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Cognitive outcome after epilepsy surgery in children: A controlled longitudinal study

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ABSTRACT

Objective: To analyze the determinants of cognitive outcome two years after surgery for drug-resistant epilepsy in a cohort of 31 children when compared to a control group of 14 surgical candidates who had yet to undergo surgery two years after the first neuropsychological assessment.
Methods: Controlled longitudinal study including three evaluations of IQ (Intelligence Quotient) scores or GDQ (General Developmental Quotient) for each group depending on the patient's age: prior to surgery (T0), one year (T1) and two years (T2) after surgery for the surgical group; baseline (T0) and one year (T1) and 2 years (T2) after the first evaluation for the control-group. At follow-up, 25 children (80%) of the surgical group were seizure free, while seizure outcome was unsatisfactory in the remaining six (20%).
To analyze language, visuomotor skills, memory, reading, visual attention, and behavior, we selected 11 school age children in the surgical group and nine controls. We reported performance prior to (T0) and one year after surgery (T1).
Results: There was a significant correlation between earlier age at seizure onset and lower IQ/GDQ at T0 ($r = 0.39$; $p = 0.03$) in the overall cohort. IQ/GDQ scores did not significantly differ between the surgical and control groups when analyzed at T0 and T2. However, they evolved differently with an improved developmental trajectory becoming identifiable only in the surgical group ($F_{1,31} = 5.33$ $p = 0.028$; $\eta^2 = 0.15$). There was also a significant increase of forward digit span ($Z = 2.33$; $p = 0.02$) and Rey recall scores ($Z = 1.97$; $p = 0.049$) in the surgical school age subgroup at T1 versus T0.
Significance: We identified significantly different developmental trajectories in operated versus non- operated children with improved IQ/GDQ scores in operated children only. We also observed a significant increase of digit span scores and Rey recall scores a year after surgery. Further studies including larger samples with longer follow-ups are needed to confirm these preliminary findings.

1. Introduction

Epilepsy puts children at higher risk for cognitive, behavioral, and psychosocial impairment, compared to the population at large [1,2]. Several studies have demonstrated a high incidence of developmental delay in children with early onset drug-resistant epilepsy, high frequency of seizures, long disease duration, and chronic polytherapy [1–3]. The prognosis of childhood epilepsy is strictly linked to intractability [4,5]. A critical change in treating children with medically intractable epilepsy was the introduction of surgery. The primary goal of surgery in children is to achieve seizure control; however, the potentially added benefit for improved neurodevelopment [4] is very encouraging.

Previous studies have attempted to identify pre-surgical, surgical or post-surgical variables associated with favorable cognitive and behavioral outcomes in children. Yet the multiple variables, which might be influential, are difficult to uncouple [6].

In particular, surgery at an early age with a consequent shorter duration of epilepsy has been associated with higher cognitive scores after hemispheric disconnections [7] and lobar resections [8,9]. The extent of epileptogenic lesions is an additional factor influencing cognitive development. Children with multilobar lesions are more likely to exhibit global deficits when compared to those with frontal or temporal lesions [2].

Regarding post-surgical variables some authors were unable to find any significant correlation between postoperative seizure outcome and cognitive outcome [2,10,11], while others did [9,12].

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Additionally, studies evaluating possible changes of neuropsychological variables after surgery showed conflicting results. Vulnerability of verbal memory function to left temporal lobe resection has been reported [13,14], but has not been confirmed in other series [15,16].

Overall, stability or an improvement was reported more often than a decline in verbal and visual memory after temporal lobectomy [17]. Visual memory may be at risk after extra-temporal surgery in children according to some authors [18] while others reported no change or minor improvements [19,20]. In a cohort of 20 patients, Lendt et al., 1999 [21] documented no change in verbal fluency after surgery while others documented a decline in lexical retrieval after temporal lobe resection suggesting a functional organization comparable to adults [22]. No significant changes in reading achievements were found over the short and long term after epilepsy surgery [23–26].

Altogether, small sample size and heterogeneous etiologies preclude drawing firm conclusions on cognitive and behavioral changes after epilepsy surgery from the available studies [28]. The primary cause of the lack of conclusive evidence on postoperative cognitive outcome in children could possibly be due to flaws in the methodology, with lack of adequate controls being a major weakness in most epilepsy surgery studies. The controls in certain studies were comparable to the surgical group only in terms of age at onset of epilepsy and duration of follow-up; however not all patients in the control group were eligible for surgery [11,28] nor were they adequately described [28]. In other studies a healthy control cohort was recruited from regular schools [6].

In this study we analyzed the possible determinants of cognitive functioning two years after surgical treatment for drug-resistant seizures in a cohort of 31 children. Based on available literature, we identified age at seizure onset, seizure frequency, age at surgery, etiology and extent of the lesion as possible variables influencing post-surgical cognitive outcome [6].

We also evaluated a control group of 14 children with drug-resistant seizures potentially eligible for surgery, who, two years following the first neuropsychological evaluation, had not yet undergone surgery.

Finally, we analyzed whether the IQ/GDQ and specific measures of reading, verbal/visual-spatial memory, naming and visual attention of children in the surgical group evolve differently from those of the control group.

2. Material and methods

2.1. Participants

We studied 31 children (20 males/11 females; mean age at surgery 8.73, standard deviation [SD] 4.33; mean age of seizure onset 4.41, SD 3.66) undergoing surgical treatment at the Meyer Children's Hospital between 2007 and 2011 ('surgical group'). Inclusion criteria for the surgical group were: a) drug-resistant seizures; b) at least two years follow-up post surgery; c) cognitive evaluations at one year and two years after surgery; d) no previous neurosurgery; e) cognitive skills and behavioral profile of the child allowing reliable testing. We used as a control group 14 children ('control group') with drug-resistant seizures (9 females/5 males, mean age at first evaluation 10.26, SD 3.3, mean age of seizure onset 4.89, SD 3.44) who were potential surgical candidates and were tested according to the same time scale of the study group, but had not been operated on two years after the first neuropsychological evaluation. Inclusion criteria for the control group were: a) drug-resistant seizures; b) at least two years of neuropsychological follow-up after surgery; c) no previous epilepsy surgery at the time of the second neuropsychological assessment; d) no previous brain surgery; e) cognitive skills and behavioral profile of the child allowing reliable testing.

We excluded nine operated patients from the analysis, as we could not complete the neuropsychological testing at T0 due to very severe behavioral disorders or refusal to complete the assessment. Three other patients were excluded as they underwent palliative surgery (callosotomy).

Children in the control group were also eligible for ablative surgery but were not operated on at T2 for different reasons, including parental requests to try all available drugs before considering surgery, parental refusal of surgery or a prolonged waiting period for surgery due to additional non-invasive and invasive tests to assess the link between the epileptogenic zone and eloquent areas.

The ethical committee of the Children's Hospital Meyer approved the study. Informed consent forms were obtained for all patients.

2.2. Procedures

We performed three evaluations of IQ/GDQ scores for each group: prior to surgery (T0), one (T1) and two years (T2) after surgery for the surgical group and at baseline (T0) and one (T1) and two (T2) years after the first evaluation for the control group. Clinical features, IQ/GDQ scores and surgical variables of the surgical group are summarized in Table 1; clinical and IQ/GDQ data of the control group are summarized in Table 2. The significant improvements or worsening of IQ/GDQ scores (change in IQ greater than 7 points) were defined by excluding the practical effect of test-retest and for higher scores to differences of average stability coefficients across all ages, as reported in technical reference manuals of cognitive scales [29,30].

At T2, statistical analyses were performed only in the 37 children (23 surgical children, 14 control children) in whom a complete and reliable assessment was available (mean of missing IQ/GDQ scores at T0: 89.12, SD: 15.36, range: 57–105; mean of completed IQ/GDQ scores at T0: 74.34, SD: 19.96, range: 45–109).

Incompleteness of cognitive and neuropsychological measures was determined by several factors such as, for example, poor cooperation or clinical constraints. Some children in the surgical group underwent neuropsychological assessments in other settings (i.e. rehabilitation clinics), especially if they lived in remote areas from the study center. The analysis did not include the results of these neuropsychological assessments in order to maintain the score's reliability.

To analyze how specific neuropsychological variables evolved i.e. language, visuomotor skills, memory, reading, visual attention and behavior, we selected 11 school age children (mean age at T0: 11.89, SD: 2.30; range: 9.25–15.3) in the surgical group ('surgical subgroup') and nine (mean age at T0: 12.08, SD: 2.99; range: 8.25–15.5) in the control group ('control subgroup'). All children within the subgroups were evaluated at T0 and T1 (but not at T2) in a 2×2 study. Subgroups were made up of school age children in order to minimize age influence and maximize comparability between the groups. Clinical variables and cognitive features of these 20 subjects are summarized in Tables 1 and 2.

General cognitive abilities were tested using GMDS-ER [31] (Griffiths Mental Developmental Scales-Extended Revised) and Italian versions of the Wechsler Scales [32,33]. Non-verbal function was measured with the Leiter-r Scale [34]. Since a relatively rare population and its peculiar clinical features do not permit maximum homogeneity in a cognitive scale, we used a single psychometric measure (IQ/General Developmental Quotient). We evaluated language function using tasks of naming and fluency and assessed the ability to name drawings of objects using the Boston Naming Test [35]. To assess verbal and semantic fluency we used the word fluency test [36].

We used two tasks taken from Wechsler scales (digit span forward and digit span backwards) as part of the assessment of verbal and working memory. Incidental semantic memory was assessed presenting 20 animals names. Each child was requested to name the color of the animal but was not instructed to remember the animal itself. At the end of the incidental learning phase children were asked to report as many animals as they could.

We used two tasks (word list reading and non-word list reading) taken from Battery for the evaluation of Dyslexia and Dysorthographia [37] to assess reading abilities.

We used the Rey Figure [38] to assess drawing abilities in copying and visual memory.