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Complete Corpus Callosotomy Brings Worthwhile Seizure Reduction in Both Pediatric and Adult Patients

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Received, February 09, 2024; **Accepted,** May 17, 2024; **Published Online,** July 2, 2024.

Neurosurgery 96:410–415, 2025

<https://doi.org/10.1227/neu.0000000000003092>

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BACKGROUND AND OBJECTIVES: The influence of the age at which complete corpus callosotomy (CC) surgery is performed on seizure outcomes remains unclear. This study aimed to evaluate the age-dependent aspects of long-term seizure outcomes after complete CC.

METHODS: We reviewed 41 patients who underwent one-stage complete CC. Seizure outcomes were analyzed for age at epilepsy onset and at complete CC, focal MRI abnormality, and etiology.

RESULTS: The median age was 7 months at epilepsy onset and 93 months at complete CC. The median follow-up duration was 67 months. Sixteen patients had focal MRI lesions and 4 had only general atrophy. Etiology was identified in 20 patients. For overall seizure outcomes (N = 41), complete seizure freedom was achieved in 5 patients, excellent seizure reduction (>80%) in 11, good (50%–80%) in 5, and poor (<50%) in 20. Freedom was correlated with younger age at complete CC and unknown etiology ($P \leq .05$). Freedom was only achieved in patients aged younger than 7 years. Worthwhile ($\geq 50\%$, freedom, excellent, and good) and not worthwhile (<50%, poor) overall seizure reduction showed no statistical difference in age at complete CC. No related factor was found for worthwhile overall seizure reduction. For drop attack outcomes (N = 31), freedom was achieved in 22 cases, excellent in 5, and poor in 4. Freedom was correlated with younger age at complete CC ($P < .05$) although freedom was achieved in 4 of 7 patients older than 20 years. Age at complete CC showed no statistical difference between worthwhile ($\geq 50\%$) and not worthwhile (<50%) drop attack reduction. Worthwhile drop attack reduction was correlated with unknown etiology ($P < .05$). Complications were mild and transient.

CONCLUSION: Complete CC is an excellent surgical option based on favorable seizure outcomes and acceptable complications in our present study.

KEY WORDS: Corpus callosotomy, Drug-resistant epilepsy, Epilepsy surgery

Corpus callosotomy (CC) can be performed as a palliative surgical treatment for patients with drug-resistant epilepsy, particularly those with multifocal or generalized epilepsy, because focal resection is impractical in these patients.^{1–4} Partial

CC has been recommended, especially in patients older than 10 years, to avoid transient disconnection syndrome.^{5–8} Later, one-stage complete CC was reappraised because a large meta-analysis found that transient disconnection syndrome was not so common in comparison with partial CC.⁹ This meta-analysis⁹ and a recent systematic review⁴ also noted that complete CC provided better seizure outcomes than partial CC. The meta-analysis suggested that complete CC achieves superior drop attacks remission (63.3%) compared with partial CC (42.6%).⁹

ABBREVIATIONS: ADL, activities of daily living; CC, corpus callosotomy; E, excellent; EEG, electroencephalographic; F, freedom; G, good; P, poor.

However, most previous reports⁵⁻⁷ indicated complete CC mainly for pediatric cases. The outcomes of seizures in adults after undergoing complete CC have remained unclear due to a lack of concrete evidence largely because surgery has often been avoided on account of the patients' age.⁵ Therefore, it is necessary to examine the seizure outcome of complete CC, including adult patients.

We recently reported that good recovery based on 5 basic categories of activities of daily living (ADL) was achieved after one-stage complete CC, even in adults with severe mental retardation.¹⁰ This study used both pediatric and adult patients to analyze the age-dependency of seizure prognosis.

METHODS

Ethics

This retrospective study received approval from our hospital's institutional review board. All patients and their caregivers participating in this retrospective study were informed about and consented to the opt-out policy concerning comprehensive presurgical and surgical procedures for potential scientific research.

Patient Selection and Preoperative Assessment

Between August 2009 and April 2019, 41 patients at our hospital underwent a one-stage complete CC for medically intractable seizures

TABLE 1. Comparison of Patient Demographics by Overall Seizure Outcome

	Worthwhile			Not worthwhile Poor (P)	P Value (95% CI)	
	Freedom (F)	Excellent (E)	Good (G)		F vs E + G + P	F + E + G vs P
Total (N = 41)	5 (12.2%)	11 (26.8%)	5 (12.2%)	20 (48.8%)		
Sex					1.00 ^a (0.26-3.07)	1.00 ^a (0.20-9.02)
Female (N = 22)	3 (13.6%)	5 (22.7%)	3 (13.6%)	11 (50.0%)		
Male (N = 19)	2 (10.5%)	6 (31.6%)	2 (10.5%)	9 (47.4%)		
Age at complete CC, y					0.04 ^b	0.99 ^b
Mean ± SD	4 ± 1.7	11.4 ± 9.8	15.2 ± 5.8	11.4 ± 9.0		
Median	4	7.5	15	7.5		
Range	1-6	2-34	6-24	2-31		
Age at epilepsy onset, mo						
Mean ± SD	12.2 ± 10.0	39.6 ± 47.5	18.4 ± 20.5	10.6 ± 8.9	0.95 ^b	0.26 ^b
Median	7	14.5	9	7		
Range	0-28	0-156	3-58	0-30		
Postoperative follow-up, mo						
Mean ± SD	67.2 ± 10.5	64.7 ± 36.2	94.8 ± 40.5	72.6 ± 35.3		
Median	65	64	117	66		
Range	53-82	13-120	30-141	8-143		
Focal MRI findings					0.14 ^a (0.46-172.02)	0.52 ^a (0.69-9.08)
Normal (N = 25)	5 (20.0%)	6 (24.0%)	4 (16.0%)	10 (40.0%)		
Abnormal (N = 16)	0 (0.0%)	5 (31.3%)	1 (6.3%)	10 (62.5%)		
Etiology					0.05 ^a (0.00-1.42)	0.21 ^a (0.12-1.44)
Known (N = 20)	0 (0.0%)	6 (30.0%)	2 (10.0%)	12 (60.0%)		
Unknown (N = 21)	5 (23.8%)	5 (23.8%)	3 (14.3%)	8 (38.1%)		

CC, corpus callosotomy.

^aFisher exact test.

^bMann-Whitney *U* test.

Data are expressed as numerical values (%) for categorical variables.

associated with drop attacks, infantile spasms, and/or bilaterally synchronized electroencephalographic (EEG) discharges. All patients received a preoperative epilepsy evaluation that encompassed long-term video EEG monitoring, 3 T MRI, and fluorodeoxyglucose positron emission tomography to rule out resectable foci. All patients had severe disturbances in preoperative psychomotor development. We assessed their developmental quotient before the one-stage complete CC using the Kinder Infant Development Scale type T.^{11,12} Developmental assessments began in May 2010 and were conducted on patients younger than 7 years in this study. For all adult patients (age at surgery 16 years and older), the Wechsler Adult Intelligence Scale-Third Edition¹³ was used, except for those with severe developmental delays who were unable to be tested. All patients were deemed qualified for CC during management conferences. One-stage complete CC was indicated for 16 of the 20 patients aged 11 years and older and for all 25 children younger than 11 years. Anterior CC was indicated in the other 4 patients due to high ADL in 3, high (>40) intelligence quotient in 2, and/or left handedness in 1. As a result, 41 of the 45 patients (23 males) underwent one-stage complete CC.

Drop attacks were defined here as seizure-related falls resulting in injuries to the body or head, rather than as a specific type of seizure.¹⁴ Infantile spasms, tonic seizures, or atonic seizures can cause drop attacks.

One-stage CC was performed by 2 neurosurgeons (MI and SO), both board-certified by the Japan Neurosurgical Society and the Japan Epilepsy Society. Our surgical procedure was previously described in detail.¹⁴ Postoperative MRI was performed on all 41 patients to confirm the complete sectioning of the corpus callosum.

Postoperative Follow-up and Outcome Evaluation

Postoperative overall seizures outcome and drop attacks were evaluated at the outpatient clinic, both measured as reduction of the frequency relative to the preoperative state. Seizure outcomes at the final follow-up were categorized into 5 grades based on Williamson's criteria.^{15,16}: (i) seizure freedom (F), 100% reduction in seizure frequency; (ii) excellent (E), >80% reduction; (iii) good (G), 50%-80% reduction; (iv) poor (P), <50% reduction; and (v) worse, unacceptable neurological deficit and/or worsening of seizure frequency. The F, E, and G classes were considered to represent worthwhile improvements.¹⁶ Seizure freedom was defined as having no seizures for a period exceed 12 months. If new epilepsy surgery was performed after one-stage complete CC, the day before the operation was the last evaluation date. The following variables were investigated from the medical records: (i) sex, (ii) age at one-stage complete CC, (iii) age at epilepsy onset, (iv) MRI findings, and (v) etiology. The Mann-Whitney *U* test (ii, iii), Fisher exact test, and χ^2 test (i, iv, and v) were used for statistical analysis. Statistical significance was assumed for $P \leq .05$. Statistical analyses were performed using JMP Pro version 14.2.0 (SAS Institute Japan Ltd.)

RESULTS

Characteristics of Patients

The 41 patients (22 females) were aged at complete CC from 1 year to 34 years (mean 132.9 months, median 93 months), and age at seizure onset ranged from 0 months to 156 months (mean 19 months, median 7 months). The follow-up time ranged from 8 to 143 months (mean 72.5 months, median 67 months). Thirty-nine patients were followed up for more than 2 years. The other 2

patients were limited to evaluation within 2 years because of further surgery. One patient underwent hemispherotomy because of localized EEG abnormality after CC. The other patient underwent vagus nerve stimulation device implantation due to poorly controlled epileptic seizures. Thirty-one of the 41 patients had drop attacks preoperatively. Sixteen patients had focal structural lesions on MRI, and 4 patients had general atrophy without focal lesions. Twenty patients were diagnosed with various etiologies of epilepsy (neuronal migration disorders in 7 cases, tuberous sclerosis in 5, chromosomal or genetic anomaly in 3, ischemia in 2, trauma in 2, and viral encephalitis in 1), and 21 patients had unknown etiology. Interictal EEG was characterized by generalized and/or multifocal epileptiform discharges in all patients. Focal ictal EEG onset was not seen in any patient. Preoperative psychomotor development was severely disturbed in all patients. Developmental quotient ranged from 11 to 83 (median 21) in 9 of the 41 patients. The other 32 patients were unable to undergo the neuropsychological tests because of moderate-to-severe psychophysical dysfunction.

Overall Seizure Outcomes

Table 1 summarizes the overall seizure outcomes graded as F in 5 patients (12.2%), E in 11 (26.8%), G in 5 (12.2%), and P in 20 (48.8%). No patient had worse outcome. Worthwhile seizure

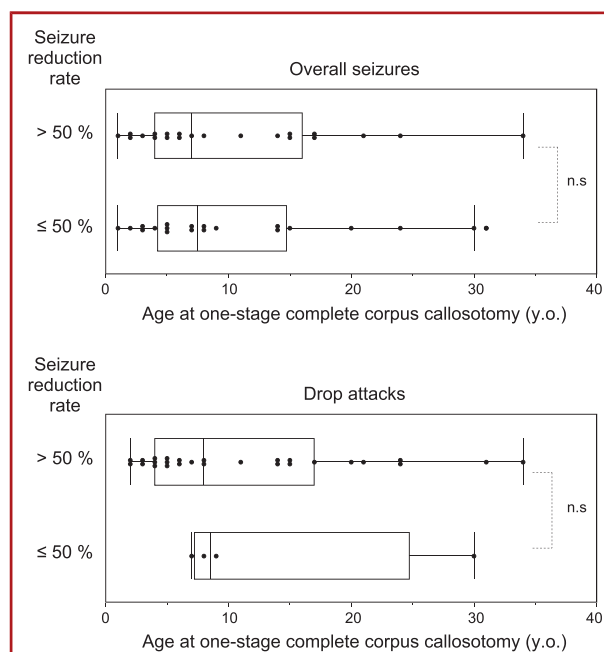


FIGURE. Overall (upper) and drop attack (lower) seizure reduction rates and age at complete corpus callosotomy. No statistical difference (Mann-Whitney *U* test) was found between worthwhile (>80%) and not worthwhile (≤80%) seizure reduction rates for both groups. Note that freedom from drop attacks was achieved in 4 and poor freedom in only 1 of the 7 adult patients.

reduction (F + E + G) was achieved in 21 patients (51.2%). Age at one-stage complete CC ($P = .04$) and unknown etiology ($P = .05$, 95% CI: 0.00-1.42) were significantly correlated with overall seizure freedom. We found no age-dependency of worthwhile seizure reduction (Figure). No other factors were significantly correlated with worthwhile outcomes.

Drop Attack Outcomes

Table 2 summarizes the overall seizure outcomes in 31 patients with preoperative drop attacks. Outcomes was graded as F in 22 patients (71.0%), E in 5 (16.1%), G in 0, and P in 4 (12.9%). Worthwhile seizure reduction (F + E + G) was achieved in 27

patients (87%). Age at complete CC was significantly correlated with drop attack freedom ($P = .02$). Unknown etiology ($P = .03$, 95% CI: 0.00-1.37) was significantly correlated with worthwhile outcomes. No patient had worse outcome. We found no age-dependency of worthwhile seizure reduction (Figure). No other factor was significantly correlated with worthwhile outcomes.

Surgical Complications

There were no perioperative deaths, and no significant neurological deficits persisted. One patient, a 24-year-old man, experienced the alien hand sign postoperatively, which resolved spontaneously after a few months.

TABLE 2. Comparison of Patient Demographics by Drop Attack Outcome

	Worthwhile			Not worthwhile Poor (P)	P Value (95% CI)	
	Freedom (F)	Excellent (E)	Good (G)		F vs E + G + P	F + E + G vs P
Total (N = 31)	22 (71.0%)	5 (16.1%)	0	4 (12.9%)		
Sex					0.25 ^a (0.07-8.42)	1.00 ^a (0.11-7.59)
Female (N = 15)	9 (60.0%)	4 (26.7%)		2 (13.3%)		
Male (N = 16)	13 (81.3%)	1 (6.3%)		2 (12.5%)		
Age at complete CC, y					0.02 ^b	0.46 ^b
Mean ± SD	9.4 ± 7.2	21 ± 9.5		13.5 ± 9.6		
Median	6	15		8.5		
Range	2-24	11-34		7-30		
Age at epilepsy onset, mo						
Mean ± SD	25.2 ± 35.7	24.6 ± 14.7		17.8 ± 17.7	0.78 ^b	0.59 ^b
Median	8	24		12.5		
Range	3-156	3-48		0-46		
Postoperative follow-up, mo						
Mean ± SD	78.3 ± 34.1	43.4 ± 20.4		84.75 ± 42.0		
Median	74	43		86		
Range	24-143	13-67		28-139		
Focal MRI findings					0.68 ^a (0.35-8.42)	0.12 ^a (0.64-79.27)
Normal (N = 20)	15 (75.0%)	4 (20.0%)		1 (5.0%)		
Abnormal (N = 11)	7 (63.6%)	1(9.1%)		3 (27.3%)		
Unknown etiology					0.69 ^a (0.12-2.65)	0.03 ^a (0.00-1.37)
Known (N = 14)	9 (90.0%)	1(10.0%)		4 (40.0%)		
Unknown (N = 17)	13 (61.9%)	4 (19.0%)		0 (0.0%)		

CC, corpus callosotomy.

^aFisher exact test.

^bMann-Whitney *U* test.

Data are expressed as numerical values (%) for categorical variables.

DISCUSSION

Our study has the following specific characteristics: (1) all subjects underwent one-stage complete CC, (2) 7 of the 41 subjects were older than 20 years, and (3) worthwhile seizure reduction was achieved age-independently for both overall seizures and drop attacks. We would like to emphasize that freedom from drop attacks was achieved in 4 and poor freedom in only 1 of the 7 adult patients.

First, we investigated the patients who underwent only one-stage complete CC. In our institute, we have always performed one-stage complete CC in children indicated for callosotomy. In addition, we included the adult patients who underwent one-stage complete CC, excluding those who underwent partial CC, ie, anterior 3-fourths CC, because of high ADL, high intelligence quotient (>40), and/or left handedness. Previously, partial CC has been most commonly performed for the management of drop attacks, especially patients older than 10 years, to avoid transient disconnection syndrome.⁵⁻⁸ However, a meta-analysis in 2018 demonstrated no significant difference in the occurrence of transient disconnection syndrome between complete CC and partial CC, with seizure outcomes exhibiting distinct advantages for complete CC.⁹ This finding is supported by a systematic review in 2023.⁴ Therefore, this study focused on the surgical outcomes of complete CC. We achieved overall seizure freedom in 12% and drop attack freedom in 71% of patients. Furthermore, no problematic neurological deficits persisted. Previously, overall seizure freedom and drop attack freedom were achieved in 0% to 10% and 39% to 84% of patients in larger series including partial CC and complete CC.¹⁷⁻²⁰ This study demonstrated excellent seizure outcomes after one-stage complete CC. We believe that one-stage complete CC is less risky than multiple-stage CC. Some target patients for CC may present with unstable general condition. In fact, several deaths have been reported from CC.^{18,21}

Second, this study included 7 adult cases and indicated satisfactory drop attack outcomes. Previously, complete CC was performed for adult patients in a large case series.²⁰ However, neither the number of adult patients who underwent complete CC nor the seizure outcomes were specified. This study is the first series of long-term seizure outcomes of one-stage complete CC including adult cases. Our study clearly indicated the effectiveness of one-stage complete CC for the treatment of patients including adults who are not candidates for resective surgery, particularly with drop attacks.

Third, this study showed worthwhile seizure reduction was age-independent whereas seizure freedom was age-dependent, for both overall seizures and drop attacks. One-stage complete CC should not be abandoned solely based on the patient's age. However, we should be aware that overall seizure freedom was not achieved in the present adult cases. In the future, it will be necessary to consider and compare additional extraventricular anterior commissurotomy with CC.²²

Limitations

Our study included only a small number of adult participants (7 of 41 patients) older than 20 years. This small sample size of adult patients limits the generalizability of our findings to the broader adult population. Nevertheless, we would like to emphasize that complete CC should not be abandoned even in adult cases.

CONCLUSION

One-stage complete CC is an excellent surgical option for medically intractable epilepsy, based on the favorable seizure outcomes obtained as well as the acceptably mild and transient complications shown in our present study.

Funding

This work was supported by MHLW research program on rare and intractable diseases, Grant number JPMH20FC1039 (Kazutaka Jin).

Disclosures

Kazutaka Jin has received speaker's fees from Daiichi-Sankyo and UCB Japan. Nobukazu Nakasato is Chair of Donated Fund Laboratory from eMind and speaker's fees from Daiichi-Sankyo, UCB Japan, and Eisai Co., Ltd. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

Author Contributions: Conception and design: Ukishiro, Osawa, Iwasaki, Yamamoto, Tominaga, Endo, Nakasato. Acquisition of data: Ukishiro, Jin. Analysis and interpretation of data: Ukishiro. Drafting the article: Ukishiro, Osawa, Kakisaka, Uematsu, Nakasato. Critically revising the article: all authors. Reviewed submitted version of the manuscript: all authors. Approved the final version of the manuscript: all authors. Statistical analysis: Ukishiro. Study supervision: Tominaga, Nakasato.

COMMENTS

The authors report a retrospective study on one stage complete corpus callosotomy using an open surgical technique, limited by small

numbers of a mixed population of both children and adults with different seizure types, of drop attacks, infantile spasms, and or bilateral synchronized electroencephalographic (EEG) discharges. The majority of patients had good outcomes, notable since, many of these patients had long histories of seizure burden and failed medical therapy. These seizure outcomes were age independent in that the adult sub-group, while small, still had worthwhile seizure freedom from their drop attacks and did not have worse seizure outcomes compared to the children. These outcomes were achieved with minimal surgical complications, including disconnection syndrome. In this series and others, disconnection syndrome did not seem to be a significant component of the complete callosotomy post operatively despite age at surgery. Their results highlight the potential for expanding the use of this procedure, complete transection of the corpus callosum upfront in one stage, rather than stage with anterior transection first, await results, followed by complete transection for later failures for this often difficult to treat population of patients. Additionally, staging does not seem to improve the efficacy for these patients that are already likely treated “conservatively” with medical therapy long past the conclusion that further medical therapy has failed and may actually increase the potential for surgical complications.

Because this series was collected over a long period of time, it does not include newer alternative approaches to achieving the complete transection of the corpus callosum (i.e.) laser interstitial thermal therapy (LITT) and endoscopic. As they found no increase in morbidity with the open procedure, more minimally invasive techniques can be further explored to improve outcomes for socioeconomic reasons, (i.e.) length of stay, or more acceptance by patients and or families to undergo this procedure.

Additionally, newer MR imaging techniques (i.e.) diffusion tensor imaging (DTI) that were not included in this study, may be useful for patients who did not achieve their expected seizure outcomes to determine if there are any remaining connections as part of the post operative evaluation.

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