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Predictors of language skills in the long term after pediatric epilepsy surgery

Klajdi Puka [a], Mary Lou Smith [a,b,c,*]

[a] Department of Psychology, The Hospital for Sick Children, Toronto, Canada
[b] Department of Psychology, University of Toronto Mississauga, Mississauga, Canada
[c] Neurosciences and Mental Health Program, The Hospital for Sick Children, Toronto, Canada

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ABSTRACT

Objective: The objective of this study was to evaluate language skills in a heterogeneous cohort of patients who underwent or were considered for epilepsy surgery in childhood 4–11 years earlier. The few existing studies that have evaluated cognitive function in the long term after surgery have examined intelligence and memory.
Method: Participants were 97 patients, of whom 61 underwent surgery. They completed standardized tests of picture naming, vocabulary, letter fluency, semantic fluency and intelligence at baseline and, on average, 7 years later.
Results: Among all patient groups, scores across language tasks were similar at baseline and follow-up. Language skills were largely independent of surgical status but were associated with seizure control. Seizure freedom and/or a longer proportion of life without seizures were associated with higher scores across all language tasks at follow-up. However, few patients showed meaningful improvements or deterioration at the individual level. Older age at epilepsy onset, higher IQ, and higher baseline scores were associated with higher follow-up scores on all language tasks. Localization and lateralization of epileptogenic foci and language lateralization were associated with higher scores on some language tasks at follow-up. Most of these variables were also predictive of change in scores over time on some of the language tasks.
Significance: Language skills largely remained similar at baseline and follow-up. Seizure freedom was associated with a modest advantage at the group level, and no significant change at the individual level, suggesting an abnormal neural substrate or epileptic activity prior to seizure control may hinder the long-term capacity for improvement, even in the absence of seizure activity.

1. Introduction

For children with drug-resistant epilepsy surgery is one of the few treatment options with the potential to eliminate or significantly reduce seizures and thereby possibly lead to improved cognitive functioning [1]. The assessment of cognitive functioning following pediatric epilepsy surgery has primarily focused on short-term outcomes (usually one to two years after surgery), and for the most part, these studies have found similar functioning at baseline and follow-up. However, a minority of studies have found improvements or deterioration in the short term following surgery (for review see Smith et al. [2]); the differences in results across studies are likely due to the diverse patient samples and the short postoperative period in which improvements could occur. The few studies that have examined long-term outcomes have reported on intellectual functioning [1,3–5], memory [5,6], and academic skills [7]. Other aspects of cognition, including language, have yet to be sufficiently addressed in the long term. It cannot be assumed that intelligence, memory, and language will exhibit similar outcomes over the long term; even different facets of memory exhibit different outcomes following surgery [6,8]. Therefore, there is a need for long-term outcome studies evaluating a range of cognitive domains following epilepsy surgery in childhood, and the present study focused on this gap in the outcome literature by investigating a variety of language skills.

Studies evaluating language after relatively short-term follow-up intervals largely find similar scores at baseline and follow-up and no advantage associated with surgical status or seizure status [9]. Very few studies have evaluated longer-term outcomes. One study followed patients with frontal (n = 12) and temporal lobe (n = 12) resections for a mean of 2.83 years (range: 14 months to 7 years) after surgery [10]. In this report, there was a suggestion of improved picture-naming scores in some patients with temporal lobe resections [10]; however, this finding should be interpreted cautiously because of the small sample size and the large range of time over which outcomes were assessed. In addition, these findings contrast with those of some short-term outcome studies which have either found no significant differences over time [11] or declines following left temporal lobectomies [12]. Vocabulary has also been evaluated in the long term (a minimum of two years after surgery), with improvements over time observed among

* Corresponding author at: Department of Psychology, University of Toronto Mississauga, 3359 Mississauga Road, Mississauga ON L5L 1C6, Canada. Fax: +1 905 569 4326.
E-mail address: marylou.smith@utoronto.ca (M.L. Smith).

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all patient groups and the lowest performance observed among surgical patients with uncontrolled seizures [5].

Identifying the long-term cognitive outcomes of pediatric epilepsy surgery is essential in providing physicians, families, and patients with prognostic indicators and allowing for informed decision-making in pursuing epilepsy surgery. This information may further prepare the patient and family in coping with potential outcomes and may provide realistic expectations and timelines following surgery. We investigated the long-term outcome of a cohort of patients, which was heterogeneous in terms of epileptogenic foci, who underwent evaluations to determine surgical candidacy in childhood, some of whom subsequently had surgery. We followed patients who had undergone preoperative neuropsychological testing and compared language functioning at the time of surgical evaluation and four to eleven years after. Comparing the outcomes of patients who underwent surgery with those who continued medication management allows for the examination of the possible causes of change following epilepsy surgery, whether it is a result of ongoing development of the child, seizure control, or the surgical intervention itself. Past studies have shown that surgical and nonsurgical patients with medically intractable epilepsy do not significantly differ in multiple cognitive and psychosocial domains at baseline [13]. Language was evaluated using measures of picture naming, vocabulary, letter fluency, and semantic (animal) fluency. We evaluated language skills over time at the group and individual levels and evaluated epilepsy-related predictors of language skills at long-term follow-up.

2. Methods

2.1. Participants and study design

All patients underwent evaluations to determine surgical candidacy between 2002 and 2009 at the Hospital for Sick Children in Toronto, Ontario, Canada. Prior to surgical evaluation, all patients had been unable to achieve adequate seizure control from at least two trials of antiepileptic drugs (AEDs). Patients who subsequently underwent surgery formed our surgical group; these patients had a clear unilateral seizure focus which did not involve the eloquent cortex. Exclusion criteria for the surgical group included hemispherectomy or corpus callosotomy procedures as these individuals tend to have marked neurological impairment, and these procedures may be performed for reasons other than complete seizure control, such as alleviating drop attacks. Patients who declined surgery or were not surgical candidates, formed our nonsurgical comparison group; patients with epilepsy syndromes that would not normally be treated with surgery or epilepsy associated with neurodegenerative disorders were excluded.

As part of routine clinical care, all patients had completed a neuropsychological assessment during the evaluation for surgical candidacy (baseline assessment); these data were extracted from patients' clinical records. Therefore, the choice of measures used at follow-up was not theoretically based but was determined by the availability of the clinical baseline measures. For a variety of reasons (e.g., time constraints, poor cooperation, or age at baseline), some patients had not completed all language tests at baseline; for this reason, data were not available for all participants on all tasks.

Four to eleven years after surgery or after the baseline assessment for nonsurgical patients, patients were contacted and offered an abbreviated neuropsychological assessment as part of a larger project examining various cognitive, affective, behavioral, and quality-of-life outcomes following surgery [1,7,14–17]. At that time, 152 individuals (92 surgical) met criteria for participation, 17 (6 surgical) could not be contacted, 2 (1 surgical) were deceased, and 36 (24 surgical) declined or were unable to participate because of distance. In sum, 97 individuals (61 surgical, 36 nonsurgical) completed the neuropsychological assessment at long-term follow-up. Participants were classified not only in terms of their surgical status but also in terms of whether or not their seizures had been controlled in the 12 months prior to their participation in the study. When possible, patients who did not wish to participate were asked whether they had had seizures in the preceding year and if they were taking any AEDs.

Patient- and epilepsy-related variables were obtained from patients' medical charts, including pathology among surgical patients and type of surgical resection. As part of the presurgical evaluation, laterality of speech representation was determined by functional MRI, the intracarotid amobarbital procedure, etomidate speech and memory (eSAM) test, or magnetoencephalography in 69 patients; of the 28 patients who did not undergo any of these procedures, 22 were right-handed. Thirty-four patients had left hemisphere (typical) speech representation, 21 had bilateral representation (of which 14, 5 and 2 had a left, right and bilateral epileptogenic foci, respectively), and 14 had right hemisphere representation (of which 10, 3, and 1 had a left, right and bilateral epileptogenic foci, respectively). We evaluated the impact of typical (left hemisphere) vs. atypical (right hemisphere or bilateral) language representation. Additionally, we evaluated the impact of side of seizure onset with respect to whether it was in the dominant or nondominant language hemisphere. In the latter categorization, patients with a bilateral seizure focus ($n = 5$) were excluded, and patients with bilateral language representation were included in the "dominant" group.

The study was approved by the Research Ethics Board of the Hospital for Sick Children, and informed consent/assent was obtained from patients and/or their parents. All cognitive assessments were conducted by experienced psychometricians or trained research assistants. Study data were managed and stored using REDCap [18].

2.2. Neuropsychological assessment

At each assessment, language was measured using 1) picture naming with the Boston Naming Test [19], where the patient is asked to name line drawings of objects, 2) the vocabulary subtest of the Wechsler Intelligence scales [20,21], where the patient is asked to verbally define single words, and 3) letter and semantic (animal) fluency, where the patient is given 60 s to name as many words as possible that begin with a given letter (three trials with the letters F, A, S) and name as many animals as possible, respectively. Normative data for the Boston Naming Test were drawn from Halperin et al. [22] for children ≤14 years of age and from Martielli and Blackburn [23] for participants >14 years. Normative data for letter fluency were taken from Delis et al. [24]. Normative data for semantic (animal) fluency for children ≤15 years of age were taken from Halperin et al. [22] and from Tombaugh et al. [25] for participants >15 years. The results of the picture naming, letter fluency and semantic fluency tests are presented as z-scores (mean: 0; SD: 1). The vocabulary subtest generates scaled scores (mean: 10; SD: 3); however, to present a common metric across all tasks, these scores were converted to z-scores. Intelligence Quotient was assessed using the Wechsler Intelligence Scales [20,21].

2.3. Statistical analyses

Demographic and epilepsy-related variables among the four patient subgroups were compared using 2 (surgical status) × 2 (seizure status) analyses of variance (ANOVA), χ^2 or Fisher's exact test, as appropriate. Change from baseline to follow-up at the group level was evaluated using 2 (surgical status) × 2 (seizure status) × 2 (time) mixed measures ANOVA. We also evaluated change at the individual level to identify the proportion of patients that showed a clinically meaningful change from baseline to follow-up, identified by a change of at least one standard deviation, a criterion used previously in studies evaluating cognition after pediatric epilepsy surgery [26]. Potential differences relating to surgical status or seizure status at the individual level were evaluated using χ^2 or Fisher's exact test, as appropriate. Next, we evaluated epilepsy-related predictors of change scores (baseline scores subtracted from follow-up scores) and of follow-up scores. Since there is a lack of long-term