preoperative evaluation for epilepsy surgery which included the following: neurological examination, video-electroencephalograph monitoring, magnetic resonance imaging (MRI), and the developmental assessment (described in the following sections). Fluorodeoxyglucose-positron emission tomography and single-photon emission computed tomography using 99 mTc-ethyl cysteinate dimer were performed as needed. All 106 patients were considered ineligible for resective surgery because their interictal electroencephalography (EEG) abnormalities were generalized, bilateral, or multifocal, no clear focus could be identified on EEG during seizures, and no focal lesions were found through MRI or functional imaging.

2.3. Patient selection for corpus callosotomy

To be a candidate for the CC procedure, we considered patients with drug-resistant epilepsy who had no exact localization on EEG or imaging, and whose seizure types include generalized seizures, focal bilateral motor seizures, focal epileptic spasms, or focal to bilateral tonic-clonic seizures. If these patients are in stable general condition, we suggested CC as a treatment option, to their caregivers. If the caregiver agreed, CC was decided as the treatment of choice.

2.4. Extent of corpus callosotomy

In our hospital, we initially performed anterior 2/3 callosotomy (ACC) or two-staged total callosotomy (TCC). However, as of April 2003, the preferred strategy for children under the age of 10 shifted to one-staged TCC as this approach is more effective in suppressing seizures than ACC [23]. Additionally, there are less complications of disconnection symptoms in younger children compared to adults [24]. The five patients who underwent ACC in this study were all operated on before April 2003. Evaluation of the extent and completeness of the CC was performed by one radiologist and at least two neurosurgeons, confirming the postoperative MRI.

2.5. Developmental assessments

The participants' preoperative and postoperative development was evaluated using the Kinder Infant Development Scale (KIDS) type T (Center of Developmental Education and Research, Tokyo, Japan, 1989), which is one of the major tests in Japan for assessing the development of patients under the age of seven. In this rating scale test, parents and caregivers evaluate a patient's behavior on nine subscales: physical motor (37 behaviors), manipulation (37 behaviors), receptive language (37 behaviors), expressive language (37 behaviors), language concepts (25 behaviors), social relationships with adults (37 behaviors), social relationships with children (25 behaviors), discipline (25 behaviors), and feeding (22 behaviors). Developmental performance is assessed by checking the number of behaviors in each subscale that the child can exhibit and then expressed as the developmental age (DA). We used the developmental quotient (DQ), a score calculated by dividing the estimated DA by the biological age and then multiplying the result by 100, as a measure of child development. A DQ < 70 represents developmental delay, and a DQ < 35 is defined as a severe developmental delay. Scale reliability and validity of the KIDS have been previously reported as adequate to high [25]. This study used physical motor, manipulation, receptive and expressive language, social relationships with adults, and feeding subscales, as well as the total DQ. The caregivers (parents or guardians) of each patient were interviewed by experienced clinical psychologists for each question listed on the KIDS.

2.6. Data

We retrospectively reviewed the data derived from medical charts, including: sex, age at onset, age at surgery, the period from onset to surgery, history of seizure remission owing to medical treatment before surgery, number of antiepileptic drugs (AEDs) used before surgery, seizure type before surgery, surgical procedure (total or anterior CC), preoperative DA and DQ, etiology, epilepsy classification, history of epileptic encephalopathy [early infantile myoclonic encephalopathy (EME), early infantile epileptic encephalopathy (EIEE), West syndrome, Lennox–Gastaut syndrome (LGS), continuous spikes and waves during slow-wave sleep (CSWS)], DA and DQ at 1 month and 1 year after surgery, EEG findings at 1 year after surgery, seizure outcome at 1 year after surgery, and surgical complications.

The primary outcome of this study was the developmental change after CC. We evaluated the changes in the DA and DQ over the first postoperative year and determined whether the development of the patient had improved, and examined factors that influenced the developmental change. If the value obtained by subtracting the preoperative DQ from the 1 year postoperative DQ was positive, we defined it as 'DQ improved', and if negative, it was defined as 'DQ non-improved'. We also assessed seizure outcome as the secondary outcome; a good outcome was defined as a completely seizure-free state for 1 year after CC.

2.7. Statistical analyses

All tests were two-sided, and p-values ≤ 0.05 were considered statistically significant. The nominal scale was analyzed using Pearson's chi-squared test, and the continuous scale was analyzed using Wilcoxon's rank-sum test. Comparison of DQ before surgery, both 1 month and 1 year after surgery, was performed using analysis of variance. Simple regression analysis was used to predict a linear relationship between two variables. The Pearson correlation

coefficient was used to measure the strength of the linear association between two variables. The odds ratio (OR) and the 95% confidence interval (CI) were determined using logistic regression analysis. The duration of the seizure-free state was analyzed using Kaplan–Meier event-free survival curves, and compared between the two groups using log-rank statistics. All statistical analyses were performed using JMP 14 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Clinical profiles

The clinical characteristics of the 106 patients (55 male and 51 female) are shown in Table 1. The mean age at the onset of epileptic seizures was 7.4 months (standard deviation (SD), 8.3). Seizure onset occurred most often in infancy, as 87 of the 106 patients (79.2%) were 1 year of age or younger, and 101 (95.3%) were two years of age or younger at the onset. The mean age at surgery was 30.3 months (SD, 21.2), and the mean time between seizure onset and surgery was 22.4 months (SD, 18.4). Total CC was performed on 101 patients (95.3%). The etiology of the seizures was known in 41 cases (38.7%): 28 (26.4%) had a structural etiology, 17 (16.0%) had a genetic etiology, and six (5.7%) had an infectious etiology. Regarding epilepsy classification, there were two patients with focal epilepsy (1.9%), 79 with generalized epilepsy (74.5%), and 25 with mixed epilepsy (23.6%). All preoperative interictal EEGs showed generalized, bilateral, or multifocal abnormalities. The types of seizures observed were epileptic spasms in 89 patients (84.0%), generalized tonic seizures in 35 patients (33.0%), generalized tonic-clonic seizures in seven patients (6.6%), atypical absence seizures in 12 patients (11.3%), myoclonic seizures in 11 patients (10.4%), atonic seizures in 7 patients (6.6%), and focal seizures in 15 patients (14.2%); 48 patients (45.3%) had two or more seizure types before surgery. There were 77 patients (72.6%) with a severe developmental delay with a DQ < 35 before CC. The mean number of AEDs tried before CC was 4.6 (SD, 1.7), and most patients were multi-drug-resistant. Eighty-four patients (79.2%) either presented or had a history of epileptic encephalopathy at the time of surgery: 11 patients (10.4%) had EME or EIEE, 78 patients (73.6%) had West syndrome, 13 patients (12.3%) had LGS, and one patient (0.9%) had CSWS. Thirty-two patients (30.2%) had a history of temporary seizure remission as a result of medical treatments, such as AEDs, adrenocorticotropic hormone therapy, and ketogenic diets, but eventually experienced a recurrence of seizures before surgery.

3.2. Developmental outcomes after corpus callosotomy

Chronological developmental changes are shown in Table 2. The mean preoperative DA was 7.9 months (SD, 10.0), and the mean preoperative DQ was 25.0 (SD, 20.8). After CC, the mean DA increased gradually to 8.2 months (SD 8.8) at 1 month after surgery, and 10.9 months (SD 12.1) at 1 year after surgery; however, the average increase in DA was only 3.0 months per year. Regarding DQ, the mean change between 1-month postoperative DQ and preoperative DQ was +1.1 (SD, 9.4). Nevertheless, the mean change from preoperative DQ 1 year after CC was −1.6 (SD, 11.6), which indicated a stagnation in the rate of developmental after surgery. Preoperative DQ was strongly correlated with postoperative DQ, with a higher preoperative DQ, indicating a higher 1-year postoperative DQ [Pearson $r = 0.82$, $p < 0.01$]; however, 1 year after CC, 45 patients (42.5%) had a mean DQ increase of 6.5 (SD, 6.4). Univariate analysis of the DQ-improved and DQ-non-improved patient groups revealed that the following factors were significantly associated with postoperative DQ gain: preoperative DQ ($p < 0.01$), 1-month postoperative DQ change ($p < 0.01$), 1-month and 1-year postoperative seizure-free state ($p = 0.01$), and AED change after CC ($p = 0.01$).

The mean preoperative DQ was significantly lower in the DQ-improved group than in the DQ-non-improved group; however, the mean DQ increased in the DQ-improved group at 1 month after CC, whereas it decreased in the DQ-non-improved group. At 1-month postoperatively, DQ change tended to be significantly greater in the DQ-improved group ($p < 0.01$).

Comparing the seizure-free rates at 1 month and 1 year after CC, the number of seizure-free patients was significantly higher in the DQ-improved than in the DQ-non-improved group (60.0, 33.3%; 34.4, 13.1%, respectively, $p = 0.01$), which indicated that patients with improvements in DQ could be seizure free, compared to those with no improvement in DQ after CC, even if temporarily.

Regarding the effect of AEDs, 46 patients (43.4%) changed their AEDs after surgery, and significantly more patients in the DQ non-improvement group changed AEDs after surgery ($p = 0.01$). However, the number of patients who changed AEDs was significantly higher among those who continued seizures (residual seizure group): 2 of 23 patients (8.7%) in the seizure-free group and 44 of 83 patients (53.0%) in the residual seizure group ($p < 0.01$). Furthermore, in the 83 patients in the residual seizure group, there was no significant difference in developmental improvement at 1-year postoperatively when the AEDs were changed. This suggests that the change in AEDs after CC did not directly affect the developmental changes, rather the elimination of seizures was considered the main contributing factor.

The multiple logistic regression analysis identified the following factors as being relevant to the developmental improvement after CC: preoperative DQ (OR 0.95, 95% CI 0.92–0.98, $p < 0.01$), increased DQ at 1 month postoperatively (OR 1.19, 95% CI 1.08–1.35, $p < 0.01$), and 1 year postoperative seizure-free state (OR 4.26, 95% CI 1.00–18.10, $p = 0.05$) (Table 3). Conversely, sex, age at seizure onset, age at surgery, the period between onset and surgery, type of surgery, etiology, epilepsy type, seizure type, history of epileptic encephalopathy, history of temporary seizure remission before surgery, and AED change after CC were not associated with postoperative developmental improvement.

3.3. Seizure outcomes after corpus callosotomy

Forty-eight patients (45.3%) had seizure-free state 1 month after CC; however, more than half of them had a recurrence, and, finally, 23 patients (21.7%) were seizure-free 1 year after CC. Electroencephalography at 1 year after CC revealed no epileptic discharge in 5 patients (4.7%), lateralized epileptic discharges in one hemisphere in 40 patients (37.7%), and persistent multifocal epileptic discharges in 61 patients (57.6%). All patients with no epileptic discharges achieved seizure-free state 1 year after CC.

A multiple logistic regression analysis of factors common to patients who were seizure-free at 1 year after surgery, showed that patients with a history of temporary seizure remission, before surgery, were significantly more common in the seizure-free group (OR 10.60, 95% CI 1.78–63.16, $p < 0.01$). The probability of seizure-free survival at 1 year after surgery, showed a significant difference between the patient group with preoperative temporary seizure remission and the patient group without preoperative temporary seizure remission ($p < 0.01$) (Fig. 1). Sex, age at onset, age at surgery, the period from the onset to surgery, type of surgery, etiology, history of epileptic encephalopathy, and preoperative DQ, were not associated with seizure remission.

Postoperative complications included subdural effusion in seven patients (6.6%) and hydrocephalus in one patient (0.9%); a subdural-peritoneal or ventriculoperitoneal shunt was required, respectively. There was one patient who needed a debridement

Table 1
Demographic and clinical characteristics of patients ($N = 106$).

Variables	All ($N = 106$)	DQ-non-improved ($n = 61$)	DQ-improved ($n = 45$)	p-value
Male, n (%)	55 (51.9)	30 (49.2)	25 (55.6)	0.56
Age at onset, mean (SD), months	7.4 (8.3)	7.2 (7.9)	7.7 (8.9)	0.54
One year of age or younger at onset, (%)	87 (82.1)	49 (80.3)	38 (84.4)	0.62
Two years of age or younger at onset, (%)	101 (95.3)	58 (95.1)	43 (95.6)	1.00
Age at surgery, mean (SD), months	30.3 (21.2)	28.0 (20.8)	33.4 (21.6)	0.14
The period from onset to surgery, mean (SD), months	22.4 (18.4)	20.9 (18.1)	24.4 (18.7)	0.24
Type of surgery, n (%)				
Total	101 (95.3)	59 (96.7)	42 (93.3)	0.42
Anterior	5 (4.7)	2 (3.3)	3 (6.7)	0.65
Etiology, n (%)				
Known	41 (38.7)	27 (44.3)	14 (31.1)	0.23
Structural	28 (26.4)	19 (31.2)	9 (20.9)	0.27
Genetic	17 (16.0)	13 (21.3)	4 (8.9)	0.11
Infectious	6 (5.7)	4 (6.6)	2 (4.4)	1.00
Metabolic	0 (0.0)	0 (0.0)	0 (0.0)	NA
Immune	0 (0.0)	0 (0.0)	0 (0.0)	NA
Epilepsy type, n (%)				
Focal	2 (1.9)	1 (1.6)	1 (2.2)	0.54
Generalized	79 (74.5)	43 (70.5)	36 (80.0)	0.27
Combined	25 (23.6)	17 (27.9)	8 (17.8)	0.67
Seizure type, n (%)**				
Epileptic spasms	89 (84.0)	50 (82.0)	39 (86.7)	0.60
Generalized tonic	35 (33.0)	20 (32.8)	15 (33.3)	1.00
Generalized tonic-clonic	7 (6.6)	5 (8.2)	2 (4.4)	0.70
Atypical absence	12 (11.3)	9 (14.8)	3 (6.7)	0.23
Myoclonic	11 (10.4)	6 (9.8)	5 (11.1)	1.00
Atonic	7 (6.6)	5 (8.2)	2 (4.4)	0.67
Focal	15 (14.2)	10 (16.4)	5 (14.2)	0.58
Number of patients with two or more seizure types before surgery, n (%)	48 (45.3)	30 (49.2)	18 (40.0)	0.43
Number of patients with a DQ < 35 before surgery, n (%)	77 (72.6)	40 (65.6)	37 (82.2)	0.08
Number of AEDs used before surgery, mean (SD)	4.6 (1.7)	4.4 (1.6)	4.9 (1.7)	0.11
History of epileptic encephalopathy, n (%)**	84 (79.2)	49 (80.3)	35 (77.8)	0.83
EME or EIEE	11 (10.4)	8 (13.1)	3 (6.7)	0.35
West syndrome	78 (73.6)	46 (75.4)	32 (71.1)	0.66
Lennox-Gastaut syndrome	13 (12.3)	8 (13.1)	5 (11.1)	1.00
CSWS	1 (0.9)	0 (0.0)	11 (2.2)	0.42
History of temporary seizure remission before surgery, n (%)	32 (30.2)	19 (31.1)	13 28.9)	0.81
Seizure free, n (%)				
1-month postoperatively	48 (45.3)	21 (34.4)	27 (60.0)	0.01*
1-year postoperatively	23 (21.7)	8 (13.1)	15 (33.3)	0.01*
One-year postoperative EEG abnormalities, n (%)				
Disappeared	5 (4.7)	2 (3.3)	3 (6.7)	0.76
Lateralized	40 (37.7)	22 (36.0)	18 (40.0)	0.68
Multi-foci	61 (57.6)	37 (60.7)	24 (53.3)	0.45
AED change after CC, m (%)	46 (43.4)	13 (28.9)	33 (54.1)	0.01*
Surgical complications, n (%)				
Subdural effusion	7 (6.6)	5 (8.2)	2 (4.4)	0.43
Hydrocephalous	1 (0.9)	1 (1.6)	0 (0.0)	0.39
Infection	1 (0.9)	1 (1.6)	0 (0.0)	0.39
Death	0 (0.0)	0 (0.0)	0 (0.0)	NA

AEDs, antiepileptic drugs; CSWS, continuous spikes and waves during slow-wave sleep; DQ, developmental quotient; EEG, electroencephalography; EME, early infantile myoclonic encephalopathy; EIEE, early infantile epileptic encephalopathy (Ohtahara syndrome); CC, Corpus Callosotomy; NA, not applicable; SD, standard deviation.
* Indicates statistical significance.
** Indicates that multiple answers were allowed.

for a surgical wound infection. There were no surgery-related fatalities.

4. Discussion

To the best of our knowledge, this is the largest cohort of infants and younger children who underwent CC for refractory epilepsy to be evaluated for postoperative developmental changes. Our results showed that most children who underwent CC before the age of 6 years had a severe developmental delay before CC; however, 42.5% of patients showed an increase in DQ 1 year after CC, suggesting that developmental improvement could occur in some patients after CC.

Factors other than surgery and subsequent EEG changes that affected the development of children with drug-resistant epilepsy after CC included sex, age at onset, age at surgery, underlying medical conditions, and the effects of AEDs. None of these factors were significantly associated with postoperative developmental gains in

Table 2
Developmental changes after corpus callosotomy.

	All (N = 106)	DQ-non-improved (n = 61)	DQ-improved (n = 45)	p-value
DA, mean (SD), months				
Preoperatively	7.9 (10.0)	9.0 (11.4)	6.3 (7.5)	0.06
1-month postoperatively	8.2 (8.8)	8.4 (8.9)	7.8 (8.7)	0.31
1-year postoperatively	10.9 (12.1)	10.8 (13.3)	11.1 (10.5)	0.54
DQ, mean (SD)				
Preoperatively	25.0 (20.8)	30.6 (22.3)	17.4 (15.7)	<0.01*
1-month postoperatively	26.1 (19.5)	28.9 (20.4)	22.3 (17.6)	0.06
1-year postoperatively	23.4 (18.5)	22.9 (18.9)	24.1 (17.7)	0.54
DQ change, mean (SD)				
1-month postoperatively	1.1 (9.4)	−1.6 (9.4)	4.9 (8.0)	<0.01*
1-year postoperatively	−1.6 (11.6)	−8.4 (10.4)	6.5 (6.4)	NA

DA, developmental age; DQ, developmental quotient; CC, Corpus Callosotomy; NA, not applicable; SD, standard deviation.
* Indicates statistical significance.

Table 3
Results of multiple logistic regression analysis to predict developmental gain.

Factor	Multiple logistic regression analysis		
	Odds ratio	95% CI	p-value
Seizure-free state 1-year postoperatively	4.26	1.00–18.10	0.05*
Preoperative DQ	0.95	0.92–0.98	<0.01*
DQ change 1-month postoperatively	1.19	1.08–1.35	<0.01*

CI, confidence interval; DQ, developmental quotient.
* Indicates statistical significance.

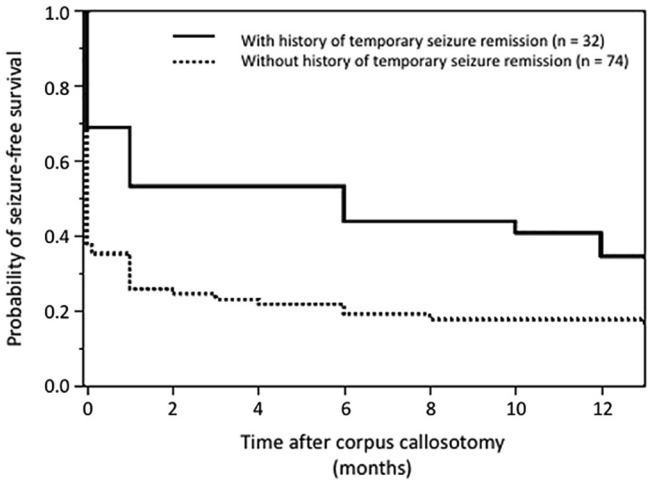

Fig. 1. Probability of seizure-free survival at one year after corpus callosotomy. Outcomes in the patients with a preoperative history of temporary seizure remission, differed significantly from the patients without preoperative remission ($p < 0.01$).

our study. Some data suggest that the nurturing environment and the use of interventions, such as rehabilitation, are also contributing factors to developmental changes, but there are many missing data in our cohort, and we were not able to extract enough information from the medical records to establish these relationships.

4.1. Developmental profile before corpus callosotomy

In our series, most patients developed seizures in early infancy and had stalled or regressed development after seizure onset. About 79.2% of patients had a history of epileptic encephalopathy before CC. The persistence of epileptic encephalopathy in infancy results in irreversible psychomotor developmental impairments with high mortality [26,27]. Most of the patients included in this study were in a desperate state, in terms of both seizures and developmental capacity, before surgery.

4.2. Developmental profile after corpus callosotomy

Although the mean DA increased slightly after CC, our results showed that the mean DQ decreased slightly over the course of a year, indicating that in most patients, the rate of development after CC remained stagnant or markedly slower than that of healthy children.

Nevertheless, there were two interesting observations in the postoperative course. First, the mean DQ subsequently increased 1 month after CC in the DQ-improved group, suggesting that residual functions were still preserved in a neural network that was exacerbated by epileptic activity before surgery, and begun to function shortly after CC. Our result, that the seizure-free rate was higher in the DQ-improved group than in the non-improved group, strongly suggests an association between epileptic seizures and development, similar to the previously reported good prognostic factors in resective surgery for epilepsy [9–12]. Moreover, an association between developmental improvement and seizure remission, both at 1 month and 1 year after CC, also indicates that the seizure-free period, even if temporary, significantly affected the developing brain during infancy. In recent years, the use of functional MRI and diffusion tensor imaging has advanced the research on the brain's functional connectivity network. Ueda et al. reported that a change in the neural network leading to more normal connectivity occurred when seizures disappeared after CC, in children with refractory epilepsy [28]. The brain in early childhood has shown plasticity depending on the seizure and EEG status, and CC may alter brain function in a very short period.

In addition to the direct effect on seizure frequency, CC's possible developmental effect may be the rapid reconstruction of networks that do not involve the corpus callosum. The preoperative interictal EEG showed generalized, bilateral, or multifocal abnormalities. In contrast, postoperatively, EEG abnormalities disappeared in 4.7% of patients and lateralized to the unilateral hemisphere in 37.7% of patients, suggesting that CC may have altered the brains' abnormal epileptic network. It has been reported that disconnection symptoms are less likely to occur in pediatric patients, and even if they do, they recover within a month [24]. Performing CC in the immature brain, which is highly plastic, may cause active modification of neuronal connectivity, which may impact development.

Second, 42.5% of patients showed an increase in DQ 1 year after CC. Due to the high degree of neuroplasticity in the pediatric brain, developmental delay in children with intractable epilepsy is not inevitable with early intervention and seizure control [29]. However, if the timing for appropriate intervention is missed, persistent poor seizure control can interfere with normal synaptic function and elaboration of neural processes, due to their high neuroplasticity, leading to the construction of abnormal epileptic networks. These children are deprived of developmental opportunities and develop irreversible neurological deficits, which is why most children with drug-resistant epilepsy that are younger than 6 years, are deemed to have "epileptic encephalopathy." As long as seizures persist, developmental improvement cannot be expected. In our series, the mean preoperative DQ was 25.0, and the patients had severe developmental delay, and almost all patients experienced uncontrolled seizures. Despite this, 42.5% of the patients still had some developmental opportunities, suggesting the importance of active intervention during the critical period, even in the presence of severe developmental delay, which is clinically very important. Because neuroplasticity is time-sensitive in the developing brain [30], for children with epileptic encephalopathy who already exhibit severe delay, more active interventions during infancy should be considered to promote development.

Factors related to improvement in postoperative DQ were 'low preoperative DQ', 'developmental gain at 1 month after CC', and 'seizure-free after CC'. Previous studies showed that preoperative DQ and postoperative DQ were strongly correlated, and that the higher the preoperative DQ level, the higher was the postoperative DQ level [10,31].

Our study observed similar results; however, regarding developmental gain, patients with lower preoperative DQ showed more considerable improvement in postoperative development. Loddenkemper et al. also reported that infants who had lower preoperative DQ had less postoperative worsening of DQ [10]. Although seemingly a contradictory causal relationship, this is reasonable given that most of the patients had developmental delay and epileptic encephalopathy. Severe developmental delay before surgery infers that the patients might have two components of disease: 'epileptic encephalopathy' due to epileptic activity and 'developmental encephalopathy' associated with the underlying disease [32]. An exceptionally low developmental level may be the result of a developmental impairment associated with 'epileptic encephalopathy' compounding the underlying condition as 'developmental encephalopathy', suggesting that there is room for improvement by attenuating epileptic activity. Although developmental changes are limited and overall development remains impaired, the reversal of epileptic encephalopathy by CC may provide patients with an opportunity for developmental progress during early childhood, which is an irreplaceable pleasure for parents or caregivers. We believe that the timing of active intervention should be early in infancy before the disability becomes permanent.

4.3. The effectiveness of corpus callosotomy for seizures

Overall, 21.7% of our patients were able to maintain seizure-free status for 1 year after CC. As CC is a palliative surgery, seizures do not entirely disappear in many cases. Previous studies reported postoperative seizure-free rates of <20%, and even lower long-term seizure-free rates [18,19,21]. This may be related both to the inclusion of older patients and those with a longer disease duration between onset and CC. Both the fact that our patients were operated on at a younger age (<6 years) and the relatively short time to surgery (22.4 months on average), may have contributed to the positive surgical results; however, our study had a short follow-up period of only 1 year after surgery. Therefore, we were unable to assess long-term recurrence rates. Moreover, long-term outcomes and the course of development need further study.

Based on our results, a predictor of seizure-free state was a history of temporary seizure remission due to medical treatment before surgery, which implied that epileptogenicity was relatively mild or the plasticity to return to a less epileptogenic neural network state was still present in the patients. There were reports that a good seizure outcome after CC could not be expected if the preoperative cognitive functioning was too low [33]; conversely, Rathore et al. found that 65% of patients with severe mental retardation had good seizure outcome after CC [34]. In our cohort, seizures disappeared in 21.7% of patients. Further, severe intellectual disability was not a contraindication to CC.

4.4. Limitations

This study has limitations. First, it was a retrospective analysis, and it is undeniable that the timing of the examination and the recruitment of the candidate patients were biased. In the future, it will be necessary to evaluate development before performing CC and to perform a prospective study with a longer follow-up period. Finally, and ideally, to prove that CC contributed to the developmental improvement, in future studies, we would need to evaluate the effect of CC by comparing the results with an unoperated patient control group.

5. Conclusions

Performing CC during infancy and early childhood for patients with drug-resistant epilepsy and severe developmental impairment was associated with improved development in 42.5% of patients. Factors associated with developmental gain were too low regarding preoperative DQ and postoperative seizure-free state. Whether development improves after 1 year can be inferred by the change in DQ within 1 month postoperatively. Remission of seizures, even if only for a short period, contributes to improved development. CC for drug-resistant epilepsy in early childhood is an effective treatment from a developmental perspective.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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