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Case Report

Corpus callosotomy in pediatric patients with non-lesional epileptic encephalopathy with electrical status epilepticus during sleep

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ABSTRACT

Epileptic encephalopathy with electrical status epilepticus during sleep (ESES) is often refractory to medical treatment and leads to poor cognitive outcomes. Corpus callosotomy may be an effective treatment option for drug-resistant ESES with no focal etiology. We retrospectively identified three patients who underwent corpus callosotomy for drug-resistant ESES in our institution. Electroencephalography (EEG) findings and cognitive functions were evaluated before surgery, at 3 months, 6 months, 1 year, and 2 years after surgery. Age at surgery was 6 years 10 months, 7 years 9 months, and 8 years 4 months, respectively. Period between the diagnosis of ESES and surgery ranged from 7 to 25 months. All patients had no obvious structural abnormalities and presented with cognitive decline despite multiple antiseizure medications and steroid therapies. One patient showed complete resolution of ESES and an improvement of intelligence quotient after surgery. Epileptiform EEG was lateralized to one hemisphere after surgery and spike wave index (SWI) was decreased with moderate improvement in development and seizures in the other 2 patients. SWI re-exacerbated from 6 months after surgery, but without subsequent developmental regression in these 2 patients. Corpus callosotomy may become an important treatment option for drug-resistant ESES in patients with no structural abnormalities.

Introduction

Epileptic encephalopathy with electrical status epilepticus during sleep (ESES) or continuous spikes and waves during slow-wave sleep is defined as epilepsy syndrome of childhood with neuropsychological impairment. The typical electroencephalography (EEG) findings of ESES are observed during at least 85% of non-rapid eye movement (NREM) sleep [1,2]. Little is known about the etiology and natural history of epilepsy with ESES. Genetic etiologies, including *GRIN2A*, *SCN2A*, *KCNA2*, *KCNB1*, and *KCNQ2* mutations [3,4], inflammatory factors, and structural factors have been reported, but the etiology remained unknown in half of cases [5]. The epileptic seizures and ESES resolve with age, but severe cognitive decline often persists [6,7]. Therefore, prevention of cognitive decline, in addition to seizure control, is important in the treatment of patients with encephalopathy with ESES.

No consensus has been established on the optimal treatment for epileptic encephalopathy with ESES. Drug treatment may be effective, but at least half of patients develop permanent cognitive decline even with modern medication [6–8]. The efficacy of surgical treatment for patients with ESES with diverse backgrounds is little reported [5]. Most surgically-treated patients were suspected to have focal etiologies of epilepsy [9].

We report our experience of three patients with ESES without focal etiology who were treated with corpus callosotomy.

Material and methods

This study was conducted with the approval of the Institutional Review Board, National Center of Neurology and Psychiatry (NCNP). We retrospectively identified three cases of corpus callosotomy performed for the treatment of ESES from the NCNP neurosurgical database between October 2010 and October 2020. A total of 121 corpus callosotomies were performed during the same period. The clinical information of the patients was extracted from the electronic medical record. The diagnosis of epileptic

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encephalopathy with ESES was made based on at least 85% ESES during NREM sleep and developmental regression with or without clinical epileptic seizures. Comprehensive presurgical evaluation including high field magnetic resonance imaging and long-term video EEG monitoring (VEEG) was performed in all patients. The indication for surgery was decided after a patient management conference attended by pediatric neurologists, neurosurgeons, and certified epileptologists. Corpus callosotomy was indicated for patients with ESES resistant to multiple medical treatments, presented with obvious cognitive decline, and had no focal etiology of epilepsy requiring resective epilepsy surgery.

All 3 patients were evaluated at 3 months, 6 months, 1 year, and 2 years after surgery with one-night VEEG and cognitive tests. Patient characteristics, neuroradiological findings, VEEG findings, medications, and cognitive functions before and after the surgery were evaluated. The spike and wave index (SWI) was measured by a pediatric neurologist and reanalyzed by author SY based on a previous report [10]. The EEG of the first one hour of NREM sleep was used for calculating SWI. Spike wace complexes were visually identified. SWI was defined as the percentage of 1-second bins with at least one spike and wave among all 1-second bins during NREM sleep EEG. Developmental quotient (DQ) and developmental age (DA) were assessed with the Kinder Infant Development Scale (Center of Developmental Education and Research, Tokyo, Japan, 1989) [11]. The KIDS consists of approximately 130 Japanese questions answered by the parent or caregivers and evaluate the child's development in nine domains including motor function, manipulative function, receptive/expressive language functions, conceptualization, social relationships with children/adults, self-discipline, and feeding. General developmental quotient (DQ) was calculated as the subject's summated DA across all domains divided by the chronological age. The KIDS is typically used for assessing the DA between one month and 7 years old. Intelligence quotient (IQ) was assessed with the Wechsler Intelligence Scale for Children fourth edition. Seizure outcome was classified by the International League Against Epilepsy classification [12].

Results

The clinical characteristics of the 3 patients who underwent corpus callosotomy for epileptic encephalopathy with ESES are summarized in Table 1. Preoperative slow wave sleep EEG was characterized by continuous generalized spike waves in all three patients. Focal structural abnormalities were found in none of the patients. All 3 patients had been treated with 6 or more types of antiseizure medications and steroid therapy. Two patients had a history of intravenous immunoglobulin therapy. However, neither steroid therapy nor immunoglobulin therapy had succeeded in improving ESES. The duration of epilepsy from the onset to the diagnosis of ESES ranged from 25 to 27 months. The period between the diagnosis of ESES and the corpus callosotomy ranged from 7 to 25 months. Two patients underwent one-stage total callosotomy and one patient underwent anterior two-third callosotomy.

Table 2 summarizes the postoperative courses of SWI, DQ/IQ, antiseizure medications, and seizure outcomes. DQ or IQ declined from the time of diagnosis to the time of surgery in all patients. ESES completely disappeared and IQ was improved after corpus callosotomy in one patient (Patient 1). SWI was improved at 3 months after surgery in the other two patients, associated with improvement in DQ and DA (Table 2). Subsequently, both patients showed re-exacerbation of SWI associated with stagnation, but no further decline, in development (Fig. 1). Interestingly, epileptiform discharges were lateralized to the left in these two patients after corpus callosotomy (Fig. 2).

Epileptic seizures were controlled before surgery and no recurrent seizures were observed after surgery in Patient 1. Generalized tonic-clonic seizures decreased from once a week to once a month after surgery, but atypical absence continued at two to three times a day in Patient 2. Weekly generalized tonic-clonic seizures were controlled after surgery, and atypical absences decreased from two to three times a month to one to two times a month in Patient 3. The number of antiseizure medications decreased in two patients after surgery. No perioperative complications occurred in any patient. Chronic disconnection syndromes, such as diagnostic dyspraxia and alien hand signs, were not observed in any patient.

Discussion

Early diagnosis and remission of ESES through effective treatment are important to improve the long-term prognosis. Epileptic encephalopathy with ESES is defined as a disorder characterized by epilepsy with focal and apparently generalized seizures, neuropsychological impairment in the form of global or selective regression of cognitive functions, motor impairment, and typical EEG findings of a diffuse spike and wave pattern occurring in up to 85% of slow sleep periods [8]. Such seizures are known to improve with age regardless of the severity. Continuous spike and wave activity during sleep also improves until age 11 years [2]. Cognitive function and behavioral status return to the previous level in 50–70% of patients as ESES disappears [8,13]. However, severe cognitive decline persists or continues to progress even after ESES disappears. No clear evidence demonstrates the effect of epileptic seizures on cognitive function in epileptic encephalopathy with ESES. Early onset and long duration of ESES are the main factors indicating poor prognosis for cognitive and behavioral function [6,14]. Patients who did not achieve complete resolution of ESES

Table 1
Clinical characteristics of patients.

Patient No.	Sex	Past history	Comorbidities	Previous ASMs	Previous steroid and immuno-therapies	Age at epilepsy onset (month)	Age at diagnosis of ESES (month)	Age at surgery (month)	Seizure type	Surgical procedure
1	F	Precocious puberty	-	CLB, CZP, ESM, LEV, NZP, VPA	mPSL-P IVIG × 2	61	86	93	Atypical absence, Facial tonic seizure	Anterior 2/3 CCS
2	F	Neonatal intraventricular hemorrhage	-	CBZ, CLB, CZP, ESM LEV, LTG, ST, VPA, ZNS	mPSL-P × 2	46	72	82	Atypical absence, GTCS	Total CCS
3	M	-	Attention deficit hyperactivity disorder	AZM, CBZ, CZP, LEV, LCM, LTG, PB, TPM, VPA, ZNS	mPSL-P × 2 IVIG × 3	48	75	100	Atypical absence, GTCS	Total CCS

Table 2
Postoperative courses of SWI, DQ/IQ, ASMs, and seizure outcome.

Patient No.	Method of evaluation	SWI (%)						DQ/IQ						ASMs		Seizure outcome*
		At diagnosis of ESES	At surgery	3 months	6 months	1 year	2 years	At diagnosis of ESES	At surgery	3 months	6 months	1 year	2 years	At surgery	2 years	
1	WISC-IV	96	90	0	0	0	0	76	66	na	na	75	87	CZP 1.5 mg ESM 300 mg VPA 600 mg	CZP 1.5 mg VPA 600 mg	1
2	KIDS	90	85	60	64	80	100	52	30	44	47	47	38	CLB 6 mg ESM 350 mg LTG 20 mg VPA 500 mg	CLB 6 mg ESM 350 mg LEV 250 mg VPA 500 mg	4
3	KIDS	97	95	40	85	75	79	85	54	60	55	47	46	LCM 50 mg TPM 6 mg VPA 700 mg	VPA 900 mg	4

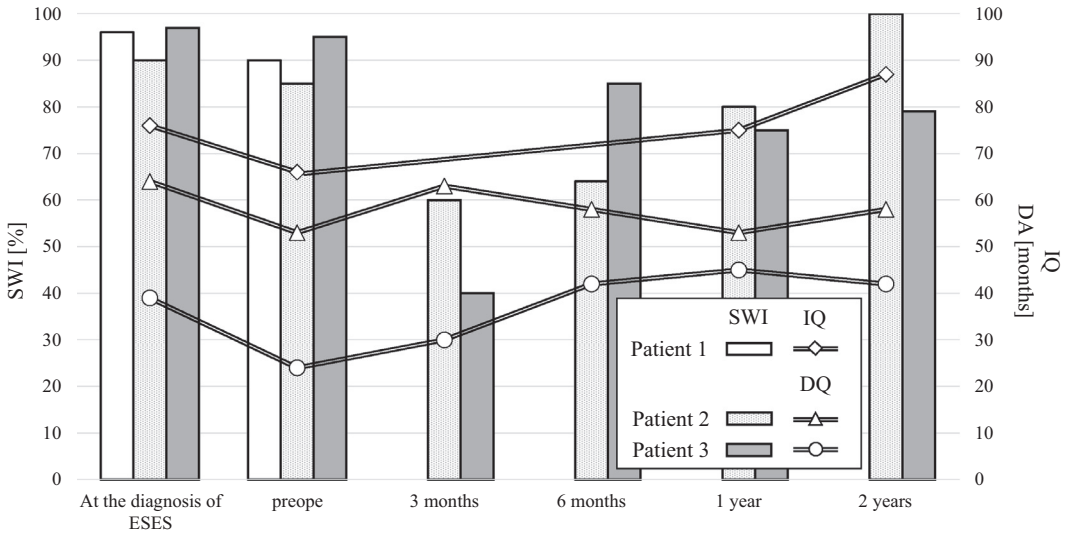

Fig. 1. Graph showing the relationship between spike and wave index (SWI) and intelligent quotient (IQ) in Patient 1 or developmental age (DA) in Patients 2 and 3. DA was maintained despite the exacerbation of SWI. Electrical status epilepticus during sleep completely disappeared and SWI went to zero after surgery in Patient 1.

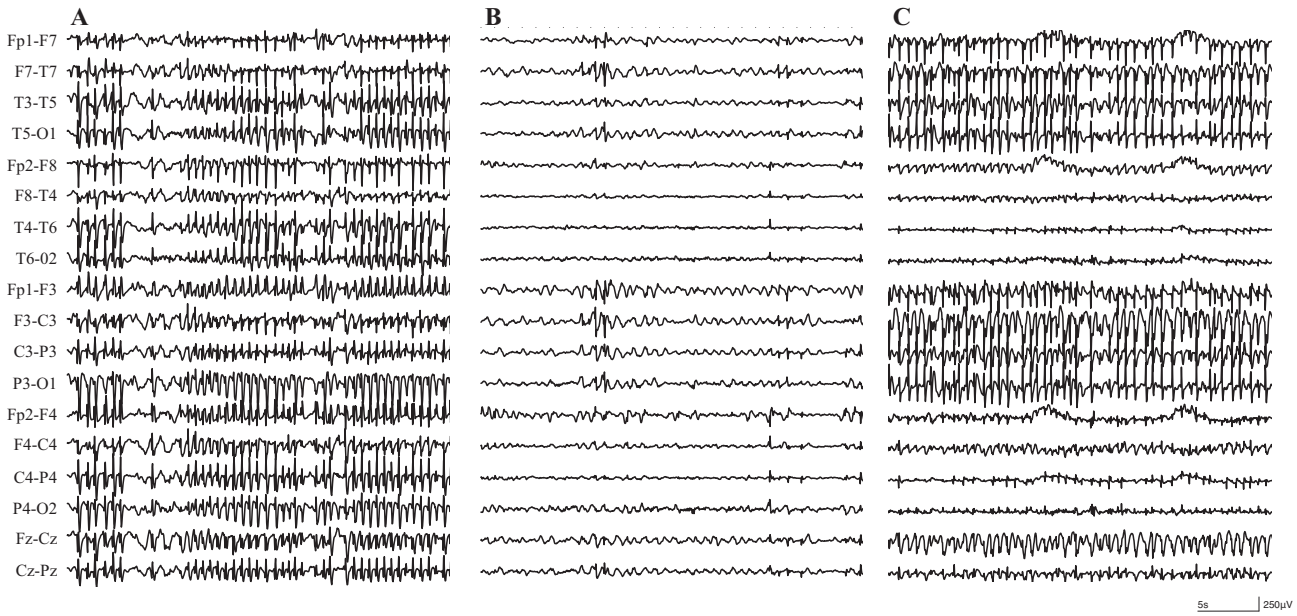

Fig. 2. Postoperative changes of electroencephalography (EEG) in Patient 2. A: Frequent generalized spike waves were seen during sleep preoperatively. B: EEG at 3 months after surgery showed improvement in the spike and wave index from 85% to 60%. Epileptiform discharges were lateralized to the left hemisphere. C: Epileptiform discharges were still lateralized, but became more frequent at 2 years after surgery.

after drug treatment had low IQ at the diagnosis and progressive cognitive decline in the long term [7].

Various retrospective studies have investigated the treatment of epileptic encephalopathy with ESES. Absence of structural abnormalities is a possible predictor of better outcome. Medication is more effective in cases of unknown etiology than in those with structural abnormalities [5]. ESES with structural abnormalities is often refractory to medication so surgical treatment becomes an important option. Pooled analysis of treatments for ESES demonstrated that steroids and surgical treatment were more effective than conventional antiseizure medications [5]. Surgical procedures include multiple subpial transection [15] and hemispherectomy/hemispherotomy [16,17], both of which have been reported to be highly effective for patients with structural abnormalities, resulting in improvement in cognitive function.

Corpus callosotomy for ESES has rarely been reported. Peltola et al reported that surgical treatment including corpus callosotomy was performed in patients in whom focal resection of the epileptogenic zone was not feasible. Eight of 9 patients who underwent corpus callosotomy did not regress during the 2-year follow-up period, and two patients showed significant improvements in IQ postoperatively [18]. All nine patients had cerebral palsy and structural abnormalities, including five with bilateral or hemispheric polymicrogyria, three with intrauterine or perinatal cerebrovascular disease, and one with postoperative frontal tissue loss without further description. Corpus callosotomy was only indicated in a limited population of patients.

Our experience suggests that corpus callosotomy has some efficacy against drug-resistant ESES without structural abnormalities. ESES disappeared in one patient immediately after the surgery and

cognitive function improved to the preoperative level. DQ was improved as SWI decreased at 3 months after surgery in the other two patients (Patients 2 and 3), suggesting that the severity of ESES determined cognitive outcomes. Such improvement was temporary and SWI worsened to the preoperative level by 6 months after surgery, but the DA showed no further decline (Fig. 1). The final DQ was below 50 in Patients 2 and 3, meaning that their development was below half expected for their chronological age. The two patients failed to gain their age-appropriate development over time, but further developmental regression was prevented.

The improvement of DQ and SWI could be attributed to the desynchronization of EEG abnormalities after corpus callosotomy. Corpus callosotomy attenuates the bilateral synchrony of epileptic discharges and increases the amplitude asymmetry [19,20]. Reduction of SWI and resolution of epileptiform discharges in at least one hemisphere probably had positive effects on cognitive function in our three cases. This finding of EEG lateralization after corpus callosotomy for epileptic encephalopathy with ESES may be important. Peltola et al reported that the propagation area of ESES decreased after surgery in two of nine patients, but showed no clear relationships to the cognitive outcome [18]. This difference with our patients may be due to the presence of structural abnormalities. High SWI affects sleep-related memory consolidation [21], although no clear evidence indicates any relationship between partial improvement of ESES and cognitive outcome. Epileptic activity during sleep is known to influence sleep homeostasis and cognitive decline [22].

The major limitation of this report is that it is a retrospective study of a small number of patients with limited follow-up. The surgical indication was not controlled and there was no comparison with medical treatment. Further accumulation of experience from multiple institutions is needed to confirm our findings. Long-term outcome should also be clarified.

Conclusion

Corpus callosotomy may be an effective treatment for drug-resistant epileptic encephalopathy with ESES in patients with no structural abnormalities. Corpus callosotomy reduces epileptic seizures, but apart from the efficacy on seizures, it may prevent cognitive regression partly owing to the reduction of ESES. CC may become an important treatment option in some patients with drug-resistant epileptic encephalopathy and ESES.

Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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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