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Long-term follow-up after epilepsy surgery in infancy and early childhood – A prospective population based observational study

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ABSTRACT

Purpose: To describe 2-year and long-term outcomes (five or ten years) after resective epilepsy surgery in children operated before the age of four years.
Methods: This prospective, population based, longitudinal study is based on data from the Swedish National Epilepsy Surgery Register 1995–2010. The following variables were analysed: seizure frequency, antiepileptic drug treatment (AED), neurological deficits, type of operation, histopathological diagnosis and perioperative complications.
Results: During the study period 47 children under four years had resective surgery. A majority had seizure onset within the first year of life, and the median age at surgery was two years and one month. Two thirds had neurodevelopmental abnormalities. Temporal lobe resection, frontal lobe resection and hemispherotomy predominated. A majority had malformations of cortical development. There was one major perioperative complication. At the 2-year follow-up, 21/47 children (45%) were seizure free, eight of whom were off medication. At the long-term follow-up, 16/32 (50%) were seizure-free and 11 of them off medication. Another ten (31%) had ≥75% reduction in seizure frequency. Fourteen children (44%) had sustained seizure freedom from surgery to the long-term follow-up.
Conclusion: This is the first prospective, population based, longitudinal study to show that a favourable seizure outcome is achievable in a majority of infants and young children undergoing resective epilepsy surgery and that the improvements are consistent over time. Many can also stop taking AEDs. The findings emphasise the importance of early referral to epilepsy surgery evaluation in cases of medically intractable epilepsy in infants and young children.

1. Introduction

Early resective surgery has emerged as an established treatment of selected children with severe intractable epilepsy starting during the first years of life. Having been regarded as an option of last resort associated with considerable risks of perioperative morbidity, resective procedures in infants and young children are now considered relatively safe due to advances in neurosurgery, anaesthesia and paediatric intensive care. Furthermore, modern neuroimaging and neurophysiological techniques permit better selection of suitable candidates for epilepsy surgery [1–3].

The primary goal of epilepsy surgery is freedom from seizures, if possible together with antiepileptic drug discontinuation. In addition to the obvious benefits of seizure relief, the case for early intervention largely rests upon the assumption that these often severely impaired children can achieve a better developmental trajectory if they are spared the harmful effects of

Abbreviations: AED, antiepileptic drug; FCD, focal cortical dysplasia; FLR, frontal lobe resection; MCD, malformations of cortical development; MLR, multilobe resection; MRI, magnetic resonance imaging; OLR, occipital lobe resection; PLR, parietal lobe resection; PMG, polymicrogyria; TLR, temporal lobe resection; TSC, tuberous sclerosis complex; VNS, vagus nerve stimulator.

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uncontrolled epileptic seizures and AED treatment during the crucial stages of brain development [4–9]. Moreover, postsurgical adverse neurological effects, typically verbal memory impairment after mesial temporal lobe surgery, are considered less prominent in younger patients due to brain plasticity [10].

There are consistent reports supporting that a favourable seizure outcome is achievable in a majority of infants and young children undergoing resective surgery; seizure freedom rates range from 48% to 73% [9,11–17]. However, longitudinal data on long-term results are scarce as previous studies are almost exclusively retrospective and cross-sectional.

The aims of this study are to describe aetiology, surgical procedures, perioperative complications and outcome in terms of seizure frequency and antiepileptic drug use in a prospective, population based, observational cohort of children under four years of age undergoing resective epilepsy surgery in Sweden between 1995 and 2010.

2. Methods

This study is an analysis of data from the Swedish National Epilepsy Surgery Register. Pre-, peri- and postoperative data on all patients undergoing epilepsy surgery have been reported to the register since 1990 and data reporting has been entirely prospective since 1995. Patients or, when applicable, their parents have given informed consent prior to the start of data collection. The 2-year follow-up is conducted at each epilepsy centre whereas the 5- and 10-year follow-up data are collected in structured telephone interviews. Five- and 10-year follow-ups have been conducted since 2005. Thus, in children operated on between 1995 and 1999, only 10-year follow-up data are available. When both 5- and 10-year follow-ups have been performed in one child (children operated on 2000–2003) only data from the 10-year follow-up were analysed. The study was approved by the Regional Board of Medical Ethics at the University of Gothenburg.

For this study, data related to the following variables were analysed: seizure frequency (mean number of monthly seizures during the year preceding surgery), AED treatment, neurological deficits or other clinical findings, type of surgical procedure, histopathological diagnosis and perioperative complications. Seizure outcome was graded as follows: seizure-free (without or with aura), ≥75% reduction, 50–74% reduction, 0–49% reduction in seizure frequency and increased seizure frequency after surgery. In case of persisting seizures, the change in mean monthly frequency was calculated based on data from the year before the follow-up.

In cases of reoperation, 2-year follow-up was conducted two years after the second operation. AED use is described as median number of AEDs used preoperatively and at follow-up. As to aetiologies, the children with malformations of cortical development were classified as having either FCD (type I, II or unspecified), PMG or hemimegalencephaly. Further categorisation was not possible. One of the reasons for this is that the classifications of FCD and hence the categorisations in the register have changed over time. Perioperative complications were graded as major (remaining sequelae >3 months after surgery) or minor (no sequelae 3 months after surgery), as earlier defined [18]. Long-term outcomes include data from the 5- or 10-year follow-ups.

2.1. Statistical methods

The results are described by means of frequencies and percentages. The number of children included in the study was considered too small to conduct any further analyses.

3. Results

Forty-seven children (23 males, 24 females) underwent a total of 55 operations in Sweden during the study period. Notably, in one region with 1.6 million inhabitants (out of 9.5 million) only one child under the age of four was operated. All 47 were followed up two years postoperatively. Thirty-two children completed long-term follow-up (Fig. 1).

Preoperative characteristics are presented in Table 1. Onset of epilepsy was during the first year of life in the majority. The median age at first operation was 2 years 1 month (range 2 months–4 years). The median duration of epilepsy was 1 year 3 months (range 1 month–3 years 11 months) and did not differ significantly between the periods 1995–1999, 2000–2004 and 2005–2010. The median preoperative seizure frequency was 150/month (range 3–3000) and most children were treated with more than one AED. In addition, several AEDs had previously been tried without success. Neurodevelopmental impairments were common, including motor deficits and intellectual disability. Fifteen (32%) had no neuroimpairment at the preoperative assessment.

Surgical procedures and aetiologies as determined by the results of the histopathological examinations are shown in Table 2. One type of operation is listed per child; in cases of reoperation, the second procedure is listed. The most common surgical procedures were temporal lobe resection (TLR) ($n = 12$), frontal lobe resection (FLR) ($n = 12$) and hemispherotomy ($n = 12$). Out of the eight reoperated children, four had completion of the initial hemispherotomy, one initially a multilobe resection (MLR) followed by hemispherotomy. Two children underwent extended FLR and one extended parietal lobe resection (PLR). In addition, one child underwent FLR as a reoperation after a first operation prior to the study period. The aetiology was classified as MCD in 29/47 children, making it the predominant aetiology. Unspecified FCD (11 children) was the most prevalent histopathological diagnosis in the MCD group and in the whole study group.

Two perioperative complications, one major (epidural abscess) and one minor (pneumonia) were registered. In addition, two children received a ventriculoperitoneal shunt, one within two years after a hemispherotomy and the other seven months after a MLR.

3.1. Two-year follow-up: seizure outcome and AED use (n = 47)

Twenty-one children (45%) were seizure-free and 12 children (26%) had ≥75% reduction in seizure frequency. Eight children (17%) had 50–74% reduction and two children (4%) 0–49% reduction in seizure frequency. Four children (9%) had an increased seizure frequency. In all, 33 children (70%) had a favourable outcome (seizure-free or ≥75% reduction of seizure frequency) at the 2-year follow-up.

Twenty-five children (53%) used a lower number of AEDs at the 2-year follow-up than preoperatively. Eight of those (17%) were completely off AEDs and they were all seizure-free. Although the median number of AEDs was unchanged at follow-up, the median change in number of AEDs used was −1 (range −3 to +4). One child had received a vagus nerve stimulator (VNS) within two years after surgery and one child was treated with ketogenic diet.

3.2. Two-year follow-up: seizure outcome and type of surgical procedures

Seizure outcome in relation to type of surgical procedure is shown in Fig. 2. The TLR group had the best seizure outcome