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Original Article

Improvement of intellectual outcomes in 20 children with refractory epilepsy after individualized surgery

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Abstract

Background: Refractory epilepsy is a common and troublesome neurosurgical disease. This study is designed to compare seizure control and degrees in intellectual outcome in children with refractory epilepsy after surgical treatment.

Methods: 20 children with refractory epilepsy were treated with tailored epilepsy surgery or vagus nerve stimulation (VNS). We used the Engel Epilepsy Surgery Outcome Scale to evaluate seizure control and the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV), to test the children's intellectual outcomes 7-day preoperative and 3-, 6-, and 12-month postoperative.

Results: In total, 14 cases were seizure free (Engel I) and 2 cases to have suffered few attacks since surgery (Engel II). In two cases, the frequency of seizures decreased by >90% (Engel III). In the remaining two cases, the effects of surgery on seizure control were not obvious (Engel IV). All children completed the WISC-IV test. On average, postoperative intelligence quotient (IQ) increased by 6.35 points 12-month postsurgery compared with the results of the preoperative tests ($P < 0.01$). Second, intellectual outcomes after surgery in the Engel I and II groups increased by >3.88 points compared with in the Engel III and IV groups ($P < 0.05$). Finally, there were no fatal complications over the long-term follow-up except for intracranial infection of two cases; postoperative subcutaneous hematoma occurred in one case and hoarseness in one case.

Conclusion: Individualized epilepsy surgery is safe and effective for children with refractory epilepsy. It can control or reduce the frequency of postoperative attacks as well as improve postoperative intellectual outcomes to different degrees.

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Key Words: Engel epilepsy surgery outcome scale, individualized surgery, intellectual outcome, refractory epilepsy children, Wechsler intelligence scale for children fourth edition

INTRODUCTION

The prevalence of epilepsy in China may be as high as 7%. There are about 10 millions of people with epilepsy, 5% of whom have active epilepsy; for about 60% of epileptic patients, symptoms begin to appear in childhood. Almost two-thirds of secondary-epilepsy cases gradually evolve into intractable epilepsy.[8] Children with long-term and recurrent epileptic seizures suffer from cognitive dysfunction and mental disorders to different degrees preoperatively. The physical and mental health and quality of life for children with epilepsy have gained more attention in recent years.[2,4] Many researchers have focused on preoperative evaluation and choice of surgical procedures. Recently, the subjects of improvement in cognitive function after surgical treatment and individualization of surgical procedures have caused more and more attention.

The purpose of this study is to compare presurgical with postsurgical cognitive function in children with epilepsy who underwent individualized surgery by using the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV). Simultaneously, by using the Engel Epilepsy Surgery Outcome Scale, we investigated the effect of epilepsy surgery on postoperative intellectual-outcome improvement.[10]

METHODS

Study population

We analyzed 20 pediatric patients with intractable epilepsy who were admitted to the Department of Neurosurgery, Provincial Hospital Affiliated, Anhui Medical University, Hefei, China, from January 2014 to December 2016 retrospectively. In total, 11 cases were male and 9 cases were female. Age range was 6–16 years old (mean 11 ± 3.3-year old). Disease course was 3 months to 9 years, and average duration was 5.3 years [Table 1]. Epileptic episodes appeared in a variety of forms: simple partial seizure occurred in six cases, complex partial seizure in two cases, partial-onset seizures with secondary comprehensive attacks in five cases and clonus attack with overall stiffness in seven cases. All 20 had been *partus maturus*. Epilepsy was poorly controlled by combinations of a variety of drugs, including valproate and levetiracetam. All 20 patients experienced obvious intellectual deficiency preoperatively, based on the WISC-IV assessment.

Multimodal imaging examination

We examined the 20 children by multimodal imaging before surgery, using normal head computerized

Table 1: Demographic and clinical characteristics and Engel classifications of 20 cases

	Raw or mean (SD)	Range	Percentages (% of cases)
Sex			
Male, *n*	11		55
Female, *n*	9		45
Average age	(In years) (SD)		
Male, year	11.6 (3.7)	8-16	
Female, year	10.1 (3.5)	6-16	
Follow-up time, M	22.1 (4.7)	12-36	
Seizure characteristics presurgery			
Duration of epilepsy, year	4.24 (3.23)	0.3-9	
Number of AEDs, *n*	2.2 (0.71)	1-4	
Surgery characteristics			
VNS	6		30
D-EP + ECOG + EFR	2		10
NAVI + ECOG + EFR	3		15
ECOG + EFR	9		45
Classification Postsurgery			
Engel I, *n*	0		0
Engel II, *n*	14		70
Engel III, *n*	1		5
Engel IV, *n*	5		25

AED: Antiepileptic drug, VNS: Vagus nerve stimulation, D-EP: Depth -electrode placement, NAVI: Neuronavigation, ECOG: Electrocorticography, EFR: Epileptogenic focus resection, Engel I: Seizures completely disappear, Engel II: Episode frequency ≤3 times/year, Engel III: Episode reduction ≥90%, Engel IV: Episode reduction <90%

tomography (CT) scan, head magnetic resonance imaging (MRI) scan and enhancement, MRI fluid-attenuated inversion recovery sequence, MR spectroscopy imaging, and diffusion-weighted imaging. Results suggested that abnormal lesions of the frontal lobe occurred in two cases, which tended to be space-occupying cysts and astrocytoma. Abnormal lesions of the temporal and occipital lobes occurred in 10 cases, which tended to be space-occupying cysts, cortical dysplasia, cavernous hemangioma, and neuroepithelial tumors. No obvious abnormalities appeared in four cases. Abnormal signaling in the peripheral region of the lateral ventricle occurred in one case. Abnormal signaling in both hippocampi occurred in two cases, which tended to be hippocampal sclerosis. Cerebral developmental deformity occurred in one case [Figure 1].

Electrophysiological examination

All 20 patients, once admitted to the hospital, received long-term video electroencephalography (VEEG) monitoring of the scalp in the epilepsy surgical ward. Monitoring time was 24–98 hours (average time, 50.3 ± 19 hours). Abnormal discharge was recorded clearly for all the patients, and epileptogenic focus was determined elementary combined with imaging examination. We could not locate specific epilepsy areas in two cases, since the monitoring results of the long-term scalp VEEG mainly showed diffuse slow waves extended throughout the bilateral frontotemporal lobe, so we decided to conduct depth-electrode placement to fully understand the relationship of time and space of epileptic seizures according to the deep-discharge sequences of the electrodes. Similarly, a typical attack was also recorded at least; simultaneously, intraoperative electrocorticogram (ECOG) cleared and defined epileptogenic focus any further and determined if the tumor is resected totally.[14,17]

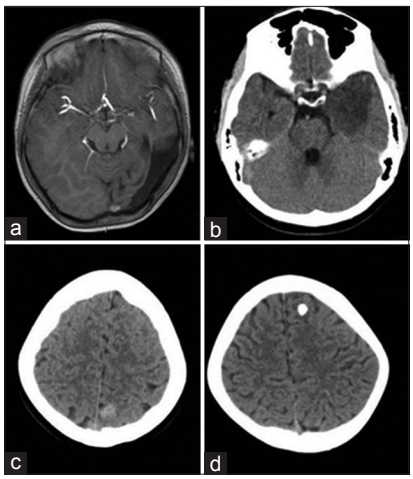

Figure 1: Multimodal Imaging Examination. (a) Local low signaling in left temporal and occipital lobes hint at dysplasia. (b) Low-density shadow is indicated for low-grade glioma of temporal lobe. (c) Identical density focus shows parietal cavernous hemangioma. (d) High density shows frontal calcification focus

Intellectual-outcome assessment

This study used the Chinese edition of WISC-IV adjusted to 6- to 16-year-old to evaluate intellectual outcomes in all 20 cases. Scale classifications of intelligence were high (110 points), medium (90–109 points), average (80–89 points), borderline (70–79 points), and extremely low (<69 points).[12] Professional pediatric physicians assessed the intellectual outcomes of the 20 patients 7 days before surgery and 3, 6, and 12 months after surgery based on WISC-IV.

Surgical procedures

Overall, eleven cases accepted intraoperative ECOG and epileptic-focus resection, six cases accepted vagus nerve stimulation (VNS), one case accepted parietal-lobe cavernous hemangioma resection under neuronavigation, one case accepted ependymal-tumor resection by subfrontal approach, and the final case accepted ECOG and anterior temporal-lobe and hippocampus resection [Table 1]. All surgical specimens were sent for pathological examination to determine their definitive properties.

Statistical methods

We used SPSS version 19.0 statistical software for statistical processing. Measurement of data were expressed with x ± SD. The *t*-test was used to compare preoperative and postoperative data. We set the standard inspection level at $\alpha = 0.05$, and $P < 0.05$ was regarded as statistically significant.

RESULTS

Seizure control

We recorded seizure-control status in all 20 cases through outpatient review or telephone follow-up for 12–36 months (average, 22 months). Results based on Engel classification are shown in Table 1.

Postoperative pathology

Fourteen children underwent surgery, and postoperative tissue specimens received pathological diagnoses. Results were as follows: four cases had focal cortical dysplasia with histopathological involvement of glial-cell vacuolar hyperplasia, layer pyramidal neuron proliferation, inflammatory-cell infiltration, lymphocytes, and foam cell infiltration. Three cases had dysembryoplastic neuroepithelial tumors, two cases had cortical dysplasia with microglial-nodule formation, one case had pilocytic astrocytoma (WHO I), one case had cavernous hemangioma with surrounding glial-cell hyperplasia, one case had ependymoma, one case had hippocampal sclerosis, and one case had mixed glial–neuronal tumors.

Intellectual-outcome assessment

Intellectual-outcome variation before and after surgery. We assessed all 20 cases using WISC-IV before and after surgery. Postoperative intelligence quotient (IQ) scores increased by various degrees during different postoperative periods. Twelve months postoperation, IQ increased by 6.35 points compared with the results of the preoperative test ($P < 0.01$). Intellectual-outcome improvement was statistically significant following surgical intervention [Table 2].

Surgical procedures affected post-operative intellectual outcomes. In the 6 cases that underwent VNS, cognitive function 12 months after surgery increased by 3.70 points compared with the results of the preoperative test, and the improvement was statistically significant ($P < 0.01$; Table 3). In the seven cases that underwent temporal-lobe lesion resection, cognitive function 12-month postoperative increased by 7.72 points, and the improvement was statistically significant ($P < 0.01$; Table 4). In the three cases of frontal-lobe epilepsy, cognitive function increased by 8.67 points 12-month post-operation compared with the results of the preoperative assessment, and the difference was statistically significant ($P < 0.01$). The other four cases underwent occipital and parietal lobe lesion resection, and in all of them, intelligence increased by varying degrees. These results indicated that intellectual outcomes in children with refractory epilepsy improved to different extents, if appropriate individual epilepsy surgery was accepted.

Effects of postoperativ Engel grading on intellectual outcome. The results showed that intellectual outcomes in the Engel I and II groups increased by 3.88 points more than in the Engel III and IV groups ($P < 0.05$). Engel grading had a positive effect on the prognosis by improving intelligence. This effect could be time dependent; recurrent attacks of epilepsy influenced brain development [Table 5].

Effects of age group on intellectual outcome. Results showed that intellectual outcomes in the age group of 6–10 years decreased by 0.44 points compared with those in the age group of 11–16 years ($P > 0.05$). Time of surgery did not result in obvious differences in prognosis for improving intelligence between the two age groups [Table 6].

Postoperative complications and adverse effect. All operations were completed successfully. Postoperative head CT scan revealed that secondary bleeding, postoperative infection, cerebrospinal-fluid (CSF) leakage and other severe complications did not occur. Postoperative fever occurred in two cases, in which intracranial infection was

Table 2: Intellectual-outcome scores of 20 cases (WISC-IV)

Time	Intellectual-outcome score (mean±SD)
7-day preoperation	40-105 (71.55±23.17)
3-month postoperation	42-105 (73.00±23.43)
6-month postoperation	45-106 (74.95±23.37)#
12-month postoperation	48-109 (77.90±23.45)**

**$P<0.01$ vs. 7-day preoperation group; #$P<0.01$ vs. 7-day preoperation group

Table 3: Intellectual-outcome scores of six cases with vagus nerve stimulation

Serial number	Age (y)	Gender	Preoperative 7 Days	3-Month Postsurgery	6-Month Postsurgery	12-Month Postsurgery	Postsurgery Engel level
1	16	M	40	40	41	43	IV
2	9	M	40	40	42	42	IV
3	13	M	40	40	41	43	III
4	8	M	90	91	93	95	I
5	14	M	98	100	101	102	II
6	8	F	100	102	104	105	III
Mean±SD	11.3±3.15		68±28.17	68.8±29.03	70.3±27.13#	71.7±26.13**	

**$P< 0.01$ vs. Pre-operative 7 Days group; #$P<0.05$ vs. Pre-operative 7 Days group

Table 4: Intellectual-outcome scores of seven cases with temporal lobe epilepsy

Serial number	Age (y)	Gender	Preoperative 7 Days	3 Months Post-surgery	6 Months Post-surgery	12 Months Post-surgery	Post-surgery Engel level
1	6	F	40	42	45	48	I
2	11	F	40	42	45	49	I
3	10	F	40	41	43	46	I
4	14	M	75	76	79	85	I
5	13	M	75	76	78	83	I
6	16	F	82	85	86	89	I
7	8	F	94	95	97	100	I
Mean±SD	11.1±3.48		63.71±22.87	65.29±23.00	67.57±22.61#	71.43±22.88**&	

**$P<0.01$ vs. Pre-operative 7 Days group; #$P<0.05$ vs. Pre-operative 7 Days group; &$P<0.05$ vs. 3 Months Post-surgery group.

Table 5: Intellectual-outcome scores of different Engel levels

Time	Engel I and II Levels (Mean±SD)	Engel III and IV Levels (Mean±SD)
7-day preoperation	40-105 (76.31±20.83)	40-90 (52.50±25.00)
12-month postoperation	46-108 (83.44±19.90)	42-95 (55.75±26.17)

Table 6: Intellectual-outcome scores of different age groups

Time	6-10 Years old (Mean±SD)	11-16 Years old (Mean±SD)
7-day preoperation	40-98 (71.78±20.07)	40-105 (71.36±22.56)
12-month postoperation	42-102 (77.89±19.20)	43-109 (77.91±21.17)

Table 7: Complications after individualized surgery

Signs and symptoms	No. of patients	Percentage
Postoperative fever	2	10
Intracranial infection	0	0
Cerebrospinal-fluid leakage	0	0
Subdural hematoma	1	5
Intraparenchymal hematoma	0	0
Hemiparesis	0	0
Hemianopia	0	0
Hoarseness	1	5

eliminated as a cause via CSF examination. However, postoperative subcutaneous hematoma occurred in one case; the hematoma was reabsorbed after 1 week of treatment with a pressure bandage. In one case, hoarseness occurred temporarily after VNS and vanished four days later. There was no death over the long-term follow-up. Long-term hemiplegia, aphasia, or other complications did not appear [Table 7].

DISCUSSION

The International League Against Epilepsy defines refractory epilepsy as that for which symptoms are not controlled by a combination of two standard antiepileptic drugs (AEDs).[15] However, refractory-epilepsy diagnosis and therapy in children remain complex, as they differ from such diagnoses and therapies in adults. Once two standard types of AEDs have been proven unable to control seizures in a patient, the physician should consider a diagnosis of intractable epilepsy.[11] It is reported that the incidence of drug resistance rises to 67% when neuroimaging results of the brains in epileptic children are abnormal, and only 11% of patients can completely prevent an attack.[16] Thus, early diagnosis and treatment are essential for avoiding irreversible damage to the central nervous system (CNS) and for developing cognitive function in children with refractory epilepsy.

Age is frequently regarded as an extremely important determinant of preoperative evaluation, surgical occasion, surgical indications, and choice of individualized surgical procedure. The rapid development and maturation of the CNS in young children is a major cause of the manifestation of clinical complications.[18] However, clinical examination of the CNS and assessment of psychological developmental in children are very difficult and must be conducted by specialist physicians. Brain plasticity develops rapidly in young children, reaching its peak between ages 3 – 7.[9] Related literature reports five risk factors for cognitive disorders and growth retardation in epileptic children: seizure type, age of onset, seizure frequency, seizure duration, and type and dose of AEDs.[3] Epileptic encephalopathy caused by these factors is irreversible in most cases.[7] Hence, early surgical intervention is an important way to terminate seizures in very young epileptic children when antiepileptic drugs cannot be controlled seizures. Individualized surgical procedures are adopted through imaging manifestations, long-term VEEG, and neuropsychological assessment in the platforms of some epilepsy centers.[6] VNS is also the operative plan when the location of the structural lesion is unclear, or lesions are located in functional areas. It is reported that the epilepsy remission rate is 72%–90% postsurgery.[5] In this study, all 20 cases underwent successful surgery, after choosing different individual operations. Surprisingly, the rate of seizure control was as high as 86% postsurgery, and scarcely any threatening complications appeared. These results fully reflected the safety and efficacy of epilepsy surgery for children.

Previous studies have shown that surgery for temporal-lobe epilepsy (TLE) performed in childhood results in excellent long-term seizure control and favorable cognitive outcomes along with positive effects on brain development.[11] However, some researchers hold the opposite view that both emotion recognition and social cognition were impaired in TLE patients and that earlier age at epilepsy onset, longer disease duration, and history of early-childhood brain injury predicted social-cognition problems in these patients. Epilepsy surgery within the temporal lobe seems to be neutral in its effect on patients' performances in both domains.[1] In contrast, the seizure-control effect of successful and timely surgery for intractable epilepsy in children was obvious, and the intellectual outcomes of these children improved by different degrees. In this study:

- The average IQ of the 20 children was 40–105 (71.55 ± 23.17) 7 days before surgery and reached 48–109 (77.90 ± 23.45) 12 months after surgery; their intellectual ability increased by 6.35 points above their highest previous scores ($P < 0.01$). Average IQ was closely associated with postoperative recovery time and tended to increase over time based on comparison of multiple time points

- Intellectual outcomes in the six cases treated with VNS increased by 3.70 points 12 months after surgery compared with the results of the preoperative test ($P < 0.01$). In the seven cases that underwent temporal-lobe lesion resection, it increased by 7.72 points ($P < 0.01$) 12-month postoperation. Two kinds of different surgical options both have positive effects on intellectual outcomes
- Intellectual outcomes in children in the Engel I and II groups increased by 3.88 points post-surgery compared with those in the Engel III and IV groups ($P < 0.05$). Engel grading had a positive effect on prognosis by improving intelligence, which further corroborates the finding that recurrent attacks of epilepsy influence brain development
- Postoperative intellectual outcomes in children in the age group of 6–10 years decreased by 0.44 points, which was more than in the age group of 11–16 years ($P > 0.05$). Surprisingly, the choice of surgery did not result in obvious differences in prognosis for improving intelligence between the different age groups.

The anterior temporal lobe and hippocampus play important roles in learning, memory, and other cognitive functions. If the bilateral anterior temporal lobe and hippocampus are damaged, patients may suffer severe cognitive impairments, including impairments to learning and memory.[13] Fortunately, there were no lethal postoperative complications, and intellectual outcomes increased among refractory epilepsy children by reasonable surgical procedures in this study. The reasons for this are as follows:

- Preoperative detailed assessment and focal epileptogenic localization are key factors in the reduction of complications
- Epilepsy control in children reduces secondary impairments caused by abnormal discharge of brain tissue
- The reduction of the AED can decrease medication side effects include central nervous system damage
- The better physical and psychological status of children permits them to better integrate into society and a more enjoyable environment to improve their cognitive function further.

There are some limitations to our research. WISC-IV is a test designed to measure intelligence, rather than the other cognitive domains. It is insufficient for measuring types of cognitive problems beyond its defined testing range, such as those of memory, continuous attention, executive function, and language, which are often reported in epileptic children.

CONCLUSIONS

Early and individualized surgical intervention is an effective method for treatment of refractory epilepsy in children, and the effects of surgery on intellectual outcomes should be given greater attention. The positive effects of surgery are of great significance to improving intellectual outcomes for epileptic children, which are namely to minimize seizures and reduce adverse effects caused by long-term medication.

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Conflicts of interest

There are no conflicts of interest.

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