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Intellectual functioning in pediatric patients with epilepsy: a comparison of medically controlled, medically uncontrolled and surgically controlled children

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Abstract

Objective: To compare the intellectual coefficient (IQ) of three groups of children with epilepsy: 1) medically controlled, 2) medically uncontrolled and 3) surgically controlled.

Methods: From December 2007 until July 2008, 98 pediatric patients were selected, with an age range between 6 and 12 years. Neuropsychological assessment included the Wechsler Intelligence Scale for Children – third edition (WISC-III). Results are related to epileptic syndrome, etiology of epilepsy, drug therapy, age at epilepsy onset and epilepsy duration.

Results: WISC scores were significantly better in the medically controlled group when compared to the medically uncontrolled group. The medically controlled group performed significantly better in the majority of the WISC subtests when compared to medically uncontrolled group: vocabulary, arithmetic, comprehension, digit span, picture completion, picture arrangement, and block design. A significantly higher number of idiopathic epilepsy and monotherapy cases was observed in the medically controlled group when compared to the medically uncontrolled group. Surgically controlled children had no significant differences in IQ performance when compared to medically controlled children.

Conclusions: Children with good seizure control have higher general, verbal and performed intelligence when compared to children with refractory epilepsy. These results may be influenced by clinical factors such as use of monotherapy, drug type and epileptic syndrome and etiology. Epilepsy surgery can have a positive impact on cognitive performance of children who were free of seizures after surgery.

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Introduction

Epilepsy is one of the most common neurological diseases in children.[1] Its correct treatment involves many issues beyond seizure control, including cognitive and social aspects.[2] It is fairly common that children with epilepsy have educational problems and cognitive deficits.[3] The cognitive problems of epileptic patients are multifactorial, including clinical and demographic factors such as: age of onset, frequency of seizures, type of seizure, cause of epilepsy, antiepileptic drugs and duration of epilepsy.[4] The heterogeneity of different types of epilepsy is one of the

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major obstacles to understanding the cognitive impairment of the epileptic syndrome. The impairment intensity caused by each isolated variable needs to be better established.[5]

Although the cognitive deficits may be influenced by these multiple factors, it seems that seizure frequency has a significant impact on their progression and may restrict children's academic skills and daily life activities.[6] Recurrent seizures can modify a wide range of cerebral processes during development that are essential for the correct formation and functioning of brain circuits.[7] Therefore, there is solid evidence that patients with intractable epilepsy have more diffuse and severe cognitive deficits than patients with good seizure control.[8] Cormack et al.[9] observed that 57% of children with intractable epilepsy are intellectually dysfunctional. In another retrospective study including comprehensive neuropsychological assessment of severe medically intractable patients with epilepsy for over 10 years, Thompson & Duncan[10] reported a decline in a range of cognitive functions. Furthermore, these same authors observed that periods of seizure remission were associated with better cognitive performance, thus showing the adverse impact of seizures on cognition.

Seizure remission can be obtained in approximately 70% of patients with epilepsy through the use of antiepileptic drugs.[11] Previous studies have indicated that even these well-controlled patients could have some cognitive impairment.[7,12] An important therapeutic option for the remaining 30% of patients with medically intractable epilepsy is epilepsy surgery, particularly among patients with focal seizures.[13] Although previous studies have already indicated that epilepsy surgery in children is as effective as in adults,[14] the ultimate impact of this procedure on cognitive functions requires further investigation. At present, there is a lack of comparative studies assessing children with medically intractable seizures, well-controlled seizures and post-surgical seizure-free children with epilepsy. The current study was conducted to compare the cognitive performance of these three groups of children with epilepsy: 1) medically controlled group; 2) medically uncontrolled group; and 3) surgically controlled group.

Methods

Patients

From December 2007 until July 2008, 98 pediatric patients were selected, with an age range between 6 and 12 years, and regularly followed-up at the Controlled Epilepsy Child Outpatient Clinic and Refractory Epilepsy Child Outpatient Clinic, at Hospital das Clínicas de Ribeirão Preto, Universidade de São Paulo, Brazil. All patients had a diagnosis of epilepsy. The study was approved by the Hospital Ethics Committee of the Hospital das Clínicas de Ribeirão Preto, Universidade de São Paulo, Brazil. Patients with severe visual, auditory or language deficits, severe psychiatric disorders, and severe mental deficiency that would prevent the understanding of the task were excluded.

All patients underwent clinical evaluation with a physician experienced in the area.

Demographic data included epileptic syndrome, etiology of epilepsy, drug therapy, age at epilepsy onset, and duration of epilepsy. The duration of epilepsy was assessed on individual basis for each group. For the surgically controlled group, it consisted of child's age at epilepsy surgery minus child's age at epilepsy onset. For the medically uncontrolled group, duration was given by child's age on the day of neuropsychological assessment minus child's age at epilepsy onset. Within the medically controlled group, two subgroups were established: for children who had been completely seizure-free for at least two years, duration of epilepsy was determined by child's age at the last seizure minus child's age at epilepsy onset; for children who had not been completely seizure-free for at least two years, duration was calculated as child's age on the day of neuropsychological assessment minus child's age at epilepsy onset. Epileptic syndrome classification was carried out according to Engel,[15] and probable etiology was defined considering magnetic resonance imaging findings.

In this study, the medically controlled group consisted of patients who had, on antiepileptic medication, experienced 0-4 seizures in the last two years. The medically uncontrolled group consisted of children experiencing at least one seizure per month, despite an optimal antiepileptic drug regimen, and the surgically controlled group referred to patients who were classified as Engel Class I after epilepsy surgery for, at least six months. The Engel Class I classification refers to patients who are seizure-free, or have only non-disabling simple partial seizures, or an occasional generalized convulsion associated to antiepileptic drug withdrawal.[15]

A patient's educational background was classified as low if patient's educational level was below that which would be expected for their age because of abandonment, repetition or enrollment at a special education school. If patients were in the educational level expected for their age, their educational background was classified as average.

Cognitive assessment

All children had a single neuropsychological assessment of about two hours after a routine medical examination at the Controlled Epilepsy Child Outpatient Clinic or the Refractory Epilepsy Child Outpatient Clinic, at Hospital das Clínicas de Ribeirão Preto, Universidade de São Paulo, Brazil. All assessments were made by the same psychologist (CSO), experienced in the area.

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. IQ is divided into verbal IQ and performance IQ and comprises a total of 12 subtests. Verbal IQ evaluates one's ability to express and receive verbal and abstract reasoning, and is culturally biased. The Verbal IQ test is made up of six subtests: Information, Similarities, Arithmetic, Vocabulary, Comprehension and Digit span. The Performance IQ assesses capacity planning, integration and perceptual processing speed, and most activities require measuring the time spent to complete them. Performance IQ consists of seven subtests: Picture completion, Coding, Picture arrangement, Block design, Object assembly, Symbol search (additional) and Mazes (additional).

The score is found by obtaining the raw score of each subtest and converting it into a score according to the age of the child; this score is, in turn, converted into an IQ value. Level of intelligence was classified as superior range (IQ score ≥ 110), normal range (IQ scores of 90-109), inferior range (IQ scores of 80-89), borderline (IQ scores of 70-79) and mentally challenged (IQ ≤ 69), according to the rules of the test manual.

The weighted scores of subtests were classified according to the percentile obtained in accordance with the norms of neuropsychological tests[16]: very superior range (96-99 percentile), superior range (85-95 percentile), bright normal range (64-84 percentile), normal range (26-63 percentile), dull normal range (10-25 percentile), low range (< 10th percentile). Based on this classification, a categorical division of the subtests was applied, in which they were classified on a two level scale: satisfactory performance, when the weighted percentile scores were greater than or equal to 26; or unsatisfactory performance when the weighted percentile scores were less than 26.

Data analysis

Demographic categorical variables were evaluated using the chi-square test. Numeric variables were analyzed using the independent samples *t* test. All statistical analysis was performed using SPSS, version 13.0. The results were considered statistically significant when $p < 0.05$.

Results

Clinical data, demographic data and cognitive characteristics of the three groups are summarized in Table 1. There were 36 (36.7%) patients in the medically controlled group, 24 (24.4%) in the surgically controlled group and 38 (38.8%) in the medically uncontrolled group. The mean age at neuropsychological evaluation was significantly low ($p = 0.03$) in the medically controlled group (mean = 9.18, SD = 1.9) when compared to the surgically controlled group (mean = 10.32, SD = 1.8). The groups did not differ significantly in terms of gender, epilepsy onset, epilepsy duration, and educational level (Table 1). Considering the number of antiepileptic drugs, the medically controlled group had a higher statistically significant number of patients using monotherapy than the surgically controlled and medically uncontrolled groups ($p = 0.001$). Regarding specific antiepileptic drugs, no significant difference was observed in the groups in relation to the use of carbamazepine. The use of valproate was significantly higher in the medically controlled group when compared to the surgically controlled group ($p = 0.02$). The use of benzodiazepines was significantly higher in the surgically controlled and medically uncontrolled groups in relation to the medically controlled group ($p = 0.001$). There was a higher statistically significant use of others drugs in the surgically controlled group ($p = 0.006$) and the medically uncontrolled group ($p = 0.004$) in relation to the medically controlled group.

Regarding epileptic syndrome, the medically controlled group had a higher statistically significant number of cases of idiopathic epilepsies than the surgically controlled and medically uncontrolled groups ($p = 0.0001$). Probably symptomatic focal epilepsies were statistically more frequent in the medically uncontrolled group ($p = 0.0001$) and symptomatic focal epilepsies were more frequent in the surgically controlled group ($p = 0.0001$).

According to magnetic resonance imaging, a large number of probable etiologies were recognized in this study (Table 1). For patients in the medically controlled group, findings included atrophy, cerebral ischemia, cortical dysplasia and mesial temporal sclerosis. For the surgically controlled group, findings included atrophy, cavernous angioma, cerebral ischemia, cortical dysplasia, mesial temporal sclerosis, tuberous sclerosis and benign tumors. The magnetic resonance images of the uncontrolled group revealed atrophy, arachnoid cysts, cerebral ischemia, cortical dysplasia, mesial temporal sclerosis, periventricular leukomalacia and Rasmussen encephalitis. Brain abnormalities were found in 21/36 of the medically controlled patients and in 18/38 of the medically uncontrolled patients. These data were statistically significant when compared to the surgically controlled group ($p = 0.0001$). Brain imaging was not carried out for six patients, five within the medically controlled group, all of them with benign epilepsies and one patient with probably symptomatic focal epilepsy.

The mean IQ was significantly higher in the medically controlled group when compared to the medically uncontrolled group ($p = 0.001$). The mean verbal IQ and the mean performance IQ were significantly higher in the medically controlled group when compared to the medically uncontrolled group ($p = 0.02$). There were no significant differences between the medically controlled group and the surgically controlled group regarding general IQ, verbal IQ and performance IQ (Table 1).

A summary of the performance in the WISC-III subtests by the three groups is shown in Table 2. Performance in

WISC-III subtests was classified according the percentile obtained in each of the subtests and subdivided into two groups: satisfactory performance (percentile greater than or equal to 26) and unsatisfactory performance (percentile less than 26). The medically controlled group showed significantly better performance in the following subtests: Vocabulary (p = 0.04), Arithmetic (p = 0.002), Comprehension (p = 0.002), Picture Completion (p = 0.02), Digit Span (p = 0.002), Picture Arrangement (p = 0.009) and Block Design (p = 0.01) when compared to the medically uncontrolled group. The performance of the medically controlled group was significantly better in the Digit Span subtest when compared to the surgically controlled group (p = 0.002). The results also indicated that no statistically significant difference existed between the medically controlled group and the surgically controlled group regarding performance in the other subtests.

Discussion

Cognitive impairment in children with epilepsy can present different patterns and severities depending on numerous factors involved in this syndrome, such as etiological variability, different types of seizures, age at onset, duration of epilepsy, therapeutic regimen and seizure frequency. Our study compared the cognitive performance

Table 1 - Clinical, demographic and cognitive characteristics of the three patient groups

	Medically controlled (n = 36)	Surgically controlled (n = 24)	Medically uncontrolled (n = 38)	p1	p2
Gender (male/female)	18/18	13/11	20/18	0.80	0.82
Age at neuropsychology evaluation (years); mean ± SD	9.18±1.9	10.32±1.8	9.23±1.59	0.03	0.90
Epilepsy onset (months); mean ± SD	44.67±27.98	37.75±35.35	37.21±24.71	0.40	0.23
Epilepsy duration (months); mean ± SD	61.92±32.16	71.00±40.75	73.24±26.43	0.34	0.10
Etiology					
Atrophy	2	–	9	0.51	0.009
Arachnoid cyst	–	–	3	1	0.28
Cavernous angioma	–	1	–	0.40	0.38
Cerebral ischemia	2	2	1	1	1
Cortical dysplasia	1	5	2	0.03	0.09
Mesial temporal sclerosis	5	7	2	0.19	0.02
Normal	21	–	18	0.0001	0.0001
Periventricular leukomalacia	–	–	1	1	1
Rasmussen encephalitis	–	–	1	1	1
Tuberous sclerosis	–	2	–	1	0.14
Tumor (benign)	–	7	–	0.0009	0.0007
Not done	5	–	1	0.08	1
Epileptic syndrome					
Idiopathic	23	–	–	0.0001	1
Focal probable symptomatic	3	–	18	0.27	0.0001
Focal symptomatic	10	24	20	0.0001	0.0001
Number of antiepileptic drugs				< 0.001	< 0.001
Monotherapy	34	07	13		
Polytherapy	02	17	25		
Antiepileptic drugs					
Carbamazepine	22	19	20	0.14	0.46
Valproate	10	01	14	0.02	0.40
Benzodiazepines	1	13	17	0.001	0.001
Others	5	11	17	0.006	0.004
Educational level				0.07	0.84
Average	30	15	31		
Low	6	9	7		
IQ; mean ± SD	89.58±19.12	80.08±23.69	73.92±20.35	0.09	0.001
VIQ; mean ± SD	90.36±16.90	82.54±21.93	76.81±18.95	0.12	0.002
PIQ; mean ± SD	90.28±21.05	80.00±28.15	74.58±21.03	0.11	0.002

IQ = intellectual coefficient; p1 = medically controlled X surgically controlled; p2 = medically controlled X medically uncontrolled; PIQ = performance IQ; SD = standard deviation; VIQ = verbal IQ.

Table 2 - WISC-III subtests performance classification among the three groups: medically controlled, surgically controlled and medically uncontrolled

	Medically controlled (n = 36)	Surgically controlled (n = 24)	Medically uncontrolled (n = 38)	p1	p2
VIQ					
Information					
Satisfactory	12	08	05		
Unsatisfactory	24	16	32	1.00	0.08
Vocabulary					
Satisfactory	22	10	14		
Unsatisfactory	14	14	24	0.14	0.04
Arithmetic					
Satisfactory	21	11	09		
Unsatisfactory	15	13	29	0.34	0.002
Comprehension					
Satisfactory	25	12	13		
Unsatisfactory	11	12	25	0.13	0.002
Similarities					
Satisfactory	13	11	07		
Unsatisfactory	23	13	31	0.45	0.09
Digit span					
Satisfactory	21	05	07		
Unsatisfactory	15	19	31	0.002	0.002
PIQ					
Picture completion					
Satisfactory	21	15	12		
Unsatisfactory	15	09	26	0.75	0.02
Picture arrangement					
Satisfactory	13	06	04		
Unsatisfactory	23	18	34	0.36	0.009
Block design					
Satisfactory	20	08	10		
Unsatisfactory	16	16	28	0.09	0.01
Object assembly					
Satisfactory	17	09	10		
Unsatisfactory	19	15	28	0.46	0.06

p1 = medically controlled X surgically controlled; p2 = medically controlled X medically uncontrolled; PIQ = performance intellectual coefficient; Satisfactory performance = scores were weighted percentile greater than or equal to 26; Unsatisfactory performance = scores were weighted less than 25 percentile; VIQ = verbal intellectual coefficient; WISC-III = Wechsler Intelligence Scale for Children – third edition.

of children in medically controlled, medically uncontrolled and surgically controlled groups, considering clinical, social and demographic aspects.

In this study, idiopathic epilepsy was only found in the medically controlled group and the number of patients with probably symptomatic and symptomatic focal epilepsy was significantly higher in the surgically controlled and the medically uncontrolled groups when compared to the medically controlled group. Bhise et al.[17] reported cognitive impairments, mainly in attention tasks, in a group of children with idiopathic epilepsy, regardless of seizure type. Berg et al.[18] showed that impaired cognitive performance in children with symptomatic focal seizures is more specific and closely related to the most affected brain region.

Similar to etiologies of epilepsies in our patients, cortical dysplasia and benign tumors were more often seen in the surgically controlled group when compared to the medically controlled group. Atrophy, mesial temporal sclerosis and tumors were more common in the medically uncontrolled group when compared to the medically controlled group. Sarkar et al.[19] reported that, for their series of patients undergoing epilepsy surgery, the most

common etiologies found were mesial temporal sclerosis, followed by tumors and dysplasia. Most studies have confirmed these findings and report satisfactory seizure control after the surgical procedure.[14,20] On the other hand, cortical and hippocampal atrophy is often associated with medically uncontrolled epilepsy and more general cognitive deficits.[21]

Some authors have noted negative influences on cognitive processes with the use of polytherapy leading to high serum antiepileptic drug levels.[4,22] In our study, there were a significantly greater number of patients using polytherapy in the surgically controlled group and the medically uncontrolled group when compared to the medically controlled group.

Scientific evidence supports the hypothesis that the side effects caused by different antiepileptic drugs may contribute to the occurrence of cognitive deficits.[23] The results of our study have demonstrated that the majority of patients in the medically controlled group were on carbamazepine or valproate monotherapy. Moreover, the medically uncontrolled group and the surgically controlled group had a higher number of patients on polytherapy and using benzodiazepines, when compared to the medically controlled group. Meador et al.[24] reported that some antiepileptic drugs, like phenobarbital and benzodiazepines, seem more likely to lead to the development of cognitive deficits than carbamazepine, valproic acid and the newer antiepileptic drugs. According to these authors, patients on phenytoin, carbamazepine and valproic acid monotherapy in the therapeutic range did not show adverse cognitive effects in concentration, attention and psychomotor abilities when compared to healthy volunteers.

There is evidence supporting the idea that patients with refractory epilepsy have greater intellectual disabilities than medically controlled patients and the general population.[10] Our findings indicated that the mean IQ, verbal IQ and performance IQ were significantly higher in the medically controlled group when compared to the medically uncontrolled group. Engelberts et al.[7] have previously investigated cognitive performance in patients with chronic well-controlled epilepsy and healthy controls and did not observe deficits in selective attention, memory and executive functions when comparing both groups. Their findings contrasted with a study by Henkin et al.[25] who have shown that children with well controlled epilepsy (2.3 seizures per year) performed worse than healthy children in all cognitive domains, despite their normal IQ.

In this study, we did not find a significant difference in mean IQ, verbal IQ and performance IQ between the medically controlled group and the surgically controlled group. Some studies emphasize the positive relation between seizure control and maintenance or cognitive improvement after epilepsy surgery highlighting the importance of preventing the cumulative cognitive deficits caused by recurrent seizures in a brain that can still be in its development process.[26,27]

Results indicated that the medically controlled group had significantly better performance in vocabulary and comprehension subtests when compared to the medically uncontrolled group. Both the subtests are part of verbal IQ and involve the capacity of abstraction, episodic memory and knowledge acquired through cultural issues, closely related to crystallized intelligence. Worse performance in the medically uncontrolled group seemed to be due to social issues, as epilepsy often leads to a more limited social and cultural life due to the limitations imposed by a disease with such a high frequency of seizures.[28]

In the current study, no differences in performance between the three groups were found in the similarities subtest. The majority of patients in the three groups showed unsatisfactory performance in the similarities subtest. According to Simões,[16] the similarities subtest requires the examination of the abstraction ability and the establishment of logical relations, skills that are difficult for any child who presents even a slight IQ deficit.

This study found that the medically controlled group had significantly satisfactory performance in the digit span subtest in relation to the medically uncontrolled and surgically controlled groups. The digit span subtest is a task of short term auditory memory, simple verbal expression and working memory. Although the effect of recurrent seizures on these abilities is not completely clear, some evidence has been reported indicating a correlation between high seizure frequency and impairment in these functions. This is probably because these functions require attention focus, an ability often impaired in children with epilepsy, particularly in those undergoing polytherapy. It was also found that the medically controlled group had significant satisfactory performance in the block design and picture arrangement subtests when compared to the medically uncontrolled group. Poor performance by this group could be due to recurrent seizures and polytherapy. These factors could affect the speed of information processing, an essential skill for good performance in both subtests due to their time-dependent nature.

In spite of performing a single neuropsychological assessment per child with epilepsy, a correction for time with controlled seizures could not be performed because some patients of the medically controlled group presented up to four seizures in period of the last two years. Another limitation refers to the small number of patients in each group, which prevented other classifications of epilepsy syndrome considering the multifactorial aspects and could influence cognition.

Nevertheless, we believe this study contributes to demonstrating that children with good seizure control have higher general, verbal and performed intelligence when compared to children with refractory epilepsy. These

results may be influenced by clinical factors such as use of monotherapy, drug type and epileptic syndrome and etiology. Additionally, it seems that epilepsy surgery can have a positive impact on cognitive performance of children who became seizure-free. Although this subject is widely discussed in the international literature, it appears that few Brazilian studies have carried out these comparisons using tests adapted to the population.

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