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Treatment for patients with recurrent intractable epilepsy after primary hemispherectomy

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ABSTRACT

Background: Hemispherectomy is useful for treating patients with intractable epilepsy caused by diffuse unilateral hemispheric disease. Few patients develop recurrent seizures after hemispherectomy, but managing epilepsy by medical means alone is challenging for these patients, and it is also difficult to determine the treatment options and assess the need for reoperation.
Objective: To present the treatment strategies and outcomes of patients who developed recurrent intractable epilepsy after initial hemispherectomies that were performed at a single institution by a single surgeon between 2004 and 2014.
Method: The preoperative medical records, operative reports, imaging findings, and follow-up data for patients with recurrent epilepsy who underwent hemispherectomy for intractable epilepsy between 2004 and 2014 at Sanbo Brain Hospital Capital Medical University were retrospectively reviewed. The baseline characteristics, cause of seizures, imaging findings, electrophysiological findings, primary surgery-related complications, treatments for recurrent epilepsy and long-term seizure outcomes were evaluated. A reduction of seizure frequency greater than 90% was considered a favorable outcome.
Results: In the cohort of 17 patients who suffered recurrent epilepsy after primary hemispherectomy, 11 had undergone reoperative surgery, whereas 6 patients took medication alone. No major complications occurred in this series. At the last follow-up, favorable outcome was noted in 10 (91%) patients who underwent reoperative surgery and in 1 (17%) patient who received only medication for treatment (Table 1, p = 0.005). Patients with malformation of cortical development tended to have worse seizure outcomes.
Conclusions: Reoperative hemispherectomy is an effective and safe treatment for patients who still have seizures after primary hemispherectomy for epilepsy caused by unilateral cortical lesion.

1. Introduction

Anatomic hemispherectomy was first introduced as a final medical treatment for intractable epilepsy patients in the 1950s (Krynauw, 1950). Subsequently, functional hemispherectomy and hemispherotomy (hemisphere disconnection) were described as methods for reducing the risk of late-onset superficial cerebral hemosiderosis and hydrocephalus (Falconer and Wilson, 1969). According to the most recent systematic review (Griessenauer et al., 2015), the type of hemispherectomy does not affect the seizure outcome, and hemispherotomy procedures involve some complications.

Although most patients are seizure free after primary hemispherectomy, a recent systematic review indicated that 26.6% of patients developed recurrent epilepsy after surgery. This high recurrence rate poses a significant dilemma to epilepsy surgeons. Preoperative electroencephalography (EEG) provides little help with distinguishing between an incomplete disconnection and a contralateral epileptogenic focus (Greiner et al., 2011). In some cases, the semiology is atypical, which makes it difficult to locate the epileptogenic side. Only magnetic resonance imaging (MRI) can confirm incomplete disconnection for the

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frontal basal cortex and white matter, but the decision to perform reoperative hemispherectomy is still challenging. Thirty-six percent of patients who underwent reoperative hemispherectomy showed no improvement in seizure outcome (Vadera et al., 2012). However, sufficient clinical evidence for the indication of reoperative hemispherectomy is still lacking. Therefore, we reviewed all cases with recurrent epilepsy after hemispherectomy. The objective of this study is to report the management of patients with recurrent intractable epilepsy who underwent primary hemispherectomy performed by a single surgeon at our epilepsy center between 2004 and 2014 and to analyze the long-term outcomes of these patients.

2. Methods

2.1. Clinical cohort

Medical records including EEG, MRI, and magnetoencephalography (MEG) findings, operative reports, and follow-up data were retrospectively reviewed for patients who suffered from recurrent epilepsy after any type of hemispherectomy including anatomical hemispherectomy, functional hemispherectomy, and hemisphere disconnection for intractable epilepsy between 2004 and 2014 at the Sanbo Brain Hospital, Capital Medical University. Postoperatively, all patients were asked to return as inpatients for follow-up at 12 weeks, 6 months, and 12 months. Postoperative MRI and EEG were performed for all patients. Patients who continued to have intractable epilepsy 3 months after hemispherectomy were recognized as having a recurrence of epilepsy. Patients with seizures due to irregular antiepileptic drug (AED) administration, fevers, or plasma electrolyte disturbance were excluded because of their occasional seizure onset, and they received regular management. Approval from the Sanbo Brain Hospital Capital Medical University Internal Review Board was obtained before this retrospective analysis was conducted.

2.2. Treating strategy

All patients were asked to be hospitalized for the assessment of seizures that occurred after primary hemispherectomy. For patients with existing frequent intractable epilepsy (more than monthly), reoperative hemispherectomy was considered. Before surgery, the patients underwent a standard epilepsy protocol MRI that included a fluid-attenuated inversion recovery (FLAIR) sequence in the axial, coronal and sagittal planes. All patients who were suspected to need reoperation underwent preoperative video EEG recording to record the seizure pattern and ictal origin, and a detailed history and physical examination were recorded. Each reoperative case was discussed at least once before surgery in a management conference with a multidisciplinary epilepsy team that included neurosurgeons, epileptologists, radiologists, and neuropsychologists. Assessment of the previous hemispherectomy, the reason for recurrence, the management options, and the necessity of a repeated hemispherectomy were discussed. Any patient with obvious incomplete disconnection as well as ipsilateral EEG origin was a candidate for reoperation. The operation was postponed if one or more participants disagreed. Neuronavigation was recommended to determine the postsurgical anatomy of the previously operated side. However, the postsurgical anatomy is difficult to distinguish, which makes it difficult to identify and disconnect the residual tissue.

2.3. Surgical technique

The surgical technique for reoperative hemispherectomy included redisconnection of brain tissue or anatomic hemispherectomy. Redisconnection was defined as a secondary disconnection of the cortex of the involved hemisphere. Anatomic hemispherectomy was defined as removal of all cerebral tissue in the previously operated side, sparing the thalamus, brainstem, and basal ganglia. Neuronavigation was recommended first because the postsurgical anatomy becomes complex after disconnective hemispherectomy. Anatomical resection was selected if the bone flap was large enough.

2.4. Data analysis

The semiology, EEG pattern, cause of epilepsy, surgical complications, pathology, postoperative seizure outcomes, and postoperative EEG outcomes were reviewed. For the imaging study, preoperative and postoperative imaging results were reviewed to evaluate disconnection. The data were summarized with descriptive statistics that included the mean, median, and standard deviation for continuous variables and the frequency of categorical variables. A univariate analysis was performed with the χ^2 test and Fisher's exact test to compare patients who showed improvement with those who experienced a recurrence of seizures. More than 90% reduction in seizure frequency was considered a marker of a favorable outcome.

3. Results

3.1. Patient characteristics

A review of the records for 182 patients who had undergone any type of hemispherectomy revealed 65 patients who still experienced seizures three months after primary hemispherectomy. In 48 of these 65 patients, the recurrent seizures were due to irregular AED administration, fever, or plasma electrolyte disturbance and vanished after regular treatment. These patients were excluded, leaving 17 patients in the analysis. The mean age of the included patients at seizure onset was 4.4 years, and their mean age at surgery was 10.01 years (range, 1.9-28.6 years; median, 4.7 years). Among these patients, 53% were male and 35% underwent a left-side hemispherectomy (Table 1).

The causes of the seizures included perinatal stroke (n = 1), malformation of cortical development (MCD) (n = 3), and Rasmussen's encephalitis (n = 13). Conservative therapy was selected in 6 patients, mainly because their seizures were infrequent. Reoperative hemispherectomy was performed in the other 11 patients. The mean interval between the first and second hemispherectomies was 2.1 years (range, 0.1-6.2 years; median, 2 years).

3.2. Primary hemispherectomy and perioperative characteristics

Focal seizures were noted in 12 (71%) of the patients; 2 (12%) had both focal and generalized seizures, whereas the exact seizure type could not be determined in 3 (17%) patients. Nine (53%) patients had severe hemiplegia (cannot walk without the help of others) before their original surgery; 6 (35%) patients had mild to moderate hemiplegia (can walk independently but changing in gait); and 2 (12%) children were recorded as having no obvious hemiplegia (walk without changing in gait). Concordant ipsilateral ictal EEG patterns were seen in 9 (53%) patients. Ictal EEG was nonlateralized in 8 (47%) patients (Table 1).

A review of the preoperative MRI findings showed that 8 (47%) patients manifested severe hemisphere atrophy, 6 (35%) had mild to moderate hemisphere atrophy, and 3 (18%) had almost symmetrical brain development.

The majority of patients had undergone a functional hemispherectomy (n = 9); the others had undergone hemisphere disconnection (n = 6) or anatomical hemispherectomy (n = 2). No major intraoperative complications or mortalities were encountered. Fever was noted in all 17 patients during the postoperative period, with a mean duration of 17 days (range, 7–29 days; median, 18 days), although no patient had a confirmed intracranial infection.

Table 1
Clinical features of patients with recurrent epilepsy after hemispherectomy.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Sex	M	M	F	F	M	M	M	F	M	F	F	M	F	F	M	F	M
Pre-existing event	Pox	N	N	Fever	N	N	N	N	Injury	N	Fever	N	N	N	TOF	Vaccine	Fever
Age at RE onset (y)	6.58	6.5	5.5	11.83	4.67	2.08	1.02	1.67	7.75	2.83	1.08	5.75	6.75	4	0.83	0.08	7
Epilepsy characteristics[a]	F + Un	F	F	F	GTCS + Un	F	F + Un	F	F	F	Un	F	F	F	GTCS	F	F
Hemiplegia	Mild	Middle	Mild	Middle	Mild	Middle	Mild	Middle	Mild	Middle	N	Middle	Severe	N	Severe	Middle	Mild
Hemisphere atrophy																	
Ictal discharge lateralization	Right	Bilateral	Left	Bilateral	Right	Bilateral	Bilateral	Right	Bilateral	Left	Bilateral	Left	Right	Unknown	Right	Bilateral	Bilateral
Concordant ipsilateral ictal EEG	No	No	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	No	Unknown	Yes	Yes	Yes
MEG discharge lateralization	R	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	R	L	Nil	L	R	Nil	R	Nil
PET low metabolism	Nil	Nil	Nil	Nil	Nil	*	Nil	Nil	R	Nil	Nil	Nil	L	R	Nil	Nil	Nil
Side of hemispherectomy	R	R	L	L	R	L	R	R	R	L	R	L	L	R	R	R	R
Type of hemispherectomy[b]	FH	FH	FH	AH	Dis	FH	FH	FH	FH	FH	FH	AH	Dis	FH	Dis	Dis	FH
Pathology	RE	RE	RE	RE	RE	RE	RE	RE	RE	RE	HHE	RE	RE	RE	Infarct	FCD&GMH	MCD
Recurrence time after primary hemispherectomy	2.7 y	6 m	3 y	6 m	5 m	1 w	1 d	2 m	1 m	6.1 y	3 m	1 d	11 m	8 m	6 m	2 d	1 d
Same with the original pattern	N	N	N	Y	N	N	Y	N	Y	N	Y	Y	N	Y	Y	Y	N
Treatment[c]	AH	SD	AH	MT	MT	AH	AH	AH	AH	SD	MT	MT	FH	AH	MT	MT	SD
Follow up period since initial hemispherectomy	4.5 y	3 y	5 y	10 y	3 y	5 y	8 y	5 y	7 y	7 y	7 y	4 y	1.5 y	4 y	2 y	3.5 y	1.5 y
Follow up period since secondary hemispherectomy	1.2 y	2 y	1.5 y	N	N	4.6 y	7.8 y	4.4 y	6.1 y	0.9 y	N	N	0.5 y	3 y	N	N	1.4 y
Seizure outcome at last follow up	Engle 2	Engel 3	Engel 2	Engel 3	Engel 3	Engel 2	Engel 1	Engel 2	Engel 1	Engel 1	Engel 1	Engel 3	Engel 3	Engel 1	Engel 2	Engel 3	Engel 2

*Left side focal high metabolism.
[a] GTCS: generalized tonic-clonic seizure; Un: uncertain pattern; F: focal epilepsy.
[b] Dis: disconnection; FH: functional hemispherectomy; AH: anatomical hemispherectomy.
[c] AH: anatomical hemispherectomy; SD: secondary disconnection; MT: medical treatment.

Table 2
Possible location of incomplete disconnection.

Location	n
Frontal base	7
Rostrum corporis callosi	2
Insular lobe	1
Brain tissue near middle line	1

3.3. Assessment and treatment strategies for patients with recurrent seizures

In this series of 17 patients, the mean period from primary hemispherectomy to the recurrence of seizures was 11.2 months (range, 1 day-6.1 years; median, 6 months). Nine patients (53%) developed different types of seizures after the first hemispherectomy, whereas other patients showed a similar seizure pattern but with a decrease in frequency and duration to different degrees. Within a three-month period of observation after the report of recurrence, the majority of patients (59%, n = 10) presented with daily seizures after the initial surgery, whereas the remainder of the patients had weekly seizures.

Medical treatment was recommended first, including an adjustment of dose and administration of new AEDs. Possible explanations for the seizure recurrence included incomplete disconnection, an epileptic origin in the contralateral hemisphere, remaining cortical tissue, and unknown reasons (Table 2). A review of the postoperative MRIs showed that 9 in total 17 (53%) of the disconnections appeared to be incomplete (including 7 patients at the frontal base, 2 patients at the rostrum corporis callosi and one patient at the insular lobe), and 2 in total 17 (12%) patients were suspected to have remaining cortical tissue near the midline (Fig. 1). Reoperative hemispherectomy was finally performed in those 11 patients.

3.4. Reoperative surgery and perioperative characteristics

The average blood loss during the reoperative hemispherectomy was 1035 ml (range, 250–2700 ml). The mean operational time was 5.9 h (range, 4.2–8 h). Among the 11 reoperative patients, 7 (64%) patients underwent anatomic hemispherectomy, whereas 4 (36%) patients underwent secondary disconnection.

No major intraoperative complications or mortalities were encountered. All postoperative MRIs showed complete disconnection at the frontal base without any notable infarction. All patients had a postoperative fever; the mean time for the body temperature to return to normal was 18.9 days.

3.5. Seizure outcome

The average follow-up period after the first hemispherectomy was 4.03 years, and the average follow-up period after the reoperative hemispherectomy was 3.04 years. At last follow-up, 11 (65%) out of 17 patients had at least a 90% reduction in their seizure frequency, which was considered a favorable outcome. Within that series, favorable outcome was noted in 10 (91%) patients who underwent reoperative surgery and in 1 (17%) patient who received only medication for treatment ($p = 0.005$).

All 3 patients with obvious bilateral cortical lesion (MCD) before the first operation still had seizures after the selected treatment (medication or reoperation), while 21% (3 out of 14) of patients with unilateral cortical lesion failed to achieve a favorable outcome after the selected treatment. Sixty percent of the patients who continued to have similar semiology after the first surgery reported favorable outcomes, compared with 71% of the patients whose types of semiology changed after the first surgery ($p = 0.829$). The outcome was not significantly correlated to age at the onset of seizures, age at surgery, or type of reoperative hemispherectomy. The original seizure semiology and interictal spike distribution before and after primary hemispherectomy did not show any correlation with seizure-free outcomes postoperatively. The presence and duration of postoperative fever did not correlate with long-term seizure outcomes.

4. Discussion

Patients with diffuse unilateral hemisphere glioma and intractable epilepsy caused by multifocal cortical dysplasia, hemimegalencephaly, hemiconvulsion–hemiplegia–epilepsy syndrome (HHE), Rasmussen's encephalitis, or Sturge-Weber syndrome are candidates for hemispherectomy (Alvarez et al., 2011; Caraballo et al., 2011; Yum et al., 2011). Approximately 20% patients develop seizures again after hemispherectomy for a variety of reasons, and the treatment of such patients is still challenging.

In our analysis of patients with recurrent intractable epilepsy after hemispherectomy, 29% of the patients achieved long-term freedom from seizures, and 65% of the patients achieved a 90% reduction in seizures. Patients with bilateral cortical lesion had worse seizure outcomes regardless of the treatment selected.

Our data indicate that patients with nonlocalizable or generalized ictal EEG patterns before their first hemispherectomy and those with ipsilateral ictal EEG patterns have similar outcomes. This result is consistent with the outcomes reported by Vadera et al. (2012). Additionally, Greiner et al. reported on 54 patients who underwent hemispherectomy and found that a lack of EEG lateralization did not predict a poor outcome in any of the etiology groups evaluated (Greiner et al., 2011). Considering these previous findings along with our present findings, we suggest that in patients with diffuse hemispheric lesion, MRI could be more helpful than ictal EEG activity for localizing the epileptic side. According to our study, a patient who had unilateral ictal origin with bilateral cortical lesion according to the MRI was likely to have worse seizure outcomes, which means that this patient is not a good candidate for hemispherectomy.

We ascribed the recurrence of seizures to incomplete disconnection, epileptogenicity in the contralateral hemisphere, or both. As semiology is of great importance for localizing the epileptogenic zone, the recording and analysis of video EEG can provide an enormous amount of useful information for differentiation. If the semiology, EEG, and MEG do not all suggest the same side, the patient should be reassessed after three to six months.

In an analysis of 36 patients who underwent reoperative hemispherectomy, Sumeet et al. found that patients with malformation of cortical development tended to have a lower rate of seizure-free outcomes than patients with other pathologies [5]. In our study, three patients with malformation of cortical development were studied. Both medication and reoperation were noted to be unsuccessful. Based on the experience of our center, bilateral MCD is a potential indication of bilateral epileptogenicity, even though some patients had a clear unilateral ictal origin.

With respect to the MRI findings after disconnective hemispherotomy or functional hemispherectomy, the areas most likely to have incomplete disconnections were the frontal base and the rostrum corporis callosi. For patients with mild or moderate hemisphere atrophy, cortical tissue was likely to remain near the middle following transventricular corpus callosotomy procedures (Fig. 2).

At follow-up, no patients had developed postoperative hydrocephalus after reoperative hemispherectomy. There were no significant differences in mortality, operation time, blood loss, or postoperative fever period between the first and second operations. The absence of hydrocephalus may be related to the fact that the cerebrospinal fluid (CSF) circulation was altered after the first surgery, making hydrocephalus unlikely to occur after reoperative hemispherectomy.

The relatively small number of patients in this study may have prevented the detection of other significant correlations. Moreover, the variation among patients made these correlations less convincing.

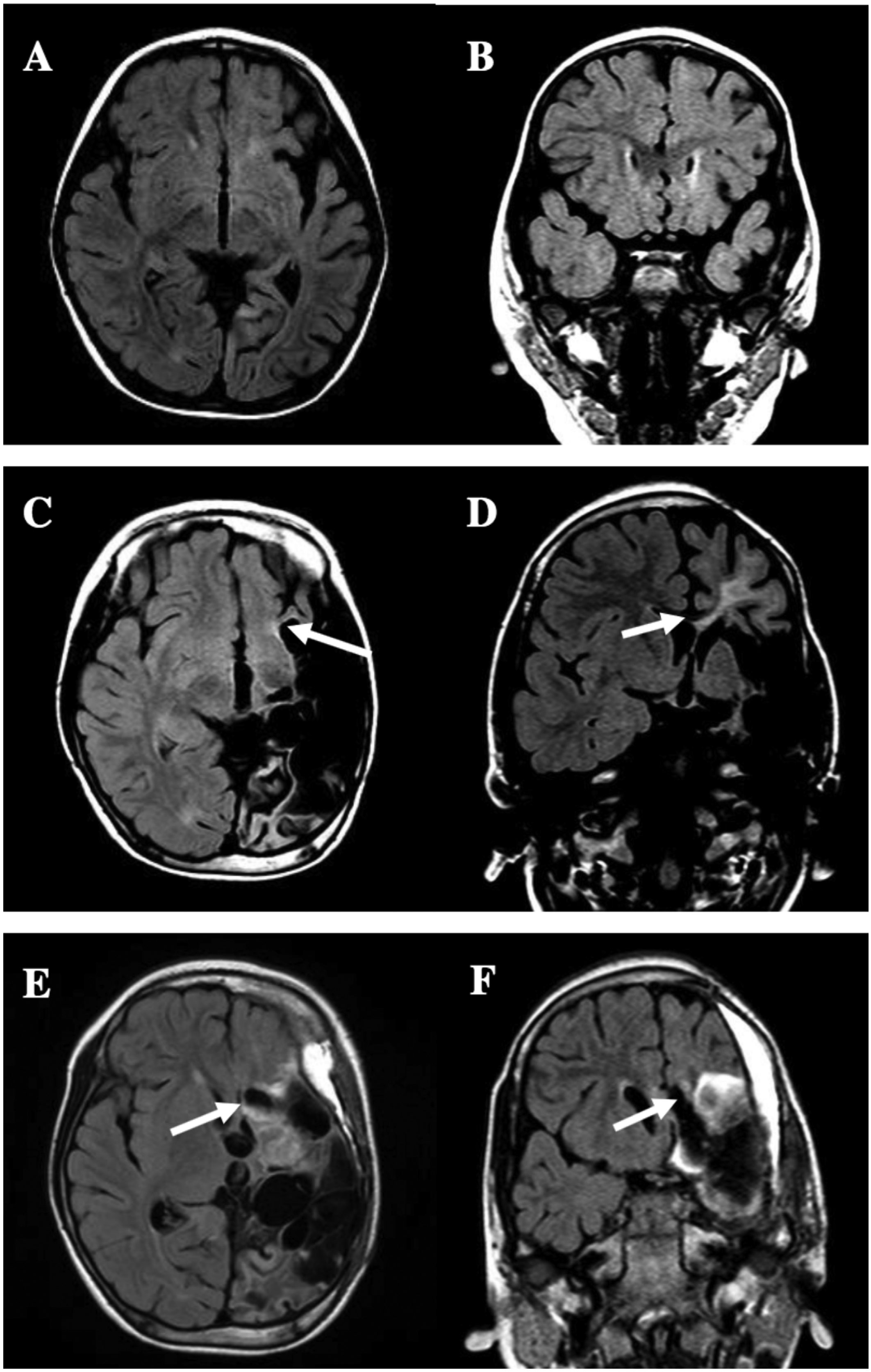

Fig. 1. MRI obtained before and after hemispherectomy.
Preoperative FLAIR in the axial plane (A) and the coronal plane (B). Incomplete disconnection at the frontal base (white arrow, C) and corpus callosum (white arrow, D) six years after primary hemispherectomy. Complete disconnection at the frontal base (white arrow, E) and corpus callosum (white arrow, F) two weeks after secondary disconnection.

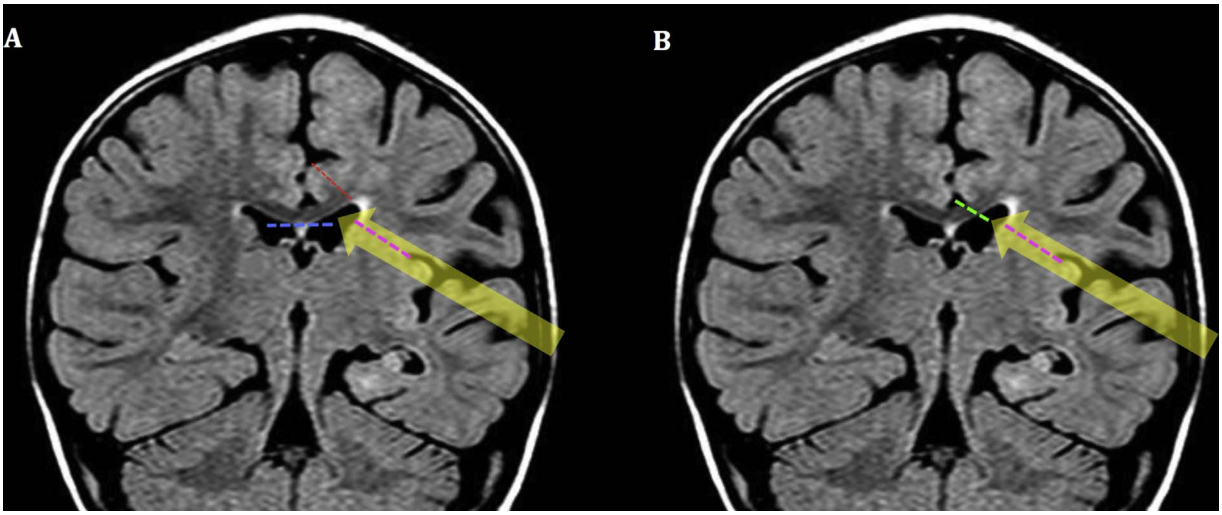

Fig. 2. Cortical tissue remaining after transventricular corpus callosotomy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
After the lateral ventricle was exposed through the Sylvian fissure (yellow arrow, pink line, A, B), we identified the corpus callosum and brain tissue remaining near the midline after resection performed at sites distant from the midline (red line, A); a vertical resection may have damaged the septum pellucidum (blue line, A). An appropriate angle would lead to a better outcome (green line, B)

However, only about one thousand patients underwent this aggressive surgery, and 10%–20% of these cases were reported to have a recurrence of seizures (Griessenauer et al., 2015). This high recurrence rate is challenging and troublesome for surgeons operating on patients with epilepsy, and recurrence is disastrous for the patients and their families. For this reason, it is important that an honest and direct discussion occurs between the epilepsy team and the patient about the potential for freedom from seizures after reoperative surgery. As some patients with recurrent seizures may be lost to follow-up, continuous follow-up for all patients who have undergone hemispherectomy is of great importance to identify additional correlations.

4.1. Limitations

This research inevitably had some limitations. The aim of this study was to report the possible reason for the recurrence of epilepsy after hemispherectomy and the outcome of those patients after conservative or surgical treatment, with the goal of finding a method to avoid incomplete disconnection and identifying the proper indication for reoperation. Although the sample size was comparatively large considering that only a minority of surgeries failed, it was still inadequate to reach a high statistical standard. Additionally, for economic reasons, the preoperative examination could not be standardized, which made it difficult to assess the accuracy of MEG on evaluation of secondary surgery. Additionally, future areas of study could focus on analyzing the effectiveness of different types of hemispherectomy and the long-term complications of such procedures, with the aim of finding the best surgical method and optimizing the surgical outcome for patients with epilepsy caused by hemisphere lesion.

5. Conclusions

Our study shows that reoperation was an effective treatment for patients with unilateral cortical lesion before primary hemispherectomy. Perioperative mortality and morbidity were no higher for the reoperative procedure than for the primary hemispherectomy. Further observation is needed to find potential correlations that might indicate a better seizure outcome.

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Conflict of interest

All authors report that they have no conflict of interest.

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