Impact of pediatric epilepsy surgery on intellectual efficiency

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Introduction. Epilepsy surgery may be a promising alternative therapy for seizure control in patients with refractory seizures, resistant to medication. Cognitive outcome is another important factor in favor of the surgical decision.

Aim. To investigate the correlation between seizure outcome and cognitive outcome after epilepsy surgery in a pediatric population.

Patients and methods. A total of 59 pediatric patients were retrospectively assessed with the WISC-III (Full Scale, Verbal Scale and Performance Scale) before and, at least, 6 months after surgery. Patients were divided into two groups according whether or not improvement of seizure control after surgery. Data collected for each child included: epileptic syndrome, etiology, age at epilepsy onset, duration of epilepsy and seizure frequency.

Results. Comparison using a MANOVA test revealed significant differences across pre-operative Full Scale, Verbal Scale and Performance Scale ($p = 0.01$) with seizure reduction group performing better than no seizure reduction group. Seizure improvement group achieved significant Performance Scale improvement ($p = 0.01$) and no seizure improvement group showed significant Verbal Scale worsened after surgery ($p = 0.01$).

Conclusions. Our results suggest that the success of the epilepsy surgery in childhood when the seizure control is achieved may also provide an improvement in the Performance Scale whereas the seizure maintenance may worsen the Verbal Scale.

Key words. Children. Cognitive. Epilepsy. Intelligence. Refractory. Seizures. Surgery.

Introduction

Epilepsy is the most common neurological disorder in childhood and the highest rates are found in children up to the first year of life [1-3]. It is defined as a group of chronic central nervous system diseases, characterized by recurrent and unprovoked seizures with varied etiologies and clinical manifestations [4, 5].

Despite advances in pharmacology and the appropriate use of antiepileptic medication about 25% of these children and adolescents have refractory seizures, resistant to medication [6]. In these cases epilepsy surgery may be a promising alternative therapy for seizure reduction or seizure control particularly in patients with focal or hemispheric seizures [7]. Numerous studies indicate that surgery for epilepsy in children often provides a satisfactory outcome, similar to results found with adults [8-10].

Patients with refractory epilepsy may benefit from surgery, however an extensive workup, which includes video EEG, structural and functional MRI, clinical, social, psychiatric and neuropsychological evaluations, needs to be performed. In this context, neuropsychological assessment may be useful to define the basic cognitive profile, to determine the adaptive skills of the children, to guide parents and teachers in understanding the impact of epilepsy on cognition, to provide assistance in individualized educational training programs, in planning cognitive rehabilitation and, in some cases, to contribute to the identification of the lateralization and localization of the cognitive dysfunction [11,12].

From a neuropsychological perspective, the majority of studies indicated that risk of cognitive deficits is increased in medication-resistant pediatric epilepsy considering that, in general, theses are children with high seizure frequencies, subject to high doses of antiepileptic medication, the frequent use of polytherapy and limited social and academic life [13,14].

Other factor, such as duration of epilepsy, age at epilepsy onset, seizure frequency, the use of mono or polytherapy and the underlying etiology, appear to contribute to cognitive deficits [15-17].

There is evidence that seizure occurrences over time have significant deleterious effects on the cognitive processes and this fact is particularly relevant in children [4,18].

In addition to the impact of seizure reduction or extinction after epilepsy surgery, another important factor in favor of the surgical decision is the cognitive outcome. Therefore, when considering a surgical procedure, aspects of motor, cognitive and behavioral development must also be taken into account since children are often engaged in activities that require learning and cognitive tasks [19].

However, despite the significance of epileptic surgery, it was identified that there are few studies which correlate seizure outcome and cognitive outcome, especially in pediatric populations [20]. The objective of this study was to investigate the correlation between seizure outcome and cognitive outcome after epilepsy surgery in a pediatric population.

Patients and methods

Sample

A total of 59 pediatric patients were retrospectively analyzed, with an age range between 6 and 16 years, with medically intractable epilepsy, who underwent resective epilepsy surgery between march 2005 and January 2010. They were assessed at the Ribeirão Preto Clinical Hospital, University of São Paulo, Brazil, using the previously described presurgical workup, approved by the Ethics Committee of the Institution. Presurgical evaluation included a detailed clinical history review and a neurologic examination, video-EEG monitoring (VEEG), structural and functional neuroimaging and neuropsychological testing. Children with epilepsy were excluded from the study for the following reasons: severe visual, auditory or language deficits, severe psychiatric disorders, and severe mental deficiency that would prevent the understanding of the tasks.

Epileptic syndrome classification was carried out according to Engel [21] classification and the probable etiology was defined considering magnetic resonance imaging findings. Demographic and clinical data collected for each child included: epileptic syndrome, etiology of epilepsy, surgery localization (temporal and extratemporal), medication therapy (use of monotherapy or polytherapy), age at epilepsy onset (age of the child during first seizure), and duration of epilepsy (time period between the first seizure and the date of pre operative neuropsychological assessment), seizure frequency (daily or otherwise: monthly or weekly), age of the child at the date of the neuropsychological pre and postoperative evaluation and time to retest (period between the day of surgery and the day of postoperative neuropsychological test).

Cognitive assessment

The neuropsychological assessment began with a clinical interview with those responsible for the child regarding issues related to school, academic achievement, cognitive complaints, behavioral and psychosocial aspects and some issues related to epilepsy (age of onset, epilepsy duration, seizure frequency and antiepileptic medication).

After the clinical interview, depending on the age and cognitive profile of the child, an experienced neuropsychologist applied an adaptive behavior scale with their parents or performed a complete neuropsychological evaluation with the patient. The neuropsychological battery included: a full scale IQ test, verbal memory test (immediate and 30 minutes), non-verbal memory test (immediate and 30 minutes), semantic and verbal fluency, naming ability, attention tests, executive functions and visuoperception organization.

In this study, all children underwent two neuropsychological evaluations: the first before the epilepsy surgery and the second, at least, six months after surgery. The intellectual efficiency data of the patients before and after epilepsy surgery were analyzed as follows: the intellectual coefficient (IQ) was calculated from the application of the Wechsler Intelligence Scale for Children – third edition (WISC-III), a scale of standardized intelligence tests, adapted for Brazilian children aged 6 to 16 years and 11 months. The WISC-III provided a standardized measure of current cognitive intelligence: Full Scale (FSIQ), Verbal (VIQ) and Performance (PIQ). The WISC-III subtests are organized into two groups: verbal subtests and execution subtests. The child's performance on these subtests results in three composite measures: VIQ (weighted sum of verbal subtests points), PIQ (weighted sum of execution subtests points) and FSIQ (weighted sum of verbal and execution subtests points). Weighted score according to the age of the child is obtained by converting the raw number of each subtest. The sum of weighted scores, in turn, is converted into IQ values, according the rules of the manual. VIQ is composed of six subtests: information, similarities, arithmetic, vocabulary, comprehension and digit. PIQ is composed of seven subtests: picture completion, cod-

Table I. Clinical and demographic information of group 1 and group 2.

	Group 1 (*n* = 46)	Group 2 (*n* = 13)	*p*
Gender (male/female)	33/13	8/5	0.48
Age of the child at the date of the neuropsychological pre operative evaluation (years)	10.90 ± 2.56	9.80 ± 3.57	0.44
Age of the child at the date of the neuropsychological post operative evaluation (years)	12.30 ± 2.54	11.46 ± 3.26	0.31
Epilepsy onset (months)	54.97 ± 49.09	47.69 ± 44.70	0.32
Epilepsy duration (months)	77.32 ± 50.83	76.76 ± 33.33	0.12
Seizure frequency before surgery			
Daily	24	11	0.04
Other	22	2	
Medication therapy on pre-operative evaluation			
Monotherapy	9	2	0.73
Polytherapy	37	11	
Medication therapy on post-operative evaluation			
Monotherapy	12	0	0.04
Polytherapy	34	13	
Time to retest (months)	10.74 ± 7.10	10.46 ± 7.48	0.81
Surgery localization			
Temporal	27	2	0.00
Extratemporal	19	11	

ing, picture arrangement, block design, cubes, object assembly, symbols search and mazes (the latter two are supplementary). Qualitatively levels of FSIQ, VIQ and PIQ are classified into: superior range (IQ score ≥ 110), normal range (IQ score 90-109), inferior range (IQ score 80-89), borderline (IQ score 70-79) and cognitive disabilities (IQ score ≤ 69), according to the standards of the WISC-III.

Outcome measures

The method used to determine the effectiveness of surgery was the occurrence of postoperative seizures according to the Engel [21] classification:

- *Class I:* complete seizure remission after surgery, or the presence of only non-disabling simple partial seizures for at least two years, or the occurrence of tonic-clonic seizure triggered by withdrawal from antiepileptic drugs.
- *Class II:* rare disabling seizures since surgery, or for at least the past two years, or the presence of exclusively nocturnal seizures.
- *Class III:* significant improvement more than 75% reduction in seizure frequency when compared to the preoperative situation, or prolonged seizure-free intervals greater than half of the follow-up period, but not less than two years.
- *Class IV:* refers to non-significant reduction, no change in seizure frequency or worsening.

In this study, patients were divided into two groups according whether or not improvement of seizure control after surgery was achieved:

- *Group 1:* patients classified as Engel I or II, considered as seizure improved group.
- *Group 2:* patients classified as Engel III or IV, considered as seizure unimproved group.

The Engel classification was performed at least 6 months after surgery and was updated during visits with the medical staff.

Data analysis

Demographic categorical variables were evaluated using the chi-square test. Numeric variables were analyzed using the independent-samples *t* test. For comparisons, with respect to pre and post neuropsychological evaluation in both groups, the linear regression model (MANOVA) was used with mixed effects (fixed and random effects), since the responses are grouped (repeated measures for the same individual). The model adjustment was performed using SAS software v. 9.0.

Results

Demographic and clinical data

Patient data are summarized in table I. The sample consisted of 59 patients. Overall, 78% of the patients became seizure-free or had a worthwhile improvement after surgery (group 1) and 22% of patients had no appreciable reduction in seizure frequency (group 2). Seventy per cent of the total sample were male, the mean age before surgery was 10.6 ± 2.82 years, ranging from 6 to 16 years and the mean age after surgery was 12.08 ± 2.70 years showing the same age variation of the pre surgical evaluation. The mean age of epilepsy onset was 53.4 ± 47.88 months in the total sample, ranging from 1 month to 186 months and the mean duration of

epilepsy was 77.20 ± 47.27 months, ranging from 4 to 189 months. Eighty per cent of the group 1 and 84.6% of group 2 used polytherapy with antiepileptic drugs before surgery.

Considering the number of post operatory antiepileptic drugs, evaluation group 2 had a statistically significant higher number of patients using polytherapy than group 1 (p = 0.04). After surgery, 74% of the patients in group 1 and all patients in group 2 used polytherapy. Regarding the seizure frequency there was a significant difference (p = 0.04) between group 1 and 2. Fifty two per cent of patients in group 1 had daily seizure before surgery and 48% had weekly or monthly seizures. In group 2, 84.6% of patients had daily seizure before epilepsy surgery and 15.4% had weekly or monthly seizures. In the total sample, temporal and extratemporal resection was performed in 30 (51%) and 29 (49%) patients, respectively. Analyzing the surgery localization, 93% of patients (n = 29) that underwent temporal lobe resection and 63% (n = 19) of patients that underwent extra temporal resection presented seizure improvement (p = 0.00). No statistically significant differences were found between the groups regarding gender, age at pre and post neuropsychological evaluation, epilepsy onset, epilepsy duration, number of antiepileptic drug at pre surgery evaluation and retest.

The correlation between cognitive development and seizures evolution after surgery was evaluated using two types of analysis: first the values of FSIQ, VIQ and PIQ were compared in group 1 and 2 separately and subsequently the comparison of FSIQ, VIQ and PIQ was made between groups 1 and 2, with the results presented in table II.

Pre and postoperative intellectual efficiency within each group

When the data were evaluated in order to verify the impact of seizure control after epilepsy surgery on cognitive performance within each group separately as measured by the intelligence test it was observed that the test t for independent samples did not show an effect of surgery on the FSIQ measure of group 1, FSIQ of group 2, PIQ of group 2, VIQ of group 1. It was also observed that there was a significant statistical difference in the values of PIQ in group 1 between the pre and post operative neuropsychological evaluation (p = 0.01). The post operative values of PIQ in group 1 were higher than the pre operative evaluation values. There was significant difference between pre and post operative VIQ in group 2 (p < 0.01). Post operative VIQ values in group 2 were smaller than the pre operative values.

Intellectual efficiency between groups 1 and 2

When the data were evaluated with the aim of comparing the mean results of FSIQ, VIQ and PIQ in group 1 in relation to group 2, it was shown that there was a significantly better intelligence test performance in group 1 (FSIQ, PIQ and VIQ) when compared to group 2, both in the preoperative evaluation and in the evaluation performed after epilepsy surgery (p < 0.05) (Table II).

Discussion

Intellectual efficiency was compared between two groups of pediatric patients with epilepsy who were matched according to seizure outcome: group 1 with Engel I or II and group 2 with Engel III or IV. All patients underwent neuropsychological evaluation before and at least 6 months after surgery in order to establish the cognitive profile base before surgery, to provide an objective measurement of cognitive changes and to guide parents and teacher in understanding the cognitive impact of epilepsy.

It can be concluded from the results that the pre operative FSIQ, PIQ and VIQ means in group 1 were higher than the means in group 2. Patients who presented extinction or a significant reduction in seizure frequency after epilepsy surgery had better cognitive performance before surgical procedure. Gleissner et al [20] confirmed these findings in a study that investigated the relationship between preoperative IQ and seizure control after epilepsy surgery in three groups of patients divided according to IQ score and concluded that a high percentage of children became seizure free from the group which presented better IQ results prior to surgery. However the authors state that the better preservation of cognition alone could not be regarded as a predictor for a good prognosis. Other studies also found similar results [22,23].

In the present study it was noted that two clinical variables were significantly different in both groups of patients before surgery: seizure frequency and surgery localization. Regarding the seizure frequency it was observed that almost all the patients in group 2 had daily seizures prior to epilepsy surgery. Longitudinal studies reinforce the idea that recurrent seizures in a developing brain may be crucial for the stagnation of cognitive deterioration over time [24,25]. In addition to these clinical as-

Table II. FSIQ, VIQ and PIQ pre- and postoperatively in group 1 and 2: comparison within and between groups.

	Group 1	Group 2	*p* [a]
FSIQ			
Pre-surgery	88.78 ± 22.06	69.31 ± 20.01	0.01
Post-surgery	90.37 ± 25.54	63.77 ± 19.17	< 0.01
p [b]	0.28	0.05	
PIQ			
Pre-surgery	87.26 ± 22.46	67.69 ± 17.29	0.01
Post-surgery	92.59 ± 22.47	69.31 ± 18.37	< 0.01
p [b]	0.01	0.67	
VIQ			
Pre-surgery	91.28 ± 20.83	73.69 ± 21.99	0.02
Post-surgery	89.46 ± 27.29	61.54 ± 20.25	< 0.01
p [b]	0.44	< 0.01	

[a] Comparative performance of FSIQ, PIQ and VIQ between group 1 and group 2. [b] Comparative performance of FSIQ, PIQ, and VIQ pre and post surgery in each group (group 1 and group 2)

pects, social factors are also strongly related to learning issues in children with epilepsy because having more seizures may lead to increased social isolation, a poorer quality of life, and decreased school attendance [26].

Concerning surgery localization, the present study indicated that group 2 showed a significant number of extratemporal cases compared with group 1 and these results are similar to those observed in the literature. In the sample of Zentner et al [27] 68.3% of extratemporal resections became seizure-free whereas in the Srikijvilaikul et al [28] study, 92% of patients had seizure reduction after temporal surgery. In the study by Gilliam et al [29], 72% of children became seizure free after temporal surgery and 60% after extratemporal resections. According to these authors, the cure rate achieved in extratemporal resections was similar to that seen in surgeries performed on adults. Téllez-Zenteno et al [11] reported that the results of extratemporal resections were not as satisfactory, with the possibility of secondary deficits considering coincidence of the epileptogenic region and eloquent cortical areas.

The present study revealed that the FSIQ, VIQ and PIQ scores of group 2 after surgery were consistent with mild cognitive impairment. Cognitive impairments resulting from epilepsy are described in several studies [30-33]. In the study by Amano et al [34] severe mental retardation was found in 72.2% of epileptic patients, of whom, 61.5% had intractable epilepsy. According to Hermann et al. [2], more diffuse cognitive impairment is related to the neurobiological effects of the early onset of seizures, long periods of exposure to seizures, and prolonged use of antiepileptic drugs. Moreover, these losses can be cumulative over time, thus it is important to perform early intervention to reduce or minimize this cognitive effect.

Our data indicated that there the mean scores of FSIQ and VIQ were maintained in group 1 after surgery. Gillian et al [29] conducted a study with a group of children with epilepsy in which 76% of them had seizure control after surgery but presented no significant improvement in IQ considering pre and post surgery measurements. In agreement with these findings Mukahira et al [35] observed that there was a subjective improvement in behavior, and that this factor could be related to a better quality of life for these patients. Another authors analyzed a group of surgically treated children with epilepsy and found that 82% of them remained stable, using a behavioral development scale, after surgery and that 22% of the patients showed a significant improvement in IQ when they were seizure free and claim that cognitive gains can be accumulated over time and, sometimes, may not be clear immediately after surgery [23].

In the present study a significant improvement in PIQ in group 1 after surgery was found, suggesting an impact of recurrent seizures on execution ability in patients with epilepsy. The deficit in PIQ performance in children with epilepsy can be due to the pharmacotherapy, the recurrent seizures and the possibility of brain damage. These factors can cause various cognitive deficits, such as deficits in information processing speed [36]. The decrease in speed of information processing can cause lower PIQ scores since the majority of tasks are time-dependent, therefore seizure control after surgery could justify the improvement in PIQ performance.

In the present study a significant worsening of VIQ in group 2 after surgery was observed. According to Modi et al [26] recurrent seizures cause a damaging psychosocial impact and these effected children are more likely to have a reduced quality of life. From the cognitive standpoint, social constraint may hinder the performance of some of the VIQ subtests such as vocabulary and information since they are dependent to crystallized intelligence.

This is based on consolidated knowledge acquired through educational and social experiences [37]. Children with recurrent seizures after epilepsy surgery continue to be socially isolated, making it difficult to acquire new knowledge and cultural scholars increasingly, hampering the performance in the subtests that depend on this type of learning.

A limitation of this study was that comparisons of the results of other neuropsychological tests such as memory, attention and executive functions before and after surgery were not possible. This occurred due to the cognitive limitations of children with epilepsy that prevented almost all of them to carry out all tests that compose neuropsychological battery. Nevertheless we believe that this study contributed to identify the cognitive improvements in PIQ in children with good seizure control after surgery (Engel I or II) and worsening of VIQ in children who had no satisfactory seizure control after surgery (Engel III or IV). According to Helmstaedter et al [8] patients who had significant seizure reduction or became seizure free and also had improved cognitive functions are considered 'double winners'. Moreover the patients can be considered 'double losers' when they have no significant reduction in seizure frequency after surgery and have maintenance or worsening of cognition after surgery.

We concluded that the intelligence of children with pharmacological refractory epilepsy depends on numerous clinical and psychosocial factors that are dependent and are intrinsically linked. In this way, epilepsy surgery in childhood may be a good alternative for seizure reduction or seizure control and also may provide a cognitive improvement leading to better cognitive outcome of these children.

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Impacto de la cirugía de la epilepsia infantil en el rendimiento intelectual

Introducción. La cirugía de la epilepsia podría ser una opción terapéutica muy prometedora para el control de las crisis en pacientes con crisis refractarias que no responden a la medicación. Otro factor importante a favor de la opción quirúrgica son los resultados cognitivos.

Objetivo. Investigar la correlación entre los resultados tanto de las crisis como cognitivos tras la cirugía para tratar la epilepsia en una población pediátrica.

Pacientes y métodos. Se evaluó de manera retrospectiva a un total de 59 pacientes pediátricos antes y al menos seis meses después de la cirugía mediante la tercera edición de la escala de inteligencia para niños de Wechsler (escala global, escala verbal y escala manipulativa). Se dividió a los pacientes en dos grupos en función de la presencia o ausencia de la mejoría del control de las crisis tras la cirugía. Los datos que se recogían de cada niño incluían: tipo de epilepsia, etiología, edad de comienzo de la epilepsia, duración de la epilepsia y frecuencia de las crisis.

Resultados. Al comparar los datos mediante un análisis multivariado de la varianza se observaron diferencias significativas en las escalas global, verbal y manipulativa preoperatorias (p = 0,01) con unos resultados mejores en el grupo con reducción de las crisis que en el grupo sin reducción de las crisis. El grupo con mejoría de las crisis consiguió una mejoría significativa en la escala manipulativa (p = 0,01) y el grupo sin mejoría de las crisis obtuvo un empeoramiento significativo en la escala verbal (p = 0,01).

Conclusiones. Nuestros resultados sugieren que el éxito de la cirugía para el tratamiento de la epilepsia en la infancia cuando se logra un control de las crisis podría conllevar también una mejoría en la escala manipulativa, mientras que la persistencia de las crisis podría empeorar la escala verbal.

Palabras clave. Cirugía. Crisis. Cognitivo. Epilepsia. Infantil. Inteligencia. Refractario.