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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

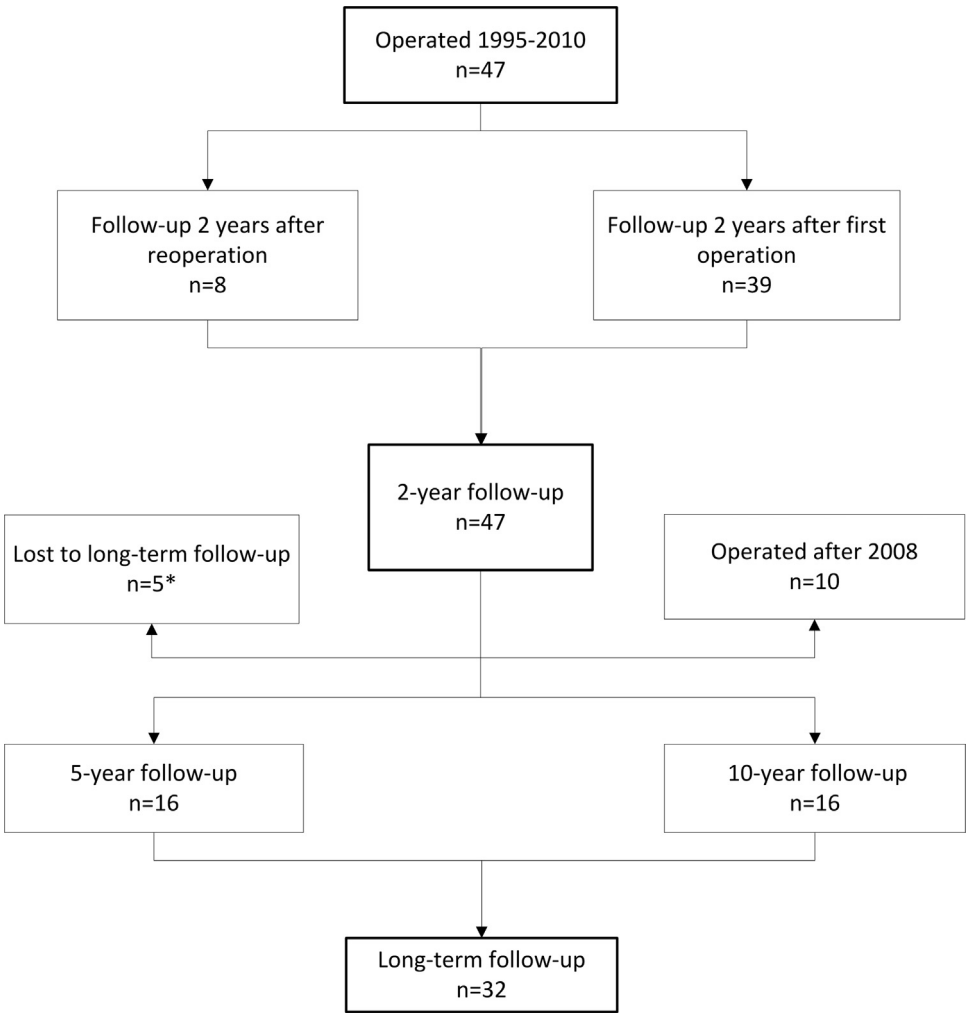

Fig. 1. Flow chart of operations and follow-ups in 47 children operated 1995–2010. *one emigrated, two were reoperated >2 years after first operation, one missing data (lost to 10-year follow-up), one died of reasons unrelated to epilepsy (lost to 5-year follow-up).

with 8/12 seizure-free, followed by the hemispherotomy group (7/12 seizure-free). The corresponding numbers in the FLR group were 4/12 and in the MLR group 1/8. Two children underwent PLR; both had ≥75% reduction in seizure frequency. The one child undergoing occipital lobe resection (OLR) was seizure-free.

Table 1
Preoperative characteristics (n = 47).

	Median	Mean	Range
Age at epilepsy onset	3 m	7 m	0 m–3 y 4 m
Age at first operation	2 y 1 m	2 y 1 m	2 m–4 y
Epilepsy duration	1 y 3 m	1 y 6 m	1 m–3 y 11 m
Seizure frequency (per month)	150	298	3–3000
Number of AEDs used	2	2,2	0–4
Number of AEDs previously tried	1	1,8	0–9
	n (%)		
Motor impairment	17 (36)		
Speech impairment	5 (11)		
IQ 50–69	10 (21)		
IQ <50	4 (9)		
Developmental delay	4 (9)		
Not assessed	2 (4)		
No neurodevelopmental impairment	15 (32)		

Abbreviations: n: number; m: month; y: year; AED: antiepileptic drug.

3.3. Two-year follow-up: seizure outcome and aetiology

Seizure outcome in relation to aetiology is shown in Fig. 3. The children with low-grade tumours (n = 4) were all seizure-free at the 2-year follow-up. None of the children with tuberous sclerosis complex (n = 4) were seizure free. In the MCD group (n = 29), 13 children were seizure-free. The children with unspecified FCD had the best outcome among the MCD subgroups. Three children in the gliosis/other non-specific pathology group (n = 7) were seizure-free, as was the one child with a vascular malformation. The child with a cystic malformation had a 0–49% reduction in seizure frequency, whereas the child without a histopathological diagnosis had an increased seizure frequency.

3.4. Long-term follow up: longitudinal seizure outcome and AED use (n = 32)

Fig. 4 shows the seizure outcome at the long-term follow-up. Sixteen out of thirty-two children were seizure-free, 14 of whom had been so since surgery (44%). Over the years between 2-year- and long-term follow-up, there were four cases of late seizure recurrence and two cases of late remission. Of the four children showing late seizure recurrence, two had only rare focal seizures with impairment of consciousness (≥75% reduction compared to preoperatively), one had focal seizures with secondary

Table 2
Aetiologies and types of surgical procedures ($n = 47$).

	TLR *n* (%)	FLR *n* (%)	PLR *n* (%)	OLR *n* (%)	MLR *n* (%)	Hemispherotomy *n* (%)	Total *n* (%)
MCD							29 (61.7)
Hemimegalencephaly					1	7	8 (17.0)
PMG				1		2	3 (6.4)
FCD I						1	1 (2.1)
FCD II	2	2	1		1		6 (12.8)
FCD uspecified	3	5			2	1	11 (23.4)
Gliosis/non-specific	2	2			2	1	7 (14.9)
Low-grade tumour	4						4 (8.5)
TSC	1	2	1				4 (8.5)
Vascular malformation		1					1 (2.1)
Cystic malformation					1		1 (2.1)
No pathology report					1		1 (2.1)
Total *n* (%)	12 (25.5)	12 (25.5)	2 (4.3)	1 (2.1)	8 (17.0)	12 (25.5)	

Abbreviations: *n*: number; TLR: temporal lobe resection; FLR: frontal lobe resection; PLR: parietal lobe resection; OLR: occipital lobe resection; MLR: multiple lobe resection; MCD: malformation of cortical development; PMG: polymicrogyria; FCD: focal cortical dysplasia; TSC: tuberous sclerosis complex.

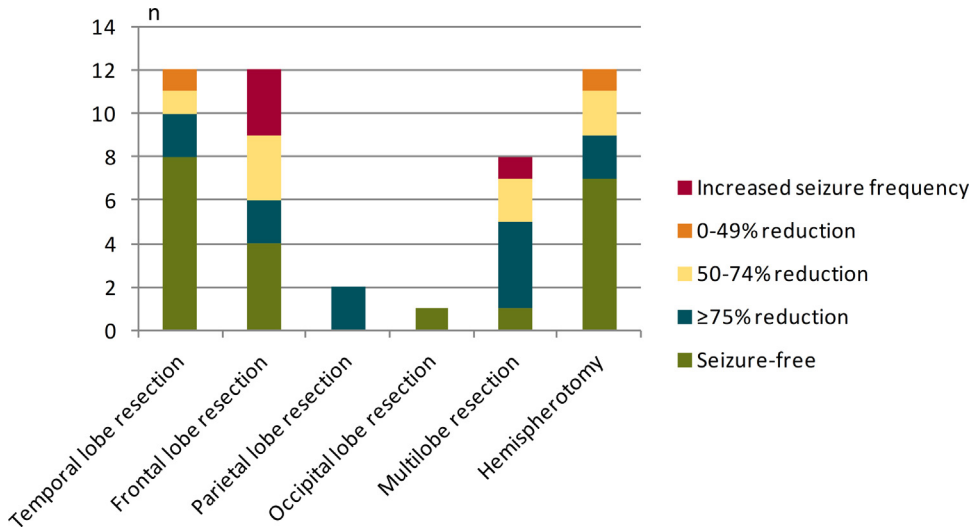

Fig. 2. Seizure outcome at 2-year follow-up related to type of surgical procedure ($n = 47$) *n*: number.

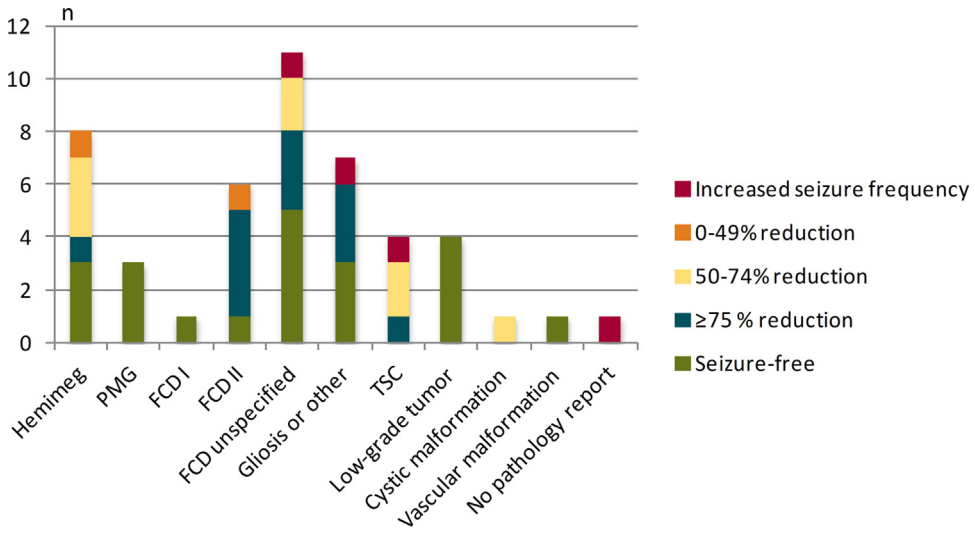

Fig. 3. Seizure outcome at 2-year follow-up related to aetiology ($n = 47$). *n*: number; PMG: polymicrogyria; FCD: focal cortical dysplasia; TSC: tuberous sclerosis complex.

generalisation (0–40% reduction) and one had an increase in seizure frequency compared to preoperatively (focal seizures without impairment of consciousness). A favourable outcome was observed in altogether 26 children (81%) at the long-term follow-up.

The median number of AEDs used at the long-term follow-up was 1 (range 0–4). Eleven children (34% of all, 69% of the 16 seizure-free), all of whom were seizure-free, had stopped AED treatment. The child on ketogenic diet had a VNS implanted

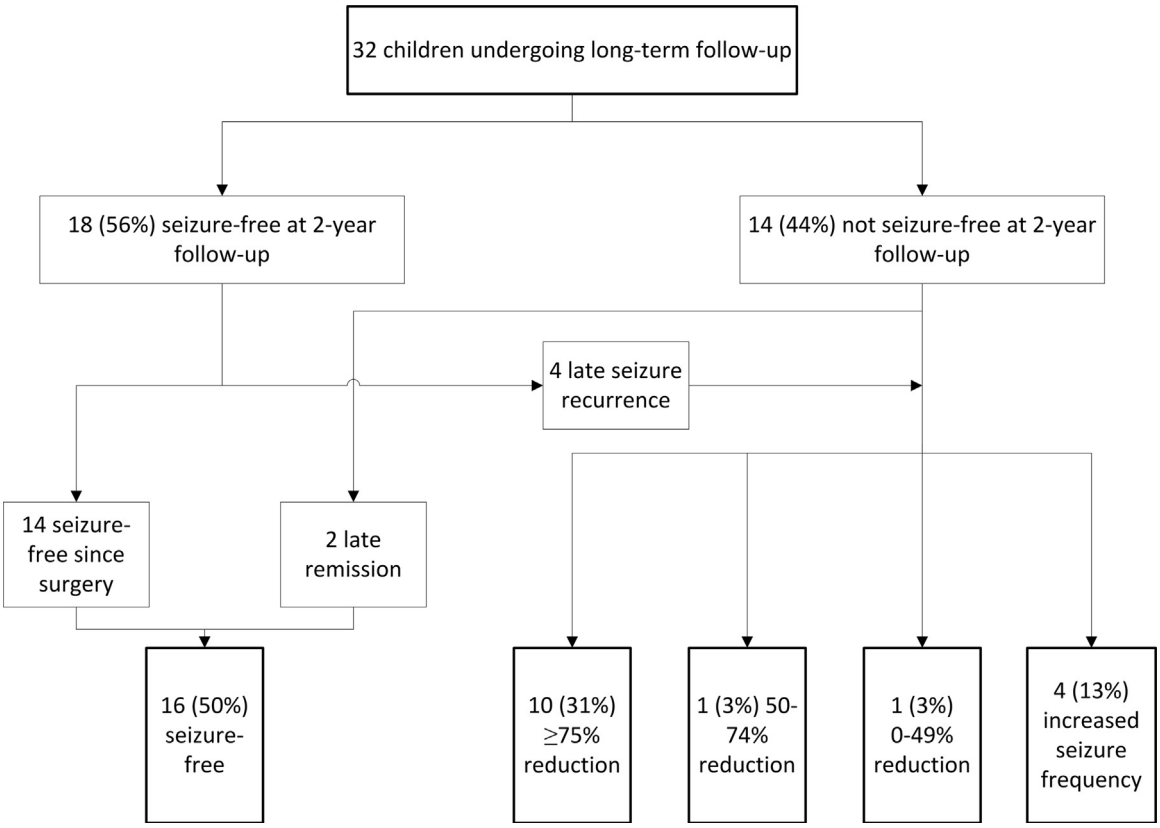

Fig. 4. Flow chart of long-term seizure outcome in 32 children.

before the long-term follow-up. Both that child and the one with a VNS implanted within two years had a ≥75% reduction in seizure frequency.

4. Discussion

This is the first prospective, population based, longitudinal study to show that resective epilepsy surgery yields persistent seizure freedom or worthwhile reduction of seizure frequency in a majority of cases when performed in infants and young children with severe medically intractable epilepsy. This is in agreement with previous retrospective cross-sectional studies on seizure outcomes in the age group in which rates of seizure freedom ranging from 48% to 73% have been reported [10–17]. With the exception of the study by Steinbok et al., all studies to date in the age group are small, making it hard to draw any definitive conclusions about differences in seizure outcome [15]. Aetiologies, localisation of resection and preoperative MRI findings have been shown to predict seizure outcome and the distribution of these variables within a study group therefore influences the results. Consequently, inclusion criteria related to these variables must be taken into account when assessing outcomes. For example, the study by Bittar et al. (73% seizure-free, $n = 11$) only included children with an identifiable lesion on MRI as well as a normal contralateral hemisphere [14]. In contrast, this study is population based and thus includes all children operated during the study period. Moreover, the differences in study design should be taken into account as cross-sectional data on seizure outcomes, collected during a rather wide time span, are not directly comparable to either the 2-year- or the long-term outcomes in this study.

When it comes to comparisons of seizure outcome after specific resection types and aetiologies, the numbers are small in our series, as is the case in most previous studies on epilepsy surgery in the very young. Maton et al. reported seizure outcomes after TLR in 20 children below 5 years of age. At follow-up at least two years after surgery, 65% were seizure free, a finding in line with our results (67% seizure free at the 2-year follow-up) [19]. Hemispherotomy is one of the most frequent types of surgery in studies on infants and young children; rates of seizure freedom ranging from 57% to 73% have been reported [9,13,15]. In our series, 58% of the children were seizure-free two years after hemispherotomy. In line with most surgical series in the age group, MCD was the predominant aetiology in this study and 13 out of 29 children (45%) were seizure-free at long-term follow-up. In a retrospective, cross-sectional study by Otsuki et al. on 56 children with different forms of MCD, 66% were seizure-free at last follow-up. The follow-up period ranged from 1 to 11 years and 55% had been seizure-free since surgery [20].

The proportion of seizure-free children in this series was largely preserved between 2-year- and long-term follow-ups. This finding is important as it implies that the risk of late seizure recurrence is not higher in infants and young children compared to older children and adults. Edelvik et al. reported a decrease in rate of seizure freedom from 55% to 50% and 50% to 41% in children 0–18 years and adults, respectively, between 2-year and long-term follow-ups [21]. In a recent study by Moosa et al. on seizure outcome after hemispherotomy in children 0–18 years, the seizure freedom rate decreased from 70% at two years to 60% five years postoperatively which is in accordance with the present study [22].

In this series, there was one major complication and no deaths. Results from early studies suggested a considerable risk of peri- or intraoperative mortality (1/12 and 2/32 children died respectively) [11,12]. However, more recent studies, have not reported any intra- or perioperative mortality with the exception

of one death in the large cohort reported by Steinbok et al. [14–17].

A considerable proportion of the seizure-free children in this series could discontinue antiepileptic medication (69% at long-term follow-up). Previous studies of epilepsy surgery in this age group have reported 25–50% of children to be off medication at follow-up [11,13–16]. The development of children with symptomatic epilepsy starting in the neonatal period or during infancy often tends to take a detrimental course. In part this is due to the underlying brain pathology, but the effects of AED treatment and ongoing seizure activity are also considered to have an influence [23,24]. The relative impacts of these factors vary depending on the condition and even though there is not yet any decisive data on the long-term effects of AED treatment on the developing brain, freedom from both seizures and medication is desirable. It is of interest to note that the proportion of seizure-free children entirely off medication increased from 17% to 34% between the 2-year- and the long-term follow-ups. It remains to determine if attempts of withdrawal from antiepileptic medication should be done earlier in the postoperative period. A recently published retrospective multi-centre study including 766 children concluded that early attempted postoperative AED withdrawal in seizure-free children did not affect seizure outcome at the end of the study period. Thus, many children could possibly be spared unnecessary and potentially harmful AED treatment, if earlier withdrawal attempts were introduced into standard clinical practice [25].

No significant change in time from epilepsy onset to surgery over the study period was observed in this study which is unfortunate as a short duration of epilepsy has been shown to predict an improved developmental trajectory [4–9]. This further emphasises the importance of early referral of children with early onset intractable epilepsy of suspected symptomatic aetiology for epilepsy surgery evaluation [26]. Moreover, our finding of an uneven distribution of operated patients over the country indicates the possibility of a surgical treatment gap.

In keeping with previous studies, the neurological co-morbidity in this series was high. Neurodevelopmental deficits were observed in a majority, including 14 children with intellectual disability of varying degree. This number is to be considered a minimum, since the developmental assessments in infants with a catastrophic seizure situation may be difficult. Even though seizure freedom is the most comprehensively investigated outcome measure in studies on paediatric epilepsy surgery, other postoperative variables are equally important and thus warrant further evaluation. As mentioned above, a bearing hypothesis in early resective surgery is that the disruption of uncontrolled seizure activity improves the postoperative neurodevelopmental trajectory. There is some evidence supporting this view but the studies suffer from methodological drawbacks (small cohorts, heterogeneous aetiologies, retrospective, cross-sectional design, different methods of assessing neurodevelopment across studies) [4–9]. Consequently, further studies, preferably multi-centre, prospective and longitudinal, as pointed out by Beghi and Tonini, are needed to assess neurodevelopmental, behavioural and quality of life outcomes after epilepsy surgery in infants and young children [27].

The major strength of this study is that, in contrast to most studies, it is prospective and population based, including all children operated in Sweden within the study period. The longitudinal design with multiple structured follow-ups makes it possible to give a more detailed account of the postoperative period, including late remissions, seizure recurrences and changes in AED use. The small size of the study cohort and its different subgroups is a weakness, as is the lack of yearly monitoring of the seizure situation.

5. Conclusion

This study shows that a favourable seizure outcome is achievable in a majority of infants and young children undergoing resective epilepsy surgery, with few complications. The results are consistent over time and a majority of the seizure-free children had also discontinued antiepileptic medication at the long-term follow-up. Finally, the findings of this study emphasise the importance and gains of early referral to epilepsy surgery evaluation in cases of medically intractable epilepsy in infants and young children.

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Conflict of interest statement

Prof. Malmgren has served on an educational advisory board for UCB and has received speaker's honoraria from UCB and from BiogenIdec. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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