Pediatric intractable epilepsy syndromes: Reason for early surgical intervention

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Abstract

Drug-resistance in several childhood epilepsy syndromes is common, and these patients may tolerate epilepsy surgery. In this study, the surgical outcomes of 24 pediatric patients with various intractable epilepsy syndromes and three patients with tuberous sclerosis were examined at Xinqiao hospital between 1997 and 2004. The study included nine cases of Lennox–Gastaut syndrome, two cases of Rasmussen's syndrome, one case of Sturge–Weber syndrome, three cases of West syndrome, three cases of tuberous sclerosis and nine cases of mesial temporal lobe epilepsy syndrome. In each case, different surgical procedures were performed according to preoperative evaluation and ECoG. At an average of 4.5 years after surgery, 14 out of 27 patients (51.9%) had an Engel Class I outcome after surgery, and an additional eight patients (29.6%) had rare seizure (Engel ClassII). Three patients showed a significant decrease in seizure frequency (Engel Class III). The mean IQ increased from 61.4 ± 12.2 to 75.0 ± 11.0, and greater IQ increase was seen in patients with shorter seizure history and drug-resistance. Temporary complications were observed in four patients and there were no deaths. In conclusion, early surgical intervention in pediatric intractable epilepsy syndromes may results in a favorable outcome in a high percentage of cases and may provides an important opportunity to prevent irreversible decline in intelligence and disability.

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Keywords: Intractable epilepsy; Epilepsy syndromes; Epilepsy surgery; Multilobe resection; Pediatric patients

1. Introduction

Drug-resistance in some childhood-onset epilepsy syndromes such as Lennox–Gastaut syndrome, Rasmussen syndrome, Sturge-Weber syndrome, West syndrome, and mesial temporal lobe epilepsy syndrome is common, and is also predictable in a certain extent [1–3]. Although each of these syndromes manifests in an age-specific manner and is defined by distinct electroclinical features, they are all refractory to antiepileptic drugs and are invariably associated with psychomotor deficits [1–5]. In the most severe cases, these pediatric epilepsy syndromes can lead to either epileptic encephalopathy or progressive neurodegeneration. Due to the poor response to antiepileptic drugs (AEDs), early surgical interventions represents an important part of a comprehensive treatment plan for this group of children, especially in regard to the developmental delays and mental retardation that are the hallmarks of these syndromes [5–7]. This study reports the surgical outcome of 27 pediatric patients with intractable epileptic syndromes.
2. Methods

The study population consisted of 27 pediatric cases which accounted for the 13.9% of all pediatric surgical patients at same term (194 cases), including nine cases of Lennox–Gastaut syndrome, two cases of Rasmussen syndrome, one case of Sturge–Weber syndrome, three cases of West syndrome, and nine cases of mesial temporal lobe epilepsy syndrome. Three cases of tuberous sclerosis also included due to their some similarities with pediatric syndromes, such as the child-onset epilepsy, drug-resistance epilepsy and mental retardation in childhood. Tuberous sclerosis patients in this group did not manifest as above pediatric syndromes. The syndrome diagnoses in this study have been described by many authors and ILAE (international league against epilepsy, ILAE). Briefly, West syndrome is characterized by infantile spasms, hypsarrhythmia and mental retardation [2]. Lennox–Gastaut syndrome is defined by the triad of (1) multiple seizure types including tonic, atomic and myoclonic seizures, and atypical absences, (2) slow spike-and-wave EEG disturbance, and (3) mental deficiency [1,4]. Rasmussen syndrome patients demonstrate epilepsy partialis continua, slowly progressive intellectual deterioration, and hemiparesis, with radiologic evidence of non-specific hemispheric brain atrophy [8]. Sturge–Weber syndrome is characterized by a facial port wine stain, contralateral hemiparesis, mental retardation, and seizures as a result of leptomeningeal angiomatosis. CNS disorder and lesion of tuberous sclerosis include cortically located tubers and/or subependymal nodules, refractory epilepsy and mental retardation [10]. Mesial temporal lobe epilepsy syndrome involves seizures in the mesial temporal regions at the onset. The EEG of such patients shows temporal focal discharge, and magnetic resonance imaging (MRI) is suggestive of hippocampal sclerosis [11].

Criteria for epilepsy surgery: (1) frequent or severe seizures interfering with patient’s life; (2) drug-resistance for at least one year (at least two AEDs failure of first- and second-line antiepileptics to control seizures); (3) seizure has been demonstrated to originated from a single focus or multiple foci at same hemisphere; (4) lesion or lobe resection should be surgical accessible and without severe deficit to patients; and (5) parents understand the risks and benefits of procedures.

All patients in the study underwent a comprehensive evaluation including detailed history and neurological examination, routine and ambulatory EEG, long-term video EEG monitoring, and magnetic resonance imaging (MRI). Nineteen patients underwent single-photon emission computed tomography (SPECT) scan. Preoperative and postoperative neuropsychological testing was assessed by a psychologist. Three patients required invasive intracranial monitoring with subdural plates and depth electrodes to further delineate the epileptic zone. The patients were discussed at a multidisciplinary Epilepsy Conference and then those that were deemed suitable candidates were subjected to surgery. Surgical incisions were designed according to the preoperative evaluation of each patient, and potential epileptogenic foci should be involved in exposed area. Single lobe resection or lesionectomy, and/or multiple subpial transection (MST) was performed when focal epileptic discharge was indicated according to preoperative evaluation and ECoG, but multilobe resection with MST and/or corpus callosotomy were chosen to deal with hemispheric multiple epileptogenic foci. Antiepileptic drugs were continued for at least two years and then gradually tapered. The patients were postoperatively assessed at 6 months, 1 year, and then annually. The duration of follow-up was between 1 and 8 years with a mean of 4.5 years. Seizure outcome was assessed using Engel’s criteria. All subjects were the patients underwent surgery but had follow-up at least one year, and those who had follow-up less than one year were excluded. Statistical analysis was performed using independent-samples t-test and paired-samples t-test on SPSS software, P < 0.05 was taken as statistically significant.

3. Results

3.1. Patient information

Sixteen patients underwent single lobe resection or lesionectomy, and eleven patients received multilobe resection. Among the 11 patients with multilobe resection, four patients received partial corpus callosotomy. The age of the Patients at surgery ranged from 3 to 15 years. All patients showed drug-resistance for at least two AEDs (failure of first- and second-line antiepileptics to control seizures) ranging from 1 to 10 years. The AED-resistant periods were for 1–2 years in eight patients, 2–4 years in 10 patients and over 4 years in nine patients (see Table 1). The lag between onset and surgery of epilepsy ranged 1–11 years.

3.2. Electroencephalograms

Routine EEG results were abnormal in 25 of 27 cases, indicating epileptic discharge in 19 patients, and generalized slowing in six patients. Ambulatory EEG monitoring demonstrated unilateral epileptic discharge in 23 patients. Long-term video electroencephalographic monitoring localized the epileptic zone in 24 cases. Three patients required invasive recording with intracranial electrodes to delineate the epileptic zone. The epileptic foci were determined by ictal EEG and interictal EEG finding. Bemegride was used to induce seizure when ambulatory EEG and video EEG observed no seizure, and use of this drug was limited to children older
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**Abbreviations:** CPS, complex partial seizure; EEG, electroencephalogram; HS, hippocampal sclerosis; LGS, Lennox-Gastaut syndrome; L. Left; MRI, magnetic resonance imaging; MTLE, Mesial temporal lobe epilepsy; RS, Rasussen’s syndrome; rt., Right; SPS, simple partial seizure; SWS, Sturge-Weber syndrome; sz., seizure; TSS, tuberous sclerosis syndrome; WS, West syndrome.
than 9 years and at low dose because it may be risky for the immature and developing brain.

Ambulatory EEG and video EEG monitoring demonstrated hypsarrhythmia in three patients with West syndrome (Fig. 1A). Slow spike-and-wave EEG disturbance were seen in nine patients with Lennox–Gastaut syndrome, and EEG monitoring of these patients indicated fast paroxysmal rhythms, especially during sleep EEG (Fig. 1B). One patient with Sturge–Weber syndrome displayed depressed background activity over the left hemisphere with continuous slowing, as well as interictal and ictal spikes. Two patients with Rasmussen syndrome showed hemispheric slowing and frequent solitary spikes (Fig. 2E). In all nine mesial temporal lobe epilepsy patients, sphenoidal electrode monitoring was performed to determine epileptic discharge onset. Out of all cases, a single epileptogenic focus was demonstrated in 16 patients, but multiple foci were found in 11 patients (summarized in Table 1).

### 3.3. Neuroimaging

All patients underwent magnetic resonance imaging (MRI), and 22 patients also had computed tomographic scan. MRI was abnormal in 24 patients and normal in three. In those with abnormal MRI, eight patients had hemisphere atrophy (Fig. 2), nine had hippocampal sclerosis, two had focal cortical dysplasia, and one had a perforating ventricle malformation. In one case, MRI with gadolinium demonstrated marked enhancement but also leptomeningeal angiomatosis over areas of the right hemisphere (Fig. 3). MRI and computed tomographic scan showed that three patients had cortex tubers and subependymal nodules, and these cases demonstrated co-localization of the cortical lesions and the epileptic zone. The pathology missed by neuroimaging included focal cortical dysplasia in one case and vascular malformations in two cases.

A total of 19 patients underwent interictal (19 patients) or ictal (12 patients) SPECT scans. SPECT results were reported as abnormal in 16 patients and normal in three patients, and indicating interictal hypoperfusion in 13 cases and ictal hyperperfusion in 10 cases. Focal SPECT abnormalities were congruent with EEG and neuroimaging abnormalities in 13 of 16 patients.

### 3.4. Neuropsychology

Comprehensive pre- and postoperative intellectual assessments were conducted on 23 of the 27 children.

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Fig. 1. (A) EEG for a patient with West syndrome demonstrating hypsarrhythmia. (B) EEG for a patient with Lennox–Gastaut syndrome showing fast paroxysmal rhythms during sleep. (C) and (D) EEG for a patient with Lennox–Gastaut syndrome pre- and postoperatively. (C) Demonstrating the slow spike-and-wave in the right temporal region before surgery, and (D) showing a normal EEG one and a half year after surgery.
included in this study, and the remaining four patients were disoperative before surgery. Children aged from 6 to 13 were administered the Wechsler intelligence scale for children-revised (WISC-R), and Children between ages 4 and 6 were administered the Wechsler preschool and primary scales of intelligence (WPPSI). Children ranged in age from 4 to 16 years at the time of initial assessment. The postoperative assessment was performed 9–23 months (14.2 months on average) after surgery. Mean intelligence quotient (IQ) before surgery was 61.4 ± 12.2, and increased to 75.0 ± 11.0 at the time of postoperative assessment. The numbers of patients with below normal intellectual functioning (IQ < 70) were 18 preoperatively, but this number
dropped to 7 postoperatively. Patients with a shorter drug-resistance and seizure history were correlated to the increase of IQ, and the patients with shorter seizure history and drug-resistance correlated with IQ increase (Table 2). In the group of patients with 1–2 years drug-resistance, 6 out of 7 patients acquired normal intellectual functioning (IQ > 70) after surgery. However, in the group of patients with 2–4 years drug-resistance, 4 out of 8 patients acquired normal intelligence functioning. In the group of patients with more than 4 years of drug-resistance, 3 out of 8 patients acquired normal intelligence functioning (see Table 3).

Memory was assessed in 22 patients using the Rey Auditory-Verbal Learning Test and the Rey–Osterrieth Complex Figure Test. Eleven patients received the Halstead–Reitan Battery because of poor cooperation. In the Rey Auditory-Verbal Learning Test, the pre- and postoperative immediate recall scores were 24.1 ± 9.5 and 28.3 ± 8.4, respectively. The delay recall scores were 4.4 ± 1.5 and 5.8 ± 2.1, respectively, which suggests increase but no significant difference (P > 0.05). In the Rey–Osterrieth Complex Figure Test, the pre- and postoperative copy scores were 22.1 ± 4.4 and 25.3 ± 3.8, the delay recall scores were 16.3 ± 2.5 and 18.1 ± 2.9, also showed the increase but no significant difference, P > 0.05. In 11 patients received Halstead–Reitan Battery, the pre- and postoperative HRB index were 0.42 ± 0.15 and 0.33 ± 0.15, respectively (see Fig. 4 and Table 4).

3.5. Pathology

Specific abnormal pathology was observed in 20 patients, whereas seven patients had either nonspecific gliosis or was considered normal. Abnormal pathology at operation included hippocampal sclerosis in nine patients, focal cortical dysplasia in three patients, tuberous sclerosis in three cases, Rasmussen’s encephalitis in two cases, Sturge–Weber syndrome in one case, vascular malformations in two cases. One patient with West syndrome and two patients with Lennox–Gastaut syndromes demonstrated the focal cortical dysplasia.

3.6. Surgical outcome

According to Engel’s criteria, 14 patients (51.9%) achieved an Engel Class I status, and eight patient (29.6%) had an Engel Class II outcome. An additional three patients (11.1%) had a significant decrease in seizure frequency (Engel Class III), and two patients (7.4%) had no change in seizure frequency (Engel Class IV). When the outcome was examined according to syndrome type, mesial temporal lobe epilepsy syndrome demonstrated the best outcome. Six patients with mesial temporal epilepsy became seizure-free (Engel Class I) and two patients had rare seizure (Engel Class II) after surgery. One patient with Lennox–Gastaut syndrome had Engel Class III outcome, and another showed no change in seizure frequency. One patient with West syn-

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Number of epileptogenic foci</th>
<th>Duration of drug-resistance</th>
<th>Engel’s grading of surgical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single</td>
<td>Multifoci</td>
<td>≤2 years</td>
</tr>
<tr>
<td>West syndrome</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lennox–Gastaut syndrome</td>
<td>9</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Sturge-Weber syndrome</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rasmussen syndrome</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Mesial temporal epilepsy syndrome</td>
<td>9</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>16</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 3
Pre- and postoperative intellectual assessments of 23 cases categorized by the drug-resistance period

<table>
<thead>
<tr>
<th>Duration of drug-resistance</th>
<th>Number of cases</th>
<th>Intellectual assessments (mean IQ)</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-operation</td>
<td>Post-operation</td>
</tr>
<tr>
<td>≤2 years</td>
<td>7</td>
<td>64.1 ± 13.2</td>
<td>82.4 ± 11.1a</td>
</tr>
<tr>
<td>&gt;2 years and ≤4 years</td>
<td>8</td>
<td>57.8 ± 10.2</td>
<td>70.6 ± 5.8a</td>
</tr>
<tr>
<td>&gt;4 years</td>
<td>8</td>
<td>62.9 ± 13.8</td>
<td>72.8 ± 12.5a</td>
</tr>
</tbody>
</table>

a Compare with pre-operation, paired-samples t-test, P < 0.05.

b There was a significant difference between ≤2 years group and >4 years group, independent-samples t-test, P < 0.05.
drome also had Engel Class IV outcome. These results are summarized in Table 1. Besides the increase of intelligence quotient, many patients and families reported increase in cognitive abilities, behavior, and quality of life after the surgery. Most of patients demonstrated the marked increase in EEG at follow-up, and epileptic discharge disappeared in 13 cases, and only one patient showed contralateral epileptic discharge (Fig. 1C and D).

Temporary complications were observed in four patients and including one case of acute disconnection syndrome, two cases of partial aphasia, and one case of contralateral partial hemiplegia. All patients made recovery within 3 weeks. Three patients who underwent occipital pole resection demonstrated contralateral hemianopia (one patient had a pre-existing condition before the surgery), all patients adapted to hemianopia gradually. There were no deaths. Six patients with multilobe resection showed no hemosiderin deposition after 4 years follow-up.

4. Discussion

The question of “drug resistance” warrants further discussion when epilepsy surgery is considered, and at what point can we determine to be truly intractable? In adult practice, “intractability” may be considered as failure to respond to at least two AEDs over a 2-year period, at least four seizures every month, and impresses the everyday life but without progressive CNS diseases [10,12]. However, in pediatric practice, these rules may not be appropriate. In an infant with catastrophic-onset epilepsy, there may be pressure in such cases to suppress seizures as early as possible to try to reduce developmental morbidity [7]. Moreover, drug-resistance in some childhood syndromes such as Lennox–Gastaut syndrome, Rasmussen syndrome, Sturge-Weber syndrome, West syndrome and mesial temporal lobe epilepsy syndrome is common, and more than 80% of such patients are drug-resistance even if greater number of AEDs are tried [1–3]. Drug-resistance in such childhood epilepsy syndromes is predictable in a certain extent before exhaustive drug trials. Therefore, definition of “intractability” that failure to AEDs over a 2-year period may be too strict for such epilepsy syndromes when surgery is considered. In this study, early surgical intervention of eight cases in which drug-resistance period was less than two years demonstrated a good result. In 7 out of the 8 cases achieve an Engel Class I or II outcome, while remaining case showed a marked decrease at seizure frequency. The results indicate that pediatric patients with intractable epilepsy syndromes who may benefit from epilepsy surgery should not be viewed too restrictively, and subsets of children with localizable epileptic discharge may be surgical candidates with a good seizure outcome prognosis [9]. Engel et al. argue that some drug-resistant epilepsies are highly responsive to surgery, and early surgical intervention is highly cost-effec-

Table 4
Pre- and postoperative intellectual assessments of 23 cases categorized by the lag between onset and surgery of epilepsy

<table>
<thead>
<tr>
<th>Duration of seizure</th>
<th>Number of cases</th>
<th>Intellectual assessments (mean IQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-operation</td>
</tr>
<tr>
<td>≤3 years</td>
<td>8</td>
<td>63.8 ± 12.3</td>
</tr>
<tr>
<td>≤6 years</td>
<td>11</td>
<td>56.9 ± 9.7</td>
</tr>
<tr>
<td>&gt;6 years</td>
<td>4</td>
<td>69.5 ± 15.9</td>
</tr>
</tbody>
</table>

* Compare with pre-operation, paired-samples t test, P < 0.05.

b There was a significant difference when compared with ≤3 years group, independent-samples t test, P < 0.05.
tive for patients with surgically remediable syndromes, so there is no need to pursue exhaustive drug trials with these patients [5,13,14].

Some childhood epilepsies halt cognitive and social development with permanent long-term effects [1]. More than one third of patients with childhood epilepsy have intellectual and cognitive problem. This is particularly true in some severe epilepsy, such as Lennox–Gastaut syndrome, in which only few children (<10%) are intellectually normal [1,7]. Although some authors claim that intellectual performance and memory remains either unchanged or further impaired after surgery, a growing body of evidence suggests that early seizure control might have a positive effect on cognitive development and social adjustment. Thus, surgical intervention for intractable epilepsy may provides a good opportunity to prevent irreversible decline of intelligence and cognitive function [1,15–17]. In this study, pre- and postoperative intellectual assessments demonstrate pediatric patients with intractable epilepsy syndromes benefit from surgery, and mean IQ increases. Memory tests and the Halstead–Reitan Battery also indicated increase, and many patients and families reported increase in cognitive abilities, behavior, and quality of life after the surgery. Moreover, the results here demonstrate that the patients with shorter seizure history and drug-resistance time correlate with higher IQ, and this maybe the reason that we have more patients who had IQ gains of $\geq 15$ IQ than Freitag’s group, because the duration of seizure in 8 cases is no more than 3 years in this study (6/8 patients had IQ gains of $\geq 15$ IQ) [14]. This suggests that early surgical intervention in pediatric patients with intractable epilepsy syndromes means not only good seizure control, but also better intelligence. Nine patients had IQ gains of $\geq 15$ IQ in this group after surgery, and most patients demonstrated the postsurgical IQ increase, but these IQ increase need to be further reexamined, because other factors, such as test–retest effect, practice effect, disease severity and maturation will affect the postsurgical IQ [18].

A subset of pediatric patients with intractable epilepsy syndromes demonstrate focal epileptic discharge, as in mesial temporal lobe epilepsy syndrome [11]. Lennox–Gastaut syndrome and West syndrome are generally accepted as generalized seizure, but some patients with such syndromes are localizable and manifest multilobar or hemispheric diffuse epileptic discharge, especially emerges in some symptomatic seizure [1,19–21]. Traditional anatomic or functional hemispherectomy has been advocated for children with hemispheric-dominant multilobar or diffuse epileptic discharge. However, the majority of these candidates have preexistent hemiplegia associated with a structural abnormality of the contralateral hemisphere and seizures proven to arise from that hemisphere [9,21,22]. The strict indications for hemispherectomy may lead to exclusion of some patients without preexistent hemiplegia, and challenge are also exist in such patients with hemispheric multilobar epileptic discharge [17,22,23]. The results of this study indicates that multilobe resection with MST or/and corpus callosotomy is a reasonable alternative to hemispherectomy. In 11 cases, 8 patients achieved an Engel Class I or II outcome. These outcomes are similar to the hemispherectomy results of Kossoff et al., but show lesser complication [22,23]. Our results also show that surgical patients have better seizure control and cognitive function in contrast to single corpus callosotomy, MST or vagus nerve stimulation alone [24]. The results of this study highlight the advantages of multilobe resection combined with MST and/or corpus callosotomy in severe intractable hemispheric epilepsy [21].

Using Engel’s criteria, approximately 80% of patients achieve an Engel Class I or Class II outcome after surgery. When the results are examined by syndrome type, patients with mesial temporal lobe epilepsy syndrome demonstrated the best outcome compared to other patients with intractable epilepsy. Pediatric patients with other intractable epilepsy syndromes also had good results, with 60% achieving the Engel Class I or Class II outcome at least. These results suggest that aggressive surgical intervention for such patients is considerable for more practice [13,25].

5. Conclusion

Epilepsy surgery in children with intractable epilepsy syndrome is effective and safe. The results here suggest that pediatric patients with intractable epilepsy syndromes that may benefit from epilepsy surgery should not be viewed too restrictively, and subsets of such pediatric patients with localizable epileptic discharge may be good surgical candidates. Early surgical intervention in pediatric intractable epilepsy syndromes may results in a favorable outcome in a high percentage of cases and may provides an important opportunity to prevent irreversible decline in intelligence and disability.

References