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Corpus callosotomy for drug-resistant spasms associated with tuberous sclerosis complex

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ABSTRACT

Background: Corpus callosotomy (CC) has recently been adopted for the treatment of drug-resistant epileptic spasms and tonic spasms. In the present study, we investigated CC outcomes among patients with drug-resistant epileptic spasms or tonic spasms associated with tuberous sclerosis complex (TSC).
Methods: We retrospectively collected data from seven patients (3 women, 4 men) with diagnosed TSC and who were treated using CC at Seirei Hamamatsu General Hospital in Japan. All patients had experienced drug-resistant epileptic spasms (<3 s of muscular contraction) or tonic spasms (>3 s) prior to CC, which were confirmed via video-electroencephalogram monitoring.
Results: All patients exhibited multiple bilateral cortical tubers on brain magnetic resonance imaging. The main seizure types were epileptic spasms in four, tonic spasms in one, and both seizure types in two patients. Patients underwent total CC between the ages of 25 months and 21.5 years. Additional resection or disconnection was performed in two patients. The follow-up period after CC ranged between 9 months and 3.5 years. Three patients achieved remission from spasms following CC alone. Two other patients became free from spasms several months after CC but required an additional focus disconnection or medical treatment. The remaining two patients continued to show spasms or asymmetrical tonic seizures.
Conclusion: Total CC resulted in freedom from drug-resistant epileptic or tonic spasms in several patients with TSC. Stepwise progression from CC to additional resection or disconnection surgery may aid in the treatment of spasms secondary to TSC.

1. Introduction

Tuberous sclerosis complex (TSC) is a neurocutaneous disorder caused by mutations in either *TSC1* or *TSC2*, which encode the protein products hamartin and tuberin, respectively; TSC is characterized by tumors in multiple organs, including the brain [1]. Eighty-five percent of patients develop epilepsy, while 38% develop infantile spasms [2]. Among those with infantile spasms, 39% are resistant to medications and develop Lennox–Gastaut syndrome or similar conditions [2]. Tuberous sclerosis complex results in the formation of multiple cortical tubers, which lead to the development of multiple/widespread epileptic networks, in turn resulting in drug-resistant multifocal seizures or epileptic spasms [3]. Resection may be a therapeutic option for a subset of patients with TSC who experience drug-resistant seizures, as 56% of patients with TSC report freedom from seizures following resection surgery [4].

Corpus callosotomy (CC) is a palliative surgery for intractable epilepsy, especially among patients who cannot be treated via resection surgery [5]. Maehara and Shimizu reported that seizure freedom was achieved in 85% of patients with drop attacks, while the seizure-free rate range was 13–21% for patients with other types of generalized seizures [6]. The procedure has been adopted for use among pediatric patients with epileptic spasms or tonic spasms, which are associated with longer muscular contractions than epileptic spasms. Baba et al. reported CC outcomes for 56 Japanese pediatric patients with epileptic spasms due to West syndrome [7]. Seizure freedom was achieved in 18 patients (32.1%), with excellent outcomes (>80% reduction in seizure frequency) occurring in 15 additional patients (26.8%). Itamura et al. also reported favorable outcomes (>90% reduction in seizure frequency) for 10 of 25 patients who underwent anterior or total CC for epileptic or tonic spasms [8].

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Corpus callosotomy is effective against epilepsy not only in patients without structural brain abnormalities, but also in patients with bilateral cortical malformations [8,9]. Tuberous sclerosis complex is characterized by the development of intractable epilepsy due to bilateral cortical abnormalities [1,2]. Liang et al. reported that 55% of patients with TSC achieved seizure freedom following CC plus resection surgery [10]. However, no previous studies have investigated the efficacy of solitary CC for the treatment of spasms in patients with TSC. Therefore, in the present study, we examined clinical data and outcomes for seven patients with TSC who underwent total CC for drug-resistant epileptic or tonic spasms at our hospital.

2. Methods

2.1. Patients

We retrospectively collected data for patients with diagnosed TSC and who were treated via CC at Seirei Hamamatsu General Hospital (Japan) between November 2014 and December 2018. All patients had drug-resistant epileptic or tonic spasms prior to CC, which were confirmed via long-term video-electroencephalogram (vEEG) monitoring.

2.2. Clinical information

We reviewed clinical information including gender, age at epilepsy onset, gene analysis results, lesion findings on brain magnetic resonance imaging (MRI), age at CC, age at and methods of additional surgical treatments after CC, cognitive development, medications for seizures before CC, seizure types before CC, follow-up period, and seizure outcomes. The numbers of cortical tubers on brain MRI were counted separately for each hemisphere. We also evaluated the presence of subependymal nodules and subependymal giant cell astrocytoma. All data were retrospectively collected from medical records.

Development was classified using the developmental quotient (DQ): severe delay, <30% of expected value; moderate delay, ≥30% yet <50% of expected value; mild delay, ≥50% yet <70% of expected value; normal, ≥70% of expected value. Development was evaluated using the Enjoji Analytical Development Test, Tanaka-Binet Intelligence Scale, and Kyoto Scale of Psychological Development. One adult patient (patient #3, 21-year-old woman) was not evaluated using these tests because of severe developmental delays (no meaningful speech).

2.3. EEG findings

Prior to CC, all patients underwent long-term interictal and ictal vEEG monitoring. To evaluate changes in the electroencephalogram (EEG) findings following CC, long-term vEEG was performed 2 to 16 weeks after CC in six patients. We carefully confirmed epileptic and tonic spasms in these recordings, as these seizure types were the primary target for treatment with CC.

Epileptic spasms were defined as short muscular contractions of <3 s (epileptic spasms) or >3 s (tonic spasms) with rhombus-like or tadpole shapes on electromyography of the neck or shoulder. Spasms were also defined based on the presence of diffuse polyphasic delta or theta waves at the beginning of the muscular contractions on vEEG. The ictal EEG findings for other types of seizures, including focal seizures, symmetrical/asymmetrical tonic seizures, myoclonic seizures, atypical absence seizures, and atonic seizures, are described in Table 2.

2.4. Seizure outcomes

We evaluated seizure outcomes at the last visit of the follow-up in accordance with Engel's outcome classification scheme (Engel class). Outcomes were evaluated after CC and before additional surgeries or medical treatments. Outcomes were categorized as follows: Engel class I, complete freedom from the seizure types; Engel class II, ≥90% seizure reduction; Engel class III, ≥50% seizure reduction; Engel class IV, <50% seizure reduction. Outcomes were evaluated separately for the main seizures (epileptic or tonic spasms) and other seizure types.

2.5. Ethical approvals

This study was approved by the ethics board of Seirei Hamamatsu General Hospital. Informed consent was obtained from the guardians of each patient. Details for patient #1 were presented in a previous case report [11], while some data for patients #2 and #7 were included in our previous study [8].

3. Results

3.1. Patients and clinical information

The clinical details are presented in Table 1. We collected data for six children (2 girls; 4 boys) and one adult woman who developed West syndrome during infancy. Gene analyses were performed in three patients and revealed mutations on the *TSC2* gene in all the patients. One patient (patient #1) developed viral infection-associated acute encephalopathy at 1 year and 3 months of age. Mild, moderate, and severe developmental delays were observed in two, one, and four patients, respectively. Six patients (all except Patient #6) presented with autistic behavior.

All patients developed West syndrome, with the age at onset ranging from 2 to 6 months (median: 3 months). Patients were treated with a range of 3–10 (median: 6) antiepileptic drugs prior to CC. Two patients (patient #3 and 4) were treated with everolimus. Four patients (patient #3, 5, 6, and 7) received adrenocorticotropic hormone therapy before CC. Three patients exhibited transient remission from epileptic spasms, with relapse occurring between the ages of 8 months and 2 years and 10 months. Seizure types at the time of CC included epileptic spasms in six patients (all except patient #3), tonic spasms in three patients (patients #1–3), focal seizures in two patients (patients #2, 3), atypical absence seizures in two patients (patients #6, 7), myoclonic seizures in one patient (#4), and atonic seizures in one patient (patient #6). The focal seizures in patient #2 sometimes evolved to generalized tonic seizures.

Patients underwent total CC, between the ages of 25 months and 21.5 years (median: 3 years and 8 months). Additional surgeries were performed for two patients, whose seizures lateralized to one hemisphere (details given in Section 3.4.). Patient # 2 was treated with vigabatrin, 13 months after CC, while patient # 5 was treated with everolimus, 11 months after CC.

3.2. Presurgical evaluations before CC

We used brain MRI, 123I-iomazenil single photon emission computed tomography (IMZ-SPECT), fluorodeoxyglucose-position emission tomography (FDG-PET), and interictal and ictal scalp vEEG for presurgical evaluation.

Brain MRI was performed for all patients. Multiple bilateral cortical tubers were observed on the brain MRI of all patients (Supplementary Fig. 1). Six patients (all patients, except patient #3) exhibited more than 10 cortical tubers in each hemisphere, while one patient (patient #3) exhibited eight cortical tubers (six in the left and two in the right hemispheres). Subependymal nodules were observed in all patients. Subependymal giant cell astrocytoma was observed in one patient (patient #5).

An IMZ-SPECT was performed for four patients (patient #1, 2, 4, and 6). The images showed low-uptake regions corresponding to the cortical tubers on brain MRI. Patient #1 showed large low-uptake regions in the frontal lobe, bilaterally, indicating the damage caused by previous acute encephalopathy. Patient #2 showed a large low-uptake region in the right temporal lobe. Patient #6 showed large low-uptake regions

Table 1
Clinical profiles, gene analysis, and brain MRI findings.

Patient #	Age at West syndrome onset	Age at CC	Gender	Gene	Cortical tuber (lt:rt hemisphere)	Development	Medications before CC
1	6m, 1y4m[a]	3y8m	Male	*TSC2*	>10:>10	Severe delay, autism	VPA, PB, ZNS, LEV
2	2m	5y6m	Male	*TSC2*	>10:>10	Severe delay, autism	VGB, NZP, LTG, LEV, CBZ, VPA, RFN
3	2m, 8m[a]	21y6m	Female	*TSC2*	6:2	Severe delay, autism	VB6, ACTH, VPA, CZP, CBZ, GBP, LEV, LTG, TPM, PER
4	4m	8y5m	Female	NA	>10:>10	Mild delay, autism	VPA, PB, ZNS, CZP, CLB, LEV, CBZ, TPM, LTG
5	3m	2y7m	Male	NA	>10:>10	Severe delay, autism	VB6, VPA, ZNS, CLB, VGB, LEV, TPM, LTG
6	3m	2y1m	Male	NA	>10:>10	Moderate delay	VPA, ZNS, VGB, CZP, LEV
7	6m, 2y10m[a]	3y5m	Female	NA	>10:>10	Mild delay, autism	VPA, TPM, LEV

Patient #	ES/TS (seizure freq.)	Other seizure types (seizure freq.)	Additional surgery (months after CC)	Others	Follow-up period	Outcome of Engel's classification	
						Spasms	Other seizures
1	ES/TS (H)	–	–	Acute encephalopathy (1y3m)	3y4m	I	Focal seizure (only once)
2	ES/TS (H)	FS ; → tonic spasms (D)	–	VNS (3y6m), VGB (6y7m)	3y6m	IV[b]	IV → II
3	TS (D)	FS (D)	Resection in left frontoparietal area (1)	–	2y10m	IV	IV
4	ES (D)	MS (D)	–	–	2y0m	I	I
5	ES (H)	–	–	Everolimus (3y6m)	2y1m	II[c]	–
6	ES (H)	AS (D), AA (D)	Left posterior disconnection (4)	–	1y5m	II[d]	AS: II ; → I AA: I
7	ES (D)	AA (D)	–	–	9 m	I	I

lt: left; rt.: right; CC: corpus callosotomy; SEN: subependymal nodules; SEGA: subependymal giant cell astrocytoma; AED: antiepileptic drugs; ACTH: adrenocorticotropic hormone; m: months; y: years; NA: not analyzed; VPA: valproate; PB: phenobarbital; ZNS: zonisamide; LEV: levetiracetam; VGB: vigabatrin; NZP: nitrazepam; LTG: lamotrigine; CBZ; carbamazepine; VB6: vitamin B6; CZP: clonazepam; GBP: gabapentin; EVE: everolimus; PER: perampanel; CLB: clobazam; ES: epileptic spasms; FS: focal seizures; TS: tonic spasms; MS: myoclonic seizures; AS: atonic seizures; AA: atypical absences; H: hourly; D: daily; VNS: vagus nerve stimulation.

[a] Age at relapse of ES.
[b] CC was ineffective, and VGB reduced the seizures.
[c] CC reduced spasms markedly, and additional everolimus treatment achieved seizure freedom.
[d] CC reduced spasms markedly and achieved freedom from other seizures, and additional disconnection achieved freedom from the spasms.

in the left parietooccipital lobes. An FDG-PET was performed for two patients (patient #3 and 5). The images also showed low-uptake regions corresponding to the cortical tubers. Patient #3 showed large low-uptake regions on the left parietal lobe.

The details of the presurgical EEG findings are described in Section 3.3. and Table 2. The EEG did not show apparent lateralization or asymmetrical findings during the ictal and interictal phases.

The decision to perform CC was made after discussion and consideration of these investigations. Complete CC was performed for the all patients, since the main seizures were epileptic or tonic spasms, and the abnormal findings showed bilateral distribution on brain imaging. We planned to perform additional resection or disconnection surgery, after CC in cases where the seizures did not undergo complete remission and were lateralized to one hemisphere.

3.3. EEG findings before and after CC

The EEG findings before and after CC are described in Table 2. Patient #2 did not undergo long-term vEEG after CC in our hospital.

During the interictal periods, all seven patients exhibited multifocal spikes and/or sharp waves, while six patients (all except patient #6) exhibited diffuse spike-and-wave or polyspike-and-wave bursts prior to CC. Three patients (patients #2, 5, 6) exhibited hypsarrhythmia. In all six patients who underwent postoperative vEEG, diffuse discharge and

Table 2
EEG before and after corpus callosotomy.

Patient #	Interictal discharges		Ictal discharges	
	Before CC	After CC	Before CC	After CC
1	Multifocal spikes, diffuse slow SPW burst	Multifocal SPW, polyspikes	ES/TS: HV theta/delta → ;DA	No ictal recording (seizure-free)
2	Multifocal spikes, diffuse slow SPW burst, hypsarrhythmia	ND	ES/TS: HV theta ; → DA FS ; → tonic sz: rhythmic alpha (rf frontal) ; → diffuse spikes ; → DA	ND
3	Multifocal spikes, diffuse SPW burst	Multifocal spikes	TS: diffuse theta ; → DA (FS was not captured)	Asymmetrical tonic sz (lt/rt): rt./lt spike burst
4	Multifocal spikes, irregular diffuse SPW, diffuse polySPW burst	Multifocal spikes	ES: polyphasic diffuse delta ; → DA MS: diffuse SPW	No ictal recording (seizure-free)
5	Multifocal spikes/sharp waves, hypsarrhythmia	Multifocal spikes/sharp waves (lt > rt)	ES: polyphasic diffuse delta wave (rt > lt) ; → DA FS:rhythmic alpha (rt occipital)	ES: polyphasic theta (lt > rt./bil frontal dominant) FS: rhythmic alpha (rt occipital)
6	Multifocal spikes, diffuse slow SPW burst, hypsarrhythmia, rapid rhythm	Multifocal spikes in lt hemisphere	ES/AS: polyphasic diffuse theta AA: diffuse slow SPW	ES/AS: diffuse theta (lt > rt) (AA: not captured)
7	Multifocal spikes, diffuse polySPW burst	Multifocal spikes	ES: HV theta/delta AA: slow SPW	No ictal recording (seizure-free)

lt: left; rt.: right; CC: corpus callosotomy; SPW: spike-and-wave; polySPW: polyspike-and-wave; HV: high-voltage; DA: diffuse attenuation; ES: epileptic spasms; TS: tonic spasms; MS: myoclonic seizures; AS: atonic seizures; AA: atypical absence; FS: focal seizures; ND: not done.

hypsarrhythmia were no longer observed following CC. In all patients, multifocal discharge remained after CC.

Epileptic and tonic spasms were confirmed via vEEG prior to CC in five and two patients, respectively. Three patients (patients #1, 4, 7) exhibited no spasms following CC, while two (patients #5, 6) continued to exhibit ictal EEG findings similar to those observed prior to CC. Patient #3 exhibited asymmetrical tonic seizures (both left- and right-dominant) with contralateral hemispheric spike bursts on EEG.

Focal seizures were confirmed in two patients (one in the right frontal area (patient #2) and one in the right occipital area (patient #5)) prior to CC. Postoperative vEEG revealed focal seizures similar to those observed prior to CC in one patient (patient #5).

Prior to CC, myoclonic seizures (patient #4) and atypical absence seizures (patients #6, 7) were observed in one and two patients, respectively. These seizures were associated with bilateral diffuse discharges on ictal EEG. Atonic seizures were observed in patient #6, who exhibited diffuse polyphasic slow waves resembling epileptic spasms on pre-CC vEEG. Seizure remission was observed following CC (i.e., absence of seizure activity on vEEG).

3.4. Seizure outcomes

The follow-up period after CC ranged from 9 months to 3 years and 6 months (median: 2 years). Regarding the outcomes of spasms, Engel class I outcome was observed in three patients, and Engel class II, and IV outcomes were observed in two patients, each. Three patients (patient #1, 4, and 7) achieved remission from spasms by CC alone. In patient #2, CC did not reduce the frequency of spasms or other seizures; however, treatment with vigabatrin beginning 13 months after CC markedly reduced the frequency of both spasms and other seizure types. In patient #5, spasm frequency gradually decreased from hourly (30–50/day prior to CC) to daily (5/day) prior to beginning treatment with everolimus. In this patient, seizure freedom was achieved 20 months after CC (9 months after initiating everolimus treatment).

Patient #3 and 6 underwent additional surgeries. Patient #3 experienced relapse in the form of bilaterally independent asymmetrical tonic spasms (right side > left side), following CC. Four weeks after the CC, we placed intracranial electrodes on the left hemisphere. Cortical resection in the left temporoparietooccipital cortices that exhibited high-gamma activity on ictal EEG and hypoperfusion on arterio-spin labeling MRI was performed (Supplementary Fig. 2A). Although, the seizures transiently disappeared, focal motor seizures appeared in the left upper extremity, one month later. Bilaterally independent asymmetrical tonic seizures reappeared 11 months after the second surgery. In patient #6, CC markedly reduced the epileptic spasms and lateralized the seizure to the left hemisphere. We placed intracranial electrodes on the left hemisphere and the left posterior quadrant area exhibited high-gamma activity on ictal EEG. This patient underwent left posterior disconnection 4 months after CC (Supplementary Fig. 2B) and experienced remission from seizures after the disconnection.

Five patients had other types of seizures, besides spasms, prior to CC. Myoclonic seizures (patient #4), atonic seizures (patient #6), and atypical absence seizures (patient # 6 and 7) ceased following CC (Engel class I). Focal seizures recurred only once in patient #2 (Engel class II) and remained in patient #3 (Engel class IV) following CC. Patient #1 experienced one focal seizure after CC.

4. Discussion

In the present study, we retrospectively analyzed clinical data and outcomes for seven patients with TSC who underwent total CC for epileptic or tonic spasms, all of whom exhibited bilateral cortical tubers on brain MRI. Remission from spasms was observed in three patients following solitary CC. These findings suggest that, even in patients with multiple bilateral cortical tubers, CC can aid in alleviating spasms in a subset of patients with TSC. Furthermore, one patient achieved seizure freedom with adjunctive everolimus treatment, while another experienced lateralization of spasms following CC, enabling an additional surgery that led to seizure freedom. Thus, even in patients without remission after CC alone, the CC procedure may play a role in reducing epileptogenesis or isolating the epileptogenic hemisphere.

Corpus callosotomy has been widely utilized in the treatment of medically intractable epilepsy in patients with drop attacks who are not eligible for focal cortical resection [6]. One meta-analysis reported that the presence of MRI lesions was associated with poor outcomes for generalized seizures, focal seizures, and infantile spasms following CC [12]. Only a few studies have evaluated several cases of CC for spasms (or drop attacks) associated with TSC. Liang et al. reported data for 11 patients who underwent total CC adjunctive to resection surgery. Six (54%) and five (45%) patients achieved seizure freedom at 1 year and 5 years from CC, respectively [10]. In addition, Liu et al. reported data for 17 surgical cases of West syndrome secondary to TSC, seven of whom underwent CC adjunctive to multilobe resection or multiple lesionectomy. Three (43%) of these patients achieved seizure freedom, and two patients (29%) achieved a >75% reduction in seizure frequency [13].

In these previous studies, CC was performed adjunctive to cortical resection. Although we initially intended to perform stepwise surgeries from CC to resection of the hemisphere exhibiting residual seizure activity, we observed that solitary CC resolved epileptic spasms and other generalized seizures in several patients. These findings suggest that, in the generation of spasms or generalized seizures, the corpus callosum promotes bilateral synchrony or interhemispheric recruitment of epileptic activity in patients with epileptogenesis in both hemispheres [14]. Even in patients who do not develop focal seizures in each hemisphere because of the use of antiepileptic drugs, the interhemispheric promotion of epileptic activity via the corpus callosum can increase epileptogenesis throughout the cerebrum, leading to epileptic spasms. Thus, CC may eliminate the interhemispheric promotion of epileptic activity, enabling control of the residual epileptogenesis in each hemisphere using antiepileptic drugs. This study has some limitations. This is a retrospective study with a small number of patients. The follow-up periods were of short duration in several patients.

In conclusion, our findings support the notion that patients with TSC experiencing drug-resistant epileptic spasms can initially be treated with solitary CC, even when multiple bilateral cortical tubers are observed on brain MRI. Stepwise progression from CC to additional resection or disconnection surgery may aid in the treatment of spasms secondary to TSC.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.06.007.

Declaration of Competing Interest

The author(s) declare no competing interests.

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Author contributions

T.O., A.F., S.B., K.O., N.I., and H.E. conceptualized the study. T.O. designed the study, wrote the first draft of manuscript, and contributed to all other aspects of the study. T.O., A.F., H.E. evaluated MRI data. T.

O., S.B., N.I., and M.N. performed data acquisition. All authors performed data interpretation and revision of manuscript.

Data availability

The anonymized clinical information and the MRI results for individual participants are available from the corresponding author (T. Okanishi) upon reasonable request and following approval by the ethical board of Seirei-Hamamatsu General Hospital. The data will be available beginning 3 months and ending 3 years following article publication.

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