DEVELOPMENT AFTER EPILEPSY SURGERY IN CHILDREN

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Development after epilepsy surgery in children

Ontwikkeling na epilepsiechirurgie bij kinderen

(met een samenvatting in het Nederlands)

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geboren op 26 juni 1960
te Rotterdam

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Chapter 1

General introduction

General introduction

With 118 new cases per 100,000 children a year in developed countries, epilepsy is the most common neurological disorder presenting during childhood.[1] The incidence is highest in the first year of life. Types of seizures, underlying causes of epilepsy, and its comorbidities vary widely. In most children epilepsy is treatable with medication, but almost 30% of children with epilepsy continue to have troublesome seizures despite trying antiepileptic drugs (AEDs).[2,3] Over the past 30 years, epilepsy surgery has become an important treatment option for children with lesional focal epilepsy in whom pharmacological treatment does not achieve seizure control, i.e., if two or three appropriate drugs fail to achieve seizure freedom or have disabling side effects.[3-6]

The most frequently used techniques intended to abolish seizures and 'cure' the epilepsy are functional hemispherectomy (hemispherotomy) and resective surgery. Functional hemispherectomy, a complete disconnection of one half of the brain with limited resection, is indicated when seizures originate from, and underlying pathology affects, an entire cerebral hemisphere. Children who may benefit from this procedure usually have a preexisting hemiparesis and other focal deficits. Resective surgery is considered when the area of the brain from which the seizures originate is well demarcated or confined to a single lobe. Whereas in the past epilepsy surgery was predominantly performed to remove temporal lobe lesions, children increasingly undergo surgery for extra-temporal lobe epilepsy. Additional types of surgery that are not intended to cure epilepsy but to improve seizure status – also referred to as 'palliative procedures' – are multiple subpial transections and corpus callosotomy. The studies described in this thesis only address childhood resective epilepsy surgery and functional hemispherectomy.

Children with pharmacoresistant epilepsy, particularly infants and toddlers, often have developmental problems, either due to the underlying epileptogenic pathology, to the frequent seizures themselves, or to the chronic use of (in most cases) multiple AEDs.[7] Mental retardation is no longer a contraindication for surgery, and over the years an increase of young patients with a generalized epileptic encephalopathy operated on has been reported. Outcome after childhood epilepsy surgery is preferably not solely expressed in terms of seizure freedom; cognitive development has become an equally important outcome measure.[4,8] When evaluating the outcome of epilepsy surgery, an important question is whether surgery has altered the course of development as it would have unfolded had the child continued to have seizures.[9] Is the surgery itself another threat, or does it provide new developmental opportunities? Years of working in the field of epilepsy surgery in children have broadened our knowledge of the course and predictors of cognitive development after epilepsy surgery. However, there are still important queries that require answers.

How can we detect change in mental development or intelligence in low functioning children?

The development of many young children with pharmacologically intractable epilepsy, especially those who undergo hemispherectomy, is severely delayed both before and after surgery.[10,11] After hemispherectomy, parents report a considerable change for the better in their children. The amelioration is difficult to measure and is not reflected in so-called developmental index scores. Standardized instruments for assessing developmental level are not apt to measure differentially on this low level, which renders quantifying the actual cognitive level of these children, let alone change, difficult.

How healthy is the remaining hemisphere after hemispherectomy in children?

After hemispherectomy, children's functioning is mediated by their remaining hemisphere, the functional and structural integrity of which may influence seizure outcome and cognitive development. The influence of contralateral MRI abnormalities on cognitive outcome after hemispherectomy has not been systematically studied before.

How do children function after hemispherectomy in the long term?

Parents faced with the information that their child is a candidate for hemispherectomy, often inquire after the long-term functional perspectives. What can be expected with respect to cognitive, academic and job achievements? Will the child be educable, lead an independent life, and how would she/he judge her/his quality of life?

What is the influence of antiepileptic drug withdrawal on cognitive development?

Withdrawal of AEDs can be envisaged shortly after epilepsy surgery when it is anticipated that the intervention was curative.[12] Tapering off medication has been shown to be safe with respect to long-term seizure outcome.[13] It may also be beneficial with regard to cognitive functioning, since AEDs are known to have cognitive side effects.[14] Research on medically treated cohorts of seizure-free patients has suggested that AED discontinuation leads to increased psychomotor speed and higher alertness in children.[15,16] Less is known about cognitive benefits of AED withdrawal after epilepsy surgery.

What is the influence of environmental variables on cognitive outcome?

From studies in normally developing childhood populations, it is clear that environment is of utmost importance for development of children's cognitive and academic achievements, e.g., children from low-income households scoring 4 to 7 points lower on standardized tests.[17] It has also been demonstrated in non-surgical epilepsy cohorts that cognitive development is often correlated not only with illness-related but also with environmental variables,[18] i.e., variables that measure some aspects of the surroundings of the child, such as parental education. It remains unclear to what extent parental education is associated with change in psychometric indices, such as IQ, after epilepsy surgery in children.

If surgery does not yield seizure freedom, are parents in retrospect satisfied with the decision to operate?

The responsibility to let epilepsy surgery be performed in one's child is, although shared with the medical team, emotionally heavy for the parent. There is little research on parents' retrospective evaluations of the decision to agree with epilepsy surgery in their children. We wanted to know how parents and patients look back upon the epilepsy surgery, also if this had not achieved the – so hoped-for – seizure freedom.

The aims of the studies described in this thesis directly relate to the questions in clinical practice as listed above. Different aspects of cognitive outcome following epilepsy surgery in children, in particular hemispherectomy, were explored. The research was embedded in the clinical care for children who underwent epilepsy surgery in the Wilhelmina Children's Hospital, University Medical Center Utrecht. With the exception of the study on the influence of AED withdrawal on intelligence quotient (IQ), that was performed on data from a large European multicenter cohort of pediatric epilepsy surgery patients (*TimeToStop* study), all studies described here are based on a standard comprehensive longitudinal assessment with fixed time intervals (shortly before, 6, 12 and 24 months after surgery) performed in a cohort of Dutch children who underwent epilepsy surgery in the UMC Utrecht between 1992 and 2009.

Outline of the thesis

Chapter 2 provides an overview of the literature regarding cognitive outcome of epilepsy surgery in childhood and the predictors of cognitive functioning after the intervention, with special attention for children with epileptic encephalopathy. **Chapter 3** reports on the attempt to detect change in mental development or intelligence over two years following functional

hemispherectomy, by separately analyzing the scores obtained with developmental scales and those derived from intelligence scales. In **Chapter 4** we explore whether EEG and MRI abnormalities in the 'healthy' contralateral hemisphere influence seizure and cognitive outcome after functional hemispherectomy. **Chapter 5** reports on functioning of (former) patients, five to eleven years after functional hemispherectomy, who were comprehensively assessed with regard to cognition, behavior, daily functioning, and health-related quality of life. We retrospectively evaluated the impact of postsurgical antiepileptic drug (AED) withdrawal on psychomotor speed (**Chapter 6**) as well as on intelligence (**Chapter 7**), in seizure-free children who had been operated on for pharmacoresistant epilepsy. In **Chapter 8** we retrospectively studied whether an important environmental variable, education of the parents, contributes to presurgical prediction of postsurgical change in the child's intelligence quotient (IQ). In **Chapter 9** we evaluate how former epilepsy surgery patients (then children, now adolescents) and their parents look back upon the decision made at least 1 year ago to proceed with epilepsy surgery. In **Chapter 10** main findings of this thesis are summarized and discussed.

References

1. Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. Epileptic Disord 2015;17(2):117-23.

2. Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, DiMario F, Smith S. How long does it take for epilepsy to become intractable? A prospective investigation. Ann Neurol 2006;60:73-9

3. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51(6):1069-77.

4. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol 2014;13(11):1114-26.

5. Pestana Knight EM, Schiltz NK, Bakaki BM, et al. Increasing utilization of pediatric epilepsy surgery in the United States between 1997 and 2009. Epilepsia 2015;56(3):375-81.

6. Lamberink HJ, Boshuisen K, van Rijen PC, et al. Changing profiles of pediatric epilepsy surgery candidates over time: a nationwide single-center experience from 1990 to 2011. Epilepsia 2015;56 (5):717-25.

7. Lah S. Neuropsychological outcome following focal cortical removal for intractable epilepsy in children. Epilepsy Behav 2004;5(6):804-17.

8. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7(6):525-37.

9. Baldeweg T, Skirrow C. Long-term cognitive outcomes after epilepsy surgery in children. In: Malmgren K, Baxendale S, Cross J, eds. Long-term outcomes after epilepsy surgery in adults and children. Springer International Publishing Switzerland; 2015:85-101.

10. Jonas R, Nguyen S, Hu B, et al. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology 2004;62(10):1712-21.

11. Althausen A, Gleissner U, Hoppe C, et al. Long-term outcome of hemispheric surgery at different ages in 61 epilepsy patients. J Neurol Neurosurg Psychiatry 2013;84(5):529-36.

12. Braun KP, Schmidt D. Stopping antiepileptic drugs in seizure-free patients. Curr Opin Neurol 2014;27(2):219-26.

13. Boshuisen K, Arzimanoglou A, Cross JH, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. Lancet Neurol 2012;11(9):784-91.

14. Loring DW, Meador KJ. Cognitive side effects of antiepileptic drugs in children. Neurology 2004;62(6):872-7.

15. Aldenkamp AP, Alpherts WC, Blennow G, et al. Withdrawal of antiepileptic medication in children – effects on cognitive function: The Multicenter Holmfrid Study. Neurology 1993;43(1):41-50.

16. Aldenkamp AP, Alpherts WC, Sandstedt P, et al. Antiepileptic drug-related cognitive complaints in seizure-free children with epilepsy before and after drug discontinuation. Epilepsia 1998;39(10):1070-4.

17. Hair NL, Hanson JL, Wolfe BL, et al. Association of child poverty, brain development, and academic achievement. JAMA Pediatr 2015;169(9):822-9.

18. Oostrom K, Smeets-Schouten A, Kruitwagen C, et al. Not only a matter of epilepsy: early problems of cognition and behavior in children with "epilepsy only" - a prospective, longitudinal, controlled study starting at diagnosis. Pediatrics 2003;112(6 Pt 1):1338-44.

Chapter 2

Cognitive outcome after epilepsy surgery in children

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Abstract

The ultimate goal of epilepsy surgery in young children is to stop seizures, interrupt the downhill course of the epileptic encephalopathy, and improve developmental capacities. Postoperative outcome after childhood epilepsy surgery should therefore not only be expressed in terms of seizure freedom, cognitive outcome is an equally important outcome measure. Insight in the mutually dependent variables that can determine pre and postoperative cognitive developmental abilities will improve prediction of outcome and presurgical counseling of parents. The purpose of this review is to discuss the literature regarding cognitive outcome and the predictors of postoperative cognitive functioning after epilepsy surgery in children, particularly those with "catastrophic" epilepsy. There are only few studies in which the relation between possible determinants and cognitive outcome or change was statistically tested in a multivariable manner. Duration of epilepsy, presurgical Developmental Quotient (DQ) or Intelligence Quotient (IQ), and postoperative seizure freedom were the only factors reported in different studies to be independently related to eventual cognitive outcome after epilepsy surgery. Underlying etiology, gender, age at surgery, presurgical DQ/IQ, postoperative seizure freedom, cessation of antiepileptic medication, and follow-up interval have all been described in different surgical cohorts to be independently related to a postoperative change of IQ or DQ scores. To appreciate how each of the preepileptic, presurgical, and postoperative variables may independently influence eventual cognitive outcome and postoperative cognitive improvement, we need multicenter studies with large homogenous surgical populations, using standardized tests and multivariable analyses.

Introduction

Up to 70% of children with intractable epilepsy have mental retardation.[1-4] Particularly in infants and young children with frequent seizures, the epilepsy syndrome may develop into a "catastrophic" course, suggesting that the developmental arrest or regression can at least partially be attributed to the ongoing seizures, and not only to the underlying epileptogenic pathology.[5] Epilepsy surgery, particularly hemispherectomy, is considered in a high proportion of these infants and children.[6] Previous studies confirm that 74–88% of patients who are candidates for hemispherectomy have a severe mental retardation, expressed as a mental developmental index (MDI), developmental quotient (DQ) or intelligence quotient (IQ) lower than 55.[7-9] Furthermore, case histories of infants and children who underwent hemispherectomy revealed that mental development had arrested or even deteriorated following the onset of catastrophic epilepsy in 82% of the patients.[10] The ultimate goal of surgery in young children with catastrophic epilepsy is to stop seizures, interrupt the downhill course of the epileptic encephalopathy, and improve developmental capacities. Postoperative outcome after childhood epilepsy surgery should therefore not only be expressed in terms of seizure freedom, cognitive outcome is an equally important outcome measure.[11] Insight in the mutually dependent variables that can determine pre and postoperative cognitive developmental abilities, will improve presurgical counseling of parents of these children. The purpose of this review is to discuss the literature regarding cognitive outcome and predictors of postoperative cognitive functioning after epilepsy surgery in children, particularly those with "catastrophic" epilepsy.

Literature search

Literature searches were carried out on PubMed, Embase and PsycINFO (January 1987 – July 2012) to identify publications on cognitive outcome in children who underwent pediatric epilepsy surgery or hemispherectomy. We used combinations of the following keywords: hemispherectomy; pediatric epilepsy surgery; childhood epilepsy surgery; intelligence, mental development; cognitive outcome; neuropsychological outcome; cognition. Studies written in English, and describing cognitive assessment of children who underwent epilepsy surgery in general and hemispherectomy in particular were included in the review of postoperative cognitive outcome. Studies were included only if they provided individual test data on pre and postsurgical assessments and described the intelligence or developmental test(s) that were used. Overviews and review articles were excluded, but their references were checked. We excluded duplicate publications, i.e. studies with overlapping patient populations from the same centre. A total of 27 publications fulfilled the criteria.

Presurgical neurocognitive development in pediatric epilepsy

Many infants and children who undergo resective or disconnective epilepsy surgery have a neurodevelopmental delay from birth, even prior to the onset of seizures, since their developmental capacities are restricted due to the underlying epileptogenic pathology. Comparable to non-epileptic patients with a stable encephalopathy, the differences between their cognitive functioning and that of healthy peers become more evident with ageing (Figure 2.1 dotted line). Once the epilepsy starts, their cognitive functions may further deteriorate, often leading to developmental arrest or even regression (Figure 2.1 shaded area). Because of the strong emotional overtone of the term "catastrophic" epilepsy in these children, the ILAE task force on classification and terminology has recommended to use the term epileptic encephalopathy,[12] defined as a condition in which the epileptic activity itself supposedly contributes to, or is responsible for, the often progressive mental developmental delay of the child. An encephalopathic course may occur in association with any form of epilepsy. Inherent to the concept of epileptic encephalopathy is the suggestion that suppression of the epileptic activity, e.g. by surgery, may improve or restart mental development (Figure 2.1).

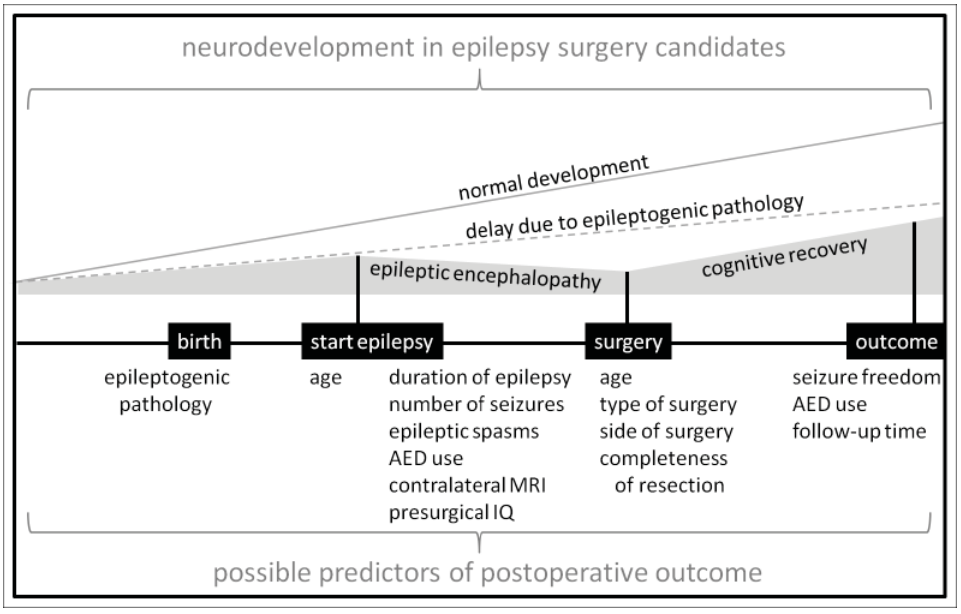

Figure 2.1 Neurodevelopment in epilepsy surgery candidates and possible predictors of postoperative outcome. AED = antiepileptic drug; MRI = magnetic resonance imaging; IQ = intelligence quotient.

Many factors have been reported to influence cognitive functioning in children with epilepsy in general and in surgical candidates specifically. Subnormal cognitive function (IQ<80) was apparent in approximately 25% of all children with newly diagnosed epilepsy in a population-based cohort, and age at epilepsy onset, a symptomatic cause, epileptic encephalopathy, and continued treatment were found to be independently associated with suboptimal cognitive functioning.[13] Especially age at onset has previously been reported to correlate with the chance of cognitive impairment; the earlier the age at onset the poorer the cognitive abilities,[3,4,14] which seems to be independent of the epileptogenic pathology.[15] Infants with longer duration and earlier onset of epilepsy performed worse on developmental testing,[9] and children with epileptic spasms had poorer developmental outcomes than those without.[16] Patients with symptomatic epilepsies were most likely to have lower intelligence quotients.[14] In a cohort of children who underwent an extratemporal resection, younger age at first seizure and longer duration of epilepsy before surgery were reported to independently correlate with lower presurgical cognitive levels.[17] Other independently significant determinants of lower presurgical cognitive functioning in the study of D'Argenzio[17] were gender and etiology, females had lower IQs and children with low-grade tumors had the highest presurgical IQ values. In addition, a higher number of presurgical AED trials correlated with lower presurgical cognitive levels.[17] In summary, the most important variables that have been reported to influence (presurgical) cognitive functioning in children with epilepsy are age at onset of seizures, the underlying epileptogenic etiology, the duration of epilepsy, the presence of epileptic spasms, the number of AED trials, gender, and evolvement into an epileptic encephalopathy. Since presurgical cognitive functioning significantly correlate with postsurgical cognitive outcome, as described below,[8,16,17] these variables may all determine eventual postoperative cognitive outcome measures.

Review of cognitive outcome after pediatric epilepsy surgery

Hemispherectomy

We included 11 studies that provided individual test data on pre- and postsurgical cognitive assessments using standardized tests of intelligence or development (Table 2.1). Eight of these studies reported solely on the cognitive outcome of hemispherectomy. From the remaining four studies that described cognitive outcome after pediatric epilepsy surgery in general, the individual scores of the pre- and postoperative assessments of hemispherectomized children could be extracted. The range of age at onset of seizures is

Table 2.1 Cognitive outcome after hemispherectomy: outcome measures, definition of change, and numbers of patients

[Study], year of publication	Nr of Pts (#)		Etiology	Age range at epilepsy onset (yr)	Age range at HS (yr)	Cognitive outcome measure	Δ IQ/DQ	Deterio-ration, n (%)	Improve-ment, n (%)	No change, n (%)	Follow-up range (yr)
[39] 1988	8		100% VAS	2.6–6.0	8.0–14.0	IQ	12	0 (0)	4 (50)	4 (50)	2.0–5.0
[18] 2002	14		100% CD	0–1.8	0.2–6.4	DQ	10*	0 (0)	4 (29)	10 (71)	Mean 2.0
[7] 2003	27	(+)	49% DEV 33% VAS, 19% PROG	0–8.0	0.33–17.0	IQ/DQ	15	0 (0)	4 (15)	23 (85)	1.0–8.0
[8] 2004	44	(+)	41% CD 14% RAS 17% HME 28% VAS	0–5.0	0.3–15.5	DQ	5	7 (16)	25 (57)	12 (27)	0.5–2.0
[27] 2004	53		28% CD 13% VAS 32% RAS	0–9.2	3.1–12.7	IQ/DQ	15	10 (19)	7 (13)	36 (68)	Mean 5.4
[26] 2005	7		14% CD 43% VASC 43 % RAS	U	3.7–11.6	VIQ	15	1 (14)	0 (0)	6 (86)	0.5–2.0
[19] 2007	8		100% SWS	0.1–0.8	0.5–10.6	IQ/DQ	Cat	0 (0)	6 (75)	2 (25)	0.8–17.4
[16] 2007	14		50% HME 36% MCD 14% SWS	U	0.2–2.2	DQ	10*	0 (0)	8 (57)	6 (43)	0.3–2.8 Median 0.5

Table 2.1 continues on next page

Table 2.1 *Continued*

[Study], year of publication	Nr of Pts (#)		Etiology	Age range at epilepsy onset (yr)	Age range at HS (yr)	Cognitive outcome measure	Δ IQ/DQ	Deterio-ration, n (%)	Improve-ment, n (%)	No change, n (%)	Follow-up range (yr)
[20] 2008	19		68% DEV 11% VAS 21% PROG	0–2.0	0.17–5.0	IQ/DQ	10	2 (11)	2 (11)	15 (78)	2.0–11.2
[40] 2009	8		100% VASC	0–5.0	4.5–10.8	IQ/DQ	Cat	0 (0)	0 (0)	8 (100)	0.2–12.0 Median 5.0
[9] 2010	34	(+)	44% DEV 35% VASC 21% PROG	0–11.0	0.2–14.3	IQ/MDI	10	3 (9)	9 (27)	22 (65)	1.0–2.0
	236							**23 (10%)**	**69 (29%)**	**144 (61%)**	

Cat = cognitive outcome was categorized; CD = cortical dysplasia; DEV = developmental lesions, including cortical dysplasia , hemimegalencephaly and other malformations of cortical development; DQ = developmental quotient; IQ = intelligence quotient; HME = hemimegalencephaly; HS = hemispherectomy; MDI = mental developmental index; n = number; Pts = patients; PROG = progressive disorders including Rasmussen encephalitis and Sturge-Weber Syndrome; RAS = Rasmussen encephalitis; SWS = Sturge Weber syndrome; U = unknown; VAS = vascular lesions, including infarcts and haemorrhages; VIQ = verbal intelligence quotient; yr = year; Δ = change of ≥ scale points or change in cognitive category; (+) = the classification of etiology is only given for the total study population and is unknown for the specific subgroup of HS patients with both pre- and postsurgical cognitive data listed here; # = number of patients in the study who underwent HS and in whom both pre and post surgical cognitive measurements are given. * = not categorized as such by the original authors, but derived for the purpose of this table from the original data.

wide. Three studies included only children with an onset below the age of two years.[18-20] In most studies, the investigators reported which change in IQ/MDI/DQ was considered relevant, varying from 5 to 15 points. In two reports, changes were not categorized by the authors. Based on the available data, we defined a change in cognitive scores in these two studies as relevant when IQ/DQ values increased or decreased with at least 10 points. Two reports were included in which the authors considered a change in predefined categorized levels of cognitive functioning as relevant (e.g. from "severely impaired" to "mildly impaired"), although individual IQ/DQ values could not be extracted from the data.

When pooling the results of these 11 studies (Table 2.1), neuropsychological outcome improved in only 29% of the children, defined as ≥5–15 points increase of IQ/MDI/DQ points or moving towards a better cognitive outcome category. Ten percent of the children showed cognitive deterioration and in 61% cognitive tests did not change after hemispherectomy.

Epilepsy surgery in general

Sixteen studies were included that provided individual test data on pre- and postsurgical cognitive assessments using standardized tests of intelligence or development (Table 2.2). In studies that also incorporated children who underwent hemispherectomy, the individual test data of these children were, if possible, excluded. In five studies, only children with an onset of epilepsy in early childhood were included,[3,16,21-23] one of which exclusively reported on outcome of children with an onset of seizures before the age of 1 year.[23] In most studies, the investigators specified which change in IQ/DQ points was considered relevant, varying from 8 to 15 points. In one report, change was not categorized by the authors. Based on the available data, we defined a relevant change in this study as at least 10 points increase or decrease of IQ/DQ values. In one study, the authors considered a change in predefined categorized levels of cognitive functioning as relevant, but individual IQ/DQ values could not be extracted from the data. In the studies of Westerveld,[24] Miranda[25] and Korkman[26] the individual scores on the verbal or performal intelligence scale were reported, without providing total IQ values. For the purpose of the present study we decided to incorporate the data of the VIQ scores.

When pooling results of these 16 studies (Table 2.2), neuropsychological outcome improved in 19% of the children, defined as an increase of ≥8–15 points in IQ/DQ points, or moving towards a better cognitive category. Eleven percent of the children showed cognitive deterioration and in 70% IQ/DQ values did not change after epilepsy surgery.

Determinants of cognitive outcome in pediatric epilepsy surgery

Table 2.3 summarizes the findings of studies in which the relation between possibly predictive variables and outcome measures was statistically tested. We differentiated between the influence of possible predictors (left column) on eventual postoperative cognitive functioning (middle column), and on the change between post- and presurgical cognitive levels (right column).

The clinically most important presurgical, surgical and postsurgical variables that may influence cognitive outcome are discussed here.

Presurgical variables

Etiology

In four of five studies that statistically tested the influence of etiology on eventual postsurgical cognitive outcome, no significant correlation was found.[8,9,16,17] In one study on cognitive outcome after hemispherectomy,[27] however, etiology was the most significant predictor of cognitive skills at follow-up, with malformations of cortical development (MCD) patients scoring lower in intelligence. When looking at etiology in relation to cognitive improvement after surgery; children with hemi cortical dysplasia (CD) showed the most progress in Vineland Adaptive Behavior Scales (VABS) DQ scores following hemispherectomy, compared to children with Rasmussen's encephalitis (RE) and vascular causes.[8] Two of the four studies that found no statistically significant relation between etiology and cognitive outcome level, also found no significant relation between etiology and a change in MDI, DQ or IQ points. In summary, children with developmental pathology seem to have worse eventual cognitive outcomes but have most to gain from surgery, with relatively high chances of postsurgical cognitive improvement. This is in line with the notion that in hemispherectomy candidates developmental lesions often are associated with early epileptic encephalopathy and developmental arrest. After surgery there is improvement of development, although the end level is limited, possibly related to a more diffuse or bilateral nature of the underlying pathology.

Timing variables (age at onset of epilepsy; duration of epilepsy; age at surgery)

A statistically significant relation between younger age at onset of epilepsy and lower cognitive outcome level was found after extratemporal resections[17] and also after surgical intervention for intractable epilepsies in children below the age of 15 years.[21] Age at onset of epilepsy was not significantly related to a change in IQ scores after temporal lobe surgery in childhood.[24,28]

Table 2.2 Cognitive outcome after pediatric epilepsy surgery in general: outcome measure, definition of change, and numbers of patients

[Study], year of publication	Nr of Pts (#)	Age range at onset epilepsy (yr)	Type of surgery	Age range at surgery (yr)	Cognitive outcome measure	Δ IQ/DQ	Deteriora-tion, n (%)	Improve-ment, n (%)	No change, n (%)	Follow-up range (yr)
[41] 1998	10	0–9.6	2 TL, 3 MST, 4 MST+ CC, 1 CC	4.6–17.2	DQ/IQ	10	1 (10)	1 (10)	8 (80)	1.2–4.6
[24] 2000	82	Mean 5.7	TL	Mean 14.2	VIQ	8	8 (10)	7 (8)	67 (82)	0.4–5.0
[25] 2001	50	0.5–14.5	TL	6.58–18.25	VIQ	8	7(14)	7(14)	36 (72)	0.5–6.5
[21] 2001	5	0–1.9	2 TL 2 Foc, 1 CC	0.3–5.33	DQ	10[a]	2 (40)	2 (40)	1 (10)	1.1–6.5
[26] 2005	31	U	23 TL, 8 ET	3.5–17.4	VIQ	15	2 (6)	3 (10)	26 (84)	2.0
[3] 2005	40	0.1–4.3	16 TL, 19 F, 18 ML, 7 HS[b]	Mean 4.9	DQ/IQ	15	2 (5)	8 (20)	30 (75)	0.5–3.0
[42] 2006	26	0–5	17 Foc, 9 ML	0.3–6.0	DQ/IQ	10	6 (23)	6 (23)	14 (54)	2.0–14.9
[43] 2006	43	Mean 3.8	30 TL, 13 ET	0.5–17.0	DQ/IQ	10	2 (7)	6 (14)	35 (81)	1.0–10.0
[16] 2007	10	U	3 F, 3 FP, 2 P, 1 PO, 1 O	0.2–2 .8	DQ	10[a]	1 (10)	5 (50)	4 (40)	0.3–2 .8 Median 0.5
[19] 2007	19	0.2–12.3	Foc	0.4–14.8	DQ/IQ	Cat	1 (5)	10 (53)	8 (42)	2.2–17.1
[44] 2009	23	0–17.7	9 T, 8 F, 2P 2 O, 3 HH	4.2–19.4	DQ/IQ	10	5 (22)	1 (4)	17 (74)	2.0

Table 2.2 continues on next page

Table 2.2 *Continued*

[Study], year of publication	Nr of Pts (#)	Age range at onset epilepsy (yr)	Type of surgery	Age range at surgery (yr)	Cognitive outcome measure	Δ IQ/DQ	Deteriora-tion, n (%)	Improve-ment, n (%)	No change, n (%)	Follow-up range (yr)
[30] 2010	22	0.3–12.0	10 ML, 11 L, 6 HS[b]	1.7–17.3	DQ/IQ	15	0 (0)	6 (27)	16 (73)	1.0–4.3
[22] 2010	9	0–2.7	6 Foc 3 PQ	0.3–4.2	DQ/IQ	10	4 (45)	3 (33)	2 (22)	3.0–6.0
[23] 2011	23	0–1.0	27 HS ^ 4 ML, 7 L, 4 Foc	0.25–3.0	DQ/IQ	15	5 (21)	2 (9)	16 (70)	2.2–13.2
[28] 2011	42	5–16	42 TL	9–16	IQ	10	1 (2)	17 (41)	24 (57)	5.0
[17] 2011	31	U	31 ET	<15	DQ/IQ	15	5 (16)	3 (10)	23 (74)	0.5–7.3
	466						**52 (11%)**	**87 (19%)**	**327(70%)**	

Cat = cognitive outcome was categorized; CC = corpus callosotomy; DQ = developmental quotient; ET = extra temporal resection ; F= frontal resection; Foc = focal resection; F = frontal resection; FP = frontoparietal resection; HH: disconnection of hypothalamus hamartoma; HS = hemispherectomy; IQ = intelligence quotient; L = lobar resection; ML = multilobar resection; MST = mesial temporal sclerosis; n = number; O = occipital resection; P = parietal resection; PO = parieto-occipital resection; PQ = posterior quadrant resection/disconnection; T = temporal; TL= temporal lobectomy; U = unknown; VIQ = verbal intelligence quotient; yr = year;; Δ = change of ≥ scale points or change cognitive category; # = number of patients in the study who underwent epilepsy surgery and in whom both pre and post surgical cognitive measurements are given.; a = not categorized as such by the original authors, but derived for the purpose of this table form the original data; b = in some studies [3, 23, 30] the available data did not allow exclusion of the individual results from HS patients.

Table 2.3 Determinants of postsurgical cognitive outcome

Possible predictors	Postoperative MDI/DQ/IQ	Change in MDI/DQ/IQ
Presurgical variables		
Etiology	MCD ↓ [27] NSR [**8**, 9, 16, **17**]	CD ↑ [**8**] NSR [9,17]
Gender	Female ↓ [17] NSR [**17**]	Male ↑ VIQ [**24**] NSR [**25**, 26]
Age at onset seizures	Younger ↓ [17, 21] NSR [**17**]	NSR [**24**, **28**]
Duration of epilepsy	Shorter ↓ [9] ↑ [**8**, 17] NSR [**17**]	Shorter ↑ [3] NSR [19, **25**, **28**]
Age at epilepsy surgery	Younger ↓ [9, 26]	Younger ↑ [16, 19, **24**] Older ↑ VIQ [**25**] NSR [26]
Preoperative seizure frequency	NSR [16]	
Epileptic spasms		↑ [16]
Contra lateral MRI abnormalities	↓ [9]	↓ [9]
Contra lateral EEG abnormalities	NSR [9]	NSR [9]
Pre MDI/DQ/IQ	Higher ↑ [8, 16, **17**]	Higher ↓ [16, VIQ **24**, **28**] Lower VIQ ↑ [**25**] NSR [26]
Surgical variables		
Type of surgery	HS ↓ [26] NSR [16, 26]	
Side of surgery	NSR [16, **17**, 26]	NSR [**24**]
Completeness of resection	NSR [17]	↑ [19]
Post surgical variables		
Postoperative seizure freedom	↑ [**8**] ↑ only for MCD [27] NSR [9, 16, 17]	↑ [19, VIQ **25**, **30**] NSR [3, 9, **24**, 26, 27, **28**]
Number of AED used at time of assessment	NSR [9, 16]	Less ↑ [**28**] NSR [9]
Follow-up interval		Longer ↓ VIQ [**25**] NSR [**24**]

Only studies in which the statistical relation between possible determinants and cognitive outcome measures was tested are listed. References in bold: multivariate or multiple regression analyses were performed. AED = antiepileptic drug; CD = cortical dysplasia; DQ = developmental quotient; EEG = electroencephalography; HS= hemispherectomy; IQ = intelligence quotient; MCD = malformation of cortical development; MDI = mental developmental index; MRI = magnetic resonance imaging; NSR = the association was tested but was found not to be significantly related; VIQ = verbal intelligence quotient; ↑ = relatively good or improvement; ↓ = relatively poor or decline.

Shorter duration of epilepsy was associated with higher postsurgical DQs after hemispherectomy,[8] and with higher IQ scores after extratemporal resection in childhood.[17] In another hemispherectomy cohort, however, shorter duration of epilepsy was predictive of poor postoperative cognition.[9] In one study with preschool children treated surgically for severe epilepsy[3] duration of epilepsy was the only significant predictor of long-term cognitive change; children with shorter intervals between onset of epilepsy and surgery had greater gains in DQ. Duration of epilepsy was not a significant predictor of IQ change after temporal lobectomy,[25,28] nor after epilepsy surgery in Sturge Weber Syndrome.[19]

The studies that statistically tested the relation between age at surgery and eventual cognitive outcome,[9,26] found that younger age was associated with lower postoperative MDI/IQ scores after hemispherectomy. In three of the five studies that statistically tested the influence of age at surgery on cognitive changes, age was found to be an important determinant of improvement in developmental status. Younger age at surgery was associated with a larger positive change in cognitive scores after epilepsy surgery in infants and young children.[16,19,24] In contrast with the study of Westerveld,[24] a later study of temporal lobectomies[25] revealed that older age at surgery was found to be predictive of more improvement in VIQ.

When summarizing the results of studies that revealed significant associations between timing variables and cognitive outcome, younger age at onset of epilepsy predicted poor outcome. Younger age at surgery predicted poor eventual outcome after hemispherectomy and extratemporal resections, but was not related to postoperative cognitive improvement. Shorter duration of epilepsy was associated with both good or poor outcome after hemispherectomy, with good outcome in a cohort of children who underwent extratemporal surgery, and with more improvement of cognitive functioning after surgery in preschool children. These findings confirm several hypotheses and assumptions that are part of everyday clinical thinking and decision making. First, early onset epilepsy reflects severe epileptogenic pathology that, by itself, restricts future cognitive abilities. Second, when hemispherectomy is indicated at very young age, the epileptic encephalopathy is severe, development has arrested or regressed and surgical treatment can induce more pronounced cognitive improvement, although eventual cognitive function is limited. Third, and most importantly, a shorter duration of active epilepsy limits the potentially irreversible effects of ongoing seizures and AEDs on brain function. This probably is independent of underlying pathology. In this context, recent animal studies have provided further evidence that seizures themselves can affect structural integrity and functional connectivity of the brain.[29]

Contralateral abnormalities

The only study that statistically tested the relation between cognitive outcome and contralateral MRI or EEG abnormalities,[9] found that children with unequivocal contralateral MRI abnormalities more often were severely retarded after hemispherectomy. Postoperative MDI/IQ scores improved in none of the children with, but in 38% of those without contralateral MRI abnormalities. Contralateral epileptic or background EEG abnormalities did not affect seizure outcome or postoperative cognitive performance. Structural integrity of the remaining hemisphere thus influences cognitive functioning after hemispherectomy.

Pre IQ/DQ

In all three studies that statistically tested the relation between pre- and postsurgical IQ/DQ, a higher IQ/DQ before surgery correlated with a higher IQ/DQ after surgery.[8,16,17] Presurgical IQ/DQ was found to be a negative predictor of changes in IQ/DQ change[16,28] and VIQ.[24] Children at the low end of the IQ spectrum improved more after surgery than those with a higher presurgical IQ/DQ level. However, IQ changes in the study of Skirrow[28] were only seen 6 or more years after surgery. More postsurgical cognitive improvement was reported in children with lower preoperative verbal IQs.[25] One other study found no significant relation between presurgical levels of cognitive functioning and postsurgical increase or decrease of IQ points.[26] In conclusion: a higher presurgical level of cognitive functioning is significantly related to higher postsurgical cognition scores, although cognitive improvement occurs less often.

Surgical variables (type of surgery; side of surgery; completeness of resection)

In a follow-up study of intelligence after pediatric epilepsy surgery IQ scores of patients in the hemispherectomy group were lower than those of patients in the extratemporal, multilobar or temporal resection group.[26] In none of the studies that tested the relation between side of surgery and cognitive outcome significant associations were found.[16,17,26] In a study on the intellectual outcome after temporal lobe surgery, side of surgery was not related to change in IQ scores.[24] In one study on surgical treatment of children with Sturge Weber Syndrome developmental improvement was significantly affected by completeness of resection,[19] but also by age at surgery. In summary: hemispherectomy is associated with the lowest IQs. Side of surgery is not related to eventual cognitive outcome or to changes in cognitive outcome levels while completeness of the resection can be a significant predictor of developmental improvement after surgery.

Postsurgical variables

Seizure freedom

Postsurgical seizure control predicted higher VABS DQ scores after hemispherectomy.[8] In another study on cognitive outcome after hemispherectomy in children, persistence and severity of seizures were significantly related to follow-up IQ for the MCD group only.[27] In three further studies that statistically tested the relation between postoperative seizure status and cognitive outcome, no predictive effect was found.[9,16,17] Postsurgical seizure control was shown to be correlated with improvement of DQ/IQ and VIQ.[19,25,30] In six other studies, however, seizure outcome did not significantly contribute to cognitive changes,[3,9,24,26-28] These findings may suggest that complete seizure freedom is not a prerequisite for cognitive improvement after epilepsy surgery.

Number of AEDs

In a study on the long-term intellectual outcome after temporal lobe surgery in childhood,[28] cessation of antiepileptic medication was an independent predictor of cognitive improvement after surgery. In patients who underwent hemispherectomy, however, the number of AEDs used at postoperative neuropsychological evaluation did not differ between the children who gained 10 or more ID/DQ points and those without postoperative improvement after surgery.[9] A change in the number of AEDs after surgery was not associated with the level of development after epilepsy surgery in infancy.[16] However, given the known cognitive side effects of AEDs,[31,32] the negative influence of many AEDs may have on brain development[33,34] and the improvement of cognitive function after discontinuation of AEDs in non-surgical cohorts[35-37] it can be expected that AED withdrawal increases the chances of postoperative cognitive improvement. It has recently been demonstrated that early postoperative AED withdrawal does not affect long-term seizure outcome after epilepsy surgery in children.[38] Further studies are needed to reveal how drug discontinuation, and its timing, may benefit cognitive development after surgery.

Conclusion

Although cognitive functioning is an important outcome measure of epilepsy surgery in children with epileptic encephalopathies, in the past 25 years only a few studies have reported developmental or intelligence scores of both pre- and postoperative assessments. When expressed as IQ, MDI or DQ values, cognitive improvement seems to be uncommon, with only 20–30% of operated children having an increase of >5–15 points after surgery. However, we should realize that many young children, especially those who undergo

hemispherectomy, are severely delayed, both before and after surgery. In those patients, subtle progression of cognitive function and an increase in mental age can probably not be quantified and expressed in formal DQ or IQ scores. The frequency of cognitive improvement may therefore be underestimated.[10]

When counseling parents of children who are considered surgical candidates, it is important to predict postoperative cognitive outcome. For that, we need to realize that outcome can be expressed in two different ways. First, how can epilepsy surgery improve cognition? The influence of surgery itself on the course of the child's neurocognitive development is reflected by the difference between post- and preoperative cognitive function scores. Second, what can we expect of the child's eventual cognitive functioning? Long-term postoperative cognitive outcome probably reflects the sum of many factors, both pre-epileptic and other presurgical variables, as well as postoperative determinants, that can each influence long-term cognitive abilities.

In this review, we summarized the studies that identified predictors of cognitive change and of eventual cognitive outcome after epilepsy surgery. The multiple and often mutually dependent variables which may influence cognitive outcome or cognitive change after surgery are difficult to uncouple. Because of small sample sizes and heterogeneity of cohorts, in most studies only simple (descriptive) statistics were allowed. We found few studies in which the relation between possible determinants and cognitive outcome or change was statistically tested in a multivariable manner. In most of these, only a limited set of variables was included in the analysis. Presurgical IQ or DQ, duration of epilepsy, and postoperative seizure freedom, were the only factors that were reported to be independently related to eventual cognitive outcome after epilepsy surgery (Table 3.3, left column). Underlying etiology, gender, age at surgery, duration of epilepsy, presurgical IQ/DQ, postoperative seizure freedom, cessation of antiepileptic medication, and follow-up interval were found to be independently related to a change in IQ or DQ scores after surgery (Table 3.3, right column).

To separate the impact of the many variables that may contribute independently to eventual cognitive outcome and to cognitive changes after pediatric epilepsy surgery, studies with a prospective design, using pre- and postoperative standardized cognitive assessments at fixed time intervals, multivariable statistical tests, and large sample sizes with pathological homogenous subgroups are urgently needed. These studies will require a multicenter collaborative approach.

References

1. Huttenlocher PR, Hapke RJ. A follow-up study of intractable seizures in childhood. Ann Neurol 1990;28:699-705.

2. Besag FM. Childhood epilepsy in relation to mental handicap and behavioral disorders. J Child Psychol Psychiatry 2002;43:103-31.

3. Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. Epilepsia 2005;46:561-7.

4. Cormack F, Cross JH, Isaacs E, Harkness W, Wright I, Vargha-Khadem F, et al. The development of intellectual abilities in pediatric temporal lobe epilepsy. Epilepsia 2007;48:201-4.

5. Shields WD. Catastrophic epilepsy in childhood. Epilepsia 2000;41(Suppl 2):2-6.

6. Cross JH. Epilepsy surgery in childhood. Epilepsia 2002;43(Suppl 3):65-70.

7. Devlin AM, Cross JH, Harkness W, Chong WK, Harding B, Vargha-Khadem F, et al. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. Brain 2003;126:556-66.

8. Jonas R, Nguyen S, Hu B, Asarnow RF, LoPresti C, Curtiss S, et al. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology 2004;62:1712-21.

9. Boshuisen K, van Schooneveld MMJ, Leijten FSS, de Kort GAP, van Rijen PC, Gosselaar PH, et al. Contralateral MRI abnormalities affect seizure and cognitive outcome after hemispherectomy. Neurology 2010;75:1623-30.

10. van Schooneveld MMJ, Jennekens-Schinkel A, van Rijen PC, Braun KPJ, van Nieuwenhuizen O. Hemispherectomy: a basis for mental development in children with epilepsy. Epileptic Disord 2011;13:47-55.

11. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7:525-37.

12. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of The ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51:676-85.

13. Berg AT, Langfitt JT, Testa FM, Levy SR, DiMaro F, Westerveld M, et al. Global cognitive function in children with epilepsy: A community-based study. Epilepsia 2008;49:608-14.

14. Nolan MA, Redoblado MA, Lah S, Sabaz M, Lawson JA, Cunningham AM, et al. Intelligence in childhood epilepsy syndromes. Epilepsy Res 2003;53:139-50.

15. Vasconcellos E, Wyllie E, Sullivan S, Stanford L, Bulacio J, Kotagal P, et al. Mental retardation in pediatric candidates for epilepsy surgery: the role of early seizure onset. Epilepsia 2001;42:268-74.

16. Loddenkemper T, Holland KD, Stanford LD, Kotagal P, Bingaman W, Wyllie E. Developmental outcome after epilepsy surgery in infancy. Pediatrics 2007;119:930-5.

17. D'Argenzio L, Colonnelli MC, Harrison S, Jacques TS, Harkness W, Vargha-Khadem F, et al. Cognitive outcome after extratemporal epilepsy surgery in childhood. Epilepsia 2011;52:1966-72.

18. Maehara T, Shimizu H, Kawai K, Shigetomo R, Tamagawa K, Yamada T, et al. Postoperative development of children after hemispherotomy. Brain Dev 2002;24:155-60.

19. Bourgeois M, Crimmins DW, de Oliveira RS, Arzimanoglou A, Garnett M, Roujeau T, et al. Surgical treatment of epilepsy in Sturge-Weber syndrome in children. J Neurosurg (1 Suppl Pediatrics) 2007;106:20-8.

20. Lettori D, Battaglia D, Sacco A, Veredice C, Chieffo D, Massimi L, et al. Early hemispherectomy in catastrophic epilepsy: a neuro-cognitive and epileptic long-term follow-up. Seizure 2008;17:49-63.

21. Matsuzaka T, Baba H, Matsuo A, Tsuru A, Moriuchi H, Tanaka S, et al. Developmental assessment-based surgical intervention for intractable epilepsies in infants and young children. Epilepsia 2001;42(Suppl 6):9-12.

22. Roulet-Perez E, Davidoff V, Major-Dubois C, Maeder-Ingvar M, Seeck M, Ruffieux C, et al. Impact of severe epilepsy on development: recovery potential after successful early epilepsy surgery. Epilepsia 2010;51:1266-76.

23. Dunkley C, Kung J, Scott RC, Nicolaides P, Neville B, Aylett SE, et al. Epilepsy surgery in children under 3 years. Epilepsy Res 2011;93:96-106.

24. Westerveld M, Sass KJ, Chelune GJ, Hermann BP, Barr WB, Loring DW, et al. Temporal lobectomy in children: cognitive outcome. J Neurosurg 2000;92:24-30.

25. Miranda C, Smith ML. Predictors of intelligence after temporal lobectomy in children with epilepsy. Epilepsy Behav 2001;2:13-9.

26. Korkman M, Granström ML, Kantola-Sorsa E, Gaily E, Paetau R, Liukkonen E, et al. Two-year follow-up of intelligence after pediatric epilepsy surgery. Pediatric Neurol 2005;33:173-8.

27. Pulsifer MB, Brandt J, Salorio CF, Vining EPG, Carson BS, Freeman JM. The cognitive outcome of hemispherectomy in 71 children. Epilepsia 2004;45:243-54.

28. Skirrow C, Cross JH, Cormack F, Harkness, W, Vargha-Khadem F, Baldeweg T. Long-term intellectual outcome after temporal lobe surgery in childhood. Neurology 2011;76:1330-7.

29. Otte WM, Dijkhuizen RM, van Meer MPA, van der Hei WS, Verlinde SAMW, van Nieuwenhuizen O, et al. Characterization of functional and structural integrity in experimental focal epilepsy: reduced network efficiency coincides with white matter Changes. PloS ONE 2012;7:e39078.

30. Lee YJ, Kang HC, Lee JS, Kim SH, Kim DS, Shim KW, et al. Resective pediatric epilepsy surgery in Lennox-Gastaut syndrome. Pediatrics 2010;125:e58-65.

31. Park SP, Kwon SH. Cognitive effects of antiepileptic drugs. J Clin Neurol 2008;4:99-106.

32. Mula M, Trimble MR. Antiepileptic drug-induced cognitive adverse effects. Potential mechanisms and contributing factors. CNS Drugs 2009;23:121-37.

33. Kaindl AM, Asimiadou S, Manthey D, Hagen MV, Turski L, Ikonomidou C. Antiepileptic drugs and the developing brain. Cell Mol Life Sci 2006;63:399-413.

34. Ikonomidou C, Turski L. Antiepileptic drugs and brain development. Epilepsy Res 2010;88:11-22.

35. Aldenkamp AP, Alpherts WC, Sandstedt P, Blennow G, Elmqvist D, Heijbel J, et al. Antiepileptic drug-related cognitive complaints in seizure-free children with epilepsy before and after drug discontinuation. Epilepsia 1998;39:1070-4.

36. Hessen E, Lossius MI, Reinvang I, Gjerstad L. Influence of major antiepileptic drugs on attention, reaction time, and speed of information processing: results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients receiving monotherapy. Epilepsia 2006;47:2038-45.

37. Lossius MI, Hessen E, Mowinckel P, Stavern K, Erikssen J, Gulbrandsen P, et al. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus Study). Epilepsia 2008;49:455-63.

38. Boshuisen K, Arzimanoglou A, Cross JH, Uiterwaal CSPM, Polster T, van Nieuwenhuizen O, et al. Timing of AED withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. Lancet Neurol 2012;11(9):784-91.

39. Beardsworth ED, Adams CBT. Modified Hemispherectomy for epilepsy: early results in 10 cases. British J Neurosurg 1988;2:73-84.

40. Scavarda D, Major P, Lorthe A, Mercier C, Carmant L. Periinsular hemispherotomy in Children with stroke-induced refractory epilepsy. J Neurosurg Pediatr 2009;3:115-20.

41. Mukahira K, Oguni H, Awaya Y, Tanaka T, Saito K, Shimizu H, et al. Study on surgical treatment of intractable childhood epilepsy. Brain Dev 1998;20:154-64.

42. Battaglia D, Chieffo D, Lettori D, Perrino F, Di Rocco C, Guzzetta F. Cognitive assessment in epilepsy surgery of children. Childs Nerv Syst 2006;22:744-59.

43. van Oijen M, de Waal H, van Rijen PC, Jennekens-Schinkel A, van Huffelen AC, van Nieuwenhuizen O. Resective epilepsy surgery in childhood: The Dutch experience 1992-2002. Eur J Pediatr Neurol 2006;10:114-23.

44. Danielsson S, Viggedal G, Steffenburg S, Rydenhag B, Gillberg C, Olsson I. Psychopathology, psychosocial functioning, and IQ before and after epilepsy surgery in children with drug-resistant epilepsy. Epilepsy Behav 2009;14:330-7.

Chapter 3

Hemispherectomy: a basis for mental development in children with epilepsy

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Abstract

Objective: To detect change in mental development or intelligence over two years following hemispherectomy in children with pharmacologically intractable epilepsy.

Participants: Seventeen infants and preschoolers (median age at epilepsy onset of 0.0 years and at hemispherectomy 1.5 years; epilepsy duration of 0.2–2.6 years) and 12 older children (median age at onset of 1.0 year and at hemispherectomy 8.3 years; epilepsy duration of 1.1–11.7 years) with pharmacologically intractable seizures due to developmental, acquired or progressive pathology.

Methods: Prospective study with consecutive inclusion of children, fixed assessment intervals (shortly before and 6, 12 and 24 months after hemispherectomy) and assessment using developmental scales and intelligence scales. Dependent variables included mental developmental index (MDI), mental age (MA) and mental developmental delay (MDD) in younger children and intelligence quotient (IQ) in older children.

Results: Mental development had arrested or deteriorated prior to hemispherectomy in 14 children (82%) assessed with developmental scales. In 14 children, it was not possible to more precisely determine MDI than 'below the lowest MDI that the test manual provided' either before or after hemispherectomy. MA, however, increased in 16 children. Overall, IQ changed negligibly over two years after hemispherectomy, although an individual approach revealed variability. Children with Rasmussen encephalitis did not recover from the significant presurgical deterioration of intelligence.

Conclusion: Removal of the affected hemisphere enables epileptic children, even those with severe mental delay, to further develop mentally.

Introduction

In terms of seizure reduction, the outcome of hemispherectomy is favourable for children regardless of their age (for a review, see Spencer and Huh[1]).

Hemispherectomy is increasingly performed in children with pharmacologically intractable epilepsy, only when seizures originate from one hemisphere. Early age is no longer considered a contraindication and children who were previously unlikely candidates for successful hemispherectomy, because mental retardation suggested widespread cerebral damage, would now have realistic chances of significant seizure reduction after hemispherectomy.

Cognitive function is another important outcome measure of hemispherectomy in children. The general impression is that cognitive function does not change much after hemispherectomy.[2] However, subtle change may be concealed for a number of reasons. The age range of children within studues varies from younger than one year to adolescence, thus, not only intelligence scales but also developmental scales are used. Developmental scales rely predominantly on sensory and motor domains, whereas intelligence scales rely more on verbal and visuo-spatial reasoning. However, with regards to developmental studies, combining the measurements obtained from these two types of scales is unwarranted.[3] Furthermore, the mental development or intelligence of these children is usually poor to a degree that cannot be quantified reliably with current scales. A child with a mental developmental index (MDI) <55 or an intelligence quotient (IQ) <48 performs below the lowest MDI or IQ for which the test offers norm values. This problem of inaccurate measurement in the lower tail of the scale distribution has consequences for longitudinal assessment. A difference between the assumed values of MDI or IQ, e.g. from 23 to 47, remains hidden since they are below the lowest value measured by the test. In such patients, any subtle improvement or increase in mental age may go unnoticed, although such a change may be relevant from the viewpoints of individual development and adaptation.

The aim of this prospective study was to detect change in mental development or intelligence over two years following paediatric hemispherectomy. To circumvent the problematic issues associated with measurement, as described above, we analysed the scores obtained with developmental scales and intelligence scales separately. We determined MDI, but also mental age (MA) and mental developmental delay (MDD), and IQ (see Methods). We investigated whether age at onset and duration of the epilepsy correlated with MDD and IQ and whether MDD and IQ were influenced by type of underlying pathology, lateralisation of epilepsy/hemispherectomy or seizure outcome.

Methods

Patients

Twenty-nine children, who were considered appropriate candidates for hemispherectomy by the national Dutch Collaborative Epilepsy Surgery Programme (DuCESP), underwent functional hemispherectomy at the University Medical Centre Utrecht (UMCU) between 1994 and 2007 and were followed by the Neuropsychology Unit. Informed consent was obtained from the parents and agreement was obtained from children aged 12 years and older. The institutional Review Ethics Committee approved the study.

Demographic and epilepsy characteristics, including age at onset, age at hemispherectomy, seizure duration, pathology, number of antiepileptic drugs (AEDs) used before surgery, seizure outcome (frequency) and cognitive level (mental developmental delay or intelligence quotient) are summarized in Table 3.1A for children assessed with developmental scales and in Table 3.1B for those assessed with intelligence scales. The strategy of the DuCESP to start withdrawal of AEDs two years after the intervention was followed in almost all cases.

In the group of 17 children assessed using developmental scales (eight girls), median age at onset ranged from 0–0.6 (median 0.0) years, and the interval between seizure onset and hemispherectomy ranged from 0.2–2.6 (median 1.1) years. Eight children underwent a left-sided functional hemispherectomy. The pathology was developmental (cortical dysplasia, hemimegalencephaly or multiple developmental anomalies) in 10, acquired (ischaemia or porencephaly) in five and progressive (Sturge-Weber syndrome) in two cases. The number of AEDs used before surgery ranged from one to three (mean 2.3). Prior to hemispherectomy, all children but one had some degree of motor impairment.

In the group of 12 children assessed with intelligence scales (nine girls), the median age at onset was 1.0 year with a broad range from 0.0–11 years, and the interval between seizure onset and hemispherectomy ranged from 1.1–11.7 (median 6.2) years. Five children underwent a left-sided functional hemispherectomy. The pathology was developmental (cortical dysplasia) in one child, acquired (ischaemia or porencephaly) in six and progressive (Rasmussen encephalitis or Sturge-Weber syndrome) in five children. One girl (Patient 18) was included who had a resection of the left occipital lobe due to severe seizures, 1½ years prior to hemispherectomy. Before hemispherectomy the participants were taking one to five (mean 2.42) AEDs. Only one child (Patient 29) had no motor impairment.

Table 3.1A Demographics, side of hemispherectomy, aetiology/pathology type, seizure outcome and mental developmental delay, before and after hemispherectomy, of 17 children assessed with Developmental Scales

Pt	Sex	Epilepsy onset (years)	Hemispher-ectomy (years)	Epilepsy duration (years)	Hemisphere resected	Aetiology/ pathology type	Previous AEDs	Seizure outcome (class)	Mental developmental delay (months)	
									Before	Two years after
1♦	F	0.25	0.75	0.5	Left	CD/Dev	3	1A	7	26
2♦	F	0	2.1	2.1	Right	HME/Dev	3	1A	12	30
3♦	M	0	0.23	0.23	Right	CD/Dev	3	1A	2	12
4	M	0	2.15	2.15	Right	PC/Acq	2	1A	15.5	32
5♦	M	0	0.5	0.5	Left	CD,TSC/Dev	1	1A*	2.5	1
6♦	M	0	1.49	1.49	Right	HME/Dev	2	1A	14	25
7♦	F	0	0.22	0.22	Right	HME/Dev	3	1A	1.5	28
8	F	0.58	3	0.28	Left	HME/Dev	1	1A	17	23
9♦	M	0.5	3.1	0.19	Right	HME/Dev	2	1A	25.5	41
10♦	F	0	0.6	0.6	Left	CD/Dev	2	1A	3	6
11♦	M	0.33	1.1	0.77	Left	Isch/Acq	3	1A	8	35
12♦	F	0.33	2.03	1.7	Left	PC/Acq	2	1A*	21	37
13	M	0.58	1.45	0.87	Right	PC/Acq	3	1A	6	30
14♦	M	0.58	2.64	2.06	Left	PC/Acq	2	1A	30	47.5
15♦	F	0	1.05	1.05	Right	SWS/Prog	3	1A	4	15
16♦	M	0	0.37	0.37	Right	SWS/Prog	2	1A	3	20
17♦	F	0.25	2.48	2.23	Left	Multi/Dev	1	2D	23.5	48

* Free of antiepileptic medication two years after hemispherectomy; ♦ Arrest or deterioration after the onset of epilepsy (from structured interviews with parents); Acq: acquired; CD: cortical dysplasia; Dev: developmental; F: female; HME: hemimegalencephaly; Isch: ischaemia; M: male; Multi: multiple developmental anomalies; PC: porencephalic cyst; Pt: patient; Prog: progressive; SWS: Sturge-Weber Syndrome; TSC: Tuberous Sclerosis Complex.

Table 3.1B Demographics, side of hemispherectomy, aetiology/pathology type, Engel classification and intelligence, before and after hemispherectomy, of 12 children assessed with Intelligence scales

Pt	Sex	Epilepsy onset (years)	Hemispher-ectomy (years)	Epilepsy duration (years)	Hemisphere resected	Aetiology/ pathology type	Previous AEDs	Seizure outcome (class)	FSIQ (VIQ, PIQ)	
									Before	Two years after
18	F	1.5	6.44	4.94	Left	CD/Dev	3	1A	73 (82;67)	61 (67;61)
19♦	F	8	14.3	6.3	Right	Ras/Prog	5	1A	68 (71;70)	57 (57;62)
20♦	F	0.33	11.8	11.47	Left	PC/Acq	1	1A	47 (51;47)	59 (65;61)
21	M	2	8.22	6.22	Left	Isch/Acq	1	1A	74 (87;68)	85 (90;84)
22	M	0.25	3.76	3.51	Right	Isch/Acq	1	1A*	72	71
23♦	F	0	6.3	6.3	Right	Isch/Acq	2	1A*	60	68
24♦	F	5.56	8.4	2.84	Right	Ras/Prog	3	3A	59 (66;59)	56 (66;51)
25♦	M	11	12.12	1.12	Left	Ras/Prog	3	1A	69 (83;61)	77 (85;73)
26♦	F	7.75	11.48	3.73	Left	Ras/Prog	3	3A	47 (47;47)	62 (67;63)
27	F	0.33	7.56	7.23	Left	SWS/Prog	3	1A	52	53
28	F	0.5	12.24	11.74	Right	PC/Acq	2	3A	63 (75;58)	63 (75;59)
29	F	0	6.96	6.96	Right	Isch/Acq	2	1A	49	60

* Free of antiepileptic medication two years after hemispherectomy; ♦ Arrest or deterioration after the onset of epilepsy (from structured interviews with parents); Acq: acquired; CD: cortical dysplasia; Dev: developmental; F: female; intell: intelligence; Isch: ischaemia; M: male; PC: porencephalic cyst; Pt: patient; Prog: progressive; RAS: Rasmussen encephalitis; SWS: Sturge-Weber Syndrome.

Assessment

The children were assessed according to a standard protocol with fixed intervals: shortly before hemispherectomy and approximately 6, 12 and 24 months thereafter. In accordance with good clinical practice, tests or test versions were selected according to the age and cognitive level of the children. Seizure outcome was recorded using Engel's Classification.[4] Histories of all children were taken through semi-structured interviews with parents. Based on these data, previous or pre-morbid levels of cognitive functioning were estimated. All children had at least three assessments including one presurgical and one final assessment (24 months after hemispherectomy).

In 17 children, mental development was measured using the Dutch versions of the Bayley Scales of Infant Development (BSID I and II).[5,6] It was anticipated that MDI (mean=100) could not be specified more precisely than 'under the lowest scale value' (of 51 or 55, depending on the scale used). Thus, for every child, we converted the raw scores to the corresponding MA, as obtained from reference data provided in norm tables of the test manual. MA gives no clue with respect to delay or advance in mental development. Therefore, we calculated MDD by subtracting the child's MA from his/her chronological age.

Twelve children were assessed using Dutch versions of intelligence scales; Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R),[7] Wechsler Intelligence Scales for Children-Revised (WISC-RN),[8] McCarthy Developmental Scales (MOS 2½–8½)[9] and the Kaufman Assessment Battery for Children (GOS 2½–4½).[10] Depending on the scale, full-scale (FS) IQ and its verbal (VIQ) and performal (PIQ) components, or the general cognitive index (GCI), were determined.

Data analysis

Data were analyzed using SPSS software version 15.0.[11] Spearman's rank correlation coefficient was used to analyse the association between the time of assessment and MA, MDD and FSIQ, and to analyse the associations between age at onset of epilepsy and duration of epilepsy with MDD and FSIQ. Differences in MDD and FSIQ between the three pathology types were analysed using the Kruskal-Wallis one-way analysis of variance and by comparing lateralisation of epilepsy /hemispherectomy with the Mann-Whitney U test. The Friedman two-way analysis of variance was used to analyse differences in FSIQ across the four assessments and the Wilcoxon matched-pairs signed-ranks test to analyse differences in FSIQ between the first and last assessment and between IQ components (VIQ versus PIQ), before and two years after hemispherectomy. The significance level, alpha, was set at $p<0.05$ (two-tailed) and the significance of correlations was evaluated according to Cohen.[12]

In order to calculate the proportion of children whose FSIQ changed significantly, a "significant change" was defined as an increase or decrease of at least 10 points, which is approximately the standard error of measurement for Wechsler intelligence scales.

Results

Children assessed using developmental scales (Table 3.1A)

The case histories revealed that mental development had arrested or even deteriorated following the onset of catastrophic epilepsy in 14 of the 17 children.

The MDI could not be quantified, either before or after hemispherectomy, more precisely than below 51 or 55, in the range where any differences are undetectable, rendering statistical analysis redundant. However, the notion of a developmental standstill was contradicted by a steady increase of MA (Figure 3.1). MA and time of assessment correlated very strongly for 12 (rho>0.9) and 4 (rho>0.5) children, which also indicated at least some development. In one child (Patient 13), the strongly negative correlation (rho=-0.775) indicated a loss of developmental skills. MDD and time of assessment were very strongly correlated in 16 children (rho>0.9), indicating that the development, as established by MA, was so poor that delay increased. One negative correlation (Patient 5) between MDD and time (of moderate strength; rho=-0.32) indicated a decrease in delay.

The correlation between age at onset and MDD, before and 24 months after hemispherectomy, were positive and moderate (rho=0.6), respectively. Longer duration of epilepsy was associated with more severe delay, both prior to hemispherectomy (rho=0.89) and 24 months thereafter (rho=0.61). A significant difference in MDD was not found between the three pathology types or between the groups with left and right-sided epilepsy and intervention, either prior to hemispherectomy or 24 months thereafter.

Two years after surgery, 16 children (94%) remained free of seizures (Class 1A). The MA of one child (Patient 17) with nocturnal seizures only (Class D) did not increase over the two years following surgery.

Children assessed with intelligence scales (Table 3.1B)

The case histories revealed that development had arrested or even deteriorated following the onset of epilepsy in six children. The four children with Rasmussen encephalitis (Patients 19, 24, 25, and 26) had developed normally and had been good students in mainstream education until the onset of seizures. Their pre-morbid FSIQs were estimated at, at least, 100.

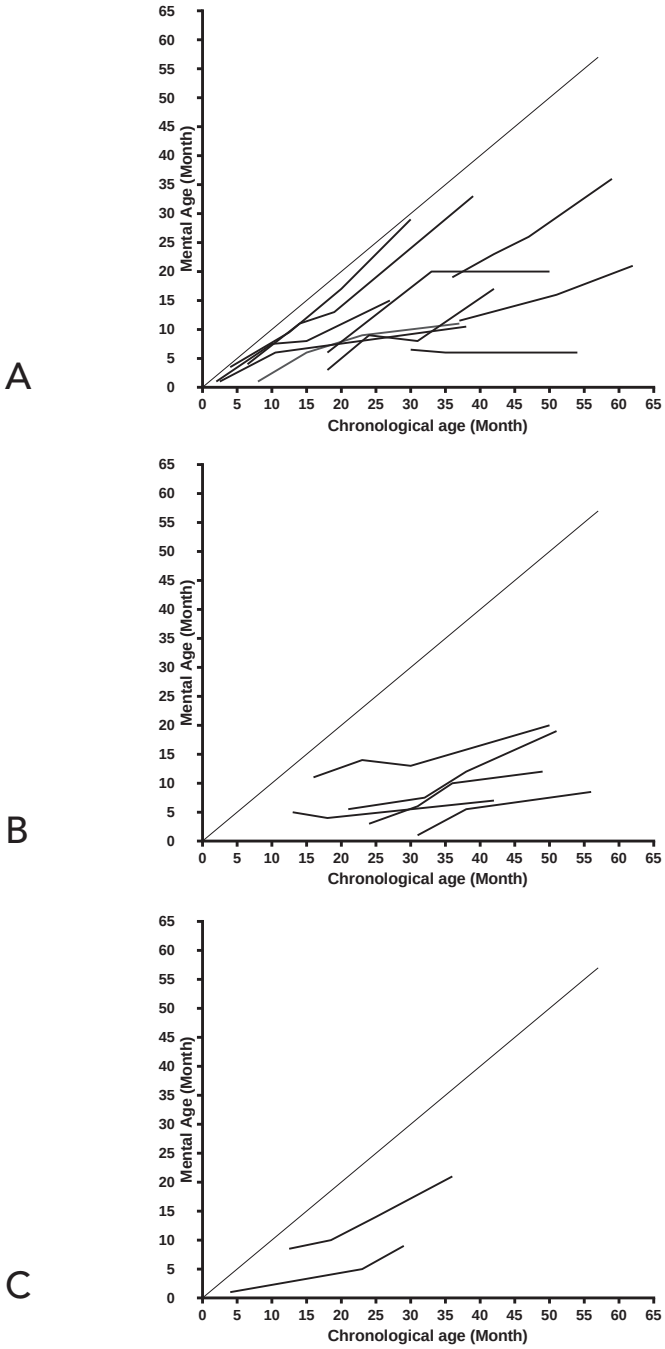

Figure 3.1 Mental development expressed as mental age before and 24 months after hemispherectomy. The initial point of each graph corresponds to the initial assessment prior to hemispherectomy. A) Infants and preschoolers with developmental pathology (n=10). B) Infants and preschoolers with acquired pathology (n=5). C) Infants and preschoolers with progressive pathology (n=2).

FSIQ did not differ significantly across the four assessment intervals. Also, no significant difference was found when the first (mean FSIQ=61.1; SD=10.3) and last assessment intervals (mean FSIQ=64.3; SD=9.3) were compared (Figure 3.2).

Prior to hemispherectomy, FSIQ ranged from 47–74. Individually, FSIQ correlated positively with time of assessment, indicating increasing FSIQ in seven children [very strongly in three (Patients 20, 21, 26; rho>0.90]). In five children, the correlation was negative, indicating diminishing FSIQ [strong in one (Patient 19; rho >0.5)].

A clinically relevant difference in FSIQ, of more than 10 points, was present in six children, with improvement in four (Patients 20, 21, 26 and 29) and deterioration in two (Patient 18 for whom the hemispherectomy was the second neurosurgical intervention and Patient 19 who developed negativistic behaviour which necessitated psychiatric treatment).

Performal IQ was lower than verbal IQ in most children, before (p=0.018) and 24 months after hemispherectomy (p=0.035), irrespective of the side of epilepsy/intervention.

The correlation between age at onset and presurgical FSIQ and FSIQ 24 months after surgery was weak. The correlation between duration of epilepsy and both presurgical FSIQ and FSIQ 24 months after surgery, was moderate and negative (rho=-0.4). A significant difference in FSIQ was not found, either prior to hemispherectomy or 24 months thereafter, between the three pathology types or between the groups with left and right-sided epilepsy/intervention.

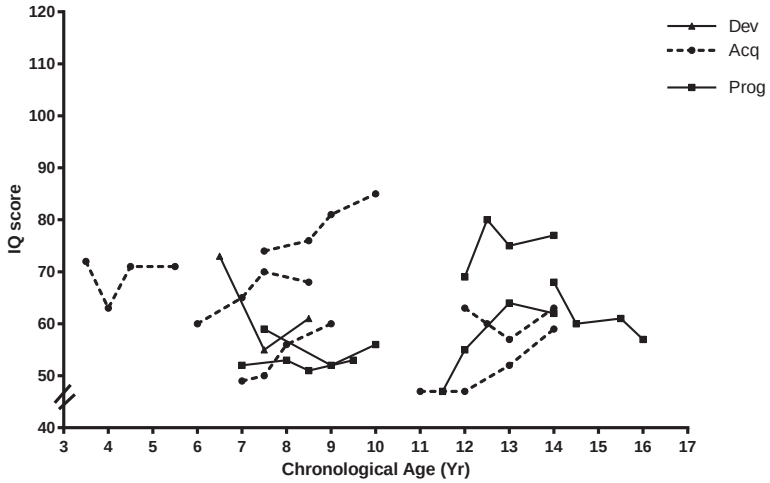

Figure 3.2 Intelligence expressed as Full Scale Intelligent Quotient (FSIQ) before and 24 months after hemispherectomy. The initial point of each graph corresponds to the initial assessment prior to hemispherectomy. Patients with developmental (Dev), acquired (Acq) and progressive (Prog) pathology are presented separately, as indicated.

During the follow-up period, seizures did not recur (Class 1A) in nine children (75%) and the remaining three children (Patients 24, 26, 28) suffered a few seizures per year (Class IIIA, 75% reduction). For two of these three children (Patients 24, 28) FSIQ did not change and for the remaining child (Patient 26) an increase of 15 points, did not compensate for FSIQ-loss before hemispherectomy.

Discussion

After hemispherectomy, the MDIs and FSIQs of the 29 children in this study remained far below the mean values of a normal peer reference group, similar to what has been reported previously (see the recent review by Samargia and Kimberly[2]). To infer that hemispherectomy may ameliorate seizure status, but not cognition, however, is premature. Subtle change may be obscured by the combined analyis of MDI and IQ[13-15] and by the fact that differences cannot be measured for a child who performs at a level which corresponds to the lower tail of the distribution of scores. These arguments compelled us to analyse results obtained by both types of scales separately.

Outcome in children assessed with developmental scales

Parents of infants and pre-school children with epilepsy and associated cognitive deficits were adamant that relevant change had occurred after hemispherectomy that had resulted in cessation or significant reduction of seizures. Yet, the unaltered low MDI did not corroborate these positive observations by parents. Measurement of mental age and mental developmental delay, however, allowed us to unveil and quantify change. Even children with catastrophic epilepsy, who had a very poor developmental prognosis with ongoing seizures, resumed mental development after hemispherectomy, which was reflected by clear increases in mental age in all but one child. Still, the increase in mental age was smaller than that of healthy peers. Thus, removal of one hemisphere did not impair mental development, but rather allowed for subsequent development without, however, undoing the damage already caused by the underlying disease and/or epilepsy.

Generally, the relationship between younger age at onset of epilepsy and mental retardation is strong.[16,17] In the present study, mental retardation was an overwhelming feature of the children. Any association between older onset age and severe mental delay is difficult to interpret and may be spurious, since age at onset is confined to only a relatively small range.

Longer duration of epilepsy (in terms of time between onset of epilepsy and hemispherectomy) was associated with more severe mental delay, both before and 24 months after

hemispherectomy. This would seem to support the plea for early hemispherectomy[18,19] in very young children with mental delays.

Performance in mental developmental scales relies heavily on sensory and motor domains. It is, however, implausible that motor impairment biased the results of the developmental scales differentially across the four assessment intervals, since motor impairment existed prior to surgery and remained almost unchanged thereafter, as reported in a study on motor outcome after hemispherectomy in the same group of children.[20]

Outcome in children assessed with intelligence scales

The overall gain in IQ scores over the two years following hemispherectomy was very small and clinically unimportant (on average less than four points). Collectively, this indicates that intelligence in these older children conformed with normal intellectual growth (under normal circumstances IQ is virtually invariant over time). However, this combined analysis masked individual variation; four of the 12 children showed a significant amelioration of IQ and two showed a significant deterioration (one for whom the hemispherectomy was the second neurosurgical intervention and one who developed negativistic behaviour).

For the four children with Rasmussen encephalitis it is important to note that, prior to hemispherectomy, the disease process had caused a dramatic decline in IQ and none of the children recovered to anywhere near their pre-morbid level after hemispherectomy. Thus, early removal of the affected hemisphere in the disease process is important for the treatment of this condition. Furthermore, the relationship between longer epilepsy duration and a worse IQ again suggests that surgery should not be unduly postponed, as urged by Freitag and Tuxhorn.[21]

In adults, verbal IQ is predominantly vulnerable to left-hemisphere damage and performal IQ to right-hemisphere damage. The present finding that performal IQ is lower than verbal IQ in children, before and after *both* left and right hemispherectomy, rather confirms that the adult pattern does not necessarily apply in children, as discussed previously.[14] In children, reorganisation of function is thought to be supported by more plasticity, compared to adults. However, the related concepts of functional plasticity and crowding are still heavily debated. As St. James-Roberts[22] convincingly argued, intelligence after hemispherectomy can be understood without both concepts. Others are also reticent with regards to the power of plasticity, especially for recovery.[23]

A significant influence of developmental, acquired or progressive underlying pathology on mental development and intelligence was not found for either the group of children

assessed using developmental scales or older children who were assessed using intelligence scales, in contrast to previously reported studies.[13-15,24] Comparison is hampered by the fact that pathology is not uniformly classified across studies. Ideally, classification should be based on pathologically homogeneous subgroups, however, this was beyond the scope of the present study.

We are aware of serious limitations of the present study. As is the case for most longitudinal outcome studies of epilepsy surgery, the one-assessment baseline limited our pre and post-hemispherectomy comparison study. However, histories were taken of all children based on interviews with their parents. Although long-term parental recall has limited validity,[25] the recollections pertaining to the younger children were of a recent nature and for the older children school career was a robust marker. The interviews yielded sufficient information to assess whether or not developmental stagnation or even deterioration had occurred. In the group of infants and preschoolers assessed using developmental scales, we measured change by means of a difference score. Difference scores present a disadvantage when comparing children of different ages, however, as our aim was to make an intra-individual comparison, the difference score was sufficient but not ideal. Furthermore, uncoupling the multiple and sometimes mutually dependent nature of variables, such as aetiology, pathology, age at onset and epilepsy duration, which may have influenced the outcome, was beyond the scope of this study. Further study is required to unravel these intricacies which have consequences for prognosis and counselling. Finally, a control group is lacking in this longitudinal study, there are, however, clear limitations in establishing such a control group in order to detect change in very young epileptic children with severe mental deficits who undergo hemispherectomy.

Notwithstanding the limitations, this prospective countrywide study with fixed time intervals contributes to refining our understanding of cognitive outcome of paediatric hemispherectomy: The approach to analyse data obtained using developmental scales and intelligence scales separately, as well as a more individual approach, has identified subtle mental improvements in younger children and variability in older children.

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References

1. Spencer, S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7:525-37.

2. Samargia SA, Kimberly TJ. Motor and cognitive outcomes in children after functional hemispherectomy. Pediatr Phys Ther 2009;21:356-61.

3. Anastasi A. Psychological testing. New York: Macmillan Publishing Company; 1988.

4. Engel JJ, van Ness P Jr, Rasmussen T, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel J Jr (Ed). Surgical treatment of the epilepsies, 2nd ed. New York: Raven Press; 1993:609-21.

5. van der Meulen BF, Smrkovský M. Bayley Developmental Scales, Dutch adaptation. Lisse: Swets & Zeitlinger; 1983.

6. van der Meulen BF, Ruiter SAJ, Lutje Spelberg HC, Smrkovský M. Bayley Scales of Infant Development-II, Dutch adaptation. Lisse: Swets Test Publishers; 2003.

7. Vander Steene G, Bos A. Wechsler Preschool and Primary Scale of Intelligence, Flemish-Dutch adaptation, provisional version, 2nd edition. Lisse: Swets & Zeitlinger; 1997.

8. van Haassen PP, de Bruyn EEJ, Pijl YJ. Wechsler Intelligence Scale for Children – Revised, Dutch adaptation. Lisse: Swets & Zeitlinger; 1986.

9. van der Meulen BF, Smrkovský M. McCarty Developmental Scales, Dutch adaptation. Lisse: Swets & Zeitlinger; 1986.

10. Neutel RJ, van der Meulen BF, lutje Spelberg HC. Kaufman Assessment Battery for Children, Dutch adaptation. Lisse: Swets & Zeitlinger; 1996.

11. SPSS for Windows, Rel. 15.0 2007. Chicago: SPSS Inc.

12. Cohen J. Statistical power analysis for the behavioural sciences, 2nd ed. New Jersey: Lawrence Erlbaum; 1988.

13. Devlin AM, Cross JH, Harkness W, et al. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. Brain 2003;126:556-66.

14. Pulsifer MB, Brandt J, Salorio CF, et al. The cognitive outcome of hemispherectomy in 71 children. Epilepsia 2004;45:243-54.

15. Lettori D, Battaglia D, Sacco A, et al. Early hemispherectomy in catastrophic epilepsy: a neuro-cognitive and epileptic long-term follow-up. Seizure 2008;17:49-63.

16. Vasconcellos E, Wyllie E, Sullivan S, et al. Mental retardation in pediatric candidates for epilepsy surgery: the role of early seizure onset. Epilepsia 2001;42:268-74.

17. Cormack F, Cross JH, Isaacs E, et al. The development of intellectual abilities in pediatric temporal lobe epilepsy. Epilepsia 2007;48:201-4.

18. Basheer SN, Connolly MB, Lautzenhiser A, et al. Hemispheric surgery in children with refractory epilepsy: seizure outcome, complications, and adaptive function. Epilepsia 2007;48:133-40.

19. Jonas R, Nguyen S, Hu B, et al. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology 2004;62:1712-21.

20. van Empelen R, Jennekens-Schinkel A, Buskens E, Helders PJ, van Nieuwenhuizen O. Functional consequences of hemispherectomy. Brain 2004;127:2071-9.

21. Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. Epilepsia 2005;46:561-7.

22. St. James-Roberts I. A reinterpretation of hemispherectomy data without functional plasticity of the brain. Brain and Lang 1981;13:31-53.

23. Duval J, Braun CM, Montour-Proulx I, et al. Brain lesions and IQ: recovery versus decline depends on age of onset. J Child Neurol 2008;23:663-8.

24. Vining EP, Freeman JM, Pillas DJ, et al. Why would you remove half a brain? The outcome of 58 children after hemispherectomy-the John Hopkins experience: 1968 to 1996. Pediatrics 1997;100:163-71.

25. Jaspers M, de Meer G, Verhulst FC, Ormel J, Reijneveld SA. Limited validity of parental recall on pregnancy, birth, and early childhood at child age 10 years. J Clin Epidemiol 2010;63;185-91.

Chapter 4

Contralateral MRI abnormalities affect seizure and cognitive outcome after hemispherectomy

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Abstract

Objective: To explore whether EEG and MRI abnormalities in the "healthy" hemisphere influence seizure and cognitive outcome after functional hemispherectomy.

Methods: This is a retrospective consecutive cohort study of 43 children who underwent functional hemispherectomy between 1994 and 2008. Results of preoperative EEG recordings were reviewed for the existence of (inter)ictal epileptic or background abnormalities in the contralateral hemisphere. Preoperative MRIs were re-examined for the existence of unequivocal contralateral abnormalities. Postoperative seizure status was assessed, and of 34 children, intelligence quotient (IQ) or mental developmental index (MDI) scores were obtained preoperatively and postoperatively. Seizure freedom was defined as Engel 1A. Contralateral EEG and MRI abnormalities were studied in relation to seizure and cognitive outcome.

Results: Thirty-three children achieved seizure freedom (77%). Of the 11 patients with contralateral MRI abnormalities, only 45% were seizure free, compared with 88% of the 32 patients without contralateral MRI lesions ($p=0.030$). Children with contralateral MRI lesions more often were severely retarded after surgery (MDI/IQ <55; 90% vs 42%, $p=0.030$). Postoperative MDI/IQ improved in none of the children with, but in 38% of those without contralateral MRI abnormalities ($p=0.034$). Contralateral epileptic or background EEG abnormalities did not affect seizure outcome or postoperative cognitive performance. Four of 6 children with bilateral epileptic encephalopathy reached seizure freedom.

Conclusion: Unambiguous contralateral MRI abnormalities are significantly associated with seizure recurrence, severe mental delay, and lack of cognitive improvement, and may be considered a relative contraindication for hemispherectomy. Contralateral EEG abnormalities do not negatively influence postsurgical outcome.

Introduction

Surgical outcome after hemispherectomy should be expressed in terms of seizure freedom and cognitive recovery,[1] because many children show developmental arrest or regression before surgery.[2,3] An appropriate selection of surgical candidates and prediction of postoperative outcome are crucial.[2-4] Postoperatively, children inherently depend on their remaining, "unaffected" hemisphere. Its functional and structural integrity may determine seizure outcome and functional recovery. We therefore expected contralateral MRI and EEG abnormalities to correlate with outcome. Previous studies suggested that bilateral or predominantly contralateral EEG abnormalities do not necessarily affect postoperative seizure outcome,[5,6] but their influence on cognitive outcome has not been systematically studied. In a recent study of 110 hemispherectomy patients,[7] contralateral, often mild MRI abnormalities were retrospectively identified in 74% of the children and were not associated with seizure outcome. In our experience, however, children with obvious contralateral magnetic resonance (MR)-visible pathology do worse after surgery. The aim of this study was to correlate unequivocal preoperative contralateral MRI and EEG abnormalities with seizure and cognitive outcome in children who underwent hemispherectomy.

Methods

This is a retrospective consecutive cohort study of all 43 children who underwent hemispherectomy for intractable hemispheric epilepsy between 1994 and 2008 in Utrecht. Preoperatively, all patients underwent a standardized evaluation programme, results of which were discussed in the countrywide epilepsy surgery meetings and reported in the Dutch Collaborative Epilepsy Surgery Programme database. The decision to perform hemispherectomy was carefully balanced against the risks of neurological deterioration. In all children at least the EEG or the MRI results were clearly lateralising; bilateral MRI abnormalities were never the sole reason to reject a child from surgical treatment. We collected data on age at epilepsy onset and surgery, side of surgery, surgical complications; antiepileptic drug (AED) use; and etiology, which was classified as developmental, acquired, or progressive.[2]

Study variables

Preoperative MRI scans were acquired on 0.5T (n=7) and 1.5T (n=36) MR systems (Philips Medical Systems, Best, the Netherlands) using a regular head coil. Scanning protocols were identical for both systems, consisting of transverse T2-weighted spin-echo images

(repetition time [TR] / echo times [TE]: 2,400 / 30, 100; slice thickness 6 mm; field of view [FOV] 230; matrix size 230×256), coronal fluid-attenuated inversion recovery images (TR / inversion time / TE: 11,000 / 2,200 / 140; slice thickness 4 mm; FOV 230; matrix size 230×256), and transverse 3-dimensional-acquired T1-weighted gradient-echo images (TR / TE / flip angle: 30 / 13 / 30; partition thickness 1.2 mm; FOV 230; matrix size 166×256). Scans were examined for the existence of unequivocal abnormalities in the "unaffected" hemisphere by an experienced epilepsy neuroradiologist (G.K.) and pediatric neurologist (K.P.B.), both blinded for seizure and cognitive outcome. In only 3 of 43 children, initial evaluation was discordant and interobserver agreement was high (kappa=0.811). Scans with possible abnormalities were then reevaluated by both investigators until agreement was reached in all. In 3 patients, small single white matter lesions or isolated areas of subtle T2 hyperintensity were found (without ventricular dilation, tissue loss, or cortical/subcortical involvement) that were not included for further analysis.

All reports of ictal, interictal, and 24-hours EEG registrations were reviewed for abnormalities in the contralateral hemisphere by 2 investigators together (K.B., K.P.B.). When they did not reach agreement on the interpretation, an experienced neurophysiologist (F.L.) re-examined the reports to reach a final conclusion. We scored the existence of preoperative contralateral 1) interictal epileptic discharges, defined as sharp waves, spikes, or (poly) spike-wave complexes that had to be detected in at least 2 EEGs, 2) background slowing, defined as slowed or inappropriate-for-age background rhythms or the absence of normal sleep phenomena, detected in at least 2 EEGs, not recorded under the influence of sedative medication, 3) ictal spreading or generalization of epileptic abnormalities to the contralateral hemisphere, and 4) an independent ictal focus in the contralateral hemisphere, which was defined as a focus producing a clinical or subclinical electrographic seizure, visible on at least 1 EEG. Diffuse epileptic encephalopathy (EE) was diagnosed when at least 1 EEG revealed bilateral severe epileptic discharges with a disturbed background pattern, including hypsarrhythmia or burst suppression.

Outcome measures

Seizure outcome

Postoperative seizure outcome was determined from the medical files and checked by telephone interviews with the parents. We differentiated between children who remained seizure free until the latest follow-up (Engel score 1A[1,8]), and those who had temporary or permanent seizure recurrences.

Cognitive outcome

Children were assessed using tests or test versions according to their age and cognitive level. IQ or mental developmental index (MDI) scores, depending on the type of tests the children were able to take, were obtained by a neuropsychologist (M.S.) in 34 children, shortly before hemispherectomy and 1 (n=6) or 2 (n=28) years after surgery. Tests to assess MDI scores were the Dutch versions of the Bayley developmental scales (Bayley ontwikkelingsschaal 2–30, Bayley Scales of Infant Development II) and McCarthy developmental scales. IQs were determined with the Groninger developmental scales, Stutsman intelligence test for infants, Snijders-Oomen non-verbal intelligence test (SON 2½–7) or Wechsler scales (Wechsler Preschool and Primary Scale of Intelligence, Wechsler Intelligence Scale for Children [WISC]–revised Dutch edition, WISC-III). Results of neuropsychological testing were categorized as normal (MDI/IQ >85), mild delay (75–85), moderate delay (55–75) or severe mental delay (MDI or IQ scores <55).[2] In the latter group were many children in whom mental development could not be determined more precisely than 'below the lowest mental developmental index provided by the manual', corresponding to values <55. We dichotomized cognitive outcome as severely delayed (MDI/IQ <55) or not.[2] To assess relevant growth in cognitive function after surgery, we identified those patients in whom postoperative cognitive scores increased with ≥10 points, compared with identical tests performed preoperatively.

Statistical analysis

Categorical data were analyzed with Fisher's exact test. We corrected for multiple comparisons between determinants (contralateral MRI or EEG abnormalities) and the three outcome measures (seizure recurrence, severe developmental delay, no cognitive improvement), using the Step-down Finner algoritm.[9] The significance level was set at $p<0.05$ (two-tailed). The relation between age (seizure onset and surgery), epilepsy duration, and outcome measures was explored by logistic regression analyses. Where possible, odds ratios (ORs) are given. Multivariate analysis was not performed because of the small size of subgroups within this cohort.

Results

Preoperative patient characteristics

Of the 43 hemispherectomized children, 18 were male. Nineteen had developmental pathology; 9 with hemimegalencephaly (1 with tuberous sclerosis complex [TSC]), 9

with multilobar or hemispheric cortical dysplasia (1 with TSC), and 1 with a complex developmental anomaly, with corpus callosum agenesis, interhemispheric cyst, and bilateral colpocephaly. Fifteen children had stable acquired pathology; 7 with perinatal ischemic lesions, 7 with porencephalic cysts, and 1 with hemiconvulsions hemiplegia epilepsy syndrome. In 9 children, etiology was considered progressive; 4 had Sturge-Weber syndrome (SWS) and 5 had Rasmussen's encephalitis. The mean age at onset was 1.2 years (SD 2.4, range 0.0–11.0), the duration of epilepsy 2.9 years (SD 3.1, range 0.2–11.7) and the age at surgery was 4.1 years (SD 4.0, range 0.2–14.3). The mean follow up time was 6.9 years (SD 3.9, range 1.0–15.7). Twenty-five of 34 patients (74%) were severely delayed; the others had a moderate developmental delay. Younger age at epilepsy onset, shorter duration of epilepsy, and younger age at surgery were associated with lower preoperative MDI/IQ scores (p=0.041 [OR 0.682, confidence interval (CI) 0.473–0.985]; p=0.032 [OR 0.736, CI 0.556–0.974], and p=0.004 [OR 0.714, CI 0.567–0.898], respectively). Preoperative cognition was not associated with pathologic subgroups; 13 (87%) patients with developmental pathology, 8 (67%) with acquired pathology and 4 (57%) with progressive pathology were severely retarded.

Preoperative MRI

Unequivocal contralateral MRI abnormalities were seen in 11 patients (2 of 7 with 0.5T scans and 9 of 36 1.5T scans) and consisted of various degrees of gliosis in combination with ventricular dilatation or white matter atrophy (n=4, acquired etiology); dilated ventricle with abnormal gyration and loss of white matter (n=2, developmental etiology); focal infarct (n=1, acquired); enlarged colpocephalic ventricle with interhemispheric cyst (n=1, developmental); bilateral hydrocephalus (one with porencephalic cyst and additional contralateral white matter lesions, the other with SWS and a contralateral ventriculoperitoneal drain), and cortical tubers (n=1). Typical examples are illustrated in Figure 4.1. In 3 patients, subtle white matter abnormalities were found, that were not included for further analysis (Figure 4.2). The existence of contralateral MRI lesions was not associated with etiology or with EEG abnormalities. The number of AEDs used before surgery and at time of neuropsychological follow-up did not differ between patients with and those without contralateral MRI abnormalities.

Preoperative EEG analysis

Contralateral interictal discharges were reported in 24 patients (56%), slowing of background activity was reported in 24 (56%), ictal spreading was reported in 18 (42%), and an independent contralateral ictal focus in 4 (9%), of whom 3 also had interictal epileptic

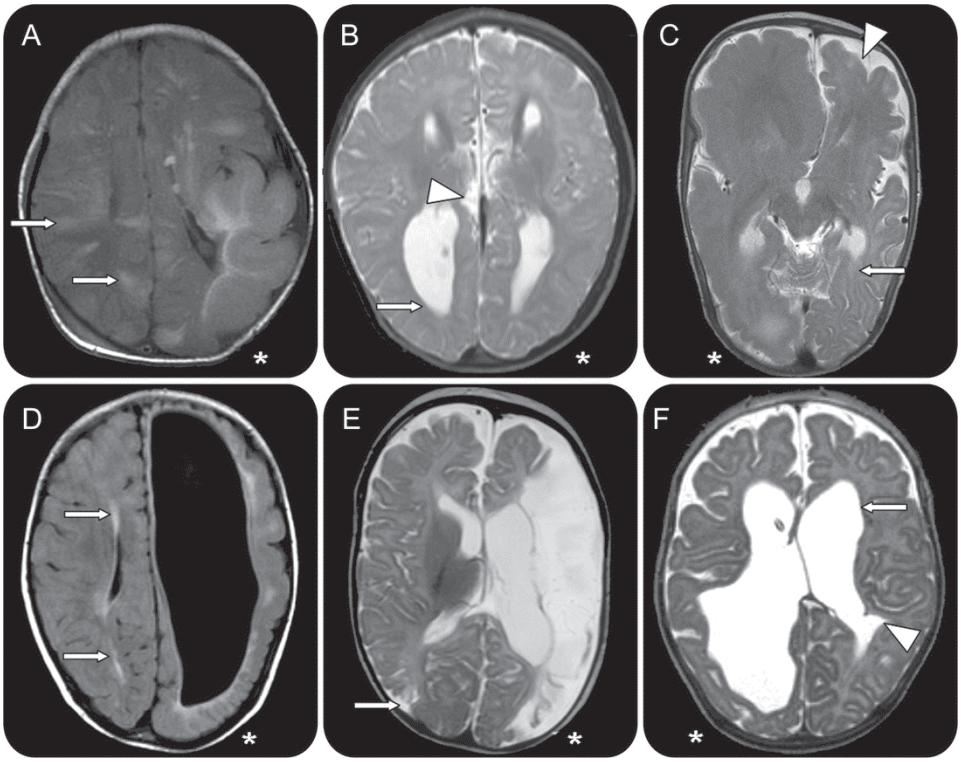

Figure 4.1 Typical examples of unequivocal contralateral MRI abnormalities.
(A) Axial T2 fluid-attenuated inversion recovery (FLAIR) image of a girl with left sided hemimegalencephaly in the context of tuberous sclerosis complex, who underwent surgery at age 16 months. In the contralateral hemisphere, multiple subcortical tubers are seen (arrows). (B) T2-weighted MRI of a 6-year old girl with a complex bilateral developmental anomaly, consisting of bilateral ventricular enlargement, colpocephaly (arrow), corpus callosum agenesis, delayed myelination and an interhemispheric cystic malformation (arrowhead). (C) Right-sided hemimegalencephaly in a boy who underwent hemispherectomy at age 6 months. T2-weighted MRI reveals a contralateral abnormal frontal gyration pattern (arrowhead) and a reduced volume of the occipitotemporal white matter (arrow). (D) Three-year-old girl, with a large left sided porencephalic cyst. T2-FLAIR MRI reveals extensive areas of periventricular hyperintensity and white matter loss, consistent with gliosis, in the contralateral hemisphere (arrows). (E) Large left-sided middle cerebral artery infarct in a boy who underwent hemispherectomy at age 13 months. T2-weighted MRI shows contralateral focal loss of occipital cortical and subcortical tissue and gliosis (arrow), consistent with infarction. (F) Bilateral posthaemorrhagic ventricular dilatation in a boy with a perinatal right hemispheric bleeding. Right-sided hemispherectomy was performed at age 2 years. T2-weighted MRI reveals contralateral ventricular enlargement (arrow) with additional cystic periventricular white matter lesions (arrowhead). * Side of surgery.

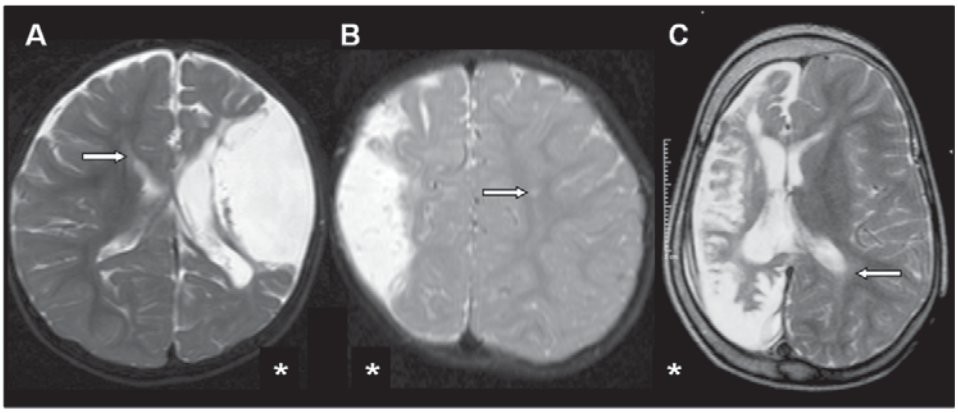

Figure 4.2 Subtle contralateral white matter abnormalities, not included for analysis.
T2-weighted axial MRI scans of the 3 children with small, isolated areas of white matter hyperintensity (arrows) in the contralateral hemisphere, with no accompanying loss of white matter, ventricular dilation, or cortical/subcortical involvement. (A) Girl with a large left-sided perinatal middle cerebral artery infarct, who underwent hemispherectomy at the age of two years. (B) Four-year old boy with perinatal right-sided middle cerebral artery infarct. (C) Extensive right-sided ischemic damage of the right hemisphere in a four-year old girl. * Side of surgery.

abnormalities. Contralateral interictal epileptic abnormalities were more frequent in patients with acquired pathology (87% compared with 37% and 44% of those with developmental and progressive diseases respectively, p=0.011). Contralateral EEG abnormalities were not associated with preoperative MDI/IQ scores. Six patients had a diffuse epileptic encephalopathy; 3 had Ohtahara syndrome with bilateral burst suppression, 2 had West syndrome with bilateral but asymmetrical hypsarrhythmia and 1 patient had bilateral but asymmetrical severe and frequent multifocal epileptic and background abnormalities.

Postoperative outcome

Thirty-three children (77%) reached permanent postoperative seizure freedom. Etiology was not related to seizure outcome, nor was gender, side of surgery, presurgical cognitive functioning, or age at onset or surgery. Mean time from surgery to seizure recurrence was 1.38 years (SD 1.67). Contralateral MRI abnormalities were associated with seizure recurrence (Table 4.1); 13% of patients without MRI abnormalities had seizure recurrence compared with 55% of patients with contralateral MRI abnormalities (p=0.030). Seizures recurred earlier in children with contralateral MRI abnormalities (0.65 years, SD 0.82) compared with those without (2.49 years, SD 2.13, p=0.020). None of the contralateral EEG abnormalities were

Table 4.1 Contralateral MRI abnormalities in relation to seizure and cognitive outcome

Contralateral MRI abnormalities	Seizure outcome (n=43)		Cognitive outcome (n=34)					
	Postoperative seizure freedom (n=33/43)		Preoperative MDI/IQ <55 (n=25/34)		Postoperative MDI/IQ <55 (n=19/34)		No postoperative increase in MDI/IQ (n=25/34)	
	n (%)	p-value[a]	n (%)	p-value[a]	n (%)	p-value[a]	n (%)	p-value[a]
Yes	5/11 (45)	0.030	9/10 (90)	0.225	9/10 (90)	0.030	10/10 (100)	0.034
No	28/32 (88)		16/24 (67)		10/24 (42)		15/24 (63)	

MDI = mental developmental index. [a] Fisher's exact test, corrected for multiple comparisons.

associated with seizure outcome (Table 4.2). Four patients with epileptic encephalopathy reached postoperative seizure freedom. At follow-up, children with contralateral MRI abnormalities less often were able to walk than those with a normal contralateral MRI (40% versus 83%, p=0.014). Contralateral EEG abnormalities did not correlate with the ability to walk after surgery. Surgical complications were seen in 18% of children with and 19% of patients without contralateral MRI abnormalities (infection [n=3], hydrocephalus necessitating ventriculoperitoneal drainage [n=2], cerebral salt wasting [n=2], and severe perioperative blood loss [n=1], none of which led to permanent neurological sequelae).

Cognitive outcome

At follow up, 19 of the 34 children who underwent repeated neuropsychological evaluation were severely cognitively delayed, 11 patients had MDI/IQ levels between 55 and 75, 3 patients were mildly delayed and 1 patient had normal cognition (MDI 95). After surgery, 9 patients (26%) showed an increase of ≥10 points in MDI/IQ scores, 22 patients remained stable, and 3 patients lost 10 points. Postoperative severe cognitive delay (n=19) correlated with low preoperative MDI/IQ scores (n=25, p=0.004). Shorter duration of epilepsy (p=0.019 [OR 0.640, CI 0.440–0.930]) and lower age at surgery (p=0.005 [OR 0.648, CI 0.478–0.879]) were also predictive for poor postoperative cognition. Cognitive function and improvement were not different between pathologic subgroups and were not related to seizure outcome. The number of AEDs used at postoperative neuropsychological evaluation did not differ between children with and those without severe cognitive delay (mean 1.0 [SD 0.94] vs 1.4 [SD 1.1], respectively; p=0.257), neither between the patients who gained ≥10 MDI/IQ points (mean 1.0 [SD 0.71]) and those without postoperative cognitive improvement (mean 1.24 [SD 1.1]; p=0.545). More children with contralateral MRI abnormalities had low postoperative MDI/IQ scores (p=0.030), and improvement in cognition scores was less frequent in these children (0%), compared with the children without contralateral MRI lesions (38%, p=0.034). Preoperative EEG variables were not associated with postoperative MDI/IQ scores or with cognitive improvement.

Seizure recurrences

Ten children had postoperative seizure recurrence. Six had contralateral MRI abnormalities (developmental [n=3], vascular [n=2], and hydrocephalus with drain [n=1]). In 4, the other hemisphere was normal. In 1 patient, recurrent seizures were proven to originate from the disconnected hemisphere; in this child, the insula was not decorticated. The patient had the same seizure semiology as preoperatively, although less severe. In 3 patients, postoperative EEGs showed a contralateral ictal focus: In 1 patient, this was already acknowledged

Table 4.2 Contralateral EEG abnormalities in relation to seizure and cognitive outcome

Contralateral EEG abnormalities	Seizure outcome (n=43)		Cognitive outcome (n=34)					
	Postoperative seizure freedom (n=33/43)		Preoperative MDI/IQ <55 (n=25/34)		Postoperative MDI/IQ <55 (n=19/34)		No postoperative increase in MDI/IQ (n=25/34)	
	n (%)	p-value[a]	n (%)	p-value[a]	n (%)	p-value[a]	n (%)	p-value[a]
Interictal epileptic								
Yes	17/24 (71)	0.470	11/17 (65)	0.438	6/17 (35)	0.107	10/17 (59)	0.172
No	16/19 (84)		14/17 (82)		13/17 (76)		15/17 (88)	
Background slowing								
Yes	18/24 (75)	0.967	11/17 (65)	0.379	8/17 (47)	0.967	13/17 (76)	1.000
No	13/16 (81)		11/14 (79)		9/14 (64)		10/14 (71)	
NI	2/3 (67)		3/3 (100)		2/3 (67)		2/3 (67)	
EEG spreading								
Yes	13/18 (72)	0.409	10/12 (83)	0.482	7/12 (58)	1.000	9/12 (75)	1.000
No	20/24 (83)		14/21 (67)		11/21 (52)		15/21 (71)	
NI	0/1 (0)		1/1 (100)		1/1 (100)		1/1 (100)	
Ictal focus								
Yes	2/4 (50)	0.536	2/4 (50)	0.281	2/4 (50)	1.000	4/4 (100)	0.702
No	31/39 (79)		23/30 (77)		17/30 (57)		21/30 (70)	
EE								
Yes	4/6 (67)	0.757	3/4 (75)	1.000	2/4 (50)	1.000	2/4 (50)	0.628
No	29/37 (78)		22/30 (73)		17/30 (57)		23/30 (77)	

EE = bilateral epileptic encephalopathy; MDI = mental developmental index; NI = not interpretable. [a] Fisher's exact test, corrected for multiple comparisons.

in preoperative ictal recordings; surgery was offered from a palliative perspective, and postoperative seizure frequency was considerably less than before. In the other 2 patients, contralateral EEG foci were not detected before hemispherectomy, and their postoperative semiology had changed. In the remaining 6 patients, postoperative ictal recordings were not performed, and localization of the epileptogenic focus was not definite. Although these 10 children did not reach seizure freedom, severity and frequency of seizures considerably decreased (Engel 2A–4A).

Discussion

In this cohort of 43 hemispherectomy patients, contralateral MRI abnormalities significantly increased the chance of seizure recurrence and were associated with severe cognitive delay and lack of cognitive improvement after surgery. Presurgical contralateral EEG abnormalities did not influence postoperative outcome.

The postoperative seizure freedom rate was 77%, which is in agreement with previously published series.[4,7,10-12] Seizure recurrences were independent of etiology but related to contralateral MRI abnormalities. Our results are similar to a previous study of 50 children operated despite abundant generalized or bilateral EEG abnormalities[6] but with predominant structural abnormalities in 1 hemisphere; 32 underwent hemispherectomy, of whom 11 (also) had contralateral MRI lesions. Seizure freedom was reached in 5 of these 11 patients (45%), compared to 18 of 21 children (86%) without contralateral MRI abnormalities. In a recent comprehensive retrospective study of 110 hemispherectomized patients from the same center, a surprisingly high number (74%) had contralateral MRI abnormalities, and no relation with seizure outcome was found.[7] Some of the lesions described in their study are similar to the unambiguous pathology we found in our patients. Their visual analysis of MRIs, however, apparently was highly sensitive and 84% of the abnormalities were subjectively classified as being of mild to moderate severity. The authors interpreted alterations of size (contralateral hemisphere, subarachnoid space, white and deep gray matter volumes) and cortical thickness as abnormal, although volumetric analysis of MRI data was not performed and age-related reference values were not available. Nevertheless, a reduced volume of the contralateral hemisphere was described in 26 patients. However, even in the most severe form of cortical malformations – hemimegalencephaly – the reduction in size of the contralateral hemisphere is only ±13% compared to age-related control brains.[13] It is therefore difficult to visually acknowledge reductions of volume in the absence of quantified control data. We focused on unambiguous contralateral MRI lesions from a clinical and "everyday practice" perspective, only including abnormalities when both experienced investigators agreed, and disregarding subjective interpretations of volumetric

changes. Therefore, the abnormalities described here probably are more severe than those in the previous study.

Contralateral interictal epileptic discharges were seen in 24 (56%) children, which is consistent with previous studies that reported such abnormalities in 36% to 61% of hemispherectomy candidates.[10,14-16] Contralateral EEG findings were not associated with seizure outcome, confirming previous results.[7,14,15] Even a bilateral epileptic encephalopathy or epileptic discharges predominating in the unaffected hemisphere, do not necessarily prevent a surgical approach, because 72 to 80% of these patients reach seizure freedom, provided that the MRI abnormalities are clearly lateralized.[5,6,17] Older children with Lennox-Gastaut syndrome may benefit from resective surgery or hemipherotomy.[18]

Previous studies reported severe developmental delay in 57 to 76% of hemispherectomy patients after surgery.[2,4,19] In 3 series with assessment of preoperative and postoperative cognition,[4,11,19] 11% to 57% of the children had postoperative improved (5–10 points) of developmental scores. In our cohort, 19 children (56%) were severely delayed postoperatively, and 26% had a marked increase in cognitive scores after surgery. Although cognitive improvement apparently is uncommon, we should realize that many children were severely delayed both before and after surgery, with MDI values <55. In those patients, subtle progression of neuropsychological functioning and an increase of mental age could not be quantified and expressed in formal MDI scores. The frequency of cognitive improvement may therefore be underestimated. The influence of contralateral MRI and EEG abnormalities on cognitive outcome has not been studied before. Patients without contralateral MRI abnormalities were less often severely delayed after surgery and their MDI/IQ scores more often increased. This suggests that continued development after surgery occurred preferentially in those whose contralateral hemisphere was relatively normal. Differences in cognitive outcome among patients with and without contralateral MRI lesions were not accounted for by the number of AEDs used at time of follow-up.

There are several limitations to this retrospective study. First, the small number of patients in the different subgroups may have prevented the detection of significant correlations among etiology, MRI abnormalities, and outcome, and between the existence of a bilateral epileptic encephalopathy or contralateral ictal focus and outcome. Second, differentiating small and possibly insignificant lesions from clinically relevant and unequivocal contralateral MRI abnormalities, may be arbitrary and depends on the subjective interpretation of the radiologist, because non-quantifiable MRI techniques are used in everyday practice. The detection of mild changes in hemispheric volumes or subtle white matter abnormalities may not relate to seizure recurrences.[7] Furthermore, MRI scans acquired at higher field (e.g. 3.0T) may reveal more subtle contralateral abnormalities, of which the clinical significance

remains to be established. Last, most children, young age or severe developmental delay did not allow the assessment of different domains of cognitive development. The use of an overall cognitive outcome measure hampers the evaluation of small but possibly important differences in specific cognitive tasks among children with and those without structural contralateral pathology.

Conclusion

When a child presents with catastrophic hemispheric epilepsy and developmental delay, the detection of contralateral MRI abnormalities is not an absolute contraindication for hemispherectomy. Almost half of the patients will still reach seizure freedom. Although these children less often improve in their cognitive development than those without contralateral MRI lesions, surgery will decrease seizure burden and stop the rapid presurgical developmental decline that is so characteristic for many hemispherectomy candidates. The decision whether or not a patient is a candidate for surgical treatment should be made by an experienced team of specialists who can determine and communicate the appropriate risk-benefit ratio.[3]

Acknowledgement

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References

1. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7(6):525-37.

2. Devlin AM, Cross JH, Harkness W, et al. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. Brain 2003;126(3):556-66.

3. Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. Epilepsia 2006;47(6):952-9.

4. Jonas R, Nguyen S, Hu B, et al. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology 2004;62(10):1712-21.

5. Gupta A, Chirla A, Wyllie E, Lachhwani DK, Kotagal P, Bingaman WE. Pediatric epilepsy surgery in focal lesions and generalized electroencephalogram abnormalities. Pediatr Neurol 2007;37(1):8-15.

6. Wyllie E, Lachhwani DK, Gupta A, et al. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. Neurology 2007;69(4):389-97.

7. Hallbook T, Ruggieri P, Adina C, et al. Contralateral MRI abnormalities in candidates for hemispherectomy for refractory epilepsy. Epilepsia 2010;51(4):556-63.

8. Engel Jj, van Nes P, Rasmussen T. Outcome with respect to epileptic seizures. Surgical treatment of the epilepsies. 2nd ed. New York: Raven Press; 1993:609-21.

9. Finner H. On A Monotonicity Problem in Step-Down Multiple Test Procedures. JASA 1993;88:920-3.

10. Limbrick DD, Narayan P, Powers AK, et al. Hemispherotomy: efficacy and analysis of seizure recurrence. J Neurosurg Pediatr 2009;4(4):323-32.

11. Lettori D, Battaglia D, Sacco A, et al. Early hemispherectomy in catastrophic epilepsy: a neuro-cognitive and epileptic long-term follow-up. Seizure 2008;17(1):49-63.

12. Van Oijen M., De Waal H, Van Rijen PC, Jennekens-Schinkel A, van Huffelen AC, Van Nieuwenhuizen O. Resective epilepsy surgery in childhood: the Dutch experience 1992-2002. Eur J Paediatr Neurol 2006;10(3):114-23.

13. Salamon N, Andres M, Chute DJ, et al. Contralateral hemimicrencephaly and clinical-pathological correlations in children with hemimegalencephaly. Brain 2006;129(2):352-65.

14. Gonzalez-Martinez JA, Gupta A, Kotagal P, et al. Hemispherectomy for catastrophic epilepsy in infants. Epilepsia 2005;46(9):1518-25.

15. Doring S, Cross H, Boyd S, Harkness W, Neville B. The significance of bilateral EEG abnormalities before and after hemispherectomy in children with unilateral major hemisphere lesions. Epilepsy Res 1999;34(1):65-73.

16. Kossoff EH, Vining EP, Pillas DJ, et al. Hemispherectomy for intractable unihemispheric epilepsy etiology vs outcome. Neurology 2003;61(7):887-90.

17. Hamiwka L, Duchowny M, Alfonso I, Liu E. Hemispherectomy in early infantile epileptic encephalopathy. J Child Neurol 2007;22(1):41-4.

18. Lee YJ, Kang HC, Lee JS, et al. Resective pediatric epilepsy surgery in Lennox-Gastaut syndrome. Pediatrics 2010;125(1):58-66.

19. Loddenkemper T, Holland KD, Stanford LD, Kotagal P, Bingaman W, Wyllie E. Developmental outcome after epilepsy surgery in infancy. Pediatrics 2007;119(5):930-5.

Chapter 5

The spectrum of long-term cognitive and functional outcome after hemispherectomy in childhood

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Submitted

Abstract

Purpose: To evaluate cognition, behaviour, daily functioning and health-related quality of life (HrQoL) five years to more than a decade after hemispherectomy (HE) in childhood.

Methods: This countrywide Dutch cohort study of 31 patients, who underwent HE between 1994 and 2009, included a semi-structured interview with parents, an assessment of cognition, and screening of behavioural problems and HrQoL.

Results: Twenty-two school-age children and young adults [median age 13.8 years (0.5 at epilepsy onset, 5.3 at HE)] were assessed with age-appropriate cognitive tests. IQ ranged from 45 to 82 (median 61). Notwithstanding results below mean norm scores, these participants could learn and remember, sustain attention, inhibit irrelevant responses, read and write. Nine more children [median age 9.7 years (0.25 at epilepsy onset, 1.4 at HE)] were so mentally retarded that age-appropriate testing was impossible. This group was almost totally dependent on others in daily activities, had the highest proportion of pre-existing contralateral MRI-abnormalities and after HE the highest rates of seizure recurrence and behavioral problems. Parents in both groups rated HrQoL surprisingly positively (mean VAS score 72.5), with a scarce low rating (40). All parents reported problems with respect to their children's self-care, daily activities and mobility.

Conclusion: At least half a decade after HE, cognitive, behavioural and daily functioning encompasses a broad spectrum that varies from profound retardation and almost total dependence to more or less unproblematic, though not normal in the statistical sense, functioning. Pre-existing contralateral MRI abnormalities hamper development after HE. Underlying pathology seems not distinctive for later functioning.

Introduction

The beneficial effect of pediatric hemispherectomy (HE) on seizure control is an established fact.[1-4] Shorter duration of epilepsy and younger age at HE are associated with higher rates of seizure freedom.[5]

The ultimate goal of epilepsy surgery in children is not only seizure freedom and discontinuation of antiepileptic medication, but also opening a gate for (better) development.[6,7] Parents generally tell us that their child's functioning and general wellbeing improve after epilepsy surgery, even although the child did not become seizure free.[8] Yet, as far as HE is concerned, formal measures of cognition such as Intelligence Quotient (IQ) or Mental Developmental Index (MDI) scores do not often acknowledge the observations of parents. Significant cognitive improvement is uncommon and 61% of the children have no measurable change in IQ/DQ points after HE (see review, Schooneveld & Braun 2013).[9] Determining mental age (MA), however, unveils and quantifies change. Even children who had a very poor development with ongoing seizures, resume mental development after HE, as demonstrated by clear increases in mental age.[3]

Shorter duration of epilepsy prior to and seizure freedom following HE are independently related to better cognitive functioning,[1] as is withdrawal of anti-epileptic drugs (AEDs).[10] Contralateral MRI abnormalities, however, are significantly associated not only with seizure recurrence but also with severe mental delay and less chance of an IQ increase of 10 points.[11] These data pertain to rather short postsurgical intervals.

To the best of our knowledge, only two studies have reported long-term functioning after HE. Both were based on retrospective postal surveys, one completed during a telephone interview. Postoperative cognitive functioning largely reflected the presurgical capacities: late (beyond age 16 years) HE was associated with higher estimated intelligence and better psychosocial achievements.[12] Reading and spoken language were frequently impaired in the majority of ambulant patients, as described by Moosa et al.[13] who found seizure recurrence and contralateral MRI abnormalities to be the major predictors of poor skills.

We performed a comprehensive cognitive re-assessment of 31 children at least five years after HE; we also addressed behavior, everyday functioning and health-related quality of life (HrQoL) by questionnaires and semi-structured interviews.

Materials and methods

In The Netherlands, epilepsy surgery in children is performed solely in the University Medical Center Utrecht.[14] Hence, we report on a countrywide cohort study. Inclusion criteria were 1) having undergone HE between 1994 and 2009, 2) age at HE younger than 18 years, and 3) neuropsychological evaluation shortly before HE, and re-evaluations two and more than five years thereafter. The medical ethical and research committee of the UMCU approved the study and concluded that the Dutch law on medical research involving subjects did not apply.

Participants

Of 47 HE patients, eight had not participated in the two-years' standardized neuropsychological follow-up. One of the 39 remaining children died. All attempts failed to establish contact with two families, and five families refused participation due to the emotional impact of seizure recurrence (n=1), severe autistic problems (n=1), or for no specified reason (n=3). Finally, 31 (former) patients and their parents decided to participate in the long-term reassessment. With respect to gender, type of pathology, presurgical contralateral MRI abnormalities, age at onset of epilepsy and at HE, epilepsy duration, side of HE and seizure freedom two years after surgery, individuals who were not included in this long-term evaluation (n=16) did not differ from those who participated. A subset of the study group has been described in papers on cognitive outcome at one to two years after surgery.[3,11]

Sources

Epilepsy status and daily activities

A semi-structured interview with parent(s) addressed epilepsy-related variables (seizure outcome, AEDs) as well as daily activities such as walking, talking, self-care, school career or employment, leisure activities and partner relationships.

Cognition

If possible, intelligence was assessed using Dutch versions of the Wechsler intelligence scales (Wechsler Preschool and Primary Scales of Intelligence III, Wechsler Intelligence Scales for Children III, Wechsler Adult Intelligence Scales III or IV. Full-scale IQ and its verbal (VIQ) and performance (PIQ) components (mean = 100, standard deviation = 15 in the general population) were determined. If age-appropriate intelligence testing was unfeasible, a developmental scale was used, either the Dutch version of the Bayley Scales of Infant Development or the Vineland Screener 0–6 years, and the raw scores were converted to

the corresponding Mental Age (MA) as obtained from norm tables of the test manuals. We calculated mental developmental delay (MDD) by subtracting the child's MA from his/her chronological age. In addition, cognitive domains[15] memory, language, calculation, processing speed, attention and executive functioning were assessed if possible (see Table 5.3).

Behavior

The parent version of the Strengths and Difficulties Questionnaire (SDQ), a screener for problems with behavioral functioning,[16] consists of 25 statements addressing pro-social behavior but also emotional problems, conduct problems, hyperactivity/inattention and problems with peer relations. Respondents select one of three categories ['not true' (0), 'somewhat true' (1), 'certainly true' (2)]. For pro-social behavior a sum score of ≤4 is considered abnormal. Summating the ratings on 20 items of the four problem domains yields the Total Difficulties (TD) score (range 0–40, ≥14 = abnormal). If possible, young adult participants (18 years and older) rated the SDQ also by themselves.

Health-related quality of life (HrQoL)

Parents rated overall HrQoL using the EuroQoL visual analog scale (EQ-VAS, minimum 0 – maximum 100), and specific HrQoL using five separate three-point [no (0), some (1), or extreme (2) problems] domain items (EQ-5D, domains mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[17,18] If possible, young adult participants (18 years and older) also rated the EuroQoL themselves.

Data management and analyses

From the patients' records, we collected age at onset of epilepsy and at HE, presence of presurgical contralateral MRI abnormalities, side of HE, pre- and two-years post-HE cognitive level, as well as seizure status and AED use two years after HE. Seizure status was dichotomized as seizure-free (no seizures since HE) or not. Use of AED and contralateral MRI abnormalities prior to HE were dichotomized as yes or no. Underlying pathology was classified as developmental (e.g., hemimegalencephaly or cortical dysplasia), acquired (perinatal ischemia or porencephalic cyst) or progressive (Rasmussen encephalitis or Sturge-Weber syndrome). For further analysis, we divided the cohort into two separate groups: those who could, and those who could not be assessed with age-appropriate intelligence tests.

Statistical analyses were performed using IBM SPSS Statistics, Version 21 (SPSS Inc., Chicago, IL, U.S.A.).[19] Descriptive statistics were used for variables including medians and ranges for continuous variables and frequencies and percentages for categorical variables. Exploratory analyses included Kruskal-Wallis One-way Analysis of Variance, Mann-Whitney U test, Wilcoxon

matched-pairs signed-rank test, Fischer exact test and Spearman's rank correlation coefficient. Nonparametric tests were chosen due to the small sample sizes. Alpha was set at 0.05 (two-tailed). The significance of correlations was evaluated according to Cohen.[20]

Results

Demographic and epilepsy-related characteristics of the study group are summarized per pathology group in Table 5.1. The median long-term follow-up interval after HE was 8.1 (range 5.5–18.0) years. The developmental group had the lowest age range at surgery compared to both the acquired (p=0.005) and the progressive group (p=0.045), and a shorter range of epilepsy duration than the acquired group (p=0.008). Age at onset of epilepsy was significantly lower in the developmental group than in the acquired group (p=0.036). Contralateral MRI abnormalities prior to HE were present in eight cases, three (25%) in the developmental, three (25%) in the acquired and two (28.6%) in the progressive group. Table 5.1 also shows per pathology group the feasibility of age-appropriate intelligence assessment at long-term follow-up. Nine children were mentally retarded to a degree that age-appropriate testing was impossible.

Epilepsy-related medical status

Twenty-three (74.2%) participants had remained seizure-free since surgery (Engel 1A) (Table 5.1). The group with acquired pathology had the highest percentage of seizure freedom, followed by the groups with developmental and progressive pathologies. Seizures had recurred in five participants within the two years after surgery and in three after the two-years' follow-up. Eight not seizure-free and one seizure-free participant(s) used AEDs at long-term follow-up. The percentage of seizure freedom was larger in the group of children who could be assessed with age-appropriate intelligence scales (Table 5.2).

Cognition

Group-wise, neither age at epilepsy onset, follow-up interval, nor current age distinguished the participants who were assessed with age-appropriate intelligence scales from those who were not. Age at HE, however, was significantly lower and duration of epilepsy was significantly shorter in children who could not be assessed with intelligence scales (Table 5.2).

Table 5.1 Characteristics of the entire group (n=31), subdivided according to pathology type

	Total (n=31)	Pathology		
		Developmental (n=12)	Acquired (n=12)	Progressive (n=7)
Age at onset epilepsy (years) median (range)	0.3 (0–11)	0.1 (0–1.5)	0.4 (0–2.5)	0.6 (0–11)
Age at surgery (years) median (range)	3.0 (0.2–12.2)	1.4 (0.2–6.4)	5.3 (1.4–12.2)	7.5 (0.3–12.1)
Duration of epilepsy (years) median (range)	2.3 (0.2–11.7)	1.4 (0.2–4.9)	3.5 (0.8–11.7)	3.3 (0.3–7.2)
Sex (male) n (%)	13 (41.9)	5 (41.7)	5 (41.7)	3 (42.9)
Side (right) n (%)	15 (48.4)	5 (41.7)	7 (58.3)	3 (42.9)
Contralateral MRI abnormalities before HE n (%)	8 (25.8)	3 (25.0)	3 (25.0)	2 (28.6)
Seizure freedom				
2 years after HE n (%)	26 (83.9)	10 (83.3)	11 (91.7)	5 (71.4)
5–11 years after HE n (%)	23 (74.2)	9 (75)	10 (83.3)	4 (57.1)
AED use				
2 years after HE n (%)	19 (61.3)	6 (50)	7 (58.3)	6 (85.7)
5–11 years after HE n (%)	9 (9.3)	2 (16.7)	4 (33.3)	3 (42.9)
After 5–11 years age-appropriate intelligence scale feasible n (%)	22 (70.9)	7 (58.3)	9 (75.0)	6 (85.7)

AED = antiepileptic drug; HE = hemispherectomy; MRI = magnetic resonance imaging; n = number; % = percentage.

Table 5.2 Epilepsy variables, intelligence, behavior, daily activities and HrQol of participants who could be assessed with age-appropriate intelligence scales and of those for whom these scales were not feasible

	Age-appropriate intelligence assessment		
	Feasible (n=22)	Not feasible (n=9)	P-value
Sex			
Male n (%)	9 (40.9)	4 (44.4)	
Female n (%)	13 (59.1)	5 (55.6)	
Age (years) median (range)	13.8 (7.1–24.5)	9.7 (7.1–12.9)	0.064
Age at epilepsy onset (years) median (range)	0.5 (0–11)	0.25 (0–0.6)	0.103
Age at HE (years) median (range)	5.3 (0.2–12.2)	1.4 (0.2–3.1)	0.007
Duration of follow-up (years) median (range)	8.2 (5.5–18.0)	8.1 (5.9–11.7)	0.012
Side of HE right n (%)	10 (45.4)	5 (55.6)	0.704
Pathology n (%)			
Developmental	7 (31.8)	5 (55.6)	0.253
Acquired	9 (40.9)	3 (33.3)	1.000
Progressive	6 (27.3)	1 (11.1)	0.639
Contralateral MRI abnormalities n (%)	2 (9.1)	6 (66.7)	0.003
Seizure freedom n (%)	19 (86.4)	4 (44.4)	0.027
AED use n (%)	5 (22.7)	5 (44.4)	0.385
Intelligence			
MA (months) median (range)	n.a.	25 (6–72)	
MDD (months) median (range)	n.a.	98 (78–111)	
FSIQ median (range)	61 (45–82)	n.a.	
VIQ median (range)	67.5 (54–93)	n.a.	
PIQ median (range)	59 (50–79)	n.a.	
Behavior			
Parent-reported SDQ TD (≥14) n (%)	4 (18.8)	5 (55.6)	0.032
Pro-social (<4) n (%)	2 (9.1)	5 (55.6)	0.007
HrQol			
Parent reported EQ VAS score median (range)	80 (40–98)	72.5 (45–90)	0.219
Young adults EQ VAS score median (range)	82.5 (70–100)	n.a.	
Most important change after HE n (%)			
Seizure freedom	6 (27.3)	0	
Restart of development	5 (22.7)	4 (44.4)	
Both	11 (50.0)	5 (55.6)	

AED = Antiepileptic drug; FSIQ = Full-scale intelligence quotient; HE = Hemispherectomy; HrQoL = health related quality of life; MA: mental age; MDD: mental developmental delay; MRI: magnetic resonance imaging; n.a. = not applicable; n = number; PIQ = performal intelligence quotient; SDQ = Strengths and Difficulties Questionnaire; TD = Total Difficulties; VIQ = verbal intelligence quotient; % = percentages.

Participants assessed with age-appropriate intelligence scales

IQ values varied widely (from 45 to even average values), with a difference between VIQ and PIQ that was significant to the disadvantage of the PIQ (p=0.00). Group-wise, IQ, nor its verbal and performance components, had changed significantly since the two-years' post-HE assessment (data not shown). Yet, seven participants showed a clinically relevant change in IQ of 10 or more points between two to at least eight years after HE, with improvement in four and decrease in three. Results on neuropsychological domains are shown in Table 5.3, separately for the young adult participants (18 years and older) and for the school-age children. Most participants obtained scores (far) below the mean age norms. However, most participants were able to recall at least three digits forward and at least two backward. They profited by repeated presentation of a word-list, achieving learning results of 19–64%; recall after a delay varied between zero and 80% of the words and recognition amounted to 67–100%. Also, participants recalled 3.2–48.4% of verbally transmitted stories; recall after a delay varied between zero (one patient) and more than half of the story contents. Word comprehension was rather poor to almost normal. On a task requiring visual attention, five young adult participants obtained accuracy scores at or above the mean norm value. Speed, however, was far below average, as also reflected in the processing speed index. When reading, six of the young adult participants were able to suppress an overlearned response in favor of a less usual one, and found all six sorting categories in a test of cognitive flexibility. Fourteen participants (6 at school-age and 8 young adults) could read connected text and write their name and a self-generated sentence. Only one participant mastered calculation skills at an age-appropriate level. For the other participants arithmetical operations were limited to counting.

Children who could not be assessed with age-appropriate intelligence scales

MA ranged from 6 to 72 (median 25) months and MDD from 78 to 111 (median 96) months (Table 5.2). MA and time of assessment (prior to HE, two years and 5–11 years after HE) correlated very strongly in six (rho=1.0), and moderately in two children (rho=0.5), which indicated at least some development. In a 9 years old girl with a complex malformation of cortical development (age at epilepsy onset 0.25 years), who was not seizure-free and used two AEDs, the strongly negative correlation (rho=- 0.9) reflected an arrest of developmental skills. One child recognized letters and digits, none of the children could read, write or calculate.

Behavior

The parent-reported TD score was in the abnormal range for 9 children: four (33%) with developmental, three (25%) with acquired and two (29%) with progressive pathology. The

number of abnormal TD scores was significantly larger for the group of children who could not be assessed with age-appropriate intelligence scales than for those who could.

Table 5.3 Neuropsychological long-term results obtained by each of the eight young adults and aggregated results of the 14 school-age participants who were tested with age-appropriate scales

	Young adult participants Range	School-age participants Range
Intelligence		
FSIQ*	56–80	52–82
PSI*	50–63	55–79
Memory		
Digit span*	2–9	1–7
Forward (n)	3–6	3–5
Backward (n)	2–6	0–5
Auditory 15 word list		
Direct learning (%)	19–63	25–53
Delayed recall (%)	0–80	20–67
Recognition (%)	67–100	93–100
Stories (TOMAL)		
Immediate recall*	4–9	3–10
Delayed recall*	2–8	0–11
Face recognition TOMAL*	3–12	1–8
(%)	30–61	
Attention/ executive functions		
WmCST		na
Categories max 6 (n)	1–6	
D2 Visual attention test		na
Speed, (n) below the mean	6	
Accuracy (n) below the mean	3	
Stroop		
Inhibition (n) below the mean	2	na
Language		
WCQ PPVT*	<55–84	56–94
Reading text[@] (+/-)	8/8+	12/14+
Writing sentence[#] (+/-)	8/8+	11/14+
Calculation[&]*	4–7	1–12

FSIQ = full-scale intelligence quotient; HE = hemispherectomy; n = number; + = yes; - = no; < = under mean norm score; ≥ = at or above mean norm score; na = not assessed; PIQ = performance intelligence quotient; PPVT = Peabody Picture Vocabulary Test; PSI = processing speed index; VIQ = verbal intelligence quotient; 15-Words Test = Auditory Verbal Learning Test; TOMAL = Test of Memory and Learning; WCQ = word comprehension quotient; WmCST = Wisconsin modified card sorting test. % = percentages; * = norm scores of the age-group (mean = 10, SD = 3). [&] = subtest Arithmetic Wechsler scales; [#] = writing a sentence on their own; [@] = technically reading a short text aloud.

Participants assessed with age-appropriate intelligence scales

Only two parents (9%) rated pro-social behavior in the abnormal range. Four parents (19%) rated TD in the abnormal range. With respect to the domains of problem behavior (data not shown), 12 parents (55%) reported hyperactivity or inattention. No young adult participant rated TD in the abnormal range. Neither parents nor young adults reported conduct problems; only one parent reported emotional problems for her young adult child and one young adult reported problems with peers.

Children who could not be assessed with age-appropriate intelligence scales

Parents of five children (56%) rated pro-social behavior in the abnormal range. Four of them and one other parent rated TD as abnormal. All 9 parents deemed their child hyperactive or inattentive. No parent reported conduct problems, one reported emotional and peer problems (11%). Problems in all domains except for conduct problems were reported with respect to one child, a boy in whom seizures had recurred more than two years after HE.

Daily functioning

Participants who could be assessed with age-appropriate intelligence scales

Nine of the 22 participants (41%) could not take a shower, dress or go to the toilet by themselves and one child was still wearing diapers. Twenty-one participants walked independently and one walked with assistance. All had speech skills to a degree that communication in daily life was not limited. Eleven school-age children were visiting a special primary or secondary school for physically and/or mentally handicapped children; one child also visited a regular primary school one day weekly. Three children in primary education received special assistance. All eight young adults had visited a secondary special school for disabled youngsters. Two of them had attended a follow-up training for disabled people to work in catering industry or administration. Currently, three worked voluntarily in an activity center for disabled people. The other five were employed as assistant in catering, a store, a nursing home or printing office. All employed adults worked two to five days weekly and received a so-called Wajong benefit (based on the Dutch law 'Jobs for young handicapped persons'). With respect to living conditions, three young adults were waiting to move into, and four already lived in, a house for assisted living, where they did their laundry, prepared their meals and paid purchases such as groceries with a bank card (rendering calculating prices redundant) and where they received professional support for two to four hours a day. All school-age children were living with their parents. Leisure activities were reported for 9 school-age participants (swimming or football) and for six young adults (disco for disabled people, dancing, membership of a church, meeting for disabled people or swimming). Two traveled by public transport. No young adult had a partner relationship.

Children who could not be assessed with age-appropriate intelligence scales
No child could take a shower, get dressed or go to the toilet without assistance. Seven of the 9 children were still wearing diapers. Three children walked independently, one walked a few steps with assistance, and five could not walk. Despite profound mental retardation, six children had developed speech to a degree that they had meaningful command of words or two- to five-word phrases. The remaining three children had no verbal utterance at all. No child was in a sheltered home. Four were visiting a day center for minimally functional children and the other five went to a special primary school for disabled children. Leisure activities were not mentioned, apart from horse riding for disabled people (one child).

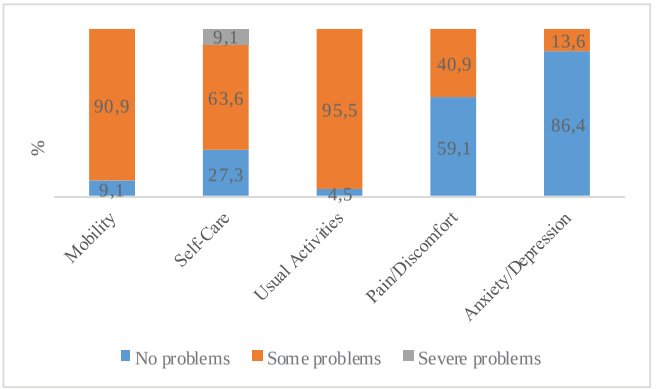
Health-related quality of life

Parents rated overall HrQoL (EQ VAS score) of their children between 40 and 90 (median 80). The distribution of the parent-reported EQ VAS -scores did not differ with respect to whether or not their child could be assessed with age-appropriate intelligence scales.

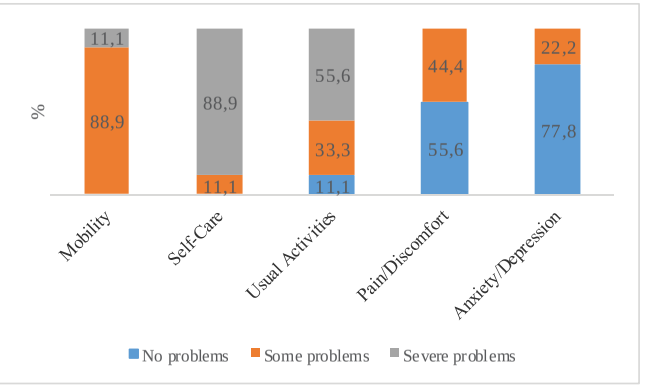
Participants who could be assessed with age-appropriate intelligence scales
Nineteen (86%) children had an EQ VAS score ≥70. The lowest score (40) pertained to a girl with Sturge-Weber syndrome who became seizure free after the HE but had continuing visual problems due to glaucoma. Almost all parents reported their children to have 'some' problems with respect to mobility and daily activities. Although some problems in self-care were frequent, severe problems in this domain were rare. Some problems with pain/discomfort were rated by 41% of the parents and 14% reported some problems of anxiety/depression.

All eight young adult participants rated their own overall HrQoL (EQ VAS score) between 70 and 100 (median 82.5). Young adults whose parents had reported some problems with mobility, self-care and pain/discomfort agreed with their parents. Far less young adults than their parents reported some problems in usual activities. Severe pain/discomfort was reported by a quarter and some pain/discomfort by half of the young adults (see Figure 5.1).

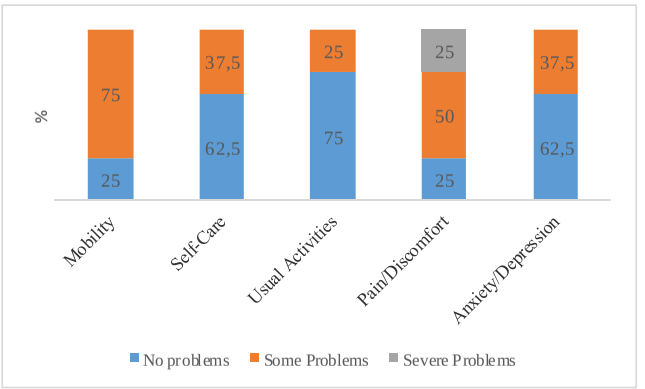
Children who could not be assessed with age-appropriate intelligence scales
Three children (33%) had EQ VAS scores >75, five (56%) between 50 and 75, and one had a score of 45. All 9 parents reported problems in mobility and self-care. Most parents reported also problems in daily activities. Some problems of pain/discomfort were reported by almost half and of anxiety/depression by less than a quarter of the parents (see Figure 5.1).



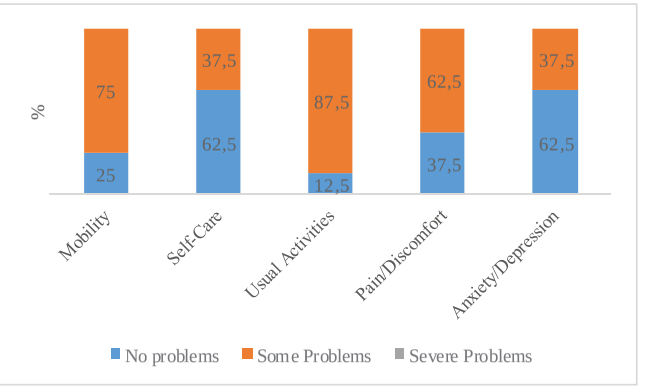
(A) As reported by the parents of participants assessed with age-appropriate intelligence scales (n=22)



(B) As reported by the parents of children who could not be assessed with age-appropriate intelligence scales (n=9)



(C) As reported by young adults themselves (n=8)



(D) As reported by the parents of the young adults (n=8)

Figure 5.1 Health-related Quality of Life (EQ-5D) Percentages of Domain-specific problems.

Associations with epilepsy-related characteristics

IQ, VIQ, PIQ, nor MDD differed significantly between participants of the three pathology types, nor between participants who were seizure free or not, who either or not used AEDs, who had left- or right-sided HE, or those with and without contra-lateral MRI abnormalities (data not shown). In the group of children who could not be assessed with age-appropriate tests, as well as in the total group, however, the parent-reported EQ VAS score differed significantly (p's=0.02) between children who were seizure free (median 80, range 75–90) and those in whom seizures had recurred (median 70, range 45–75). This difference could be traced back to a low EQ VAS score (=45) for a nearly 10 years old girl who had undergone HE at the age of 9 months for treatment of intractable seizures due to cortical dysplasia in the left hemisphere and in whom seizures had recurred but who did not use AED since 1½ years after HE. Use of AEDs, contra-lateral MRI abnormalities, side of surgery and type of pathology did not influence the EQ VAS scores significantly. Significantly more parents of participants with recurrent seizures than parents of seizure-free participants gave abnormal TD scores, reflecting behavior problems (p=0.001).

The correlations of IQ and EQ VAS scores with age at epilepsy onset, age at HE and presurgical duration of epilepsy were weak to moderate and statistically not significant. In the group of children who could not be assessed with intelligence scales, longer duration of epilepsy and higher age at HE were strongly (rho's=0.6) although not significantly associated with more severe delay.

Discussion

The attendance rate of almost 80% in our comprehensive neuropsychological reassessment long after hemispherectomy allowed us to sketch long-term (median 8 years, range 5.5–18) functioning of the Dutch population of persons who had HE in childhood. The percentage of seizure freedom (74%) was in the same range as reported previously.[4] Groupwise, children with developmental, acquired or progressive pathology types could not be distinguished with respect to long-term seizure freedom, AED use, presence of presurgical contralateral MRI abnormalities, nor with respect to feasibility of age-appropriate intelligence scales or level of cognitive functioning.

In contrast to previous findings,[12] standardized neuropsychological assessment was reliably feasible, although not in all participants. Median IQ scores were hardly meaningful, hiding ranges as large as 40 points. Corroborating earlier results,[9] overall IQ scores had not changed significantly since the assessment two years post-surgery. It should be stressed

that IQ stability is only possible when development is in agreement with normal growth. More individually, IQ of four children increased by at least 10 points, a clinically relevant change, since the assessment two years after surgery. This may indicate some catch up of development, presumably due to AED reduction and/or educational challenges. On the other hand, three children suffered similar amounts of IQ-decrease. That despite the side of surgery PIQ remained lower than VIQ confirms that the adult pattern (in which VIQ is predominantly vulnerable to left and PIQ to right hemispheric damage) does not necessarily apply in children after HE, as already signaled.[3,21] Assessment of other cognitive domains revealed that, although most results were below the mean norm score, participants were able to learn and recall verbal and visual information, and that – although their working speed was low – the young adult participants realized a surprising accuracy in tasks requiring sustained attention, response inhibition and mental flexibility. Furthermore, notwithstanding right or left HE, participants had developed usable reading skills.

Nine children were mentally retarded to the degree that age-appropriate testing was not possible. Seizure recurrence (56%) was relatively frequent in this group. Eight children had slightly increased in mental age since the two-years' postsurgical assessment, meaning some development, but the increase was far smaller than in healthy peers. Poor development was related to bilateral or diffuse underlying pathology. Although the children had been operated on at a very early age (≤3.1 years), the delay in mental development was associated with duration of epilepsy and age at surgery, supporting the plea for early HE[1,22-24] in very young children with mental delays.

Children with epilepsy have high rates of associated behavior disorders, such as attention deficits or social problems.[25,26] Almost a third of the parents in the present study rated behavior of their children as abnormal, a similar proportion as reported by Moosa et al.[13] Problematic behavior appeared to concentrate on the hyperactivity/ inattention complex; all parents of the 9 children with profound retardation and parents of 12 participants assessed with intelligence scales (in total 68%) rated this complex as problematic. In the structured, one-to-one situation of a neuropsychological assessment, however, the participants were able to address and sustain attention as needed; we took the complaints of the parents as indicating that that these children are unable to meet the more complex requirements of daily life.

With respect to daily functioning, a large majority (77%) walked independently or with assistance (6%) and almost 50% participated in leisure activities outside school or day-care, essential for acceptance within peer groups and self-confidence.[27] The group of children with profound retardation was almost totally dependent on others in daily activities. Five of them were unable to walk, three – with complex underlying epileptogenic etiologies and

contralateral MRI abnormalities – had no verbal utterances at all. Leisure activities were not mentioned, apart from horse riding for disabled people (one child).

The great majority of the parents evaluated HrQoL of their children as positive, notwithstanding remaining physical and cognitive impairments and in some children seizure recurrence. When interviewed 13.5 years (median) after their children's hemispherectomy, Swedish parents also estimated quality of life of their children as good to very good.[28] Might parents overestimate their children's functioning after HE? It is conceivable that they do, anchoring their long-term estimations in the period of devastating epilepsy. However, perceptions of the young adult patients themselves were also quite positive. Apparently, patients and their parents tend to cut their coats according to their cloths and redefine their needs, as has been suggested for parents of children with a different medical predicament.[29] Parents of the profoundly retarded children reported severe problems in domains such as self-care and daily activities, probably reflecting their increasing burden of caring for and assisting their child with her/his increasing age. Pain/discomfort, due to headache, scoliosis, glaucoma or spasticity, reported by relatively large percentages of parents as well young adults themselves, has remained underreported and urges for more extensive inquiry in order to develop means for palliation or relieve. Problems with respect to anxiety/depression are not frequently reported, which is important as managing of anxiety or depression plays an even more important role in HrQoL than seizure control, IQ or duration of follow-up.[30]

This study has limitations. The analysis of possible determinants of outcomes was constrained by the relatively small number of participants and remained explorative. We controlled for the very wide ranges of follow-up periods and ages at long-term neuropsychological reassessment by ascertaining that the outcome variables were not significantly correlated with duration of follow-up or age at reassessment. Differences in chronological ages and intelligence levels had necessitated the use of both developmental and intelligence scales, which complicated the comparison across time. To screen for generic HrQoL, we opted for the brevity of the EQ-5D. To investigate physical and psychological functioning more systematically, more specific measures are needed, like the Child Health Questionnaire (CHQ) or Pediatric Quality of Life Questionnaire (PedsQL). As we assessed HrQoL at a single point in time without a control group, we could not tap a possible response shift of parents.[31] However, we feel that assets of this study are its long-term follow-up, its comprehensive neuropsychological reassessment including formal testing of both intelligence and other cognitive domains of the (previous) patients and its emphasis on behavior, everyday functioning and HrQoL rather than focusing on intelligence only.

Conclusion

At least half a decade after childhood HE, cognitive, behavioral and daily functioning encompasses a broad spectrum that varies from profound retardation and almost total dependence to more or less unproblematic, albeit not normal in the statistical sense, functioning. Underlying pathology seems not distinctive for later functioning. Pre-existing contralateral MRI abnormalities, however, are signs of a bad brain that scarcely mediates development after HE. Notwithstanding remaining and often invalidating physical and cognitive impairments, a harmonious and rewarding life can be attained.

Acknowledgement

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References

1. Jonas R, Nguyen S, Hu B, et al. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology 2004;62(10):1712-21.

2. Hallböök T, Tideman P, Rosen I, Lundgren J, Tideman E. Epilepsy surgery in children with drug-resistant epilepsy, a long-term follow-up. Acta Neurol Scand 2013;128(6):414-21.

3. van Schooneveld MM, Jennekens-Schinkel A, van Rijen PC, Braun KP, van Nieuwenhuizen O. Hemispherectomy: a basis for mental development in children with epilepsy. Epileptic Disord 2011;13(1):47-55.

4. Griessenauer CJ, Salam S, Hendrix P, et al. Hemispherectomy for treatment of refractory epilepsy in the pediatric age group: a systematic review. J Neurosurg Pediatr 2015;15(1):34-44.

5. Schramm J, Kuczaty S, Sassen R, Elger CE, von Lehe M. Pediatric functional hemispherectomy: outcome in 92 patients. Acta Neurochir 2012;154(11):2017-28.

6. Shields WD. Catastrophic epilepsy in childhood. Epilepsia 2000;41 Suppl. 2:S2-6.

7. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. The Lancet Neurology 2014;12(11):114-26.

8. Engelhart MC, van Schooneveld MM, Jennekens-Schinkel A, van Nieuwenhuizen O. 'With the benefit of hindsight': would you opt again for epilepsy surgery performed in childhood? Eur J Paediatr Neurol 2013;17(5):462-70.

9. Van Schooneveld MM, Braun KP. Cognitive outcome after epilepsy surgery in children. Brain Dev 2013;35(8):721-9.

10. Boshuisen K, van Schooneveld MM, Uiterwaal CS, et al.; TimeToStop cognitive outcome study group. Intelligence quotient improves after antiepileptic drug withdrawal following pediatric epilepsy surgery. Ann Neurol 2015;78(1):104-14.

11. Boshuisen K, van Schooneveld MM, Leijten FS, et al. Contralateral MRI abnormalities affect seizure and cognitive outcome after hemispherectomy. Neurology 2010;75(18):1623-30.

12. Althausen A, Gleissner U, Hoppe C, et al. Long-term outcome of hemispheric surgery at different ages in 61 epilepsy patients. J Neurol Neurosurg Psychiat 2013;84(5):529-36.

13. Moosa AN, Gupta A, Jehi L, et al. Longitudinal seizure outcome and prognostic predictors after hemispherectomy in 170 children. Neurology 2013;80(3):253-60.

14. Lamberink HJ, Boshuisen K, van Rijen PC, Gosselaar PH, Braun KP; Dutch Collaborative Epilepsy Surgery Program (DCESP). Changing profiles of pediatric epilepsy surgery candidates over time: A nationwide single-center experience from 1990 to 2011. Epilepsia 2015;56(5):717-25.

15. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. New York, NY: Oxford University Press; 2012.

16. Goedhart A, Treffers F, Widenfelt B. Vragen naar psychische problemen bij kinderen en adolescenten: de Strengths and Difficulties Questionnaire. Maandblad Geestelijke Volksgezondheid 2003;58:1018-35.

17. EuroQol group. The EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.

18. Brocks R. EuroQol: the current state of play. Health Policy 1996;37 (1):53-72.

19. Cohen J. Statistical power analysis for the behavioral sciences 2nd ed. New Yersey: Lawrence Erlbaum; 1988.

20. IBM Corp. Released 2012. IBN SPSS statistics for windows, version 21.0 Armonk, NY: IBM.Corp.

21. Pulsifer MB, Brandt J, Salorio CF, et al. The cognitive outcome of hemispherectomy in 71 children. Epilepsia 2004;45(3):243-54.

22. Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: Rationale for early intervention. Epilepsia 2005;46:258-71.

23. Basheer SN, Connolly MB, Lautzenhiser A, et al. Hemispheric surgery in children with refractory epilepsy: complications, and adaptive function. Epilepsia 2007;48:133-40.

24. Cross JH, Jayakar P, Nordli D, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: Recommendations of the subcommission for pediatric epilepsy surgery. Epilepsia 2006;47;952-59.

25. Lendt M, Helmstaedter C, Kuczaty S, Scharamm J, Elger CE. Behavioural disorders in children with epilepsy: early improvement after surgery. J Neurol Neurosurg Psychiat 2000;69(6):739-44.

26. Davies S. Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. Dev Med Child Neurol 2003;45(5):292-5.

27. Longo E, Badia M, Orgaz BM. Patterns of participation in leisure activities outside of school in children and adolescents with cerebral palsy. Res Dev Disabil 2013:34:266-75.

28. Verdinelli C, Olsson L, Edelvik A, Hallböök T, Rydenhag B, et al. A long-term patient perspective after hemispherotomy – a population based study. Seizure 2015;30:76-82.

29. Steinlin M, Roellin K, Schroth G. Long-term follow-up after stroke in childhood. Eur J Pediatr 2004;163(4-5):245-50.

30. Puka K, Smith ML. Predictors of long-term quality of life after pediatric epilepsy surgery. Epilepsia 2015;56(6):873-81.

31. Sajobi TT, Fiest KM, Wiebe S. Changes in quality of life after epilepsy surgery: the role of reprioritization response shift. Epilepsia 2014;55(9):1331-8.

Chapter 6

Withdrawal of antiepileptic drugs improves psychomotor speed after childhood epilepsy surgery

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Abstract

This retrospective study evaluates the impact of postoperative antiepileptic drug (AED) withdrawal on psychomotor speed in seizure-free children, operated for medically refractory epilepsy. Postsurgical medication policy and neuropsychological assessments (performed shortly before and six, 12 and 24 months after surgery), were evaluated in 57 children (32 female, median age at surgery 13 years). Patients were divided into a withdrawal (n=29) and a no-withdrawal group (n=28). Scores of four psychomotor tests performed at 12 and 24 months after surgery were compared with those of postoperative baseline measurements, performed six months after surgery. At 24 months, the withdrawal group had improved significantly more than the no-withdrawal group on three of four tests; reaction time to light (p=0.031), reaction time to sound (p=0.045) and tapping (p=0.003). At 12 months, a non-significant tendency in the same direction was found for both reaction time tests. Drug withdrawal after surgery improves psychomotor speed and may unleash the potential for cognitive improvement.

Introduction

The ultimate goal of epilepsy surgery in children is to reach "cure", defined as both seizure- and antiepileptic drug (AED) freedom.[1] In contrast to previous suggestions that early withdrawal would be unsafe, we recently demonstrated in a large retrospective European cohort study that timing of postoperative AED discontinuation in children did not relate to long-term seizure outcomes.[2] Antiepileptic drug withdrawal might not only be safe but also beneficial with regard to cognitive functioning, since AEDs are known to have cognitive side effects,[3] with attention, vigilance and psychomotor speed being most affected.[4] From medically treated cohorts of seizure free patients, we know that AED discontinuation leads to improved complex cognitive processing under time pressure in adults[5] and increased psychomotor speed and higher alertness in children.[6,7] Less is known about cognitive benefits of AED withdrawal after epilepsy surgery, but AED cessation was recently shown to be the strongest predictor of postoperative increase in IQ in children who underwent temporal lobe surgery.[8] Here, we aimed to evaluate the effect of postoperative AED withdrawal on psychomotor speed in seizure free children after epilepsy surgery.

Material and methods

We retrospectively evaluated postoperative cognitive functioning and medication policy in children who underwent epilepsy surgery in our center between 1998 and 2010. Cognitive functioning was monitored by neuropsychological assessments at fixed time points, shortly before and six, 12 and/or 24 months after surgery (pre-NPA, NPA6, NPA12 and NPA24). Postsurgical use of AEDs was obtained from the patients' medical or neuropsychological records. Patients were included if they (1) underwent at least two postoperative NPAs, including NPA6, (2) were six years or older at the time of pre-NPA; the lowest age level at which the assessed psychomotor tests were performed, (3) had a total IQ of at least 55 at NPA6, as most children with an IQ <55 are not able to perform the psychomotor tests used, due to their low level of cognitive functioning and (4) reached complete seizure-freedom after surgery.

For each patient, available performances with their dominant hand on four psychomotor speed tasks were collected: (1) simple reaction time to light (milliseconds [ms]), (2) simple reaction time to sound (milliseconds [ms]), (3) purdue pegboard test (seconds [s]), and (4) tapping (number of taps [n]). These tasks were part of the reaction time test (1,2) and motor performance series (3,4) of the Vienna Test System (Schuhfried, Vienna).

To exclude possible bias through differential effects of the surgical procedure itself on the course of cognitive functioning between groups, we used the first postoperative time point

(NPA6) as baseline (rather than preoperative assessment). Using this baseline, changes in postoperative psychomotor speed were assessed by calculating differences in raw scores between the later assessments (NPA12 and NPA24) and baseline. Subsequently, these raw delta-scores were expressed as percentages (improvement or deterioration) of the baseline score.

Patients were categorized in two groups. "Withdrawal" was defined as complete cessation of at least one AED at the latest time of assessment (NPA12 or NPA24) compared to the number of AEDs used at NPA6. "No-withdrawal" was defined as continuation of all AEDs that were used at baseline assessment.

Statistical analyses were performed using SPSS, version 20. Mann-Whitney U and chi-square tests were used for comparing baseline characteristics of both groups. Independent-samples t-tests were conducted to compare the mean percentage deltascores of the "withdrawal" group and the "no-withdrawal" group. The significance level was set at $p<0.05$ (two-tailed).

Results

Of the 57 included patients, 29 (51%) withdrew at least one AED and 28 (49%) did not discontinue medication after NPA6. Thirteen patients (23%) were completely AED-free at NPA24. Patient characteristics of both groups are shown in Table 6.1. Extra-temporal surgery was performed more often in the "withdrawal" group than in the "no-withdrawal" group. A tumor was the most common underlying cause of epilepsy in both groups. More children in the no-withdrawal group used only one AED at baseline. Gender, age at onset and surgery, side of surgery and TIQ were not different between the two groups.

As we used mean delta-scores to compare the individual test results of latest NPA with baseline-assessment in both groups, instead of direct cross sectional comparison of the groups, we did not control for baseline differences.

Changes in scores on the four psychomotor tests are shown in percentage delta-scores in Table 6.2. Except for Purdue pegboard, there were significant differences in delta-scores between the withdrawal- and the no-withdrawal group, 24 months after surgery, in favour of the withdrawal group. At NPA24, the mean delta-score for the reaction time to light test, was -15.7% in the withdrawal group, compared to -1.8% in the no-withdrawal group ($p=0.031$); the mean delta-score for the reaction time to sound test in the withdrawal group was -12.4% versus -5.6% in the no-withdrawal group ($p=0.045$) and the mean delta-scores for the tapping test were 12.2% and 3.4% respectively ($p=0.003$). At NPA12 a non-significant tendency in the same direction was seen for both the reaction time to sound and light test.

Table 6.1 Patient characteristics

	Withdrawal (n=29)	No withdrawal (n=28)
Female; n (%)	16 (55.2)	16 (57.1)
Median age epilepsy onset (interquartile range)	8 (3.5–12)	5 (2–9.75)
Median age surgery (interquartile range)	12.1 (10.8–15.9)	14.3 (11.3–15.7)
Most frequent seizure type before surgery; n (%)		
Complex partial seizures	20 (69.0)	19 (67.9)
Simple partial seizures	6 (20.7)	6 (21.4)
Secondarily generalized tonic-clonic seizures	3 (10.3)	3 (10.7)
Etiology; n (%)		
Tumor	20 (69.0)	12 (42.9)
HS	3 (10.3)	6 (21.4)
MCD	3 (10.3)	5 (17.9)
Vascular	1 (3.4)	1 (3.6)
Other	2 (6.9)	4 (14.3)
Surgery type; n (%)		
Temporal resection	15 (51.7)	19 (67.9)
Extratemporal resection	13 (44.8)	5 (17.9)
Hemispherectomy	1 (3.4)	2 (7.1)
Multiple subpial transections	0 (0.0)	2 (7.1)
Side of surgery; n (%)		
Right	14 (48.3)	12 (42.9)
Left	15 (51.7)	16 (57.1)
Surgery in dominant hemisphere; n (%)	16 (55.2)	12 (42.9)
Median TIQ at NPA6 (interquartile range)	89 (72.5–103)	88 (73.7–97.0)
Number of AEDs at NPA6; n (%)		
1	6 (20.7)	13 (46.4)
2	15 (51.7)	10 (35.7)
3	6 (20.7)	4 (14.3)
4	2 (6.9)	1 (3.6)
Number of discontinuated AEDs; n (%)		
1	15 (51.7)	-
2	13 (44.8)	-
3	1 (3.4)	-
Commonly withdrawn AEDs; n (%)		
Clobazam	10 (34.5)	-
Carbamazepine	8 (27.6)	-
Levetiracetam	8 (27.6)	-
Lamotrigine	6 (20.7)	-
Fenytoin	4 (13.8)	-
Oxcarbazepine	4 (13.8)	-
Other	3 (10.3)	

AED = antiepileptic drug; MCD = malformation of cortical development; HS = hippocampal sclerosis; NPA6 = neuropsychological assessment six months after surgery; TIQ = total intelligence quotient.

Table 6.2 Effect of antiepileptic medication on mean percentage delta scores of psychomotor speed tests

	Withdrawal		No-withdrawal		
	Mean (SD)	n	Mean (SD)	n	p-values*
Reaction time to light					
NPA12-NPA6	-6.23 (9.82)	12	-.70 (14.17)	20	0.244
NPA24-NPA6	-15.67 (10.18)	9	-1.79 (16.79)	19	0.031
Reaction time to sound					
NPA12-NPA6	-3.48 (15.26)	12	3.67 (16.72)	20	0.236
NPA24-NPA6	-12.37 (13.11)	9	-5.56 (14.20)	19	0.045
Purdue Pegboard					
NPA12-NPA6	-0.18 (17.15)	26	0.52 (12.08)	22	0.873
NPA24-NPA6	-6.35 (11.67)	21	-2.34 (15.25)	19	0.353
Tapping					
NPA12-NPA6	4.77 (8.65)	26	3.31 (8.05)	23	0.545
NPA24-NPA6	12.15 (8.21)	21	3.36 (9.22)	19	0.003

NPA6 = neuropsychological assessment 6 months after surgery; NPA12: neuropsychological assessment 12 months after surgery; NPA24: neuropsychological assessment 24 months after surgery; n = number.
* the significance level was set at $p<0.05$ (two-tailed).

Discussion

The main finding of this retrospective study is that postoperative AED withdrawal in children significantly improves performances on psychomotor speed tests. Two years after surgery, the children who discontinued at least one AED improved significantly more on several psychomotor speed tests compared to six months postoperatively, than children who remained on medication.

Two previous AED discontinuation studies in non-surgical pediatric cohorts have reported varying effects on cognition. Chen et al.[9] found no correlation between AED withdrawal and IQ in a nonrandomized and unblinded discontinuation study in 70 seizure-free children on monotherapy. Aldenkamp et al.[6,7] reported significant improvement of psychomotor speed and observed subjective improvement in alertness in 83 seizure-free children on monotherapy who withdrew medication.

Until now, only one study has reported the influence of AED withdrawal on cognitive outcome in operated children.[8] Discontinuation of antiepileptic drugs was found to be an independent predictor of IQ increase in children who underwent temporal lobe surgery. Whereas a positive IQ change in that study only became significant after many years following surgery, the results of our study illustrate that AED withdrawal has early beneficial effects on other aspects of cognitive functioning.

Our study has limitations. It is retrospective, non-randomized, and the number of patients who underwent all tests at all time-points is limited. The number of AEDs used postoperatively may have been one of the factors that contributed to the decision whether or not to withdraw. Still being assured of the protection of at least one drug after withdrawal, children who use more than one AED are more likely to start withdrawal of one of their medications.[2] As more children in the no-withdrawal group used only one AED at baseline, they were less likely to withdraw their medication to begin with. In addition, the many other factors that may have influenced each individual's cognitive outcome and potential to improve have not been systematically accounted for in our study. Both study groups, however, were seizure free and mainly differed in terms of AED withdrawal. In this study no distinction was made between different types, the total number, dose, and blood levels of AEDs, which could all contribute to cognitive side-effects. As described in the literature, effects on cognition are worse for older AEDs.[10] Also, higher medication dosages and blood levels are associated with an increased risk of cognitive side effects.[11] The small number of patients prevented multivariable analysis of these factors that may have influenced the amount of improvement in the withdrawal group.

It remains to be established to what extent the reported improvement in psychomotor speed after drug withdrawal influences daily life and learning abilities of children. It is probable that improved psychomotor speed and attention will benefit the cognitive development of children, since even small cognitive adverse effects of AEDs may have cumulative negative consequences on eventual academic performance.[11] The results of this study and previous work[8] suggest that in seizure-free children AED withdrawal after epilepsy surgery is favourable with regard to cognition. A collaborative randomized study to prove benefits and safety of early AED discontinuation is under way.

References

1. Schmidt D, Baumgartner C, Loscher W. The chance of cure following surgery for drug-resistant temporal lobe epilepsy. What do we know and do we need to revise our expectations? Epilepsy Res 2004;60(2-3):187-201.

2. Boshuisen K, Arzimanoglou A, Cross JH, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. Lancet Neurol 2012;11(9):784-91.

3, Loring DW, Meador KJ. Cognitive side effects of antiepileptic drugs in children. Neurology 2004;62(6):872-7.

4. Meador KJ. Cognitive outcomes and predictive factors in epilepsy. Neurology 2002;58(8 Suppl 5):S21-6.

5. Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus Study). Epilepsia 2008;49(3):455-63.

6. Aldenkamp AP, Alpherts WC, Blennow G, et al. Withdrawal of antiepileptic medication in children--effects on cognitive function: The Multicenter Holmfrid Study. Neurology 1993;43(1):41-50.

7. Aldenkamp AP, Alpherts WC, Sandstedt P, et al. Antiepileptic drug-related cognitive complaints in seizure-free children with epilepsy before and after drug discontinuation. Epilepsia 1998;39(10):1070-4.

8. Skirrow C, Cross JH, Cormack F, Harkness W, Vargha-Khadem F, Baldeweg T. Long-term intellectual outcome after temporal lobe surgery in childhood. Neurology 2011;76(15):1330-7.

9. Chen Y, Chi Chow J, Lee I. Comparison the cognitive effect of anti-epileptic drugs in seizure-free children with epilepsy before and after drug withdrawal. Epilepsy Res 2001;44(1):65-70.

10. Loring DW, Marino S, Meador KJ. Neuropsychological and behavioral effects of antiepilepsy drugs. Neuropsychol Rev 2007;17(4):413-25.

11. Mula M, Trimble MR. Antiepileptic drug-induced cognitive adverse effects: potential mechanisms and contributing factors. CNS Drugs 2009;23(2):121-37.

Chapter 7

Intelligence quotient improves after antiepileptic drug withdrawal following pediatric epilepsy surgery

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Abstract

Objective: Antiepileptic drugs (AEDs) have cognitive side effects that, particularly in children, may affect intellectual functioning. With the *TimeToStop* (TTS) study, we showed that timing of AED withdrawal does not majorly influence long-term seizure outcomes. We now aimed to evaluate the effect of AED withdrawal on postoperative intelligence quotient (IQ), and change in IQ (delta IQ) following pediatric epilepsy surgery.

Methods: We collected IQ scores of children from the TTS cohort with both pre- and postoperative neuropsychological assessments (NPAs; n=301) and analysed whether reduction of AEDs prior to the latest NPA was related to postoperative IQ and delta IQ, using linear regression analyses. Factors previously identified as independently relating to (delta) IQ, and currently identified predictors of (delta) IQ, were considered possible confounders and used for adjustment. Additionally, we adjusted for a compound propensity score that contained previously identified determinants of timing of AED withdrawal.

Results: Mean interval to latest NPA was 19.8±18.9 months. Reduction of AEDs at latest NPA significantly improved postoperative IQ and delta IQ (adjusted regression coefficient [RC]=3.4, 95% confidence interval [CI]=0.6–6.2, p=0.018 and RC=4.5, 95% CI=1.7–7.4, p=0.002), as did complete withdrawal (RC=4.8, 95% CI=1.4–8.3), p=0.006 and RC=5.1, 95% CI=1.5–8.7, p=0.006). AED reduction also predicted ≥10 point IQ increase (p=0.019). The higher the number of AEDs reduced, the higher the IQ (gain) after surgery (RC=2.2, 95% CI=0.6–3.7, p=0.007 and RC=2.6, 95% CI=1.0–4.2, p=0.001, IQ points per AED reduced).

Interpretation: Start of AED withdrawal, number of AEDs reduced, and complete AED withdrawal were associated with improved postoperative IQ scores and gain in IQ, independent of other determinants of cognitive outcome.

Introduction

The ultimate goals of epilepsy surgery are to achieve freedom of seizures, enable antiepileptic drug (AED) discontinuation, and improve developmental capacities.[1-3] Early in life, at least some AEDs can interfere with normal brain development, by inducing neuronal apoptosis and impairing neurogenesis, synaptogenesis, cell proliferation and migration, and synaptic plasticity.[4,5] Furthermore, it is well recognized that many AEDs have cognitive adverse effects,[6] with attention, vigilance and psychomotor speed being most affected.[7] Cumulatively, the cognitive consequences of using 1 or more AEDs during critical stages of development may affect eventual academic achievements.[8] The possibility of improving cognitive development is an important motive to consider AED withdrawal in seizure-free patients.[9] Several studies have convincingly revealed that AED reduction improves specific cognitive measures, such as cognitive processing under time pressure,[10,11] psychomotor speed and alertness,[12-14] processing speed,[15] and verbal memory,[16] in both medically and surgically treated patients. Only 1 study has addressed the influence of AED discontinuation on intelligence quotient (IQ), in a selected cohort of children who underwent temporal lobe surgery, and found AED cessation to be associated with increase in IQ.[17]

In this study we aimed to investigate how drug withdrawal influences intelligence after epilepsy surgery in a large heterogeneous cohort of 301 children who were operated on in 11 European centers and who started AED reduction after having reached postoperative seizure freedom. We evaluated the effect of reduction and complete discontinuation of AEDs on postoperative IQ and on the postoperative change in IQ (delta IQ).

Patients and methods

The *TimeToStop* (TTS) Study[18] is a retrospective European multicenter cohort study that collected data on seizure outcome and AED withdrawal policies after pediatric epilepsy surgery. The study was initiated in 2008 within the European Taskforce for Epilepsy Surgery in Children ('U-task') and included 766 patients younger than 18 years at surgery, operated on between January 1, 2000 and October 1, 2008 in 15 medical centers from 8 countries, who started AED reduction at some point postoperatively, with at least 1 year of postoperative follow-up. The first aim of TTS was to investigate timing of postoperative AED withdrawal in relation to seizure outcomes. For further details on the study, we refer to the previous publications on the TTS study.[18,19] For the current study, we included children from the original TTS cohort for whom both a pre- and postoperative intelligence quotient (IQ) was available, and for whom the TTS investigators agreed to share the data.

Neuropsychological assessments

All patients had undergone pre- and at least one postoperative neuropsychological assessment. A range of standardized measurements, according to age and cognitive level of the child, was used, which differed between participating centers of the study. The neuropsychological tests used are shown in Supplementary Table S7.1. Normed IQ, or mental developmental index (MDI) scores, depending on the type of tests the children were able to take, were obtained. For children who scored below the lower end of the IQ/MDI norms' range and for whom a mental age could be determined, IQ was calculated as a developmental quotient, using the ratio 100 x mental age/calendar age). All obtained scores will be referred to as IQ. The main outcome variables were the latest inventoried postoperative IQ, and delta IQ, which was defined as the latest assessed postoperative IQ minus the presurgical IQ. The varying time interval from surgery to latest NPA and the number of postoperative NPAs performed were considered important to account for, and were incorporated as possible confounders in the analysis (see Statistical Analysis). To ascertain a correct interpretation of data, we performed a separate analysis including only patients for whom normed IQ scores were available (IQ>50), in addition to the analysis of the total cohort that included children with normed IQ scores as well as those who only had ratio IQ scores. In addition, we performed a separate analysis including only patients who either had been completely seizure free since surgery, or who had been Engel 1 for at least 1 year at the time of their latest NPA, to ascertain that patients with ongoing seizures who would not be (good) candidates for withdrawal of AEDs have not confounded the results. To evaluate the possible clinical relevance of findings, we performed a supplemental analysis in which the cohort was divided into patients who improved with 10 or more IQ points, those who kept stable IQ scores, and children whose IQ decreased by 10 or more points after surgery.

Data collection

When the local TTS investigators agreed to share neuropsychological data for the purpose of this study, we collected all available pre- and postoperative IQ scores of children. Epilepsy related variables, previously identified as possible predictors of postsurgical IQ or change in IQ[3,17,20,21] were inventoried and included sex, duration of epilepsy, age at surgery, etiology, seizure recurrence, and type- and side of surgery. Etiology was classified as malformations of cortical development (MCD; including all subtypes of focal cortical dysplasia, minimal malformations of cortical development, hemimegalencephaly, and tuberous sclerosis complex), tumors, vascular lesions, mesiotemporal sclerosis, and other etiologies (including Rasmussen encephalitis, postinfectious etiologies, and nonspecified etiologies). Type of surgery was classified as lobar, including frontal, temporal, parietal, occipital and tailored resections or

disconnections, multilobar resections or disconnections, and hemispherectomy. Seizure freedom at the time of the latest NPA was defined as the patient being completely free of seizures, including auras, since surgery or for at least 1 year at the time of NPA.

From the medical files we collected the following data on AED withdrawal: (1) whether at the latest NPA the process of AED withdrawal had already been started, defined as discontinuation of at least 1 AED compared to the situation at preoperative NPA; (2) whether all AEDs had been completely discontinued at the latest NPA; and (3) the number of AEDs that had been discontinued at the latest NPA. The patients who did not start AED withdrawal at the moment of NPA were used as reference. In addition to the AED withdrawal data, we collected the time intervals from surgery to start of withdrawal and to complete discontinuation of AEDs, and we noted which AEDs were discontinued and which were first withdrawn postoperatively.

Statistical analysis

To study the influence of AED withdrawal on postsurgical IQ and delta IQ, we first analyzed the crude association between (1) having started AED withdrawal; (2) having discontinued all AEDs; and (3) the number of AEDs reduced at latest NPA, and both IQ and delta IQ. Second, we adjusted for factors that were related to IQ or delta IQ in a univariate linear regression model (Supplementary Table S7.2), those being age at surgery and preoperative IQ. Additional factors we identified to be related to IQ or delta IQ were also associated with timing of postoperative AED withdrawal, and were therefore incorporated into the propensity score, as explained below. In addition to the variables we identified in the current study, variables that had previously been reported to be independently predictive of IQ or IQ change after surgery[3] were added to the model. These factors were male gender and duration of epilepsy. We also adjusted for time to latest NPA and number of postoperative NPAs. Third, we calculated a compound propensity score for both start and completion of AED withdrawal, including previously identified predictors of time to start and completion of AED withdrawal,[18] using logistic regression analysis. The final propensity score was based on the clinically most important predictors of both start and completion of AED withdrawal, or to either of them as previously identified.[18] These were shown to have large influence on timing of AED withdrawal. We therefore chose the following variables for the final propensity score: number of AEDs used at time of surgery, complete resection of the anatomical lesion and of the epileptogenic zone, epileptic electroencephalographic (EEG) abnormalities postoperatively, and underlying etiology (Figure 7.1).

With this score, we tried to capture the clinical indications for AED withdrawal, as they might by themselves influence (delta) IQ. Instead of extension of the initial model with these indications, we chose to incorporate them in 1 score to gain statistical power. The final

regression model was adjusted for this propensity score, to exclude a possibly confounding influence of these factors on cognitive outcome through timing of AED withdrawal. As type of surgery was highly correlated with preoperative IQ, we adjusted for preoperative IQ only, and not for type of surgery in the propensity model. Continuous variables were introduced as such in the models; for categorical variables, we created indicator variables. To study the relation between medication policy and IQ change of 10 or more points, analysis of variance tests were used for continuous variables and chi-square tests for categorical variables. We used SPSS Statistics version 22.0. Results are reported as a regression coefficient (RC) with 95% confidence intervals (CIs), indicating change in postoperative IQ or delta IQ with every unit or category change in the predictor. Probability values were based on 2-sided tests with 0.05 as the cutoff level for statistical significance.

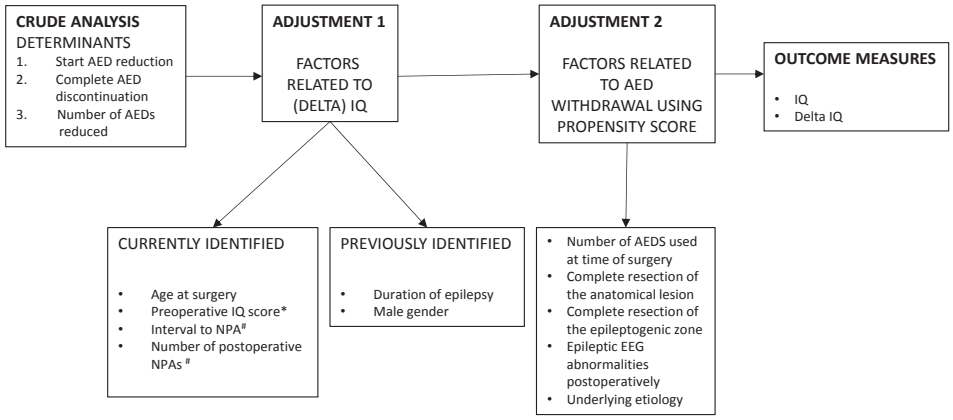

Figure 7.1 Statistical analysis.

* Only analyses with postoperative intelligence quotient (IQ) as outcome measure, were adjusted for preoperative IQ. # Not significantly associated with IQ or delta IQ, but considered possibly important confounders and necessary to adjust for. AED = antiepileptic drug; delta IQ = postoperative IQ minus preoperative IQ; EEG = electroencephalographic; NPA = neuropsychological assessment.

Results

We included 301 patients of whom both pre- and postoperative IQ values were known (Table 7.1). Mean age at surgery was 9.6±4.5 (standard deviation [SD]) years, the mean age at preoperative NPA was 9±4 years, and the latest postoperative NPA was at 11 years ±5 years. The mean interval from surgery to latest NPA was 19.8±18.9 months. Mean IQ at the latest postoperative NPA was 81.9±22.6, and mean delta IQ was 2.9±11.6. The mean IQ change for all patients who reduced or stopped AEDs, was 4.6±11.5; for patients who started reduction but did not reach complete withdrawal of AEDs it was 4.1±12.0,

Table 7.1 Clinical characteristics and seizure outcome data of the 301 patients

Characteristic	Patients			
	No. (%) or Mean±SD	Had not started AED withdrawal at time of latest NPA, n=146	Had started AED withdrawal at time of latest NPA, n=155	p
Male	147 (48.8)	77 (52.7)	70 (45.2)	0.189
Etiology	301			0.014
MCD	94 (31.2)	38 (26)	56 (36.1)	0.101
Tumor	109 (36.2)	60 (41.1)	49 (31.6)	0.112
Vascular lesions	41 (13.6)	13 (8.9)	28 (18.1)	0.012
HS	50 (16.6)	31 (21.2)	19 (12.3)	0.037
Other etiologies	7 (2.3)	4 (2.7)	3 (1.9)	0.644
EEG	299			0.025
No epileptic abnormalities	215 (71.9)	114 (79.2)	101 (65.2)	0.007
Epileptic EEG abnormalities	15 (16.1)	18 (12.5)	30 (15.5)	0.107
No EEG performed	36 (12.0)	12 (8.3)	24 (15.5)	0.058
Type of surgery	301			0.006
Lobar surgery	239 (80.5)	125 (86.8)	114 (74.5)	0.006
Hemispherectomy	45 (15.2)	12 (8.3)	33 (21.6)	0.001
Multilobar resection	13 (4.4)	7 (4.9)	6 (3.9)	0.692
Preoperative IQ score	83.2±17.6	84.6±19.8	73.5±22.6	<0.001
Number of AEDs used during preoperative NPA	1.8±0.8	1.4±0.7	2.2±0.7	<0.001
Mean IQ score at latest NPA	81.6±22.6	85.8±20.4	78.1±23.9	0.003
Number of AEDs used preoperatively	1.7±0.8	1.5±0.7	1.8±0.8	<0.001
Direct postoperative seizure freedom	273 (91.0)	131 (90.3)	142 (91.6)	0.701

Table 7.1 continues on next page

Table 7.1 *Continued*

Characteristic	Patients			
	No. (%) or Mean±SD	Had not started AED withdrawal at time of latest NPA, n=146	Had started AED withdrawal at time of latest NPA, n=155	p
Complete resection of the anatomical lesion	300			0.092
Yes	205 (68.3)	102 (70.3)	103 (66.5)	0.526
Not determined	53 (17.7)	19 (13.1)	34 (21.9)	0.042
No	42 (14)	24 (16.6)	18 (11.6)	0.227
Complete resection of the epileptogenic zone	294			0.428
Yes	75 (25.5)	39 (27.7)	36 (23.5)	0.485
Not determined	198 (67.3)	90 (63.8)	108 (70.6)	0.142
No	21 (7.1)	12 (8.5)	9 (5.9)	0.412
Stop AEDs[a]	192 (64.9)	3 (2.1)[a]	56 (36.1)	<0.001
Interval to start AED reduction, mo	18.3±13.5	21.6±13.8	15.3±12.5	<0.001
Interval to complete AED withdrawal (m)	29.6±16.7	33.3±19.0	26.6±13.9	0.006
Interval to latest NPA, mo	19.8±18.9	14.6±14.0	24.6 (21.6)	<0.001
Number of AEDs used during latest NPA	1.1±0.8	1.4±0.7	0.7±0.6	<0.001
Mean reduction of AEDs at latest NPA	0.7±0.9	0.0±0.24	1.4±0.67	<0.001
Seizure recurrence[b]	42 (14.0)	22 (15.1)	20 (12.9)	0.588
Regain of seizure freedom[b]	23 (65.7)	14 (70)	9 (60)	0.537
Engel 1 at latest NPA[c]	161 (53.8)	62 (42.8)	99 (64.3)	<0.001
Seizure free since surgery, or Engel 1 at latest NPA	271 (90.6)	129 (89.0)	142 (91.6)	0.336

Baseline characteristics were compared using chi-square test for categorical variables and independent t tests for scaled or ordinal variables.

[a] Having reached complete stop of AEDs during time frame of the TTS study.

[b] During entire follow-up period of TTS study.

[c] Defined as seizure freedom without auras for at least 1 year, regardless of AED use at time of latest NPA.

AED = antiepileptic drug; EEG = electroencephalogram; HS = hippocampal sclerosis; IQ – intelligence quotient; MCD = malformations of cortical development; NPA = neuropsychological assessment; SD = standard deviation; TTS = TimeToStop.

and for patients who achieved complete withdrawal of medication it was 5.6±10.8. For patients who had not started AED reduction, mean IQ change was 1.1±11.4. Thirty-six patients (12%) had a postoperative decrease of 10 or more IQ points, whereas 70 patients (23%) increased their IQ by 10 or more points. We checked whether patients with more NPAs postoperatively or with shorter time intervals between pre- and latest postoperative NPAs had more IQ increase due to a possible learning effect, but neither the number of postoperative NPAs nor the interval between assessments was not associated with IQ or delta IQ (see Supplementary Table S7.2). Baseline characteristics differed among patients who had started AED withdrawal compared to those who had not. These differences are mainly attributable to the intervals to start of AED withdrawal (longer for those who did not start AED reduction, and shorter for those who started) and to the time point of latest NPA (shorter for those who did not start AED reduction and longer for those who started AED reduction at time of their latest NPA), and to variables that were known to influence the postoperative timing of AED withdrawal (see Table 7.1). We adjusted for interval to NPA, and for the variables associated with intervals to AED withdrawal in the compound propensity score to limit confounding.

The influence of AED reduction on postoperative IQ and delta IQ

All patients included in the TTS study started AED reduction at some point during their postoperative follow-up interval. In the current cohort 155 (52%) had started reduction of AEDs at their latest postoperative NPA, and 59 patients (20%) had completely stopped medication at the latest NPA. The mean interval to complete cessation of AEDs was 29.6 ±16.7 months. The average number of AEDs used preoperatively was 1.7±0.8. At the latest postoperative NPA, patients used on average 1.1±0.8 AEDs.

Variables identified to be associated with IQ or delta IQ in univariate linear regression analysis were age at surgery, preoperative IQ score, etiology, number of AEDs used at time of surgery, and type of surgery (see Supplementary Table S7.2). These variables were considered possible confounders. Sex and duration of epilepsy were not significantly related in this study, but considered possible confounders.due to previously reported associations3. When adjusted for confounders and the propensity score, patients who had started AED withdrawal at latest NPA had a significantly higher postoperative IQ and more IQ increase (RC=3.4, 95% CI=0.6–6.2, p=0.018 and RC=4.5, 95% CI=1.7–7.4, p=0.002, respectively; Table 7.2). Complete discontinuation of AEDs was also significantly related to a higher IQ and IQ gain (RC=4.8, 95% CI=1.4–8.3, p=0.006 and RC=5.1, 95% CI=1.5–8.7, p=0.006). The number of AEDs that had been reduced postoperatively was linearly related to IQ and delta IQ; the more drugs withdrawn, the higher postoperative IQ and the more increase in

Table 7.2 AED withdrawal and postoperative IQ and delta IQ

	Latest postoperative IQ				Delta IQ[a]			
	Crude model		Adjusted model[b]		Crude model		Adjusted model[b]	
	RC (95% CI)	p	RC (95% CI)	p	RC (95% CI)	p	RC (95% CI)	p
Start withdrawal of AEDs, n=155/301	-7.7 (-12.8–2.7)	0.003	3.4 (0.6–6.2)	0.018	3.5 (0.9–6.2)	0.008	4.5 (1.7–7.4)	0.002
Complete discontinuation of AEDs, n=59/301	-0.5 (-7.0–5.9)	0.873	4.8 (1.4–8.3)	0.006	3.4 (0.1–6.7)	0.044	5.1 (1.5–8.7)	0.006
Number of AEDs reduced, N=301[c]	-3.3 (-6.2—0.3)	0.023	2.2 (0.6–3.7)	0.007	1.9 (0.4–3.4)	0.011	2.6 (1.0–4.2)	0.001

Analysis performed: linear regression analysis of the relation between AED withdrawal and IQ and delta IQ.

[a] Postoperative IQ minus preoperative IQ.

[b] Adjusted for age at surgery, interval to latest postoperative neuropsychological assessment, duration of epilepsy, gender, and in analyses of the latest postoperative IQ, also for preoperative IQ score. Furthermore, we adjusted for a compound propensity score that contained previously identified predictors of start or completion of medication withdrawal[18] (i.e. number of AEDs used at time of surgery, completeness of resection of the anatomical lesion and of the epileptogenic zone, postoperative electroencephalographic findings, and etiology). Because of high correlation between type of surgery and preoperative IQ, we did not adjust for type of surgery.

[c] The change in number of AEDs compared to preoperatively.

AED = antiepileptic drugs; CI = confidence interval; IQ = intelligence quotient; RC = regression coefficient, indicating the change in IQ or delta IQ with every unit or category change in the predictor.

IQ (RC=2.2, 95% CI=0.6–3.7, p=0.007 and RC=2.6, 95% CI=1.0–4.2, p=0.001), IQ points per AED reduced respectively; see Table 7.2). Start of AED withdrawal was also significantly associated with an increase of 10 or more IQ points (p=0.019). Complete cessation of AEDs and the number of AEDs withdrawn, however, were not significantly associated with a positive change in IQ of 10 or more points (Supplementary Table S7.3).

In additional analyses, including only patients with normed IQ scores (IQ>50) and thus excluding those with a calculated ratio IQ score (n=28), the relation between start and completion of AED withdrawal and (delta) IQ remained significant, as did the relation between the number of drugs reduced and IQ and delta IQ (Supplemental Table S7.4) and the relation between start AED reduction and 10 points IQ change (p=0.035). In the analysis only including patients who were seizure free at least 1 year at the time of their latest NPA or who had been completely seizure free since surgery (n=271), the relations between start- and completion of AED withdrawal, reduction of number of AEDs and (delta) IQ (Supplementary Table S7.5) and the relation between start AED reduction and 10-point IQ change also remained significant (p=0.044).

Type of AED reduced and delta IQ

With the exception of Vigabatrin, reduction of any of the AEDs given in Table 7.3 was associated with a comparable mean IQ increase of 3.0 to 6.5 points. Withdrawal of Sultiame (n=3), Phenobarbital (n=2) and Primidone (n=2) was associated with a larger IQ increase of 10 or more points. Due to the small subgroups, statistical analyses were not performed.

Discussion

The unique European multicenter collaboration of the TTS study enabled the collection of pre- and postoperative IQ data from a large group of pediatric epilepsy surgery patients (n=301) who started postoperative AED withdrawal. After correction for possible confounders, having started with AED reduction and having completely withdrawn AEDs at latest NPA were shown to predict a higher postoperative IQ and more gain in IQ, compared to children who remained on their presurgical drug regimen. The more AEDs reduced, the higher eventual postoperative IQ and the more gain in IQ. Having started AED reduction was associated with an increase of ≥10 IQ points.

Table 7.3 Type of AED reduced in relation to delta IQ

AED reduced	All patients who had started AED reduction before latest postoperative NPA, n=155	
	Patients who reduced that AED, No. (%)	Mean IQ change per type of AED reduced
Carbamazepine	18 (27)	4.2±10.7
Clobazam	17 (41)	5.0±10.7
Clonazepam	3 (38)	3.0±3.5
Gabapentin	2 (40)	5.0±12.7
Levetiracetam	15 (24)	3.3±11.2
Lamotrigine	21 (26)	6.4±10.6
Oxcarbazepine	30 (25)	5.3±14.3
Phenobarb	2 (22)	26.7±23.6
Phenytoin	7 (44)	-2.1±9.3
Sultiam	3 (43)	10.0±1.4
Topiramate	9 (27)	1.4±11.5
Vigabatrine	11 (73)	-0.1±10.6
Valproic acid	8 (42)	6.5±7.6
Primidone	2 (33)	10.0±9.9
Mean IQ change for patients who started AED reduction, n=155		4.6±11.5
Mean IQ change for patients who started reduction but did not reach complete withdrawal of AEDs, n=99		4.1±12.0
Mean IQ change for patients who completely withdrew AEDs, n=59*		5.6±10.8
Mean IQ change for patients who had not started AED reduction yet at time of NPA, n=146		1.1±11.4

Number of children who reduced a particular AED before latest NPA. The percentage given between parentheses reflects the number of children who withdrew that particular AED first, compared to the total group of children who used the drug before surgery. Mean IQ scores are given for the whole group of patients with AED change, for patients who only started reduction, for those who achieved complete AED withdrawal, and for those who had not started reduction yet.
* Three children stopped AEDs preoperatively and were coded as nonreduction, but achieved complete withdrawal.
AED = antiepileptic drug; IQ = intelligence quotient; NPA = neuropsychological assessment.

AEDs and cognition

Cognitive improvement after AED reduction has been described in both medically and surgical treated cohorts. In medically treated cohorts of seizure-free adult patients, AED discontinuation has been shown to improve complex cognitive processing under time pressure[10,11] and executive functions.[22] In children, AED withdrawal led to improvement

of psychomotor speed and alertness.[12,13] In surgical series, drug load reduction improved executive functions in a predominantly adult cohort.[23] Two years after epilepsy surgery, performances on psychomotor tests improved more in children who withdrew medication, compared to those who stayed on their original AED regimen.[14] At the long-term, significant improvements in processing speed were more pronounced in children who had stopped AEDs.[15] Finally, verbal memory development was better in children who discontinued all AEDs compared to those who stayed on AEDs.[16]

Intelligence is a multidimensional construct, and IQ subtests tap into a variety of mental abilities, including cognitive skills vulnerable for AED side effects. Until now only one study, focussing on children with temporal lobe epilepsy, reported improvement in IQ after AED discontinuation.[17] The current study is the first to show IQ improvement related to AED withdrawal in a large heterogeneous cohort including patients with different types of surgery and etiology. The above mentioned studies focused on AED withdrawal in general. The effect of specific AEDs on cognition has been assessed more systematically in adults and results are mostly extrapolated to children. Dose-related adverse effects on cognition and behaviour are frequently reported,[24] occurring not only with old but also newer generation AEDs.[25] The effect of withdrawal of specific AEDs after epilepsy surgery, especially in children, has never been studied. In the current study, we describe the effect of different types of AED withdrawal on cognition. We did not find large differences in IQ increase between different drugs, apart from Sultiame, Phenobarbital and Primidone, although for the latter 2 standard deviations were large, indicating a great variation in IQ change. The low number of children who reduced each individual drug first, however, prevented further statistical analysis.

We previously showed that early withdrawal of AEDs does not affect eventual seizure outcome.[18] The results of the current study demonstrate that withdrawal of medication influences postoperative IQ and IQ-change. The clinical relevance of the effect size (RC=3.4 for eventual IQ and RC=4.5 for delta IQ), with only 23% of patients experiencing a 10 point IQ increase postoperatively, is not certain. We did, however, find an association between AED withdrawal and IQ changes of >10 points, which are considered clinically relevant. In the future randomized controlled multicenter TTS trial, we will assess, at different postoperative time points, both safety and cognitive benefits of early versus late AED reduction in children who underwent anticipated curative epilepsy surgery. The cognitive assessment battery will include a broader domain of neuropsychological functions and quality of life measures.

Strengths and limitations

Our study has several limitations. First, as agreed by the study group, only patients were included who had started AED withdrawal at some point in the follow-up period of the TTS study, not necessarily before the latest NPA. At the moment of NPA, AED withdrawal could have been started or completed, or patients could still have been on their original presurgical dosage of AEDs. In this selected subgroup of AED withdrawing children, surgical success was anticipated and unfavourable predictors of postoperative seizure outcome were expected to be less common than in the total group of children who undergo epilepsy surgery. Therefore, cognitive outcomes could not be compared with those of children who were not candidates for a medication withdrawal attempt, either because they were not seizure free or because relapse risks were considered too high. Second, patients who had not started AED withdrawal at the moment of their latest NPA were used as a reference group to be compared with the ones who had started AED reduction. Baseline characteristics of this group, however, differed significantly from the group that had started AED reduction. Although we thoroughly adjusted for the factors that contributed to those baseline differences, we cannot rule out that baseline differences may have partly biased the results. Third, the measurements used to assess IQ, and their time points, differed between participating centres of the study, as they were performed according to the local pre- and postsurgical NPA and follow-up protocols. Fourth, the use of an overall cognitive outcome measure hampers the evaluation of possibly important differences in specific cognitive domains, such as processing speed and attention processes, which are known to be important aspects of every day learning and cognitive functioning. We could not completely rule out the possibility of an IQ increase as result of a learning effect by repeated neuropsychological testing, although the number of performed NPAs was shown not to be associated with postoperative IQ or delta IQ. A decrease in IQ due to the natural course of an epileptic syndrome cannot completely be ruled out, despite correction for study intervals and etiology. These factors are, however, also applicable to the patients who did not start AED reduction. Fifth, information about drug dosages was not available, so we could not assess whether reduction of total drug load improved cognitive outcome, as was recently reported.[23] Nevertheless, the number of AEDs that had been reduced correlated with cognitive outcome, pointing in the same direction. Sixth, postoperative reduction or disappearance of EEG abnormalities, increased sleep quality and better school attendance once seizure free, probably all contribute to IQ improvement as well. Finally, presurgical NPA results were available in a subset of the total TTS cohort for logistic reasons and in some patients neuropsychological testing was not feasible due to an extremely high seizure frequency. In most centers, however, surgical candidates routinely undergo both pre- and postoperative NPA, leading us to suggest that our findings are in principle generalizable to all patients who underwent epilepsy surgery.

There are 2 important strengths of this study. The first is the large and heterogeneous cohort of children who could be included, owing to the unique collaboration between 11 centers. Second, we thoroughly adjusted for possible confounders. With adjustment for variables that influence AED withdrawal and variables that influence IQ (change), we were able to identify the true relationship between AED withdrawal and (change of) IQ. We showed in Table 7.2 that the direction of the RC between AED withdrawal and IQ in the crude analysis was the opposite from that in the adjusted analyses. This is the result of other variables that attribute to IQ change after surgery. Only when adjusted for those did the actual direction of the relation between AED withdrawal and IQ became apparent.

In conclusion, AED withdrawal is independently associated with postoperative IQ and change in IQ scores in children who undergo epilepsy surgery. The more AEDs reduced, the higher the postoperative IQ and IQ change. This association between reduction of AEDs and IQ change may have consequences for medication policies after surgery in the future. Previously, we reported that early AED withdrawal is safe and does not influence seizure outcome in the long term. We now found that AED withdrawal improves cognitive outcome. To confirm safety and benefits of early AED withdrawal, a prospective randomized trial is needed and underway.

References

1. Shields WD. Catastrophic epilepsy in childhood. Epilepsia. 2000;41 (Suppl 2):S2-S6.

2. Cross JH. Epilepsy surgery in childhood. Epilepsia 2002;43(Suppl 3):65-70.

3. Van Schooneveld MM, Braun KP. Cognitive outcome after epilepsy surgery in children. Brain Dev 2013;35(8):721-9.

4. Kaindl AM, Asimiadou S, Manthey D, et al. Antiepileptic drugs and the developing brain. Cell Mol Life Sci 2006;63(4):399-413.

5. Ikonomidou C, Turski L. Antiepileptic drugs and brain development. Epilepsy Res 2010;88(1):11-22.

6. Loring DW, Meador KJ. Cognitive side effects of antiepileptic drugs in children. Neurology 2004;62(6):872-7.

7. Meador KJ. Cognitive outcomes and predictive factors in epilepsy. Neurology 2002;58(8 Suppl 5):S21-6.

8. Mula M, Trimble MR. Antiepileptic drug-induced cognitive adverse effects: potential mechanisms and contributing factors. CNS Drugs 2009;23(2):121-37.

9. Braun KP, Schmidt D. Stopping antiepileptic drugs in seizure-free patients. Curr opin Neurol 2014;27(2):219-26.

10. Lossius MI, Hessen E, Mowinckel P, et al. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus Study). Epilepsia 2008;49(3):455-63.

11. Hessen E, Lossius MI, Reinvang I, Gjerstad L. Influence of major antiepileptic drugs on attention, reaction time, and speed of information processing: results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients receiving monotherapy. Epilepsia 2006;47(12):2038-45.

12. Aldenkamp AP, Alpherts WC, Blennow G, et al. Withdrawal of antiepileptic medication in children--effects on cognitive function: The Multicenter Holmfrid Study. Neurology 1993;43(1):41-50.

13. Aldenkamp AP, Alpherts WC, Sandstedt P, et al. Antiepileptic drug-related cognitive complaints in seizure-free children with epilepsy before and after drug discontinuation. Epilepsia 1998;39(10):1070-4.

14. van Schooneveld MM, van Erp N, Boshuisen K, et al. Withdrawal of antiepileptic drugs improves psychomotor speed after childhood epilepsy surgery. Epilepsy Res 2013;107(1-2):200-3.

15. Hallbook T, Tideman P, Rosen I, et al. Epilepsy surgery in children with drug-resistant epilepsy, a long-term follow-up. Acta Neurol Scand 2013;128(6):414-21.

16. Meekes J, Braams O, Braun KP, et al. Verbal memory after epilepsy surgery in childhood. Epilepsy Res 2013;107(1-2):146-55.

17. Skirrow C, Cross JH, Cormack F, et al. Long-term intellectual outcome after temporal lobe surgery in childhood. Neurology 2011;76(15):1330-7.

18. Boshuisen K, Arzimanoglou A, Cross JH, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. Lancet Neurol 2012;11(9):784-91.

19. Boshuisen K, Schmidt D, Uiterwaal CS, et al. Time to relapse after epilepsy surgery in children: AED withdrawal policies are a contributing factor. Epileptic Disord 2014;16(3):305-11.

20. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7(6):525-37.

21. Prayson BE, Prayson RA, Kubu CS, Bingaman W, Najm IM, Busch RM. Effects of dual pathology on cognitive outcome following left anterior temporal lobectomy for treatment of epilepsy. Epilepsy Behav 2013;28(3):426-31.

22. Hessen E, Lossius MI, Gjerstad L. Antiepileptic monotherapy significantly impairs normative scores on common tests of executive functions. Acta Neurol Scand 2009;119(3):194-8.

23. Helmstaedter C,Witt JA. Do antiepileptic drug changes affect cognitive outcome after epilepsy surgery? Epilepsia 2014;55(suppl 2):4-246 .

24. Ortinski P, Meador KJ. Cognitive side effects of antiepileptic drugs. Epilepsy Behav 2004; 5(Suppl 1):S60-5.

25. Sarco DP, Bourgeois BF. The safety and tolerability of newer antiepileptic drugs in children and adolescents. CNS Drugs 2010;24:399-430.

Appendix

Supplemental Table S7.1 Overview of used standardized measurements of IQ and MDI

Types of neuropsychological tests used (abbreviation)
Bayley Scales of Infant Development (BSID-I en BSID-II)
Vineland Adaptive Behavior Scales (VABS)
Griffiths Mental Development Scales
Stanford-Binet intelligence Scales
Brunet-Lezine test
McCarthy Scales of Children's Abilities (MSCA, MOS)
Kaufman Assessment Battery for Children (K-ABC, GOS)
Snijders-Oomen Niet-verbale intelligentietest 2½–7 (SON 2½–7)
Snijders-Oomen Niet-verbale intelligentietest 5½–17 (SON 5½–17)
Wechsler Preschool and Primary Scale for Infants (WPPSI, WPPSI-R)
Wechsler Intelligence Scales for Children (WISC-R, WISC-III, WISC-IV or HAWIK-R, HAWIK-3, HAWIK-4)
Wechsler Intelligence Scales for Adults (WAIS or HAWIE-R)
Kaufman Adult Intelligence Scale (KAIT)
Leiter international performance scale (LEITER-R)
Prüfsystem für Schul- und Bildungsberatung (PSB-R)
Peabody Picture Vocabulary Test (PPVT-III)
Raven's Progressive Matrices (SPM)

Supplemental Table S7.2 Determinants of latest postoperative IQ and delta IQ

	Latest postoperative IQ (mean 81.9±22.6 [SD])		Delta IQ (mean 2.9±11.6 [SD])	
	Univariable analysis		Univariable analysis	
Possible determinant of (delta) IQ	RC (±95% CI)	p	RC (±95% CI)	p
Male sex	0.6 (-4.6–5.7)	0.833	-1.1 (-3.7–1.5)	0.410
Duration of epilepsy (years)	-0.7 (-1.3–0.1)	0.070	0.2 (-0.2–0.6)	0.289
Age at surgery (years)	1.4 (0.9–2.0)	**<0.001**	0.4 (0.1–0.7)	**0.005**
Nr. of AEDs at preoperative IQ test	-5.3 (-8.6–-2.0)	**0.002**	0.3 (-1.4–2.0)	0.727
Type of surgery				
Lobar resection (*reference*)				
Hemispherectomy	-26.7 (-33.3–-20.0)	**<0.001**	-0.7 (-4.5–3.1)	0.719
Multilobar resection	-3.2 (-14.7–8.2)	0.579	0.2 (-6.4–6.8)	0.952
Etiology				
MCD (*reference*)				
Tumor	13.9 (8.1–19.6)	**<0.001**	1.3 (-1.9–4.6)	0.418
Vascular	-14.2 (-21.8–-6.5)	**<0.001**	-0.8 (-5.1–3.6)	0.724
HS	6.0 (-1.1–13.1)	0.095	-0.9 (-4.9–3.2)	0.673
Other etiologies	-14.6 (-30.5–1.2)	0.070	-2.3 (-11.3–6.7)	0.619
Preoperative IQ	0.9 (0.8–1.0)	**<0.001**	-0.1 (-0.2–-0.1)	**<0.001**
Epileptic EEG abnormalities postoperatively	-1.8 (-5.5–1.9)	0.348	-3.1 (-6.7–0.5)	0.092
Interval to latest NPA (months)	0.01 (-0.1–0.2)	0.829	0.01 (-0.1–0.1)	0.772
Interval from preoperative NPA to latest NPA (months)	0.01 (-0.2–0.1)	0.955	0.1 (-0.1–0.1)	0.838
Number of NPAs performed	-0.2 (-3.1–2.8)	0.922	1.0 (-0.6–2.5)	0.215
Seizure free at time of latest NPA*	-2.1 (-7.6–3.4)	0.450	2.2 (-0.7–5.1)	0.135
Seizure free since surgery, or Engel 1 at latest NPA	1.7 (-7.1–10.6)	0.705	3.3 (-1.2–7.9)	0.151
Number of AEDs at latest NPA	-0.6 (-4.0–2.8)	0.716	-1.2 (-2.8–0.5)	0.172

Uni and multivariate linear regression analysis of latest postoperative IQ and change of IQ (delta IQ), defined as latest postoperative IQ minus preoperative IQ.
RC = regression coefficient, indicates the change in IQ or delta IQ with every unit or category change in the predictor; CI = confidence interval; MCD = malformations of cortical development; HS = hippocampal sclerosis.
* Defined as seizure freedom without auras for at least 1 year, regardless of AED use at time of latest NPA (NP Assessment).
Significant correlations are in bold. Alongside a-priori chosen confounders, determinants that were significantly associated with IQ or delta IQ were considered possible confounders for the relation between withdrawal of AEDs and (delta) IQ. We adjusted for these determinants if they were not already in the propensity score, as described in the statistical section of the methods.

Supplemental Table S7.3 AED withdrawal and clinically relevant postoperative IQ changes

Variable	Total number of patients (%)	Change of IQ of at least 10 points			p
		Decrease	Unchanged	Increase	
Number of AEDs reduced*		0.5±0.9 (36)	0.7±0.9 (195)	0.9±0.9 (70)	0.100
Having started AED reduction	155 (51.5)	15 (10)	94 (61)	46 (29)	0.019[$]
Not having started AED reduction	146 (48.5)	21 (14)	101 (69)	24 (16)	
Having stopped all AEDs	59 (20)	4 (7)	39 (66)	16 (27)	0.346[$]
Not having stopped AEDs	242 (80)	32 (13)	156 (65)	54 (22)	

ANOVA tests for continuous variables and chi-square tests for categorical variables were used. Relation between AED withdrawal and a 10 points IQ change is shown. * For number of AEDs reduced, the number of patients that had increased, unchanged or increased IQs is given. The mean number of AEDs reduced ± standard deviation is given and between parentheses, the number of patients per group. The p-value reflects the differences in mean AED reduction between the three groups, [$] P-values reflect the comparison between the patient groups who did and those who did not withdraw or completely stop AEDs.

Supplemental Table S7.4 AED withdrawal and postoperative IQ and delta IQ for patients with normed IQ scores ≥50

	Latest postoperative IQ				Delta IQ[$]			
	Crude model		Adjusted model*		Crude model		Adjusted model*	
	RC (95% CI)	p	RC (95% CI)	p	RC (95% CI)	p	RC (95% CI)	p
Start withdrawal AEDs (n=132/273)	-3.0 (-7.5–1.5)	0.194	3.8 (1.1–6.5)	0.006	3.3 (0.7–5.9)	0.013	4.5 (1.7–7.2)	0.002
Complete discontinuation of AEDs (n=52/273)	2.6 (-3.2–8.3)	0.380	5.8 (2.3–9.3)	0.001	2.9 (-0.4–6.3)	0.087	5.7 (2.1–9.3)	0.002
Number of AEDs reduced[#] (n=273)	-0.5 (-3.1–2.2)	0.735	2.9 (1.3–4.4)	<0.001	2.2 (0.7–3.7)	0.005	3.1 (1.5–4.7)	<0.001

RC = regression coefficient, indicating the change in IQ or delta IQ with every unit or category change in the predictor; CI = confidence interval. Analysis performed: linear regression analysis of the relation between AED withdrawal and IQ and delta IQ. $ Postoperative IQ minus preoperative IQ, * Adjusted for age at surgery, interval to latest postoperative neuropsychological assessment, duration of epilepsy, gender, and in analyses of the latest postoperative IQ (left panel), also for preoperative IQ score. Furthermore, we adjusted for a compound propensity score that contained previously identified predictors of start or completion of medication withdrawal[18] (i.e. number of AEDs used at time of surgery, completeness of resection of the anatomical lesion and of the epileptogenic zone, postoperative EEG findings, and etiology). Because of high correlation between type of surgery and preoperative IQ, we did not adjust for type of surgery.

[#] The change in number of AEDs compared to preoperatively.

Supplemental Table S7.5 AED withdrawal and postoperative IQ and delta IQ for patients completely seizure free since surgery, or at least 1 year Engel 1 at NPA

	Latest postoperative IQ				Delta IQ[$]			
	Crude model		Adjusted model*		Crude model		Adjusted model*	
	RC (95% CI)	p	RC (95% CI)	p	RC (95% CI)	p	RC (95% CI)	p
Start withdrawal of AEDs (n=142/271)	-8.8 (-14.2–-3.5)	0.001	3.6 (0.6–6.7)	0.020	3.7 (0.8–6.5)	0.011	5.1 (2.0–8.2)	0.001
Complete discontinuation of AEDs (n=55/271)	-2.0 (-8.8–4.7)	0.553	4.9 (1.2–8.5)	0.010	3.2 (-0.3–6.7)	0.076	5.3 (1.5–9.2)	0.007
Number of AEDs reduced[#] (n=271)	-4.3 (-7.3–-1.3)	0.006	2.2 (0.4–3.9)	0.015	1.8 (0.2–3.4)	0.028	2.8 (1.0–4.6)	0.002

RC = regression coefficient, indicating the change in IQ or delta IQ with every unit or category change in the predictor; CI = confidence interval. Analysis performed: linear regression analysis of the relation between AED withdrawal and IQ and delta IQ. $ Postoperative IQ minus preoperative IQ, * Adjusted for age at surgery, interval to latest postoperative neuropsychological assessment, duration of epilepsy, gender, and in analyses of the latest postoperative IQ (left panel), also for preoperative IQ score. Furthermore, we adjusted for a compound propensity score that contained previously identified predictors of start or completion of medication withdrawal[18] (i.e. number of AEDs used at time of surgery, completeness of resection of the anatomical lesion and of the epileptogenic zone, postoperative EEG findings, and etiology). Because of high correlation between type of surgery and preoperative IQ, we did not adjust for type of surgery.

[#] The change in number of AEDs compared to preoperatively.

Chapter 8

Parental education predicts change in intelligence quotient after childhood epilepsy surgery

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Abstract

Objective: To know whether change in the intelligence quotient (IQ) of children who undergo epilepsy surgery is associated with the educational level of their parents.

Methods: Retrospective analysis of data obtained from a cohort of children who underwent epilepsy surgery between January 1996 and September 2010. We performed simple and multiple regression analyses to identify predictors associated with IQ change after surgery. In addition to parental education, six variables previously demonstrated to be associated with IQ change after surgery were included as predictors: age at surgery, duration of epilepsy, etiology, presurgical IQ, reduction of anti-epileptic drugs, and seizure freedom. We used delta IQ (IQ 2 years after surgery minus IQ shortly before surgery) as the primary outcome variable, but also performed analyses with pre- and postsurgical IQ as outcome variables to support our findings. To validate the results we performed simple regression analysis with parental education as the predictor in specific subgroups.

Results: The sample for regression analysis included 118 children (60 males; median age at surgery 9.73 years). Parental education was significantly associated with delta IQ in simple regression analysis ($p=0.004$), and also contributed significantly to postsurgical IQ in multiple regression analysis ($p=0.008$). Additional analyses demonstrated that parental education made a unique contribution to prediction of delta IQ, that is, it could not be replaced by the illness-related variables. Subgroup analyses confirmed the association of parental education with IQ change after surgery for most groups.

Significance: Children whose parents had higher education demonstrate on average a greater increase in IQ after surgery and a higher postsurgical – but not presurgical – IQ than children whose parents completed at most lower secondary education. Parental education – and perhaps other environmental variables – should be considered in the prognosis of cognitive function after childhood epilepsy surgery.

Introduction

More than 60% of children with epileptic seizures that do not sufficiently respond to medication become free of seizures after epilepsy surgery.[1] Up to 80% of these children start medication withdrawal,[2] of whom at least 45% achieve complete discontinuation of anti-epileptic drugs within the short follow-up of published studies.[3,4] Seizures and antiepileptic medication have been demonstrated to affect cognitive function prior to surgery in some children,[5] and cognitive function may improve after epilepsy surgery.[6] Age at surgery, duration of epilepsy, etiology, presurgical intelligence quotient (IQ), postsurgical medication policy and seizure freedom are among the determinants that have previously been reported to contribute to change in IQ after epilepsy surgery in children.[7]

However, it has been demonstrated in nonsurgical epilepsy cohorts[8] as well as in other populations at risk for neuropsychological impairments[9,10] that cognitive development is often correlated not only with illness-related and demographic variables but also with environmental variables, that is, variables that measure some aspect of the surroundings of the child. Despite recent research regarding the impact of environmental variables in both surgical[11,12] and non-surgical[13,14] epilepsy populations, it remains unclear to what extent such variables are associated with change in IQ after surgery. Higher parental education is associated with higher average IQ in normally developing children.[15] Hence, if any environmental variables do indeed contribute to cognitive outcome after surgery, parental education seems a likely candidate. Both intellectual stimulation and financial resources are associated with parental education, although of course parental education – like many other environmental variables – is also correlated with parental IQ, and parental IQ in turn shares genetic determinants with child IQ.[16] We analyzed IQ change between assessments performed before and 2 years after childhood epilepsy surgery to test the hypothesis that parental education is associated with IQ change.

Patients and methods

Study design

We performed a retrospective countrywide cohort study within the Dutch Collaborative Epilepsy Surgery Program. Inclusion criteria were (1) resective or disconnective epilepsy surgery (tailored or lobar temporal or extratemporal resection or disconnection, multilobar resection or disconnection, or hemispherotomy) at the University Medical Center Utrecht between January 1996 and September 2010; and (2) age at surgery <18 years. Patients with missing data were excluded. Data were collected from neuropsychological assessments

before surgery and 2 years thereafter, and were anonymized. The study was approved by the medical ethics committee of the University Medical Center Utrecht.

Outcome variables

A range of tests selected in conformity with the mandate of best clinical practice (see Supplementary Table S8.1 for a list of tests and their frequency of application) were used to determine IQ, or – for very young or delayed children – mental developmental index. These instruments all assess (developing) intelligence by formal testing of the child and the score will be referred to as IQ. For children who scored below the lower end of the norms' range or for whom age-appropriate tests were too difficult and for whom a mental age could be determined, IQ was calculated as a developmental index, using the ratio (100 * mental age / calendar age). For the nine children with a ratio IQ above the minimum of the respective test, the lowest obtainable score according to the manual of that test was substituted. The main outcome variable was 'delta IQ' (postsurgical minus presurgical IQ, i.e., change in IQ).

Parental education

Parental education was taken from histories provided by parents at the presurgical neuropsychological assessment and classified by level and sublevel using the 2011/2012 revision of the (Dutch) Standard Education Classification 2006,[17] which is largely congruent with the International Standard Classification of Education 2011.[18] These classifications contain seven classes, but in light of the small number of parents with doctoral or equivalent education (i.e., PhD or equivalent: n=1) or with at most primary education (n=4), we recoded parental education into four classes (see Table 8.1). For analysis, the highest level of education attained by either parent was used. We also explored the importance of maternal and paternal contributions separately.

Table 8.1 Classification and distribution of parental education

SOI recoded[a]	N	ISCED 2011 description
1	15	Early childhood, primary or lower secondary education
2	54	Upper secondary; post-secondary non-tertiary
3	32	Short cycle tertiary; bachelor or equivalent
4	17	Master or equivalent; doctoral or equivalent

SOI, Standard Education Classification ('Standaard Onderwijsindeling');[17] ISCED, International Standard Classification of Education.[18]

[a] The SOI classification (seven classes) was recoded by combining the "early childhood education", "primary education", and 'lower secondary education" classes (i.e., new class 1), and the "master or equivalent" and "doctoral or equivalent" classes (i.e., new class 4).

Other predictor variables

We selected six additional variables that have previously been demonstrated to be associated with change in IQ after surgery:[7] age at surgery, duration of epilepsy, etiology, presurgical IQ, reduction of antiepileptic drugs (AEDs) and postsurgical seizure freedom.

An experienced child neurologist/epileptologist (OvN) scored disease variables. Etiology was categorized as (1) malformation of cortical development, (2) hippocampal sclerosis, (3) tumor, (4) vascular (including Sturge-Weber syndrome), or (5) other (including Rasmussen's encephalitis). Age at surgery and duration of epilepsy were scored in years. We defined medication reduction as the number of AEDs at presurgical assessment minus the number of AEDs at postsurgical assessment (i.e., 2 years after surgery). Note that this variable can be negative in cases where the number of AEDs is increased after surgery. Seizure outcome (2 years after surgery) was scored according to Engel et al.,[19] with only patients with an Engel score of Ia being considered seizurefree.

Data analysis

Statistical analysis was performed using R 3.03.[20] Loss to follow-up and selection bias were addressed by testing for differences between included and excluded patients, using Wilcoxon rank-sum tests (for age at surgery, duration of epilepsy, parental education, and reduction of AEDs), t-tests (for presurgical and postsurgical IQ) and chi-square tests (for etiology and seizure freedom).

Our primary analyses consisted of simple and multiple regressions, which we report using highest parental education and, separately, using maternal and paternal education. For each variable, simple linear regression was performed to assess relations between single predictors and delta IQ. To determine whether the contributions of particular predictors held up when corrected for other possible predictors, we then analyzed a full multiple regression model. However, in a multiple regression model for delta IQ, the inclusion of presurgical IQ would render the results uninterpretable.[21,22] For this multiple regression analysis, we therefore used postsurgical IQ rather than delta IQ as the dependent variable. The inclusion of presurgical IQ as a predictor in the model for postsurgical IQ renders the contributions of other predictors interpretable in terms of their association with change in IQ (or more precisely, change not associated with presurgical IQ).

We analyzed collinearity to make sure that observed associations between parental education and IQ change were not caused by confounding by other predictors.

To assess whether parental education actually improved prediction of delta IQ, we compared the best possible model (i.e., including parental education) with the best possible model that did not include parental education (these models were determined by testing all possible combinations of predictors to find the optimal set of predictors as measured by Akaike's Information Criterion [AIC]).

We performed simple linear regression analyses in subgroups to assess the sensitivity of the findings to differences in assessment method. Firs, because ratio IQ is known to be less stable than normed IQ,[23] we selected the subgroup for which normed IQ was available both before and after surgery. Second, we performed simple linear regression analysis in the subgroup of children who were tested with the same version of the same test before and after surgery (for some children, a different test or test version had been used after surgery than before, usually because the children had outgrown the age range of the test or because an updated version of the test had become available). Furthermore, to reduce variability caused by differences between tests, we ran a separate analysis in the subgroup of children who had been tested with (the Dutch version of) the Wechsler Intelligence Scale for Children (WISC-NL). Because differences between group sizes render direct comparison of p-values misleading, we report B-values and the associated confidence intervals (CIs) in the text for these and additional subgroup analyses.

Given previously demonstrated associations of IQ change after surgery with etiology and postsurgical seizure freedom,[7] we also explored these associations in subgroups of children with the same etiological category, and separately for seizure-free and non-seizure-free children. To further reduce heterogeneity, only seizure-free children were included in the etiology subgroups. Note that because the number of patients in these exploratory subgroup analyses is much smaller, the power is often insufficient to reliably demonstrate an association as strong as or even stronger than in the cohort as a whole. Hence, a non-significant p-value in these analyses means that the existence of such an association cannot be demonstrated reliably in this sample, but does not, by itself, suggest that there is no association.

Finally, we validated the results for delta IQ by performing simple and multiple linear regression analyses for presurgical and postsurgical IQ. We expected to find illness-related predictors for presurgical IQ, and presurgical IQ to be the strongest predictor for postsurgical IQ.

Results

Patients

During the inclusion period, 201 children underwent surgery of whom 161 (80%) were assessed at our neuropsychology department. For 126 patients (63%), IQs were available both before and 2 years after surgery. Parental information was incomplete for three patients. Normality checks showed a normal distribution of delta IQ, with five clear outliers. In these five patients, presurgical assessment was severely affected by acute and persistent epileptic and/or psychiatric disturbances, which made interpretation of the presurgical results (and hence the change after surgery) unreliable. The final analysis therefore included 118 patients (59%; Table 8.2; see also Table 8.1 for distribution of parental education) and their parents. There were no differences between included and excluded patients (Table 8.2).

Prediction of IQ change

Simple linear regression (Table 8.3) showed that highest parental education predicted delta IQ ($F_{1,116}$=8.44, p=0.004, adjusted R^2=0.06). The multiple regression model for postsurgical IQ (i.e., with all predictors included – Table 8.4, right side) showed that highest parental education was significantly associated with postsurgical IQ ($F_{1,107}$=7.30, p=0.008). Because the latter model corrects for presurgical IQ, this result also suggests that highest parental education is associated with IQ change after surgery.

Separating maternal and paternal education showed that paternal education was significantly associated with delta IQ in simple linear regression ($F_{1,116}$=13.95, p<0.001, B=3.40, 95% confidence interval [CI] 1.60–5.21, β=0.33, adjusted R^2=0.10), but maternal education was not ($F_{1,116}$=0.64, p=0.424, B=0.86, 95% CI -1.27–3.00, β=0.07, adjusted R^2=0.00). The multiple regression models for postsurgical IQ showed that paternal education (see Supplementary Table S8.3) was significantly associated with postsurgical IQ ($F_{1,107}$=12.34, p<0.001), whereas maternal education (see Supplementary Table S8.4) was not ($F_{1,107}$=1.10, p=0.298).

The B-value of parental education – that is, the amount of change in the predicted delta IQ for a one-class difference in parental education – in the simple linear regression model suggests a difference in delta IQ of 8.43 (i.e., 3 * 2.81) points (95% CI 2.67–14.19) between the children whose parents had at most lower secondary education and those with a parent who had obtained a master's degree, to the advantage of the latter. Children whose parents had at most lower secondary education tended to show minor gains (mean delta IQ=3.67; 95% CI -0.03–7.36), whereas children whose parents had obtained a master's degree gained on average 11.23 points (95% CI 5.00–17.45).

Table 8.2 Sample demographics

	Included	Excluded		
	(n=118)	n		p
Variables used in analysis				
Age at surgery: median (IQR)	9.73 (4.05–13.75) yrs	83	11.08 (3.78–13.97) yrs	0.70
Duration of epilepsy: median (IQR)	3.24 (1.75–6.13) yrs	83	4.34 (1.86–9.17) yrs	0.13
Etiology: n (%)		80		0.38
MCD	33 (28)		23 (29)	
HS	12 (10)		15 (19)	
Tumor	42 (36)		24 (30)	
Vascular	16 (14)		12 (15)	
Other	15 (13)		6 (8)	
Maternal education: median (IQR)	2 (2–2)	36	2 (1–3)	0.74
Paternal education: median (IQR)	2 (2–3)	33	2 (1–3)	0.91
Highest education: median (IQR)	2 (2–3)	36	2 (2–3)	0.62
Presurgical IQ: mean (SD)	70.9 (26.0)	26	62.8 (27.6)*	0.17
Postsurgical IQ: mean (SD)	76.2 (28.4)	17	67.2 (25.8)	0.20
Change in IQ: mean (SD)	5.3 (9.6)	-	-	-
Reduction of AEDs: median (IQR)	1 (0–2)	43	1 (0–1)	0.87
Seizure freedom: yes / no (n)	95 / 23	43	34 / 9	>0.99
Other descriptive variables				
Gender: girls / boys (n)	60 / 58	83	41 / 42	0.95
Type of surgery: n (%)		83		0.13
Multi-lobar resection	37 (31)		30 (36)	
Temporal resection	50 (42)		41 (49)	
Extra-temporal resection	31 (26)		12 (14)	
Side of surgery: left / right (n)	57 / 61		37 / 46	0.40

IQR = interquartile range; yrs = years; MCD = malformation of cortical development; HS = hippocampal sclerosis; IQ = intelligence quotient; AEDs = antiepileptic drugs; SD = standard deviation.
* Without patients excluded for non-interpretable presurgical assessment.

Collinearity analysis

Collinearity analysis suggested that lower parental education was associated with longer duration of epilepsy ($F_{1,116}$=6.17, p=0.014, adjusted R^2=0.04). Scrutiny of the data showed that very long duration of epilepsy (>8 years) occurred more frequently in patients whose parents had only primary education. Although the relatively low adjusted R^2 suggests that the risk of confounding through collinearity is small,[24] we reanalyzed the data after exclusion of all patients with duration of epilepsy >8 years – eliminating any association between parental education and other predictors – and found that parental education was still significantly associated with delta IQ ($F_{1,100}$=8.93, p=0.004, adjusted R^2=0.07; see also Table 8.6).

Table 8.3 Summary of simple linear regressions (intercept + single variable) for delta IQ

Predictor	Intercept	B[a]	95% CI	β[b]	p	adj. R^2
Age at surgery	3.61	0.19	-0.14–0.52	0.10	0.261	0.00
Duration of epilepsy	6.06	-0.16	-0.65–0.32	-0.06	0.510	0.00
Etiology (reference category: MCD)	6.38				0.493	0.00
HS		-2.55	-8.99–3.90	-0.08		
Tumor		-0.25	-4.70–4.20	-0.01		
Vascular		-0.50	-6.33–5.32	-0.02		
Other		-4.91	-10.87–1.04	-0.17		
Parental education	1.31	**2.81**	**0.89–4.73**	**0.26**	**0.004**	**0.06**
Presurgical IQ	4.03	1.43	-0.18–3.03	0.16	0.080	0.02
Reduction of AED	2.86	3.08	-1.33–7.50	0.13	0.169	0.01
Seizure freedom (reference category: seizure recurrence)	3.61	0.19	-0.14–0.52	0.10	0.261	0.00

IQ = intelligence quotient; CI = confidence interval; MCD = malformations of cortical development; HS = hippocampal sclerosis; AED = antiepileptic drugs. Values in bold correspond to predictors that are significant in the respective regression analysis.

[a] B is the unstandardized regression coefficient and can be interpreted in terms of the predictor and the outcome variable. For example, the simple regression model for parental education predicts a 2.81 point increase (95% CI 0.89–4.73 points) in delta IQ for each class increase in parental education.

[b] β is the standardized regression coefficient and facilitates comparison of the effect of different predictors.

Prediction with and without parental education

The best model for prediction of delta IQ contained three predictors: age at surgery, reduction of AEDs, and parental education (Table 8.5A). When parental education was excluded, the best model consisted of the variables age at surgery and reduction of AEDs (Table 8.5B). Although both models significantly predicted delta IQ (model including parental education: $F_{3,114}$=5.19, p=0.002; model excluding parental education: $F_{2,115}$=3.30, p=0.04), the model including parental education was significantly better ($F_{1,114}$=8.55, p=0.004) than the model that did not include parental education, demonstrating that parental education makes a unique contribution to prediction of delta IQ, which is not explained by one or more of the other variables.

Sensitivity to assessment procedures

The B-values for parental education were similar to those in the entire cohort and remarkably stable (Table 8.6), regardless of whether the analysis was restricted to children for whom normed IQs were obtained (B=2.80, 95% CI 0.87–4.73), to children who were assessed with the same test before and after surgery (B=2.75, 95% CI 0.87–4.62), or to children who were assessed with the WISC before and after surgery (B=2.91, 95% CI 0.43–5.38).

Table 8.4 Summary of simple and multiple regression analyses for postsurgical IQ

	Simple regression (intercept + single variable)						Multiple regression[a] (intercept + all variables)			
Predictor	Intercept	B[b]	95% CI	β[c]	p	adj. R^2	B	95% CI	β	p
[Intercept]							-2.76	-10.09–4.58		0.458
Age at surgery	45.45	**3.37**	**2.61–4.14**	**0.63**	**<0.001**	**0.39**	0.47	-0.06–0.99	0.09	0.081
Duration of epilepsy	72.79	0.78	-0.65–2.20	0.10	0.282	0.00	-0.02	-0.67–0.64	0.00	0.961
Etiology (reference category: MCD)	62.58				**<0.001**	**0.24**				0.505
HS		**21.67**	**5.15–38.19**	**0.23**	**0.011**		-4.00	-10.90–2.90	-0.04	
Tumor		**31.46**	**20.07–42.86**	**0.53**	**<0.001**		-1.26	-6.36–3.84	-0.02	
Vascular		0.40	-14.53–15.32	0.00	0.958		-0.27	-6.14–5.60	0.00	
Other		1.59	-13.67–16.84	0.02	0.837		-4.48	-10.29–1.32	-0.05	
Parental education	72.44	2.65	-3.19–8.49	0.08	0.370	0.00	**2.72**	**0.72–4.71**	**0.09**	**0.008**
Presurgical IQ	3.44	**1.03**	**0.96–1.09**	**0.94**	**<0.001**	**0.88**	**0.98**	**0.88–1.08**	**0.90**	**<0.001**
Reduction of AED	78.29	-2.24	-7.01–2.53	-0.09	0.354	0.00	1.53	-0.29–3.34	0.06	0.099
Seizure freedom (reference category: seizure recurrence)	61.41	**18.42**	**5.73–31.10**	**0.26**	**0.005**	**0.06**	2.09	-2.86–7.04	0.03	0.404

IQ = intelligence quotient; CI = confidence interval; MCD = malformations of cortical development; HS = hippocampal sclerosis; AED = antiepileptic drugs. Values in bold correspond to predictors that are significant in the respective regression analysis.

[a] Adjusted R^2 for the full multiple regression model: 0.89.

[b] B is the unstandardized regression coefficient and can be interpreted in terms of the predictor and the outcome variable. For example, the simple regression model for parental education predicts a 2.65 point increase (95% CI -3.19–8.49 points) in postsurgical IQ for each class increase in parental education.

[c] β is the standardized regression coefficient and facilitates comparison of the effect of different predictors.

Table 8.5 Summary of optimal regression models for delta IQ with (A) and without (B) parental education

	A: including parental education[a]				B: excluding parental education[b]			
Predictor	B[c]	95% CI	β[d]	p	B	95% CI	β	p
[Intercept]	-3.54	-8.57–1.49		0.166	0.61	-3.69–4.91		0.780
Age at surgery	**0.36**	**0.02–0.69**	**0.20**	**0.037**	**0.32**	**-0.02–0.67**	**0.18**	**0.067**
Parental education	**2.80**	**0.90–4.69**	**0.26**	**0.004**	X	X	X	X
Reduction of AED	**1.76**	**0.13–3.40**	**0.20**	**0.035**	**1.95**	**0.27–3.63**	**0.22**	**0.023**

IQ = intelligence quotient; CI = confidence interval; AED = antiepileptic drugs. Values in bold correspond to predictors that are significant in the respective regression analysis. Duration of epilepsy, Etiology, Presurgical IQ and Seizure freedom were tested but excluded because inclusion of these variables did not improve the regression model. X = variable a priori excluded from consideration for this model.
[a] Adjusted R^2 for the best model including parental education: 0.10.
[b] Adjusted R^2 for the best model excluding parental education: 0.04.
[c] B is the unstandardized regression coefficient and can be interpreted in terms of the predictor and the outcome variable. For example, the regression model for delta IQ predicts a 2.80 point increase (95% CI 0.90–4.69 points) in delta IQ for each category increase in parental education.
[d] β is the standardized regression coefficient and facilitates comparison of the effect of different predictors.

Seizure freedom, etiological category, and low IQ

In children who remained seizurefree after surgery, there was a clear association between parental education and delta IQ (B=3.82, 95% CI 1.58–6.06; see Table 8.6 for additional statistics regarding this and further subgroup analysis), but in children with recurrence of seizures the association was negligible (B=-0.44, 95% CI -3.98–3.09).

We thus analyzed in seizure-free children whether an association between parental education and delta IQ was present in etiology subgroups. Notably, no association between parental education and delta IQ appeared to exist in children with malformations of cortical development (B=0.62, 95% CI -3.93–5.16). Although the observed B-values suggested that the association was present in the other etiology groups (hippocampal sclerosis: B=2.94, 95% CI -2.75–8.63; tumor: B=4.81, 95% CI 1.19–8.44; vascular: B=10.43, 95% CI 0.43–20.44; other etiology: B=4.59; 95% CI -2.51–11.70), the results were not statistically significant for all of the groups and should therefore be treated with caution. In addition, the association was present for seizure-free children with a presurgical IQ ≥70 (B=3.80, 95% CI 1.10–6.50), but could not be demonstrated in this sample for those with a presurgical IQ <70 (B=3.71, 95% CI -0.20–7.63) although again the B-value suggested an association similar to that in the cohort as a whole.

Table 8.6 Summary of simple linear regressions (intercept + parental education) for delta IQ in specific subgroups

	N	Intercept	B[a]	95% CI	β[b]	p	adj. R^2
Collinearity							
Duration of epilepsy <8 years	102	0.29	**3.47**	**1.17–5.78**	**0.29**	**0.003**	**0.07**
Differences in assessment method							
Normed IQ obtained both before AND after surgery	90	2.19	**2.80**	**0.87–4.73**	**0.29**	**0.005**	**0.08**
Tested with the same instrument before and after surgery	99	1.58	**2.75**	**0.87–4.62**	**0.28**	**0.005**	**0.07**
Tested with the same version of the WISC before and after surgery	45	1.68	**2.91**	**0.43–5.38**	**0.34**	**0.022**	**0.09**
Seizure-freedom subgroups							
Seizure free after surgery	95	0.39	**3.82**	**1.58–6.06**	**0.33**	**0.001**	**0.10**
Not seizure-free after surgery	23	3.46	-0.44	-3.98–3.09	-0.06	0.796	-0.04
Etiology subgroups							
Malformation of cortical development and seizure-free after surgery	21	7.06	0.62	-3.93–5.16	0.06	0.780	-0.05
Hippocampal sclerosis and seizure-free after surgery	11	-0.28	2.94	-2.75–8.63	0.36	0.273	0.04
Tumor and seizure-free after surgery	37	-0.80	**4.81**	**1.19–8.44**	**0.41**	**0.011**	**0.15**
Vascular etiology and seizure-free after surgery	15	-9.03	**10.43**	**0.43–20.44**	**0.53**	**0.042**	**0.23**
Other etiology and seizure-free after surgery	11	-3.03	4.59	-2.51–11.70	0.44	0.177	0.10
IQ subgroups							
Presurgical IQ ≥70 and seizure-free after surgery	53	1.33	**3.80**	**1.10–6.50**	**0.37**	**0.007**	**0.12**
Presurgical IQ <70 and seizure-free after surgery	42	-0.61	3.71	-0.20–7.63	0.29	0.063	0.06

adj. = adjusted; IQ = intelligence quotient; WISC = Wechsler Intelligence Scale for Children. Values in bold correspond to predictors that are significant in the respective regression analysis.

[a] B is the unstandardized regression coefficient and can be interpreted in terms of the predictor and the outcome variable. For example, the regression model for seizure-free children predicts a 3.82 point increase (95% CI 1.58–6.06) in delta IQ for each category increase in parental education.

[b] β is the standardized regression coefficient and facilitates comparison of the effect of different predictors.

Pre- and postsurgical IQ

In simple linear regression analysis (Supplementary Table S8.2, left side) higher presurgical IQ was associated with etiology ($F_{4,113}$=12.58, p<0.001; patients with tumors, and to a lesser extent those with hippocampal sclerosis had higher presurgical IQs than patients with other etiologies), older age at surgery ($F_{1,116}$=84.84, p<0.001), and postsurgical seizure freedom ($F_{1,116}$=6.74, p=0.01); that is, children who became seizurefree after surgery already had higher IQs before surgery. All three variables were also associated with presurgical IQ in the multiple regression analysis (Supplementary Table S8.2, right side).

Simple linear regression analysis of predictors for postsurgical IQ (Table 8.4, left side) showed significant associations of etiology ($F_{4,113}$=10.32, p<0.001; patients with tumors and those with hippocampal sclerosis had higher postsurgical IQs than patients with other etiologies), age at surgery ($F_{1,116}$=76.77, p<0.001; older children had higher postsurgical IQs), postsurgical seizure freedom ($F_{1,116}$=8.27, p=0.005; seizure-free children had higher postsurgical IQs), and presurgical IQ ($F_{1,116}$=898.30, p<0.001; higher presurgical IQ was associated with higher postsurgical IQ). Note that these variables were already associated with presurgical IQ. The multiple regression analysis for postsurgical IQ (Table 8.4, right side) has been discussed above (section "Prediction of IQ change").

Discussion

Previous studies have mostly examined associations between illness-related variables and the outcome of epilepsy surgery.[7] Recently, however, the role of environmental variables has come under scrutiny in epilepsy surgery research.[11,12] We examined the impact of one such variable, parental education, and found that higher parental – in particular paternal – education was associated with a larger increase in IQ (delta IQ) after surgery. Children who had at least one parent with a master's degree gained on average almost 8 IQ points more after surgery than did children of parents who both had at most lower secondary education. Subgroup analyses suggested that this estimate may even understate the strength of the association, since in some more homogeneous subgroups – in particular the subgroup of children who obtained seizure freedom after surgery – the corresponding estimate would be 9–15 points (i.e., a B-value of 3–5, or 3–5 IQ points per educational class). The association could not be explained by correlations between parental education and other predictor variables, as verified by collinearity analysis and comparison of the best regression models with and without parental education.

However, the effect size for the association between parental education and delta IQ was small (adjusted R^2=0.06). This small effect size has several possible explanations beyond the obvious possibility that the association between parental education and delta IQ is fairly weak. First of all, as a measure of effect size, the adjusted R^2 depends not only on the influence of the predictor(s), but also on the variance to be explained.[25] Hence, the heterogeneity of the present cohort may be one cause of the small effect size, a suggestion that is supported by the often larger effect sizes in the analyses of more homogeneous subgroups (Table 8.4). Noise in the predictor variable (i.e., parental education) or in the outcome variable (i.e., delta IQ) would also reduce the adjusted R^2. Such noise may be caused by imperfect measurement (e.g., limited reliability of IQ tests) or because the variable captures only part of the causal mechanism. If, for example, the association between parental education and change in IQ of the child were fully caused by genetic IQ determinants shared between child and parent, then measuring parental education instead of parental IQ would increase the noise in the predictor variable.

We found no significant differences in demographic or illness-related variables between included and excluded patients. The cohort therefore appears representative of the childhood epilepsy surgery population in The Netherlands, although we could not prove this due to missing IQ and/or parental education data among the excluded patients. Over-representation of tumor patients (our sample contained more patients with tumors than cohorts from surgical centers in other countries) could have affected the estimates of average IQ and IQ change,[26] but reanalysis after excluding all tumor cases yielded similar estimates of the B-value for parental education (data not shown). Another limitation of the study concerns the selected predictor variables: to retain adequate power, not all variables that potentially contribute to change in IQ after childhood epilepsy surgery could be included. Yet the association between parental education and delta IQ appeared robust in a series of supplementary analyses.

In the general population, children of highly educated parents have higher average IQ than those of parents with lower education.[15] In the surgical candidates of our cohort, this link was not present before surgery: parental education did not contribute to prediction of their presurgical IQ. This lack of association between parental education and presurgical IQ is in line with the recent finding that IQ in children with new-onset idiopathic epilepsy is not correlated with parental IQ.[13] The present study suggests that after surgery, freed from disruption by seizures (and often from side-effects of antiepileptic drugs), the child may again develop in accord with what would be expected based on the education of his or her parents.

Perhaps surprising is the observation that in particular paternal – rather than maternal – education is associated with postsurgical IQ change. Although some studies have found

that maternal education is a better predictor of child IQ than paternal education, this is not universally the case.[26] A recent Norwegian registry study[27] demonstrated that education of stepfathers is correlated with IQ in their stepsons, even after controlling for a range of other background factors including education of the biological parents. This strongly suggests that fathers contribute through environmental as well as genetic mechanisms. Even in families where mothers are the primary caretakers and homework monitors, fathers commonly have an important role in setting the wider physical and social environment of their children (e.g., the neighborhood in which they live).

Parental education, like many other environmental variables, is not a measure of the environment alone. Although parental education is associated with intellectual stimulation in the family, as well as with the financial resources available to the family, it is also correlated with parental IQ.[16] As parental IQ in turn shares genetic determinants with child IQ, any observed association between parental education and IQ change is conceivably due to both genetic and environmental mechanisms.

Our analysis does not imply that illness-related variables do not predict cognitive outcome after surgery: although parental education contributed significantly, the strongest predictor of postsurgical IQ was presurgical IQ (as previously reported by d'Argenzio et al.[28]). Presurgical IQ in turn was best understood in terms of illness-related variables, with higher presurgical IQ in children with tumors or hippocampal sclerosis, and in children who are older at surgery. Postsurgical seizure freedom was also associated with higher IQ in this cohort, even before surgery.

The observed association between reduction of AEDs and IQ change (in the best regression model – with or without parental education), which was not unexpected given the well-known cognitive side effects of AEDs,[5] may have consequences for medication policy after surgery. Cessation of AEDs is an important predictor of postsurgical IQ change in children.[6] Recently it has also been demonstrated that AED withdrawal is associated with improved psychomotor speed[29] and with better verbal memory outcome.[30] The present study therefore adds to the mounting evidence that AED withdrawal is one of the major directly modifiable factors affecting postsurgical cognitive development in children.

To our knowledge this is the first study to report that higher parental education is associated with larger increases in IQ after epilepsy surgery in children. Hence higher postsurgical IQ implies that parental education (and perhaps related environmental and genetic factors) should be considered in future studies of cognitive outcome after surgery.

References

1. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7:525-37.

2. Boshuisen K, Braams O, Jennekens-Schinkel A, et al. Medication policy after epilepsy surgery. Pediatr Neurol 2009;41:332-8.

3. Schmidt D, Baumgartner C, Löscher W. Seizure Recurrence after planned discontinuation of antiepileptic drugs in seizure-free patients after epilepsy surgery: a review of current clinical experience. Epilepsia 2004;45:179-86.

4. Boshuisen K, Arzimanoglou A, Cross J, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. Lancet Neurol 2012;11:784-91.

5. Loring DW, Marino S, Meador KJ. Neuropsychological and behavioural effects of antiepilepsy drugs. Neuropsychol Rev 2007;17:413-25.

6. Skirrow C, Cross JH, Cormack F, et al. Long-term intellectual outcome after temporal lobe surgery in childhood. Neurology 2011;76:1330-7.

7. van Schooneveld M, Braun K. Cognitive outcome after epilepsy surgery in children. Brain Dev 2013;35:721-9.

8. Oostrom K, Smeets-Schouten A, Kruitwagen C, et al. Not only a matter of epilepsy: early problems of cognition and behavior in children with "epilepsy only"- a prospective, longitudinal, controlled study starting at diagnosis. Pediatrics 2003;112:1338-44.

9. Sullivan M, Miller R, Msall M. 17-year outcome of preterm infants with diverse neonatal morbidities: part 2, impact on activities and participation. J Spec Pediatr Nurs 2012;17:275-87.

10. Cserjesi R, van Braeckel K, Timmerman M, et al. Patterns of functioning and predictive factors in children born moderately preterm or at term. Dev Med Child Neurol 2012;54:710-5.

11. Baca C, Vickrey B, Vassar S, et al. Time to pediatric epilepsy surgery is related to disease severity and nonclinical factors. Neurology 2013;80:1231-9.

12. Hauptman JS, Dadour A, Oh T, et al. Time to pediatric epilepsy surgery is longer and developmental outcomes lower for government compared with private insurance. Neurosurgery 2013;73:152-7.

13. Walker N, Jackson D, Dabbs K, et al. Is lower IQ in children with epilepsy due to lower parental IQ? A controlled comparison study. Dev Med Child Neurol 2012;55:278-82.

14. Berg AT, Loddenkemper T, Baca CB. Diagnostic delays in children with early onset epilepsy: Impact, reasons, and opportunities to improve care. Epilepsia 2014;55:123-32.

15. Hanscombe K, Trzaskowski M, Haworth C, et al. Socioeconomic status (SES) and children's intelligence (IQ): in a UK-representative sample SES moderates the environmental, not genetic, effect on IQ. PloS one 2012;7:e30320

16. Rowe DC, Jacobson KC, Van den Oord EJCG. Genetic and environmental influences on vocabulary IQ: parental education level as moderator. Child Dev 1999;70:1151-62.

17. Statistics Netherlands. Standaard Onderwijsindeling [Standard Education Classification]. (in Dutch). Available at http://www.cbs.nl/nl-NL/menu/methoden/classificaties/overzicht/soi/2006/2006-soi-niveau-indeling-2011-12.htm. Accessed May 18, 2014.

18. UNESCO Institute for Statistics. International Standard Classification of Education 2011. Available at http://www.uis.unesco.org/Education/Documents/isced-2011-en.pdf. Accessed May 18, 2014.

19. Engel J, Van Ness PC, Rasmussen TB, et al. Outcome with respect to epileptic seizures. In: Engel J (Ed) Surgical treatment of the epilepsies. 2nd Ed. New York: Raven; 1993:609-21.

20. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2014

21. Glymour MM, Weuve J, Berkman LF, et al. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. Am J Epidemiol 2005;162:267-78.

22. Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2011.

23. Baron I, Leonberger K. Assessment of intelligence in the preschool period. Neuropsychol Rev 2012;22:334-44.

24. Chatterjee S, Hadi AS. Regression analysis by example. 4th ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2006

25. Nakagawa S, Cuthill IC. Effect size, confidence interval and statistical significance: a practical guide for biologists. Biol Rev Camb Philos Soc 2007;82:591-605.

26. Bradley RH, Corwyn RF. Socioeconomic status and child development. Annu Rev Psychol 2002;53:371-99.

27. Eriksen W, Sundet JM, Tambs K. Are stepfathers' education levels associated with the intelligence of their stepsons? A register-based study of Norwegian half-brothers. Br J Psychol 2013;104:212-24.

28. D'Argenzio L, Colonnelli MC, Harrison S, et al. Cognitive outcome after extratemporal epilepsy surgery in childhood. Epilepsia 2011;52:1966-72.

29. van Schooneveld MMJ, van Erp N, Boshuisen K, et al. Withdrawal of antiepileptic drugs improves psychomotor speed after childhood epilepsy surgery. Epilepsy Res 2013;107:200-3.

30. Meekes J, Braams O, Braun KPJ, et al. Verbal memory after epilepsy surgery in childhood. Epilepsy Res 2013;107:146-55.

Appendix

Supplemental Table S8.1 List of intelligence tests and their frequency of use

Test	Presurgical assessment	Postsurgical assessment
Bayley Ontwikkelingsschalen (BOS 2–30)[1]	10	10
Bayley Scales of Infant Development, second edition, Dutch version (BSID-II-NL)[2]	16	11
McCarthy Ontwikkelingsschalen (MOS 2½–8 ½)[3]	2	2
Stutsman Intelligentietest voor kleuters[4]	2	0
Groningse Ontwikkelingsschalen (GOS 2–4 ½)[5]	1	2
Snijders-Oomen Niet-verbale Intelligentietest 2½–7[6]	11	14
Snijders-Oomen Niet-verbale Intelligentietest 5½–17[7]	1	1
Wechsler Preschool and Primary Scales of Intelligence (WPPSI)[8]	6	2
Wechsler Intelligence Scales for Children, revised edition, Dutch version (WISC-RN)[9]	28	30
Wechsler Intelligence Scales for Children, third edition, Dutch version (WISC-III^{NL})[10]	24	24
Wechsler Adult Intelligence Scales, revised edition[11]	6	9
Wechsler Adult Intelligence Scales, third edition (WAIS-III-NL)[12]	1	2
Kaufman Adult and Adolescent Intelligence Test (KAIT)[13]	10	11

Supplemental Table S8.2 Summary of simple and multiple regressions for presurgical IQ

	Simple regression (intercept + single variable)						Multiple regression[a] (intercept + all variables)			
Predictor	Intercept	B[b]	95% CI	β[c]	p	adj. R^2	B	95% CI	β	p
[Intercept]							**29.74**	**16.95–42.53**		**<0.001**
Age at surgery	41.84	**3.18**	**2.50–3.87**	**0.65**	**<0.001**	**0.42**	**2.99**	**2.17–3.81**	**0.61**	**<0.001**
Duration of epilepsy	66.73	0.94	-0.36–2.24	0.13	0.156	0.01	-1.02	-2.25–0.22	-0.14	0.106
Etiology (reference category: MCD)	56.20				**<0.001**	**0.28**				**0.008**
HS		**24.22**	**9.51–38.93**	**0.28**	**0.001**		11.68	-1.30–24.66	0.14	0.077
Tumor		**31.71**	**21.56–41.86**	**0.59**	**<0.001**		**17.19**	**8.02–26.35**	**0.32**	**<0.001**
Vascular		0.90	-12.40–14.19	0.01	0.894		4.93	-6.24–16.09	0.07	0.384
Other		6.50	-7.09–20.09	0.08	0.345		6.06	-4.96–17.08	0.08	0.278
Parental education	71.12	-0.16	-5.53–5.21	-0.01	0.953	-0.01	1.16	-2.64–4.95	0.04	0.547
Reduction of AED	74.25	-3.67	-8.01–0.67	-0.15	0.096	0.02	-1.17	-4.63–2.29	-0.05	0.503
Seizure freedom (reference category: seizure recurrence)	58.55	**15.33**	**3.64–27.03**	**0.23**	**0.011**	**0.05**	**11.25**	**2.04–20.45**	**0.17**	**0.017**

IQ = intelligence quotient; CI = confidence interval; MCD = malformations of cortical development; HS = hippocampal sclerosis; AED = antiepileptic drugs. Values in bold correspond to predictors that are significant in the respective regression analysis.

[a] Adjusted R^2 for the full multiple regression model: 0.54.

[b] B is the unstandardized regression coefficient and can be interpreted in terms of the predictor and the outcome variable. For example, the simple regression model for parental education predicts a 0.16 point increase (95% CI -5.53–5.21 points) in presurgical IQ for each class increase in parental education.

[c] β is the standardized regression coefficient and facilitates comparison of the effect of different predictors.

Supplemental Table S8.3 Summary of multiple regression for postsurgical IQ with paternal education

	Multiple regression[a] (intercept + all variables)			
Predictor	B[b]	95% CI	β[c]	p
[Intercept]	-2.75	-9.63–4.12		0.429
Age at surgery	0.44	-0.07–0.96	0.08	0.090
Duration of epilepsy	-0.01	-0.64–0.63	0.00	0.984
Etiology (reference category: MCD)				0.549
HS	-4.25	-11.01–2.51	-0.05	
Tumor	-0.93	-5.93–4.06	-0.02	
Vascular	0.05	-5.70–5.80	0.00	
Other	-3.68	-9.41–2.05	-0.04	
Paternal education	**3.31**	**1.44–5.17**	**0.11**	**0.001**
Presurgical IQ	**0.97**	**0.87–1.07**	**0.89**	**<0.001**
Reduction of AED	1.58	-0.20–3.35	0.06	0.082
Seizure freedom (reference category: seizure recurrence)	2.31	-2.54–7.16	0.03	0.348

IQ = intelligence quotient; CI = confidence interval; MCD = malformations of cortical development; HS = hippocampal sclerosis; AED = antiepileptic drugs. Values in bold correspond to predictors that are significant in the respective regression analysis.

[a] Adjusted R^2 for the full multiple regression model: 0.90.

[b] B is the unstandardized regression coefficient and can be interpreted in terms of the predictor and the outcome variable. For example, the multiple regression model predicts a 3.31 point increase (95% CI 1.44–5.17 points) in postsurgical IQ for each class increase in paternal education.

[c] β is the standardized regression coefficient and facilitates comparison of the effect of different predictors.

Supplemental Table S8.4 Summary of multiple regression for postsurgical IQ with maternal education

	Multiple regression[a] (intercept + all variables)			
Predictor	B[b]	95% CI	β[c]	p
[Intercept]	0.10	-7.38–7.58		0.980
Age at surgery	0.53	-0.03–1.08	0.10	0.062
Duration of epilepsy	-0.17	-0.84–0.49	-0.02	0.608
Etiology (reference category: MCD)				0.539
HS	-3.49	-10.64–3.66	-0.04	
Tumor	-1.68	-7.00–3.64	-0.03	
Vascular	-0.76	-6.85–5.34	-0.01	
Other	-4.96	-10.98–1.07	-0.06	
Maternal education	1.19	-1.06–3.43	0.03	0.298
Presurgical IQ	**0.98**	**0.87–1.08**	**0.90**	**<0.001**
Reduction of AED	1.56	-0.32–3.44	0.06	0.103
Seizure freedom (reference category: seizure recurrence)	2.23	-2.91–7.37	0.03	0.391

IQ = intelligence quotient; CI = confidence interval; MCD = malformations of cortical development; HS = hippocampal sclerosis; AED = anti-epileptic drugs. Values in bold correspond to predictors that are significant in the respective regression analysis.

[a] Adjusted R^2 for the full multiple regression model: 0.89.

[b] B is the unstandardized regression coefficient and can be interpreted in terms of the predictor and the outcome variable. For example, the multiple regression model predicts a 1.19 point increase (95% CI -1.06–3.43 points) in postsurgical IQ for each class increase in maternal education.

[c] β is the standardized regression coefficient and facilitates comparison of the effect of different predictors.

Supplementary references

1. van der Meulen BF, Smrkovský M. Bayley Developmental Scales, Dutch adaptation. Lisse, the Netherlands: Swets & Zeitlinger; 1983.

2. van der Meulen BF, Ruiter SAJ, Lutje Spelberg HC, et al. Bayley Scales of Infant Development-II, Dutch adaptation. Lisse, the Netherlands: Swets Test Publishers; 2003.

3. van der Meulen BF, Smrkovský M. McCarthy Developmental Scales, Dutch adaptation. Lisse, the Netherlands: Swets & Zeitlinger; 1986.

4. Smulders, FJH. Stutsman, intelligentietest voor kleuters, Nederlandse bewerking. Nijmegen, the Netherlands: Berkhout; 1963.

5. Neutel RJ, van der Meulen BF, lutje Spelberg HC. Kaufman Assessment Battery for Children, Dutch adaptation. Lisse, the Netherlands: Swets & Zeitlinger; 1996.

6. Tellegen PJ, Winkel M, Wijnberg-Williams BJ, et al. Snijders-Oomen Niet-verbale Intelligentietest SON-R 2 ½ - 7. Lisse, the Netherlands: Swets & Zeitlinger; 1998.

7. Snijders JT, Tellegen PJ, Laros JA. Snijders-Oomen niet-verbale Intelligentietest SON-R 5½ - 17. Groningen, the Netherlands: Wolters-Noordhoff; 1988.

8. Vander Steene G, Bos A. Wechsler Preschool and Primary Scale of Intelligence, Flemish-Dutch adaptation, provisional version, 2nd edition. Lisse, the Netherlands: Swets & Zeitlinger; 1997.

9. van Haassen PP, De Bruyn EEJ, Pijl YJ. Wechsler Intelligence Scale for Children – Revised, Dutch adaptation. Lisse, the Netherlands: Swets & Zeitlinger; 1986.

10. Wechsler D. Wechsler Intelligence Scale for Children - third edition. Dutch adaptation. Harcourt Assessment; 2005.

11. Stinissen J, Willemse PJ, Coetsier P, et al. Wechsler Adult Intelligence Scale. Dutch adaptation. Amsterdam, the Netherlands: Swets & Zeitlinger; 1970.

12. Wechsler D. Wechsler Adult Intelligence Scale - third edition. Dutch adaptation. Lisse, the Netherlands: Swets & Zeitlinger; 2004.

13. Mulder JL, Dekker R, Dekker PH. Kaufman - Intelligentietest voor Adolescenten en Volwassenen (KAIT). Leiden, the Netherlands: PITS Testuitgeverij; 2004.

Chapter 9

'With the benefit of hindsight': Would you opt again for epilepsy surgery performed in childhood?

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Abstract

Background: How adolescents and their caregivers look back on epilepsy surgery performed in early life, and whether epilepsy-related restrictions are still in force years after the operation, are insufficiently known.

Aims: To obtain retrospective evaluations of the decision for epilepsy surgery at an early age, and to inventory current epilepsy-related restrictions.

Methods: Of 177 children who underwent epilepsy surgery between 1992 and 2009, 129 could be approached. They and their parents received a rating list inventorying whether, in retrospect, they would opt again for epilepsy surgery, which were motives for their answer, how successful they felt surgery had been and which, if any, epilepsy-related restrictions were still in force.

Results: Forty-one of 44 seizure-free adolescents and 9 of 10 adolescents with current seizures were inclined to (re-)opt for surgery. Parents also would in majority re-opt for surgery. Age at surgery, postsurgical interval, nor type of surgery was statistically significantly related with re-opting for surgery. Seizure-freedom was the paramount motive of seizure-free respondents; respondents with current seizures in majority mentioned amelioration of seizures and/or medication. For parents of children with current seizures, a better developmental perspective was another important motive. Rare hesitation/refusal was related to uncertainties in weighing advantages and disadvantages. Current seizures were no reason to consider surgery as a failure. Among children who were free of both seizures and anti-epileptic drugs, 42% lived with restrictions.

Conclusions: Epilepsy surgery that does not result in seizure freedom can nevertheless be beneficial. Proper advice should prevent meaningless continuation of restrictions.

Introduction

Epilepsy surgery, nowadays even in very young and mentally retarded children a safe and effective treatment of pharmacologically intractable seizures,[1] fails to obtain seizure freedom in roughly 30% of children.[2] Seizure recurrence is considered to be a consequence of failing surgery,[3] a view, however, that may reflect the surgeons' perspective rather than that of the child and his family.

Four reasons prompted the present study. First, as also noted by Chin et al., there is a need for retrospective evaluations of the decision to have epilepsy surgery in very young children.[4] The age at surgery is often not clearly specified.[5-9] In their comprehensive assessment of epilepsy surgery outcome, Gilliam et al. examined 33 children whose ages at surgery ranged from 8 months to 12 years, but with respect to satisfaction they only asked parents.[10]

Second, there is little research on retrospective evaluations of both proxies and children themselves. Children have little involvement in the decision to proceed with epilepsy surgery, but their awareness of their situation increases with age, which may be reflected in retrospective evaluations. Also, evaluation by a proxy-respondent is not equivalent to that reported by the (former) patient.[11] Benifla et al. interviewed both patients and parents, but the study did not distinguish the two sources.[5] Third, most studies focus on retrospective evaluations of temporal lobe surgery.[4-7,12] Extra-temporal resections are less well represented in the literature, and in studies of mixed groups the effect of surgery type on retrospective evaluation is not reported.[9,10] In particular, retrospective evaluations of the decision for hemispherectomy are lacking. Fourth, the duration a parent has lived with an impaired, albeit possibly seizure-free, child may in the long run change retrospective evaluations of the decision for epilepsy surgery.[6]

Our aim was to find out how (former) patients and their parents/caretakers evaluate their decision to proceed with epilepsy surgery, at least one year after the operation. Rather than asking about satisfaction, we selected an 'action approach' by asking respondents whether they, with the benefit of hindsight, 'would do it again', i.e., opt again for surgery.[4] Further aims were to explore the motives behind responses for or against surgery, and to trace the effects of age at operation, duration of postsurgical interval and type of surgery, both for children with seizure recurrence and for those who were seizure-free. Finally, we inventoried epilepsy-related restrictions imposed on children at least one year after epilepsy surgery.

Materials and methods

Respondents (Figure 9.1)

In the Netherlands, all pediatric candidates for epilepsy surgery are referred to the Dutch Collaborative Epilepsy Surgery Program (DuCESP) and all operations on eligible children are performed at the University Medical Center Utrecht (UMCU). Criteria for surgery are as recommended by Cross et al.[13] Between January 1992 and April 2009, 177 children had undergone epilepsy surgery. Demographic data and data with respect to etiology, age at surgery, date of surgery and type of surgery were retrieved from the DuCESP database.

Two children died after the postsurgical period. Parents of the surviving 175 children were approached by letter, which set out the aims and objectives of the study and asked whether the parents and, where possible, their child were willing to take part. Assurance was given that non-participation would not have any treatment implications. Also enclosed were the

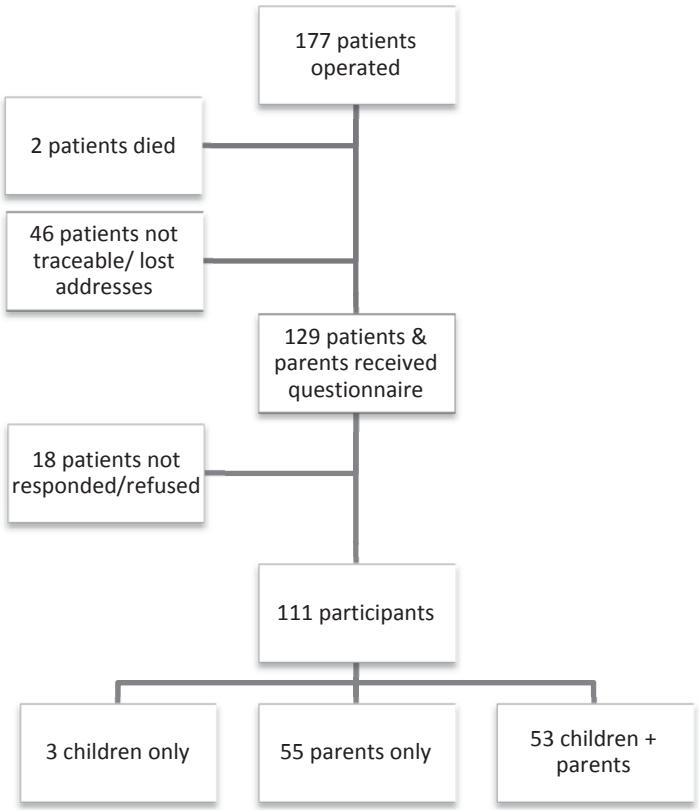

Figure 9.1 From total group to respondents.

rating list 'Would you re-opt for epilepsy surgery' (version for parents and one for children differing only in form of address), and the Euroqol questionnaire (to be reported separately). Independence of answering the questions by child and proxy was demanded but not checked. A stamped hospital envelope was included to return the completed documents.

All attempts failed to establish contact with 46 families. Eighteen of the remaining 129 families chose not to participate because their child had been seizure-free for more than 10 years (n=3), due to the emotional impact of continuing seizures (n=1), or for no specified reason (n=14). One hundred and eleven lists were filled out and returned (86% of the contacted sample), 53 completed by both parents and children, 55 by only the parents and three by only the child.

With respect to gender, etiology, type of surgery, duration of postsurgical period and seizure freedom, patients from whom no response was obtained did not differ from those who or whose parents responded. As far as could be ascertained from the medical files, intelligence quotients did not differ either, with a mean of 86 (range 50–120) in the participant group and 85 (range 47–123) in the non-participants. Ages at the time of surgery and of assessment were, however, significantly higher in the 56 children who responded (means 10.8 and 17.9 years respectively) than in the 119 children who did not respond (means 7.5 and 15.1 years respectively) (p-values <0.01). The 55 children whose parents were the only respondents were significantly younger at the time of surgery and currently (means 7.5 and 10.2 years respectively) than children of non-responding parents (means 14.8 and 18.0 years respectively) (p-values <0.01).

Instrument (see Appendix 9.1)

The three principal questions of the 'Would you do it again?' rating list were: 'With the benefit of hindsight, would you opt again for epilepsy surgery?', 'What is the main motive behind your response to the former question?' and 'How do you now evaluate the surgical outcome?'. The first and third question were framed as five-point Likert items, the second one was an open question. Twelve multiple-choice questions addressed the current status of the child with respect to epilepsy (e.g., seizures and use of anti-epileptic drugs) and to his functioning in major life areas (education, employment and living arrangements). Thirteen three-point questions ('yes', 'no', 'not applicable') recorded whether epilepsy-related restrictions in daily activities were still in force, and if so, which. The list reflected issues frequently broached in the consulting room.

Data management and analysis

Ratings were tallied per scale point and percentages were calculated. Responses to the open question were tabulated, categorized and counted; most of the motives given by children and parents could be grouped around two broad issues, one related to the 'medical predicament' (epilepsy, anti-epileptic medication, underlying disease, health perspective and/or intervention) and the other to 'functioning (social, abilities, activities) and/or wellbeing'. Two children and five parents had misunderstood the first question as to implicate a necessity for further surgery rather than a reconsideration of their initial decision; these cases were excluded from analysis of the responses to the three principal questions. The five cases of invalid filling out the restrictions list (e.g., a parent of an 8 year-old child who mentioned his child to be restricted in using alcohol and/or drugs) were excluded from calculations and analyses.

Data were processed separately for seizure-free (no seizures during at least one year up to the moment of participating) children and those in whom seizures recurred. For statistical analysis, age at operation was classed as 0–2, 3–7, 8–12 and 13–16 years and duration of postsurgical follow-up as 1–3, 4–6, 7–9 and 10 years or more. Type of surgery was classed as hemispherectomy, temporal resections and other types of surgery. Epilepsy-related restrictions were dichotomized ('no restrictions' versus 'restrictions').

SPSS software version 17.0.1 was used for statistical analysis.[14] Nominal variables were analyzed with the Chi-square test and continuous variables with the Mann-Whitney U test. Results were considered significant if the two-tailed p-value was smaller than 0.05.

Results

Notwithstanding the fact that many (ex-)patients who participated were youngsters or adults (age range 2–33 years), we denote them as 'children', except for when a more precise indication of age clarifies the point to make.

Demographic data and epilepsy-related characteristics are shown separately for seizure-free children and children in whom seizures recurred (Table 9.1). Of the 56 participating children, 46 (82%) were seizure free and of these 20 (44%) reported continued use of AED. Parents of 81 seizure-free children (75%) reported continued AED use in 27 (33%) of these children. Children and their parents gave identical information with respect to seizures and AED. The proportion of children whose level of mental functioning was incompatible with formal education was considerably larger than in the general population, and twice as large in the group with current seizures as in the group of seizure-free children. The vast majority of the children received special education, but a few seizure-free adolescents were able to

Table 9.1 Demographics, epilepsy variables and activities of seizure-free and not seizure-free respondents

		Seizure free in the past year (n=83)		Not seizure free in the past year (n=28)		Total (N=111)	
		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Current age (years)		14.8 (6.70)	2–28	14.9 (7.67)	2–33	14.8 (6.92)	2–33
Age at surgery (years)	Overall	7.7 (5.21)	0–16	7.0 (5.60)	0–16	7.5 (5.30)	0–16
	Callosotomy	-	-	12 (5.66)	8–16	12 (5.66)	8–16
	Hemispherectomy	2.4 (2.43)	0–8	3.1 (4.53)	0–12	2.6 (3.13)	0–12
	Temporal resections	10.3 (4.31)	1–16	5.8 (4.76)	3–14	9.8 (4.52)	1–16
	Extra-temporal resections	8.5 (4.75)	1–16	10.2 (4.67)	0–16	9.2 (4.69)	0–16
Duration follow-up (years)	Overall	7.0 (4.26)	1–17	7.8 (5.06)	1–17	7.2 (4.46)	1–17
	Callosotomy	-	-	16.5 (0.71)	16–17	16.5 (0.71)	16–17
	Hemispherectomy	6.8 (3.87)	1–15	6.6 (4.01)	2–13	6.7 (3.85)	1–15
	Temporal resections	6.9 (4.02)	1–16	7.6 (4.72)	2–15	6.9 (4.04)	1–16
	Extra-temporal resections	7.7 (5.60)	1–17	7.4 (5.37)	1–16	7.6 (5.40)	1–17
		n (%)		n (%)		N (%)	
Sex	Male	36 (43.4)		17 (60.7)		53 (47.7)	
	Female	47 (56.6)		11 (39.3)		58 (52.3)	
Type of surgery	Callosotomy	0 (0.0)		2 (7.1)		2 (1.8)	
	Hemispherectomy	24 (28.9)		10 (35.7)		34 (30.6)	
	Temporal resection	44 (53.0)		5 (17.9)		49 (44.1)	
	Extra-temporal resection	15 (18.1)		11 (39.3)		26 (23.4)	

Table 9.1 continues on next page

Table 9.1 *Continued*

		Seizure free in the past year (n=83)	Not seizure free in the past year (n=28)	Total (N=111)
		n (%)	n (%)	N (%)
Etiology	Cortical dysplasia	21 (25.3)	13 (46.4)	34(30.6)
	Tumor	30 (36.1)	3 (10.7)	33 (29.7)
	Vascular	9 (10.8)	3 (10.7)	12 (10.8)
	Mesotemporal sclerosis	14 (16.9)	2 (7.1)	16 (14.4)
	Porencephalic cyst	3 (3.6)	1 (3.6)	4 (3.6)
	Tuberous sclerosis	1 (1.2)	3 (10.7)	4 (3.6)
	Rasmussen encephalitis	1 (1.2)	1 (3.6)	2 (1.8)
	Miscellaneous / unknown	4 (4.8)	2 (7.1)	6 (5.4)
Seizure frequency last year	<1 in 3 months		4 (14.3)	4 (3.6)
	≥1 in 3 months		5 (17.9)	5 (4.5)
	≥1 in a month		5 (17.9)	5 (4.5)
	≥1 in a week		12 (42.9)	12 (10.8)
	Unknown		2 (7.1)	2 (1,8)
Current anti-epileptic drugs	No	54 (65.1)	2 (7.1)	56 (50.5)
	One	16 (19.3)	7 (25.0)	23 (20.7)
	Two	5 (6.0)	8 (28.6)	13 (11.7)
	Three	5 (6.0)	5 (17.9)	10 (9.0)
	Four	2 (2.4)	4 (14.3)	6 (5.4)
	Five or more	1 (1.2)	2 (7.1)	3 (2.7)

Table 9.1 continues on next page

Table 9.1 *Continued*

		Seizure free in the past year (n=83)	Not seizure free in the past year (n=28)	Total (N=111)
		n (%)	n (%)	N (%)
Highest completed education	No (only care)	7 (8.4)	5 (17.9)	12 (10.8)
	Special primary	18 (21.7)	4 (14.3)	22 (19.8)
	Primary	4 (4.8)	1 (3.6)	5 (4.5)
	Special secondary	12 (14.4)	10 (35.7)	22 (19.8)
	Secondary education	9 (10.8)	3 (10.7)	12 (10.8)
	Lower vocational	19 (22.9)	2 (7.1)	21 (18.9)
	Higher vocational or university	6 (7.2)	0 (0.0)	6 (5.4)
	Not applicable, too young	6 (7.2)	2 (7.1)	8 (7.2)
	Missing	2 (2.4)	1 (3.6)	3 (2.7)
Employment	No, too disabled	9 (10.8)	8 (28.6)	17 (15.3)
	Yes	32 (38.6)	7 (25.0)	39 (35.1)
	No, pre-school age	33 (39.8)	12 (42.9)	45 (40.5)
	In school/education	8 (9.6)	1 (3.6)	9 (8.1)
	Missing	1 (1.2)	0 (0.0)	1 (0.9)
Living arrangements	With parents, unable to live independently	3 (3.6)	3 (10.7)	6 (5.4)
	With parents, age-appropriate	62 (74.5)	18 (64.3)	80 (72.1)
	With parents, voluntarily	5 (6.0)	1 (3.6)	6 (5.4)
	Sheltered home	2 (2.4)	3 (10.7)	5 (4.5)
	Independent with support	2 (2.4)	2 (7.1)	4 (3.6)
	Independent, single	6 (7.2)	1 (3.6)	7 (6.3)
	Independent with partner	3 (3.6)	0 (0.0)	3 (2.7)

follow higher vocational or university education. About 60% of the children in both groups were of an employable age. Around 10% of the seizure-free respondents and a quarter of those with current seizures were unemployed due to disabilities. However, well over a third of the seizure-free respondents and a quarter of those with current seizures were regularly employed. The majority of the children were living with their parents, typical of children in their age range. The few seizure-free adolescents unable to live independently (<10%), were being cared for by their parents or resident in a sheltered home. At least two times more adolescents with current seizures were unable to live independently.

'Would you re-opt for surgery?' (Table 9.2.1)

Almost all (93%) of the seizure-free children and 9 out of 10 children with seizures in the past year responded 'definitely yes' or 'probably yes'. Three seizure-free children (one in whom a hemispherectomy had been performed) were unsure whether they would opt again for surgery. One of the 10 children with seizures during the past year would definitely not opt again for surgery.

Amongst the parents whose children were seizure free, 73 (96%) would definitely or probably re-opt for epilepsy surgery, whereas 23 (85%) of those whose children experienced seizures felt the same. Three parents of seizure-free children and two parents of children with current seizures were unsure whether they would re-opt for surgery. The parents of another two children with current seizures would probably not opt again for surgery.

The parents of 22 children who were seizure free after a hemispherectomy (92%) and those of nine children with current seizures after this intervention (90%) were inclined to re-opt for surgery. Parents of one out of four children with seizure recurrence after temporal resection and those of one out of 9 children with seizure recurrence after extra-temporal surgery would probably or definitely not re-opt for surgery.

Neither the four age groups nor the four groups with different postsurgical intervals could be distinguished with respect to their inclination to re-opt for epilepsy surgery. This was true both for seizure-free children and for children with current seizures.

Motives for (not) opting again for surgery (Table 9.2.2)

The majority (65%) of the 37 seizure-free children who had provided an adequate response to the question 'would you re-opt for surgery' and who provided a response to the motivation question, described their motivation to re-opt for surgery in terms of their epilepsy (frequency or severity of seizures, antiepileptic medication) and/or the underlying cause

Table 9.2 Children and parents evaluate epilepsy surgery: responses to the principal questions

	Children (N=54)		Parents (N=103) of children who were	
9.2.1 Would you do it again? n (%)	Seizure-free (n=44)[a]	Not seizure-free (n=10)	Seizure-free (n=76)[b]	Not seizure-free (n=27)[c]
Definitely yes	33 (75.0)	8 (80.0)	56 (73.7)	16 (59.3)
Probably yes	8 (18.2)	1 (10.0)	17 (22.4)	7 (25.9)
I don't know	3 (6.8)	0 (0.0)	3 (3.9)	2 (7.4)
Probably not	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)
Definitely not	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)
9.2.2 Major motive(s) to (not) re-opt for surgery n (%)[i/j]	Children (N=47)		Parents (N=97) of children who were	
	Seizure-free (n=37)[a]	Not seizure-free (n=10)	Seizure-free (n=72)[b]	Not seizure-free (n=25)[c]
Epilepsy-related				
Respondents who would definitely / probably re-opt for epilepsy surgery	24 (64.8)	7 (70)	31 (43.1)	11 (44)
Respondents who were uncertain	0	0	0	2 (8.0)
Respondents who would probably / definitely refrain from epilepsy surgery	0	0	0	0 / 2 (8.0)[z]
Functioning-related				
Respondents who would definitely / probably re-opt for epilepsy surgery	1 (2.7)	1 (10)	18 (25)	5 (20)
Respondents who were uncertain	1 (2.7)	0	0 / 1 (1.4)	0
Respondents who would probably / definitely refrain from epilepsy surgery	0	0	0	0

Table 9.2 continues on next page

Table 9.2 *Continued*

2.2 Major motive(s) to (not) re-opt for surgery n (%)[i/j]	Children (N=47)		Parents (N=97) of children who were	
	Seizure-free (n=37)[a]	Not seizure-free (n=10)	Seizure-free (n=72)[b]	Not seizure-free (n=25)[c]
Both epilepsy and functioning related				
Respondents who would definitely / probably re-opt for epilepsy surgery	10 (27)	1 (10)	20 (27.8)	5 (20)
Respondents who were uncertain	0 / 1 (2.7)[zz]	0	1 (1.4) / 1 (1.4)	0
Respondents who would probably / definitely refrain from epilepsy surgery	0	1 (10)	0	0
	Children (N=54)		Parents (N=103) of children who were	
9.2.3 Evaluation of surgery outcome n (%)	Seizure-free (n=44)[a]	Not seizure-free (n=10)	Seizure-free (n=76)[b]	Not seizure-free (n=27)[c]
Great success	38 (86.4)	3 (30.0)	64 (84.2)	9 (33.3)
Partial success	5 (11.4)	4 (40.0)	11 (14.5)	15 (55.6)
Neither success nor failure	0 (0)	1 (10.0)	1 (1.3)	1 (3.7)
Partial failure	1 (2.3)	1 (10.0)	0 (0)	1 (3.7)
Severe failure	0 (0)	1 (10.0)	0 (0)	1 (3.7)

[a] 2 answers deleted because they addressed the question whether they would envisage a second surgery.
[b] 4 answer deleted (see above).
[c] 1 answer deleted (see above).
[i/j] If answers are framed following i/j, i refers to positive motives, j to negative ones.
[z] One parent mentioned seizure increase after incident that was not related to epilepsy surgery.
[zz] Respondent doubted equilibrium of pros and cons in both epilepsy- and functioning-related domains.

of their seizures, such as a tumor in one case. One respondent in the latter group referred to improvement of a symptom (headache). Ten seizure-free children (27%) explained their decision to re-opt for surgery with reference to both an epilepsy-related advantage and a change in wellbeing (with an emphasis on 'feeling free', 'no restrictions') or the decrease and even normalization of limitations in activities or abilities prior to surgery. Answers of four seizure-free children were noteworthy. One child re-opted for surgery although she felt that her level of achievement at school had deteriorated after the intervention, one other child avoided answering the question of motive by referring back to his parents' original decision, a third one would definitely re-opt for surgery, provided that postsurgical counseling would be in place (the family had dropped out of the normal neuropsychological follow-up scheme and the girl had suffered post-traumatic stress disorder during the first two years after surgery), and a seizure-free adolescent (age 15 years, special secondary education) answered that re-opting for surgery would depend on the pros and cons of the intervention and how arduous postsurgical rehabilitation was expected to be.

Most children with current seizures referred to an amelioration of their medical condition, e.g. seizures or a growing tumor. The other two children mentioned in one case the disappearance of a symptom (nausea) and in the other case increased wellbeing. The child with current seizures who would definitely not re-opt for surgery thought there was little prospect of gaining seizure freedom and improved functioning.

Parents of seizure-free children (43%) explained their inclination to re-opt for surgery predominantly in terms of seizure freedom and/or cessation of AED or removal of the underlying cause (tumor in three cases). Almost 30% of the parents explained their answer in terms of improved wellbeing or functioning. Although the intervention had rendered his child seizure free, one parent was not sure whether he would re-opt for the intervention, because the child turned out to be autistic and mentally retarded. Another parent would 'probably not' re-opt for surgery, because of new symptoms (spasms and paralysis), which became manifest only after the intervention.

For over half of the 25 parents whose children had current seizures (52%), ameliorations such as a period free from seizures or a reduced threat of a progressive underlying disease were sufficient motives to re-opt for surgery. Another 40% were motivated by improved wellbeing or functioning or by improvement in both areas. Parents of two children with current seizures would probably not re-opt for surgery: in one case the intervention had been ineffective in terms of wellbeing and functioning, in the other the child had become wheelchair-dependent, doubly incontinent and more retarded after an incident of choking that necessitated artificial breathing, occurring some six months after epilepsy surgery and not plausibly related to the intervention.

Retrospective evaluation of surgical success (Table 9.2.3)

Eighty-six percent of the seizure-free children evaluated the surgery as a great success and 11% as a partial success. Of the 10 children with current seizures, three rated the intervention as a great success and four as a partial success.

Almost all the parents of seizure-free children (99%), but also 89% of parents whose children currently had seizures, evaluated the surgery as a success. Among parents of seizure-free children, 84% saw the surgery as a 'great success', compared to one third of the parents of children with current seizures. All parents of the hemispherectomized children rated the intervention as a success, whether the child had become seizure-free or not. The same was true for parents of both callosotomized children. Parents of one out of four children who had not become seizure-free after temporal resection rated surgery as a severe failure, whereas parents of the remaining three children rated the operation as a success. With respect to extra-temporal resections, all parents of seizure-free children rated surgery as a success, as did parents of seven out of ten children with seizure recurrence.

Neither the four age groups nor the four groups with different postsurgical intervals could be distinguished with respect to their evaluation of the outcome of surgery. This was true both for seizure-free children and for children with current seizures.

Epilepsy-related restrictions (Figures 9.2 and 9.3)

Living with epilepsy-related restrictions was reported by 78% of children who were not seizure-free and using AED. Eighty-four percent of the parents mentioned restrictions of AED-using children with seizures. Of the children who were seizure-free but still using AED, 65% reported living with restrictions and 55% of the parents of this group mentioned restrictions imposed upon their child.

More informative, 42% of children who were free of both seizures and AED and 33% of parents reported current restrictions.

All 13 restrictions were still imposed at the time of the research, those related to alcohol and/or drug use and the amount of sleep most frequently. Restrictions related to going on holiday, going out and swimming were also frequently in force. Restrictions related to making new friends and sexual intercourse were the only restrictions mentioned more by children than parents.

Neither the four age groups nor the four groups with different postsurgical intervals could be distinguished with respect to the number of currently imposed restrictions, whether

the children were seizure free or not. Similarly, the number of reported restrictions did not differ significantly between respondents who were inclined to re-opt for surgery and those who were not.

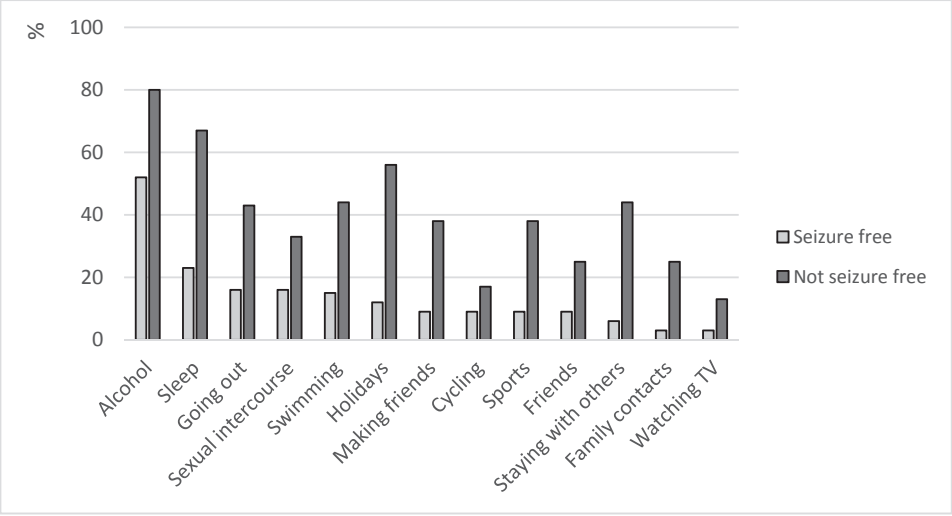

Figure 9.2 Childrens' estimations of current epilepsy-related restrictions.

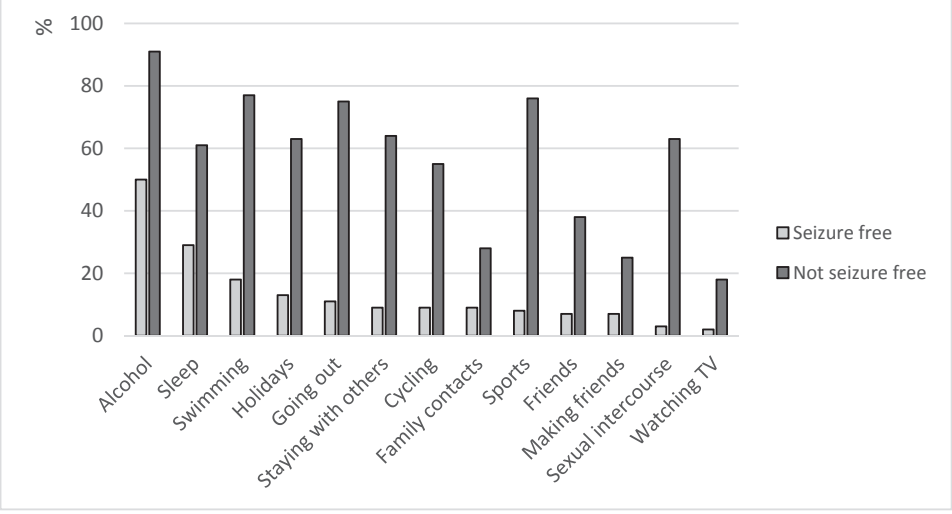

Figure 9.3 Parents' estimations of current epilepsy-related restrictions.

Discussion

Retrospective evaluations of pediatric epilepsy surgery have been framed in terms of satisfaction.[15] However, because the child or his or her caregiver decides together with the epilepsy treatment team on any treatment (pharmacological, dietary, surgical or otherwise), we followed Chin et al. by using an action orientation, questioning children and parents on whether they would, with the benefit of hindsight, opt again for surgery.[4,16]

Our study comprised children who were very young at the time of their operation and a fair proportion of the respondents consisted of parent-child pairs. Neither age at surgery, postsurgical interval nor type of surgery, affected re-opting for surgery and evaluating the outcome of surgery to a statistically significant degree, whether the children were seizure free or not. Also, the parents' ratings were not significantly influenced by their child's age at surgery, type of surgery or time after surgery. The threat of a growing tumor (in 30% of the cases the underlying etiology), was recollected by some respondents, but it was not the primary motive to re-opt for epilepsy surgery.

Is surgery a failure when seizures recur?

Epilepsy teams tend to consider surgery a failure when it does not achieve seizure freedom. This study shows, however, that the majority of (former) patients and their proxies, evaluate epilepsy surgery as a disease improving intervention even when seizures have recurred. For some children with catastrophic epilepsy, surgery may be the only chance of development. A large majority of children and parents would re-opt for surgery, even in the case of infants and babies. As the length of time between surgery and the present study did not significantly influence the responses, neither children nor parents appear to alter their evaluation of the surgical procedure and its outcome over time.[6]

Why were some children or their parents not inclined to re-opt for surgery?

Other authors have noted that visual, motor or memory deficits after temporal surgery or epilepsy surgery in general are sources of dissatisfaction, along with unfulfilled presurgical expectations of seizure elimination.[6,7,12] Our study adds that arduousness of the rehabilitation process, absence of psychosocial counseling, persisting mental retardation and autism, and new postsurgical problems such as spasms and paralysis, may be reasons for ambivalence towards or rejection of surgery. These rare exceptions to the overwhelmingly positive responses highlight the importance of informing the children's proxies, and where relevant the children themselves, before surgery about the risk of enduring cognitive and/or affective

impairments. Intensive medical and psychosocial support in the period following the first few months of intensive postsurgical medical engagement is very important, even for seizure-free children.

Restrictions and use of AED

Using a list of 13 activities relevant for children of school age as well as for adolescents, we found 42% of the children who were free of both seizures and AED since at least one year, to live with epilepsy-related restrictions. This is surprising, as many restrictions imposed on children aged six and over are usually lifted in the six months post surgery and as tapering off AED appears to be safe after one year of seizure freedom.[17] Whether the patients themselves feel safer with restrictions or whether the parents insist on their continuation is presently under study.

Limitations and strengths

The study is necessarily retrospective, as we wanted respondents to look back on their decision for epilepsy surgery, taking into account any relevant changes, set-backs and complications felt to have influenced their existence after the operation. Furthermore, although a countrywide cohort study with a rather large number of respondents, finer-grained statistical analyses were limited by smallness of sub-groups. Hemispherectomies were, however, sufficiently represented to add data to the literature. Also, the widely divergent post-surgery interval rendered statistical analysis of particular associations impossible. The response rate (86% of those who could be contacted) is felt to be reasonable, seen the – for some respondents very long (up to 17 years) – interval between surgery and this study. The low response rate (43%) from the children is understandable from the fact that 28% were younger than 12 years at the time of the study. Responding children were older at the times of surgery and of study than non-responding children, while the 55 children whose parents were the only respondents were younger on both occasions.

Seeking for bias, we checked gender, etiology, type of surgery, duration of postsurgical period and seizure freedom and found no differences between patients from whom no response was obtained and those who or whose parents responded. As far as we could find out, intelligence did not distinguish non-responding and responding children either. The rating list was not standardized, our primary objective being current feelings with respect to previous vital decisions made by families under our care. Also, we cannot rule out interaction between children and parents, since we asked parents to answer the questions and where possible to have their children answer the same questions in the list prepared for the children.

After we had finished our study, Macrodimitris et al. published a systematic review of the literature on patient satisfaction following epilepsy surgery.[18] Concluding that patient satisfaction with interventions had received little attention in epilepsy surgery they proposed guiding principles for measuring satisfaction. Having (1) used a theoretical framework for the evaluations by the respondents, (2) defined the responses as the positive or negative evaluation of the entire process of undergoing epilepsy surgery and its outcomes, (3) described possible determinants of these evaluations (amongst others, patient characteristics, type of surgery, seizure outcome), (4) presented different dimensions along which the respondents could gauge their evaluations and (5) used the response format of Likert scales rather than dichotomous response categories, we feel that the present study contributes to a better understanding of the long-term outcome of epilepsy surgery in children.

Conclusions and recommendations

With the benefit of hindsight, most patients and their parents would opt again for epilepsy surgery. The vast majority of (former) patients and their parents evaluate epilepsy surgery that did not lead to seizure freedom as a success and as a disease improving intervention. Uncertainty or (rare) unwillingness to re-opt for surgery tends to be attributed to persisting impairments in cognitive and/or social functioning and the expected arduousness of rehabilitation. Therefore presurgical information about likely outcomes and intensive medical and psychosocial counseling are of paramount importance. Finally, guidance on lifting restrictions and tapering off AED can forestall frustration and disappointment about postoperative development.

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References

1. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7(6):525-37.

2. Van Oijen M, De Waal H, Van Rijen PC, Jennekens-Schinkel A, van Huffelen AC, Van Nieuwenhuizen O, et al. Resective epilepsy surgery in childhood: the Dutch experience 1992-2002. Eur J Paediatr Neurol 2006; 10(3):114-23.

3. Marks WJ, Jr. When epilepsy surgery fails ... There is often a second chance. Epilepsy Curr 2005;5(4):149-51.

4. Chin PS, Berg AT, Spencer SS, Lee ML, Shinnar S, Sperling MR, et al. Patient-perceived impact of resective epilepsy surgery. Neurology 2006;66(12):1882-7.

5. Benifla M, Rutka JT, Otsubo H, Lamberti-Pasculli M, Elliott I, Sell E, et al. Long-term seizure and social outcomes following temporal lobe surgery for intractable epilepsy during childhood. Epilepsy Res 2008;82(2-3):133-8.

6. Dupont S, Tanguy ML, Clemenceau S, Adam C, Hazemann P, Baulac M. Long-term prognosis and psychosocial outcomes after surgery for MTLE. Epilepsia 2006;47(12):2115-24.

7. Guldvog B. Patient satisfaction and epilepsy surgery. Epilepsia 1994;35(3):579-84.

8. Jones JE, Berven NL, Ramirez L, Woodard A, Hermann BP. Long-term psychosocial outcomes of anterior temporal lobectomy. Epilepsia 2002;43(8):896-903.

9. Reid K, Herbert A, Baker GA. Epilepsy surgery: patient-perceived long-term costs and benefits. Epilepsy Behav 2004;5(1):81-7.

10. Gilliam F, Wyllie E, Kashden J, Faught E, Kotagal P, Bebin M, et al. Epilepsy surgery outcome: comprehensive assessment in children. Neurology 1997;48(5):1368-74.

11. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes 2007;5:2.

12. Wheelock I, Peterson C, Buchtel HA. Presurgery expectations, postsurgery satisfaction, and psychosocial adjustment after epilepsy surgery. Epilepsia 1998;39(5):487-94.

13. Cross JH, Jayakar P, Nordli D, Delalande O, Duchowny M, Wieser HG, et al. Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. Epilepsia 2006;47(6):952-9.

14. IBM® (2008) SPSS software version 17.0.1 (SPSS® Statistics).

15. Keene DL, Loy-English I, Ventureyra EC. Patient satisfaction with surgical treatment of refractory epilepsy done in childhood and early adolescence. Childs Nerv Syst 1998;14(1-2):30-2.

16. Kuhl J. A theory of self-regulation: Action versus state orientation, self-discrimination, and some applications. Appl Psychol 1992;(41):95-173.

17. Carpay HA, Vermeulen J, Stroink H, Brouwer OF, Peters AC, van Donselaar CA, et al. Disability due to restrictions in childhood epilepsy. Dev Med Child Neurol 1997;39(8):521-6.

18. Macrodimitris S, Sherman EM, Williams TS, Bigras C, Wiebe S. Measuring patient satisfaction following epilepsy surgery. Epilepsia 2011;52(8):1409-17.

Appendix 9.1 List of questions

Outcome of the operation

1. Suppose, your seizures are now the same as they were before the operation. And suppose also that it was completely up to you to decide whether or not to go ahead with the operation. You know from your own experience what impact such operations can have. Would you choose to have the operation? Or not?

   - ☐ Yes, absolutely
   - ☐ Probably
   - ☐ I am not sure
   - ☐ Probably not
   - ☐ No, absolutely not

2. What is the most important reason for your choice?

   _____

   _____

   _____

   _____

3. How would you describe the outcome of the operation?
   Tick the box that matches the way you think of the outcome:

   - ☐ A great success
   - ☐ Partly a success
   - ☐ Not a success but not a failure either
   - ☐ Partly a failure
   - ☐ A complete failure
   - ☐ Something else: _____

Things I take into account because of epilepsy

Answer the following questions whether you have seizures at the moment or not.

Do you still take epilepsy into account because of your (past) seizures when taking part in the following activities?:

N.b.: We are trying to find out whether you are taking into account that these activities could lead to a seizure. If you are not allowed to do these activities because you are too young, or for other reasons besides your epilepsy (such as a physical disability), please answer 'not applicable'.

I take my epilepsy into account with regards to:				
a.	Going on holiday	Yes	No	Not applicable
b.	Sleeping over (somewhere other than at home)	Yes	No	Not applicable
c.	Going out	Yes	No	Not applicable
d.	Playing sports	Yes	No	Not applicable
e.	Swimming	Yes	No	Not applicable
f.	Cycling	Yes	No	Not applicable
g.	Drinking alcohol and using drugs	Yes	No	Not applicable
h.	Watching television	Yes	No	Not applicable
i.	The amount of sleep that I need	Yes	No	Not applicable
k.	Meeting friends	Yes	No	Not applicable
l.	Making new friendships	Yes	No	Not applicable
j.	Sexual intercourse	Yes	No	Not applicable
m.	With my parents, brother(s) and/or sister(s)	Yes	No	Not applicable

Chapter 10

Summary and general discussion

Summary and general discussion

For children with lesional focal epilepsy that is refractory to pharmacological treatment, epilepsy surgery has increasingly become the treatment option par excellence. In The Netherlands, pediatric epilepsy surgery is performed solely in the University Medical Center Utrecht (UMCU). The beneficial effect of epilepsy surgery on seizure control in selected candidates has been well established, with almost three quarters of the children enjoying complete seizure freedom (Engel class 1A) at two years after surgery.[1]

The main aim of this thesis was to explore the development of children who underwent epilepsy surgery, based on a series of questions that arose from the clinical care for these patients. The thesis describes the results of studies that investigated different aspects of cognitive outcome following epilepsy surgery in children, in particular hemispherectomy. The study addressing the influence of AED withdrawal on intelligence quotient (IQ) was performed on data from a large European multicenter group of pediatric epilepsy surgery patients (*TimeToStop* study). The other studies are based on a standard comprehensive longitudinal assessment with fixed time intervals (shortly before and 6, 12 and 24 months after surgery) performed in a cohort of Dutch children who underwent epilepsy surgery in the UMCU between 1992 and 2009.

Summary

Chapter 2 provides a critical review of the literature with respect to predictors of cognitive change and eventual cognitive outcome after epilepsy surgery. We found only few studies in which the relation between presumed determinants and change of cognition or the ultimate postsurgical cognitive level was analyzed in a multivariable manner. With this caveat, we reported seven variables that were independently related to a change of mental developmental index (MDI), developmental quotient (DQ) or IQ in different surgical cohorts after surgery. These variables were gender, age at surgery, presurgical cognitive level (MDI, DQ or IQ), underlying etiology, postsurgical seizure freedom, cessation of antiepileptic medication, and follow-up interval. Straightforward cognitive improvement seems to be uncommon, with only 20–30% of surgically treated children achieving an increase of 5 to 15 MDI, DQ or IQ points after surgery. With respect to the ultimate level of cognitive functioning, duration of epilepsy, postsurgical seizure freedom and presurgical MDI, DQ or IQ, were the only independent influencing variables reported in different studies.

In **Chapter 3** we conclude that hemispherectomy can be a basis for mental development in children with epilepsy. The approach to separately analyse data obtained using

developmental scales and intelligence scales, as well as a case-by-case approach (rather than reporting group means only), enabled us to detect subtle mental development in young children (n=19), as reflected by clear increases in mental age. Still, the increases were smaller than those of healthy peers. Although the overall gain in IQ scores in older children (n=17) was very small (4 points), it indicated that cognitive development in these children kept pace with normal cognitive growth. Case-by-case, however, four children showed a significant (i.e., 10 or more IQ points) increase and two significant decrease.

In **Chapter 4** we report on the issue whether EEG or MRI abnormalities in the 'healthy' hemisphere influence outcome in terms of seizure recurrence and IQ after functional hemispherectomy. We found that unequivocal contralateral MRI abnormalities are significantly associated not only with seizure recurrence but also with severe mental delay and with a MDI or IQ increase of less than 10 points. The proportion of children with severe retardation (MDI/IQ <55) was larger in the group of children with contralateral MRI abnormalities, compared to those without (95% versus 42%). Children with MRI-abnormalities did not improve in MDI/IQ scores over the course of postsurgical follow-up. Presurgical epileptic or background EEG abnormalities in the contralateral hemisphere did neither influence seizure outcome nor cognitive outcome after hemispherectomy.

Chapter 5 reports on functioning of (former) patients five to eleven years after childhood hemispherectomy. Thirty-one persons participated in a comprehensive neuropsychological re-assessment; parents and young adult patients provided data on behavior, daily functioning and health-related quality of life (HrQoL). Twenty-two participants in school-age and young adulthood (median age 13.8 years) were assessed with age-appropriate cognitive tests. IQ ranged from 45 to 82 (median 61). Participants with far below mean norm scores, could learn and remember, sustain attention, inhibit irrelevant responses, read and write. Nine children (median age 9.7 years) were so mentally retarded that age-appropriate testing was impossible; they were almost totally dependent on others in daily activities. The proportion of pre-existing contralateral MRI abnormalities was larger in this group, as were the rates of seizure recurrence and of behavior problems after hemispherectomy. Parents of participants in both groups rated overall HrQoL surprisingly positively (mean VAS-score 72.5), with a scarce low rating (40). All parents reported problems with respect to their children's self-care, daily activities and mobility.

In **Chapter 6** we retrospectively evaluated the impact on psychomotor speed of withdrawing antiepileptic drugs (AEDs) after epilepsy surgery (both hemispherectomy and resections). The effect was only studied in children who had become seizure free. Postsurgical medication policy and neuropsychological assessments shortly before and six, 12 and 24 months after surgery were evaluated in 57 children (32 female, median age at surgery 13 years). Patients

were divided into two groups: the withdrawal group consisted of 29 children and the no-withdrawal group of 28 children. Scores on four psychomotor tests performed at 12 and 24 months after surgery were compared with postsurgical baseline scores, obtained six months after surgery. At 24 months, the withdrawal group (withdrawal defined as complete cessation of at least one AED at the latest time of assessment compared to the number of AEDs used at six months after surgery) showed significantly more improvement in psychomotor speed than the no-withdrawal group on three of four tests. At 12 months, a similar difference between groups was seen, though not statistically significant. We concluded that drug withdrawal after surgery improves performances on psychomotor speed tests.

Chapter 7 describes the results of a study that explored how intelligence changes in relationship with AED withdrawal. From the European multicenter retrospective *TimeToStop* cohort of children who reached seizure freedom after surgery and in whom AED-withdrawal was started, we collected IQ scores of children who had been assessed neuropsychologically both before and after variable postsurgical intervals (n=301). Using linear regression analyses, we studied whether reduction of AEDs prior to the last assessment was related to the last postsurgical IQ and to delta IQ (i.e., the difference in IQ between the last and the presurgical assessment). We adjusted for possible confounders, being those variables that influenced AED withdrawal policies and variables that influenced IQ and IQ-change. Reduction of AEDs significantly improved both postsurgical IQ and delta IQ, as did complete withdrawal. If a difference of 10 or more points was taken as the criterion, AED reduction again predicted an increase of IQ.

In **Chapter 8** we report on our query whether education of the parents, normally an important environmental variable, contributes to presurgical prediction of postsurgical change in the child's IQ. The sample for regression analysis included 118 children who underwent epilepsy surgery in our center, independent of seizure outcome (60 males; median age at surgery 9.7 years). Parental education proved to be significantly associated with delta IQ (defined as in Chapter 7) in simple regression analysis (p=0.004), and also contributed significantly to postsurgical IQ in multiple regression analysis (p=0.008). Parental education made a unique contribution to prediction of delta IQ, i.e., it could not be replaced by the illness-related variables. Subgroup analyses confirmed the association of parental education with IQ change after surgery for most groups. Children of higher educated parents had on average a larger increase in IQ after surgery and a higher postsurgical – but not presurgical – IQ than children whose parents had completed at most lower secondary education.

In **Chapter 9** we report how parents and patients evaluate the decision to agree with epilepsy surgery in their children. We recorded whether the intervention had or had not achieved the – so hoped-for – seizure freedom. Of the 177 children who had undergone epilepsy surgery

between 1992 and 2009 in the UMCU, two children died during the follow-up period. All attempts failed to have contact with 46 families. Eighteen of the remaining 129 families chose to not participate because their child had been seizure free for more than 10 years (n=3), due to the emotional impact of continuing seizures (n=1), or for no specified reason. One hundred and eleven (former) patients and their parents could be approached and were sent a questionnaire inventorying whether they, with the benefit of hindsight, would opt again for epilepsy surgery or not and which were the motives for their answer. Forty-one of 44 seizure-free adolescents and 9 of 10 adolescents with recurrent seizures would re-opt for surgery. The majority of parents would also re-opt for surgery. Seizure-freedom was the paramount motive of seizure-free respondents; respondents with current seizures in majority mentioned amelioration of seizures and/or medication. For parents of children with ongoing seizures, a better developmental perspective was another important motive. Hesitation and refusal were rare, and related to not knowing how to weigh advantages against disadvantages. Current seizures were no reason to consider surgery as a failure.

Three main themes of this thesis – findings in perspective and future research

Development after epilepsy surgery

The high chance of seizure freedom – as a primary aim of pediatric epilepsy surgery – is well established. Cognitive development after surgery has become another, increasingly acknowledged, outcome measure.[2,3] Up to 70% of children with intractable epilepsy are mentally retarded.[4-7] In infants and young children with frequent seizures, the epilepsy syndrome may take a catastrophic course – so-called epileptic encephalopathy[8] –, suggesting that the developmental arrest or regression can at least be attributed to the ongoing seizures and continuous electrographic epileptic abnormalities, and not only to the underlying epileptogenic pathology. When counseling parents, it is important to have empirically based knowledge of postsurgical cognitive development. This particularly holds true for the children who are about to undergo functional hemispherectomy, in whom presurgical developmental trajectories are most dramatically affected. In the relevant literature, cognitive functioning is usually defined as intelligence or development, and cognitive improvement is expressed as an increase of 5 to 15 MDI, DQ or IQ points or a shift from one to another predefined category of cognitive function, such as from below average to low average. Viewing case by case, we found a significant number of the children (61% of hemispherectomized children and 70% of those who underwent a focal resection) who had an almost unchanged cognitive level or remained in their presurgical category of functioning (Chapter 2).

To infer that epilepsy surgery may ameliorate seizure status, but not cognitive development, however, would be wrong. Subtle changes in developmental capacity may be concealed for a number of reasons. First, the age range of children within studies varies from younger than one year to adolescence. So, in most studies not only intelligence scales but also developmental scales are used. Developmental scales are applied to assess infants and young or mentally retarded children and, due to the developmental stage of the children, rely predominantly on sensory and motor domains. With development, cognitive abilities and capacities change not only quantitatively, so that in school age other capacities can be tapped. Intelligence scales used to assess older children rely more on verbal and visuo-spatial reasoning. As the components of these two types of scales are not the same, the scores on developmental scales do not correlate highly with the scores on intelligence scales. Yet, also because group numbers are usually small, data from both types of measurements are often collapsed, which should be avoided.[9] Second, when determining the development of a child, his or her test results are compared to norm scores obtained in the general population. However, the development of many children who undergo epilepsy surgery, particularly those who undergo hemispherectomy, is already delayed before surgery, in a not negligible proportion even from birth onwards, far before the onset of seizures. Once the epilepsy has become manifest, children may not have full access to their cognitive capacities. Some children may even drift into developmental arrest or even regress. Test scores of these children usually lie in the lower end of the score distribution, where it is known that the instruments do not measure accurately. Third, this problem of inaccurate measurement in the lower tail of the scale distribution has consequences for longitudinal assessment, as some increase in mental age or in raw score of an intelligence test may go unnoticed after converting to standard scores. Yet, such a change may be relevant from the perspective of an individual child's development and adaptation. Determining mental age at several time points unveils and quantifies such a change, as we could demonstrate (Chapters 3 and 5). Of course, this is an emergency measure but it suffices for intra-individual comparison when other procedures are absent.

Furthermore, it should be noticed that even an unchanged postsurgical IQ actually implies that the child has maintained her or his presurgically measured cognitive level. To maintain IQ levels, a child must continuously acquire new skills and knowledge over time, as IQ is measured relatively to normal peers and is corrected for increasing age. When pooling results of studies, we found only a minority of children whose standardized MDI, DQ or IQ values decreased significantly after epilepsy surgery: 10% of the hemispherectomy group and 11% of the focal resection group. Does this necessarily indicate loss of function in these children? IQ-decrease may indicate a true loss of skills, but in children it is possible that the conversion from raw to standard scores results in a lower IQ value, even in the presence

of some positive development. In adults a decrease of IQ usually indicates a loss of skills, whereas this is not always the case for children.[10] Catch-up of development, defined as an increase of five to 15 IQ/DQ points, is noticed at least two times more frequently (20–30%) after hemispherectomy or focal epilepsy surgery than a decrease of a similar amount of MDI/DQ/IQ points (Chapters 2, 3 and 5). To truly appreciate the meaning of unchanged or decreased MDI/DQ/IQ values, individual developmental trajectories should be assessed.

A problem of a different order is connected with the fact that results from different studies are difficult to compare. Not only are the study cohorts heterogeneous, but also this heterogeneity is different in the studies to be compared, because of an unequal representation of the pertinent variables such as underlying etiology, age at onset of epilepsy, presurgical duration of epilepsy, type and side of surgery, seizure freedom, antiepileptic drug(s) used, and presurgical cognitive level. Moreover, many of these variables are interrelated. Comparability of studies is further hampered by differences in defining change. For individual data, a change in intellectual ability over time is considered clinically significant if the observed difference is larger than two times the standard error of measurement (SEM), reflecting the test-retest reliability. However, the definition of change in published articles varied from 5 to 15 MDI, DQ or IQ points and this definition seemed to have been dictated by clinical lore rather than by the reliability of the instruments used.

It has been suggested that epilepsy surgery, ending a shorter or longer time of severe epilepsy, needs an unusually long time to entail manifest cognitive improvement or recovery.[6,11] This has been suggested to explain why previous studies that assessed outcome with relatively short time intervals after hemispherectomy (Chapters 2 and 3), reported no significant change in IQ. We found, however, that the group average of IQ scores obtained at least half a decade after hemispherectomy had not changed significantly since the assessment two years after the surgery. Yet, notwithstanding insignificant change of the group average, four of 21 participants had achieved a clinically relevant increase of at least 10 IQ points since the two-years' post-assessment. However, three children decreased 10 or more IQ points. The increase in some participants indicated some catch up of development, which was presumably due to AED cessation and/or educational challenges (Chapter 5). The children who in the long term were mentally retarded to such a degree that age-appropriate testing was not possible showed slight increase in mental age since the two-years' reassessment, implying some ongoing development, but the increase was far smaller than that of healthy peers. Poorer development in these children was related to bilateral or diffuse underlying pathology. Seizure recurrence was relatively frequent in this group of children (Chapter 5). Briefly, epilepsy surgery ameliorates seizure status and has no detrimental effect on overall cognitive development.

How will these findings help when counseling parents of children who need epilepsy surgery, in particular hemispherectomy? Queries of parents are, among others, whether surgery is another threat for the development of the child or may hold the potential to improve cognition. One should be realistic about the cognitive consequences of the intervention: early surgical intervention may halt deterioration and open the possibility for appropriate development relative to the presurgical situation. It is, however, unlikely that surgery results in major improvement of MDI/DQ/IQ values. Perhaps the most important reassurance the clinician can offer to parents is that true developmental decline, in the sense of permanent deterioration, is rare. On the other hand, particular domains of cognitive functioning, such as verbal and visual memory, may be affected by epilepsy surgery.[10,12] Long-term cognitive outcome of epilepsy surgery reflects the sum of many interconnected and independent variables. The treating physicians and surgical teams can influence some of these, such as the duration of epilepsy from seizure onset to surgery, and AED withdrawal policies. Indeed, a shorter duration of epilepsy has been associated with better outcome[6,13,14] and reducing more AEDs may lead to more gain in IQ (Chapter 7). Unlike in adults, one has to consider the effects of epilepsy surgery within the context of a developing nervous system and ongoing maturational changes, apart from structural and functional plasticity that play a role throughout life. The few parents, who in retrospect were hesitant or unwilling to re-opt for surgery, attributed their negative evaluation to persisting impairments in cognitive and/or social functioning of the child, and to the expected arduousness of rehabilitation (Chapter 9). Therefore, proper information about likely outcomes and early medical and psychosocial counseling of parents are of paramount importance prior to epilepsy surgery.

To further appreciate the impact of the many variables that may contribute independently or in concert to later cognitive outcome after pediatric epilepsy surgery, studies with a prospective design, of large sample sizes and homogeneous etiological subgroups, using standardized cognitive assessments before and at fixed time intervals after surgery, and analyses using multivariable statistical tests, are needed. Such studies require a multicenter collaborative approach. Cognitive functioning should also be followed over a longer period of time after surgery, into adolescence and even adulthood. This would be useful not only to better understand why there is in some children a catch up growth in the long-term, and in others on the contrary a decline. Attention should also be paid to so-called growing into deficits, the appearance of deficits that could not be researched in younger children because different periods of development require different skills. Whereas up till now cognitive functioning and its impairments have been the focus of neuropsychological research effort, other aspects of functioning after epilepsy surgery need to be addressed in more depth. The research presented in this thesis offers a starting point for studying the execution of age-relevant tasks and the involvement in life situations, as well as difficulties experienced

in doing so. These major domains of full human functioning, activities and their limitations and participation and restrictions therein[15] should be analyzed against the background of (impairments in) cognitive functioning, with the ultimate goal to discover barriers that can be remedied and to enhance life quality after epilepsy surgery.

Antiepileptic drug withdrawal and development after surgery

The primary aim of epilepsy surgery has long been considered to achieve seizure freedom. Seizure outcomes were expressed independently of AED use and there was no consensus – let alone evidence – on the optimal timing of AED withdrawal in patients who reached seizure freedom after epilepsy surgery. It was not uncommon to continue AEDs for unspecified time-periods after surgery. Over the last decade, the ultimate goal of epilepsy surgery in children was gradually broadened from strictly seizure-freedom to on the one hand 'cure', defined as freedom from both seizures and AED,[16] and on the other hand improvement of development (Chapter 2). With increasing insight into the anticipated curative nature of the intervention, i.e. removing the source of the seizures, AED policies were changed towards earlier withdrawal after surgery. Since AEDs are known to have cognitive side effects[17] and the cumulative effects of using one or more AEDs during critical stages of development may affect long-term academic achievement,[18,19] the idea became inescapable that relief of the suppressive effects of AEDs after withdrawal might have a positive influence on cognitive outcome after surgery. Improved cognitive development is now an important motive to consider AED withdrawal in seizure free patients.[20]

The results from the *TimeToStop* study have strongly suggested – although retrospectively – that timing of AED withdrawal is not related to long-term seizure outcome.[21] Early postsurgical AED withdrawal has the advantage that it sooner identifies patients who remain dependent on AEDs, and prevents unnecessary continuation of AEDs in many others. In children who underwent temporal lobe epilepsy, Skirrow et al.[11] found AED discontinuation to be an independent predictor of IQ increase after more than six years. We aimed to further our insight on the effects of AED discontinuation on cognitive outcome measures, such as psychomotor speed and IQ in children who became seizure free after curative epilepsy surgery, and after shorter postsurgical periods than studied by Skirrow et al.[11] From the studies performed in our Dutch and European cohorts of children, we learnt that psychomotor performances improved after AED withdrawal (Chapter 6). More importantly, eventual postsurgical IQ was higher and IQ increase was larger already after having started AED withdrawal than in children who were still on their presurgical drug regimen at latest neuropsychological assessment (Chapters 7 and 8). Due to the large number of patients included, the *TimeToStop* study had sufficient power to statistically test the correlations between AED withdrawal and IQ

outcome, while elaborately adjusting for possible confounders. The clinical relevance of the effect sizes (RCs=3.4 for IQ and 4.5 for delta IQ) may not seem convincing. However, dividing the cohort into three groups according to change of IQ (stability, improvement or deterioration – both defined as a change of more than 10 IQ points –, revealed a strong association between AED withdrawal and clinically relevant IQ improvement.

Although our findings indicate that AED withdrawal has cognitive benefits for the children in the sense of higher test scores than prior to surgery, we only have clinical impressions of the effect of AED withdrawal on the child's daily life, for instance his or her school achievements. This is still an unexplored field. The influence of AEDs on cognition must be distinguished from the influences of the underlying epileptogenic disease, and from the negative effects of the seizures themselves.[22] Our findings are promising and add to the growing body of knowledge with respect to AED effects on several aspects of functioning: AED withdrawal is associated with better outcome in many cognitive domains including psychomotor speed (Chapter 6), word fluency,[23] verbal memory[10] and intelligence (Chapters 7 and 8), after both resective epilepsy surgery and hemispherectomy and after relatively short postsurgical periods. We recently started a randomized clinical trial of which one aim was to study the effect of early withdrawal; we hypothesize that children who discontinue AED early (i.e., 4 months after surgery) have better scores in several domains of development – cognition, behavior and quality of life – than those who discontinue late (i.e., one year after surgery), and that such benefits persist. The assessment battery taps a broader range of neuropsychological functions (e.g., executive function and attention as these functions are thought to be particularly vulnerable to adverse effects of AED) as well as more elaborate behavioral and quality of life measures.

Environment and development after epilepsy surgery

There is compelling evidence, e.g., from twin and adoption studies, that intelligence level is influenced by both genes and environment, in other words, by both nature and nurture.[24] In the general population, children of highly educated parents have higher average IQ scores than those of parents with lower education.[25] The majority of previous studies with respect to the effects of epilepsy surgery examined associations between illness-related variables and the outcome of epilepsy surgery (Chapter 2). We examined the impact of the level of parental education, a variable that includes both environmental and genetic aspects, on intelligence after epilepsy surgery, and found that higher parental education was associated with a larger increase in IQ after surgery (Chapter 8). The lack of association between parental education and presurgical IQ is the more interesting in light of the recent finding that IQ in children with new-onset idiopathic epilepsy is not correlated with parental IQ.[26] These results suggest that the child after surgery, freed from the disruptive

effects of seizures and finally also from the adverse effects of AEDs, may again develop in accordance with what would be expected based on the education of his or her parents. Parental education conceivably has its effect on the child through intellectual stimulation in the family, as well as through the financial resources available to the family. However, education of the parent is of course correlated with IQ, and therefore with the genetic basis of the child's intellectual capacity.[27] What does this finding mean for the care of children who undergo epilepsy surgery? By creating an optimal environment, in which parenting as well as educational and therapeutic opportunities are tailored to the child's abilities, we can help fostering intellectual development.[28-30]

The international classification of functioning for children and youth (ICF-CY) understands functioning of children and youngsters in terms of not only physical factors, but explicitly recognizes facilitative and inhibitory environmental influences.[15] According to the ICF, not only living conditions and (the accessibility of) resources, but also support and relationships are either barriers to, or facilitators of, the person's functioning. In future studies on prognosis of functioning after childhood epilepsy surgery, parental education, and other environmental variables such as household income and the home environment, should be considered next to illness-related variables. This suggestion is supported by findings from our study on functioning five to eleven years after functional hemispherectomy (Chapter 5), showing that how the child is doing in everyday life depends not only on the nature and degree of his remaining impairments. Parental attitudes can also have either stimulating or inhibiting effects on the way of life of a child.

The main conclusions of this thesis are

- Multiple variables, of which many mutually dependent, determine cognitive development after epilepsy surgery. Unraveling their respective impacts requires studies in large cohorts and advanced statistical methodology.
- Measuring mental age as a marker of development is less than ideal, but allows one to at least unveil and quantify minor change in poor cognitive functioning. Such change may go unnoticed when relying on intelligence quotients.
- As far as development is concerned, contralateral MRI abnormalities are no contra-indications for hemispherectomy.
- At least half a decade after hemispherectomy, cognition, behavior and daily functioning vary from profound retardation and almost complete dependence on others to relatively unproblematic functioning.

- AED reduction after surgery improves psychomotor speed and IQ.
- Environmental variables such as parental education should be considered in the prognosis of cognitive change after childhood epilepsy surgery.
- With the benefit of hindsight, even epilepsy surgery that does not result in seizure freedom is felt to be beneficial. Most patients and their parents would opt again for epilepsy surgery.

References

1. Lamberink HJ, Boshuisen K, van Rijen PC, et al. Changing profiles of pediatric epilepsy surgery candidates over time: a nationwide single-center experience from 1990 to 2011. Epilepsia 2015;56 (5):717-25.

2. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol 2008;7(6):525-37.

3. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol 2014;13(11):1114-26.

4. Huttenlocher PR, Hapke RJ. A follow-up study of intractable seizures in childhood. Ann Neurol 1990;28:699-705.

5. Besag FM. Childhood epilepsy in relation to mental handicap and behavioural disorders. J Child Psychol Psychiatry 2002;43:103-31.

6. Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. Epilepsia 2005;46:561-7.

7. Cormack F, Cross JH, Isaacs E, et al. The development of intellectual abilities in pediatric temporal lobe epilepsy. Epilepsia 2007;48:201-4.

8. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005-2009. Epilepsia 2010;51:676-85.

9. Anastasi A. Psychological testing. New York: Macmillan Publishing Company; 1988.

10. Meekes J, Braams O, Braun KPJ, et al. Verbal memory after epilepsy surgery in childhood. Epilepsy Res 2013;107:146-55.

11. Skirrow C, Cross JH, Cormack F, Harkness W, Vargha-Khadem F, Baldeweg T. Long-term intellectual outcome after temporal lobe surgery in childhood. Neurology 2011;76:1330-7.

12. Meekes J, Braams O, Braun KPJ, et al. Visual memory after epilepsy in children: a standardized regression-based analysis of group and individual outcomes. Epilepsy Behav 2014;36:57-67.

13. Jonas R, Nguyen S, Hu B, et al. Cerebral hemispherectomy: hospital course, seizure, developmental, language, and motor outcomes. Neurology 2004;62(10):1712-21.

14. Basheer SN, Connolly MB, Lautzenhiser A, et al. Hemispheric surgery in children with refractory epilepsy: seizure outcome, complications, and adaptive function. Epilepsia 2007;48:133-40.

15. World Health Organisation (WHO). Nederlandse vertaling van de International classification of functioning, disability and health, version Children & Youth. Houten, Bohn Stafleu van Loghum; 2008.

16. Schmidt D, Baumgartner C, Loscher W. Seizure recurrence after planned discontinuation of antiepileptic drugs in seizure-free patients after epilepsy surgery: a review of current clinical experience. Epilepsia 2004;45(2):179-86.

17 Loring DW, Meador KJ. Cognitive side effects of antiepileptic drugs in children. Neurology 2004;62(6):872-7.

18. Park SP, Kwon SH. Cognitive effects of antiepileptic drugs. J. Clin Neurol 2008;4:99-106.

19. Mula M, Trimble MR. Antiepileptic drug-induced cognitive adverse effects. Potential mechanisms and contributing factors. CNS Drugs 2009;23:121-37.

20. Braun KP, Schmidt D. Stopping antiepileptic drugs in seizure-free patients. Current Opinion in Neurology 2014;27(2):219-26.

21. Boshuisen K, Arzimanoglou A, Cross JH, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. Lancet Neurol 2012;11(9):784-91.

22. Raspall-Chaure M, Neville BG, Scott RC. The medical management of the epilepsies in children: conceptual and practical considerations. Lancet Neurol 2008;7(1):57-69.

23. Meekes J, Chanturidze, Braams O, et al. Lexicon before and after epilepsy surgery in adolescents. In memory after epilepsy surgery in children. PhD thesis, Utrecht, the Netherlands. 2015; Chapter 4:69-82.

24. McDevitt TM, Ormrod JE. Effects of heredity and environment on Intelligence. In: McDevitt TM, Ormrod JE. Child development and education. Boston, Pearson Allyn Bacon Prentice Hall; 2007:291-296.

25. Hanscombe KB, Trzaskowski M, Haworth CMA, et al. Socioeconomic status (SES) and children's intelligence (IQ): in a UK-representative sample SES moderates the environmental, not genetic, effect on IQ. PLoS ONE 2012;7:e30320.

26. Walker N, Jackson D, Dabbs K, et al. Is lower IQ in children with epilepsy due to lower parental IQ? A controlled comparison study. Dev Med Child Neurol 2012;55:278-82.

27. Rowe DC, Jacobson KC, Van den Oord EJCG. Genetic and environmental influences on vocabulary IQ: parental education level as moderator. Child Dev 1999;70:1151-62.

28. Spittle AJ, Orton J, Doyle LW, Boyd R. Early developmental intervention programs post hospital discharge to prevent motor and cognitive impairments in preterm infants. Cochrane Database Syst Rev 2007;18(2):CD005495.

29. Falch T, Massich SS. The effect of education on cognitive ability. Econ Ing 2011;49(3):838-56.

30. Brinch CN, Galloway TA. Schooling in adolescents raises IQ scores. Proc Natl Acad Sci U S A 2012;109(2):425-30.

Nederlandse samenvatting

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Epilepsie is de meest voorkomende chronische hersenaandoening bij kinderen. Hersencellen geven voortdurend boodschappen aan elkaar door. Dat gebeurt via elektrische stroompjes en chemische stoffen. Soms raakt dit systeem verstoord. Dan treedt als het ware kortsluiting op. Een epilepsieaanval is het gevolg van zulke overmatige elektrische activiteit in de hersenen. Wanneer iemand bij herhaling last heeft van aanvallen, kun je zeggen dat hij of zij epilepsie heeft. De meeste kinderen met epilepsie kunnen goed behandeld worden met medicijnen, anti-epileptica, die de aanvallen onderdrukken. Als twee of meer anti-epileptica niet tot aanvalsvrijheid leiden, spreken we van medicamenteus moeilijk behandelbare – 'farmacoresistente' of 'refractaire' – epilepsie. Ongeveer 30% van de kinderen met epilepsie houdt aanvallen ondanks gebruik van anti-epileptica.

Voor kinderen met een plaatselijke en structurele oorzaak van de epilepsie, is het mogelijk de epilepsie operatief te behandelen. Bij een dergelijke hersenoperatie wordt de oorzaak van de aanvallen, de epilepsiehaard, verwijderd. Epilepsiechirurgie heeft alleen zin wanneer de epilepsiehaard niet in hersengebieden ligt die belangrijk zijn voor bijvoorbeeld het bewegen, het geheugen of de taal. Als de epilepsie in een groter gebied ontstaat, als bijvoorbeeld een hele hersenhelft ziek is en aanvallen veroorzaakt, kan de chirurg deze hersenhelft volledig loskoppelen van de rest van de hersenen. Dat heet functionele hemisferectomie of hemisferotomie. Alle Nederlandse kinderen die voor epilepsiechirurgie in aanmerking komen worden geopereerd in het Universitair Medisch Centrum Utrecht (UMCU). Na epilepsiechirurgie hebben de kinderen een grote kans op aanvalsvrijheid.

Veel kinderen met refractaire epilepsie hebben ontwikkelingsproblemen. Bij zuigelingen en peuters met frequente aanvallen kan de epilepsie zelfs een catastrofaal beloop nemen. Deze kinderen hebben een zogeheten epileptische encefalopathie. De stilstand of zelfs achteruitgang in hun ontwikkeling wordt – zo denkt men – tenminste gedeeltelijk veroorzaakt door de voortdurende epileptische aanvallen. In tegenstelling tot vroeger is ernstige retardatie (ontwikkelingsachterstand) tegenwoordig geen reden om van epilepsiechirurgie af te zien. Hoe bepaal je nu de uitkomst van epilepsiechirurgie? Uiteraard is aanvalsvrijheid een belangrijke maat om de uitkomst van epilepsiechirurgie bij kinderen te bepalen. Maar de cognitieve ontwikkeling is een even belangrijke uitkomstmaat. Is epilepsiechirurgie een nieuwe bedreiging, of geeft ze het kind nieuwe mogelijkheden voor ontwikkeling? Op onderzoek gebaseerde kennis van het postoperatieve (na de operatie) ontwikkelingsverloop is onontbeerlijk voor beantwoording van deze vraag. Jaren van werk op het terrein van de kinderepilepsie en de chirurgische behandeling daarvan heeft de kennis over de cognitieve ontwikkeling na epilepsiechirurgie verbreed. Er blijven echter vragen bestaan waarop antwoorden gevonden moeten worden.

Dit proefschrift beschrijft de resultaten van studies naar verschillende aspecten van de cognitieve ontwikkeling na epilepsiechirurgie op de kinderleeftijd. De meeste onderzoeken waren ingebed in de klinische zorg voor kinderen die epilepsiechirurgie ondergingen. De studie naar de invloed van het afbouwen van anti-epileptica op het intelligentiequotiënt na operatie is uitgevoerd op basis van gegevens van een groot Europees, multicentrisch cohort van pediatrische epilepsiechirurgie-patiënten (*TimeToStop*). De andere in dit proefschrift beschreven studies rapporteren de uitkomsten van gestandaardiseerd longitudinaal onderzoek dat met vaste tijdsintervallen is uitgevoerd op een cohort van Nederlandse kinderen die tussen 1992 en 2009 epilesiechirurgie hebben ondergaan in het UMC Utrecht. Behalve kort voor de ingreep, onderzochten we de kinderen 6, 12 en 24 maanden erna nog eens. Tenslotte zijn in dit proefschrift twee studies opgenomen die buiten dit stramien vallen (zie Hoofdstukken 5 en 9).

Hoofdstuk 2 geeft een overzicht van de literatuur betreffende cognitief functioneren en verandering daarin na epilepsiechirurgie bij kinderen. Meestal wordt het cognitieve functioneren uitgedrukt in een ontwikkelingsindex (OI) of een intelligentiequotiënt (IQ). Verbetering (een toename van 5 tot 15 OI/IQ punten, of een verschuiving van bijvoorbeeld benedengemiddeld naar laaggemiddeld niveau) na epilepsiechirurgie in de kindertijd, komt zoals blijkt uit onderzoeken die dergelijke maten gebruiken weinig voor. Een groot aantal kinderen (61% van de hemisferectomie-patiëntjes en 70% van de kinderen met een focale resectie) functioneert na operatie op hetzelfde cognitieve niveau als voor de ingreep. OI/ IQ na de operatie wordt beïnvloed door postoperatieve aanvalsvrijheid en preoperatief OI/ IQ. Verandering in OI/IQ na de operatie wordt beïnvloed door zeven variabelen: geslacht, leeftijd bij operatie, preoperatieve OI or IQ, oorzaak van de epilepsie, postoperatieve aanvalsvrijheid, stoppen van anti-epileptica, en follow-up interval.

Ouders nemen na de hemisferectomie een positieve verandering in functioneren van hun kinderen waar. Maar deze verbetering is moeilijk te meten. Ze wordt in elk geval niet weerspiegeld in de algemeen gebruikte ontwikkelingindices. **Hoofdstuk 3** handelt hierover. Wij deden herhalingsonderzoek bij 29 kinderen die een hemisferectomie hadden ondergaan. Zeventien van hen (leeftijdsbereik bij operatie 0.2–2.6, mediaan 1.1 jaar) werden onderzocht met ontwikkelingsschalen. De meerderheid functioneerde zowel voor als na hemisferectomie op een zeer laag niveau: OI/ IQ <55. Een minder algemeen gebruikte – en minder ideale – maat, mentale leeftijd, liet bij deze laag functionerende kinderen toch verbetering van het functioneren na de operatie zien. De vooruitgang in mentale ontwikkeling was echter duidelijk langzamer dan die van gezonde leeftijdsgenoten. De twaalf oudere kinderen (leeftijdsbereik bij hemisferectomie 3.7–14.3, mediaan 8.3 jaar) die waren onderzocht met intelligentieschalen toonden als groep weinig verandering in IQ (slechts 4 punten), wat overigens wel betekent dat zij na de operatie hun cognitieve niveau

van functioneren wisten te behouden. Bij meer individuele bestudering en bij hantering van een criterium voor significante verandering (tien of meer IQ-punten) bleken van voor tot twee jaar na de hemisferectomie vier kinderen significant vooruitgegaan en twee kinderen significant achteruitgegaan in cognitief functioneren. Deze individuele veranderingen blijven onopgemerkt als alleen op groepsniveau gekeken wordt.

In **Hoofdstuk 4** onderzochten wij of al voor de functionele hemisferectomie bestaande EEG- of MRI-afwijkingen in de vermeende 'gezonde' hemisfeer (hersenhelft) samenhangen met postoperatieve aanvalsvrijheid, OI/IQ en eventuele verandering daarin. Na hemisferectomie wordt het functioneren gemedieerd door de overgebleven hemisfeer. Het ligt voor de hand te veronderstellen dat zowel de kans op aanvalsvrijheid als het cognitieve niveau van het kind na de hemisferectomie afhangt van de functionele en structurele integriteit van de vermeende 'gezonde' hemisfeer. Van 32 van de 43 kinderen (leeftijdsbereik bij operatie 0.2–14.3, gemiddeld 4.1 jaar) die een hemisferectomie hadden ondergaan, waren zowel pre- als postoperatieve OI/IQ scores beschikbaar. MRI-afwijkingen in de overgebleven hersenhelft bleken samen te hangen met aanvalsrecidief (terugkeer van aanvallen). Het percentage kinderen met een ernstige verstandelijke beperking (OI/IQ <55) was groter in de groep kinderen met MRI-afwijkingen in de overgebleven hersenhelft dan in de groep kinderen zonder dergelijke afwijkingen (90% versus 42%). De OI/IQ scores van kinderen met de MRI-afwijkingen verbeterden na de operatie niet. Preoperatieve EEG-afwijkingen in de overgebleven hersenhelft beïnvloedden de aanvalsvrijheid en de cognitieve uitkomst na hemisferectomie niet.

Ouders van kinderen die door de Landelijke Werkgroep Epilepsiechirurgie geschikt bevonden zijn voor hemisferectomie vragen in het traject voorafgaande aan operatie vaak naar het ontwikkelingsperspectief van hun kind op de lange termijn. Wat kunnen ze verwachten ten aanzien van cognitie en opleiding? Kan hun kind een onafhankelijk leven leiden en hoe is hun kwaliteit van leven? In **Hoofdstuk 5** wordt beschreven hoe patiënten vijf tot elf jaar na de in de kindertijd verrichte hemisferectomie functioneren. Eenendertig kinderen en hun ouders namen deel aan een uitgebreid herhalingsonderzoek, waarbij zowel cognitie, gedrag, dagelijks functioneren en kwaliteit van leven in kaart gebracht werden. Tweeëntwintig kinderen in de schoolleeftijd of adolescentie werden onderzocht met leeftijdsadequate intelligentietests. De IQ-scores varieerden van 45 tot 82 (gemiddeld 61). De 22 deelnemers behaalden in andere functiedomeinen weliswaar duidelijk beneden-gemiddelde normscores, maar zij waren in staat om te leren en te onthouden, de aandacht vast te houden, irrelevante prikkels te onderdrukken, te lezen en te schrijven. Negen kinderen (gemiddelde leeftijd bij herhalingsonderzoek 9.7 jaar) waren zo ernstig verstandelijk beperkt dat zij niet onderzocht konden worden met leeftijdsadequaat testmateriaal. Deze kinderen waren voor hun dagelijkse functioneren vrijwel volledig afhankelijk van anderen.

In deze groep kwamen contralaterale MRI-afwijkingen, terugkeer van aanvallen, evenals gedragsproblemen procentueel meer voor dan in eerstgenoemde groep. Ouders van kinderen uit beide groepen beoordeelden de aan gezondheid gerelateerde kwaliteit van leven van hun kinderen verrassend positief (gemiddelde VAS-score 72.5), met voor slechts een enkeling een lage score (van 40 of 45); twee meisjes waarvan de complexe problematiek ook na de hemisferectomie continue medische zorg nodig had. Alle ouders rapporteerden problemen op de gebieden van zelfverzorging, dagelijkse activiteiten en mobiliteit van hun kinderen.

Wanneer het kind na de epilepsiechirurgie aanvalsvrij is, moet overwogen worden om de anti-epileptische medicatie geleidelijk te staken. Onnodig gebruik van anti-epileptica moet worden voorkómen vanwege hun schadelijke cognitieve nevenverschijnselen. In **Hoofdstuk 6** onderzochten wij of uitsluipen van anti-epileptica gevolgen had voor de reactietijd (snelheid van reageren). Van 57 kinderen die na hemisferectomie of resectie aanvalsvrij waren (gemiddelde leeftijd bij operatie 13 jaar; 32 meisjes) waren gegevens beschikbaar. Medicatie-mindering werd gedefinieerd als volledig staken van één anti-epilepticum, beoordeeld op het laatste onderzoeksmoment. De kinderen werden verdeeld in twee groepen. De medicatie-minderingsgroep bestond uit 29 en de niet-minderingsgroep uit 28 kinderen. De kinderen voerden vier verschillende reactietijdtaken uit. We vergeleken de reactietijden die de kinderen 12 en 24 maanden na operatie scoorden met die van zes maanden na de operatie. Vierentwintig maanden na operatie reageerden de kinderen in de medicatie-minderingsgroep in drie van de vier tests significant sneller dan de kinderen in de niet-minderingsgroep. Twaalf maanden na operatie bestond een dergelijk verschil tussen de groepen, zij het statistisch niet significant.

In **Hoofdstuk 7** bestudeerden wij, bij 301 kinderen uit de *TimeToStop* studie die na de operatie aanvalsvrij waren geworden, het effect van anti-epileptica-mindering op het postoperatieve IQ en op eventuele verandering in postoperatief IQ ten opzicht van preoperatief IQ. Zowel medicatiemindering (mindering van tenminste één anti-epilepticum), het aantal anti-epileptica dat werd verminderd als het staken van alle anti-epileptica, hingen samen met een hoger postoperatief IQ en met meer postoperatieve IQ-verbetering. Anti-epileptica-mindering bleek ook samen te hangen met toename van IQ wanneer verbetering niet werd gedefinieerd als elke toename in IQ maar – strenger – als toename van 10 of meer IQ-punten.

Het is algemeen bekend dat de omgeving een rol speelt in de ontwikkeling van zich normaal ontwikkelende kinderen. Wij vroegen ons af of de omgeving van een kind ook een rol speelt voor de ontwikkeling van het kind met medicamenteus niet behandelbare epilepsie en hoe dat zit na epilepsiechirurgie (**Hoofdstuk 8**). In een groep van 118 kinderen

(gemiddelde leeftijd bij operatie 9.7 jaar; 58 meisjes) vonden wij een verband tussen het opleidingsniveau van de ouders en verandering van IQ (het verschil tussen het laatst na operatie vastgestelde IQ en het preoperatief vastgestelde IQ). Gemiddeld toonden kinderen van hoger opgeleide ouders een grotere IQ-winst dan kinderen van lager opgeleide ouders. Ook mindering van anti-epileptica (aantal preoperatief minus aantal postoperatief) en hogere leeftijd bij operatie hingen samen met een grotere gemiddelde vooruitgang in IQ. Belangwekkend is dat het preoperatieve IQ bepaald werd door epilepsievariabelen; deze beïnvloedden zo het postoperatieve resultaat ook wel, maar ze hadden geen significante invloed op de winst na operatie.

In **Hoofdstuk 9** werd geëvalueerd hoe patiënten en hun ouders tenminste een jaar na operatie terugkijken op de beslissing tot epilepsiechirurgie. Honderdelf respondenten (55 ouders, 53 adolescenten en hun ouders, 3 adolescenten) vulden een vragenlijst in die inventariseerde of zij, met de kennis van nu, wel of niet opnieuw akkoord zouden gaan met epilepsiechirurgie en wat hun motieven voor hun huidige keuze waren. De meerderheid van zowel de adolescenten als hun ouders zou opnieuw besluiten tot operatie. Voor de aanvalsvrije respondenten was aanvalsvrijheid het meest genoemde motief. Belangrijke motieven voor niet-aanvalsvrije respondenten waren vermindering in aantal of ernst van de aanvallen en/of vermindering van de medicatie. Voor ouders van niet-aanvalsvrij geworden kinderen was een beter ontwikkelingsperspectief na de operatie ook een belangrijk motief. Twijfel over en weigering van opnieuw opereren kwamen weinig voor en waren gerelateerd aan het besef dat men de voordelen onvoldoende kon afwegen tegen de nadelen. Het feit dat de aanvallen waren teruggekomen was geen reden om de operatie als een mislukking te beschouwen.

In de afgelopen 30 jaar is epilepsiechirurgie een belangrijke behandelingsmogelijkheid geworden. Het succespercentage is opvallend hoog; twee jaar na de ingreep is ongeveer 74% van de kinderen aanvalsvrij. Het doel van epilepsiechirurgie is in de loop van de jaren verbreed. Aanvankelijk was bewerkstelligen van aanvalsvrijheid het doel. Nu beoogt men veeleer genezing, gedefinieerd als aanvalsvrijheid, en daarmee volledig stoppen van anti-epilepticagebruik, maar ook verbeterde kans op ontwikkeling. Hoe kunnen onze bevindingen helpen bij de counseling van de ouders en/of de kinderen die epilepsiechirurgie te wachten staat? We weten nu dat epilepsiechirurgie de preoperatieve stilstand of achteruitgang in ontwikkeling van sommige patiëntjes kan stoppen en dat daarmee een mogelijkheid ontstaat tot herstart van de ontwikkeling na operatie. We weten echter ook dat de operatie naar alle waarschijnlijkheid niet zal resulteren in een grote toename van OI/IQ scores. Misschien is de belangrijkste geruststelling die ouders geboden kan worden dat ontwikkelingsachteruitgang, in de zin van definitieve deterioratie, na de operatie zeer zeldzaam is. Meerdere variabelen, die veelal met elkaar samenhangen, bepalen de

cognitieve ontwikkeling na epilepsiechirurgie. Sommige van deze variabelen, zoals de duur van de epilepsie voor de operatie, en anti-epileptica-mindering, kunnen we beïnvloeden. De verwachte cognitieve verbetering is een belangrijk motief om anti-epileptica te staken bij aanvalsvrije kinderen. De 'omgeving' kan een stimulerende of beperkende werking hebben op het functioneren van een kind. Terugkijkend, wordt zelfs epilepsiechirurgie die niet leidt tot aanvalsvrijheid (door vermindering in aantal of ernst van de aanvallen en/of vermindering van anti-epileptica en een beter ontwikkelingsperspectief) als positief beoordeeld.

Prospectieve studies waaraan grote cohorten deelnemen en waarin geavanceerde statistische methodes kunnen worden toegepast zijn nodig om verder zicht te krijgen op de bijdrage van de vele, veelal onderling samenhangende, variabelen die een rol spelen in de ontwikkeling voor en na epilepsiechirurgie in de kinderleeftijd. Een gerandomiseerde klinische trial is gestart om het effect van anti-epileptica-afbouw op cognitie verder te onderzoeken. Naast IQ zullen in deze trial ook executief functioneren, aandacht, gedrag en kwaliteit van leven worden geïnventariseerd. In toekomstige studies moeten naast ziektevariabelen ook omgevingsvariabelen, bijvoorbeeld opleidingsniveau van ouders, maar ook beroepsniveau en woonomgeving meegewogen worden in de prognose van functioneren na epilepsiechirurgie in de kinderleeftijd. Beperkingen in activiteiten en problemen in participatie moeten worden afgezet tegen de fysieke en cognitieve stoornissen om barrières te ontdekken die geremedieerd kunnen worden en de kwaliteit van leven te kunnen verbeteren. Follow-up tot in adolescentie en volwassenheid is nodig om meer zicht te krijgen op bijvoorbeeld moeilijkheden die iemand heeft met het uitvoeren van dagelijkse activiteiten of de problemen die iemand heeft met deelname aan de maatschappij.

List of publications

In this thesis

Boshuisen K, van Schooneveld MM, Uiterwaal CS, Cross JH, Harrison S, Polster T, Daehn M, Djimjadi S, Yalnizoglu D, Turanli PG, Sassen R, Hoppe C, Kuczaty S, Barba C, Kahane P, Schubert-Bast S, Reuner G, Bast T, Strobl K, Mayer H, de Saint-Martin A, Seegmuller C, Laurent A, Arzimanoglou A, Braun KP; TimeToStopcognitive outcome study group. Intelligence Quotient improves after antiepileptic drug withdrawal following pediatric epilepsy surgery. Ann Neurol 2015 Jul;78(1):104-14.

Meekes J*, van Schooneveld MM*, Braams OB, Jennekens-Schinkel A, van Rijen PC, Hendrinks MP, Braun KP, van Nieuwenhuizen O. Parental Education predicts change in intelligence quotient after childhood epilepsy surgery. Epilepsia 2015 Apr;56(4):599-607.

van Schooneveld MM*, van Erp N*, Boshuisen K, Meekes J, Braun KP. Withdrawal of antiepileptic drugs improves psychomotor speed after childhood epilepsy surgery. Epilepsy Res 2013 Nov;107(1-2):200-3.

Engelhart MC, van Schooneveld MM, Jennkens-Schinkel A, van Nieuwenhuizen O. 'With the benefit of hindsight': would you opt again for epilepsy surgery performed in childhood? Eur J Pediatr Neurol 2013 Sept;17(5):462-70.

van Schooneveld MM, Braun KP. Cognitive outcome after epilepsy surgery in children. Brain Dev 2013 Sept;35(8):721-9.

van Schooneveld MM, Jennkens-Schinkel A, van Rijen PC, Braun KP, van Nieuwenhuizen O. Hemispherectomy: a basis for mental development in children with epilepsy. Epileptic Disord 2011 Mar;13(1):47-55.

Boshuisen K, van Schooneveld MM, Leijten FS, de Kort GA, van Rijen PC, Gosselaar PH, van Nieuwenhuizen O, Braun KP. Contralateral MRI abnormalities affect seizure and cognitive outcome after hemispherectomy. Neurology 2010 Nov 2;75(18):1623-30.

Other publications

Boshuisen K*, Lamberink HJ*, van Schooneveld MM, Cros JH, Arzimanoglou A, van der Tweel I, Geleijns K, Uiterwaal CSPM, Braun KPJ. Cognitive consequences of early versus late antiepileptic drug withdrawal after pediatric epilepsy surgery: a study protocol for the TimeToStop (TTS) Trial, a pragmatic randomized clinical trial. Trials 2015;16:482. DOI 10.1186/s13063-015-0989-2.

Koenraads Y, van der Linden DC, van Schooneveld MM, Imhof SM, Gosselaar PH, Porro GL, Braun KP. Visual function and compensatory mechanisms for hemianopia after hemispherectomy in children. Epilepsia 2014 Jun;55(6):909-17.

van Buuren LM*, van der Aa NE*, Dekker HC, Vermeulen RJ, van Nieuwenhuizen O, van Schooneveld MM, de Vries LS. Cognitive outcome in childhood after unilateral perinatal brain injury. Dev Med Child Neurol 2013 Oct;55(10):934-40.

de Koning T, Versnel H, Jennkens-Schinkel A, van Schooneveld MM, Dejonckere PH, van Rijen PC, van Nieuwenhuizen O; Ditch Collaborative Epilepsy Surgery Programme (DuCESP). Epilepsia 2009 Nov;50(11):2408-19.

Ritchi L, Jennekens-schinkel A, van Schooneveld MM, Koomen I, Geenen R. Behavior is not realy at risk after surviving meningitis in childhood. Acta Paediatr 2008 Apr;97(4):438-41.

van Schooneveld M. Cognitieve ontwikkeling twee jaar na hemisferectomie. Epilepsie Periodiek voor professionals 2007 Jun;5(2):12-13.

Meekes J, Jennkens-Schinkel A, van Schooneveld MM. Recovery after childhood traumatic brain injury: vulnerability and plasticity. Pediatrics 2006 Jun;117(6):2330.

Hanlo PW, Gooskens RJ, van Schooneveld MM, Tulleken CA, van der Knaap MS, Faber JA, Willemse J. The effect of intracranial pressure on myelination and the relationship with neurodevelopment in infantile hydrocephalus. Dev Med Child Neurol 1997 May;39(5):286-91.

van der Knaap MS, Valk J, Bakker CJ, van Schooneveld MM, Faber JA, Willems J, Gooskens RH. Meylination as an expression of the functional maturity of the brain. Dev Med Child Neurol 1991 Oct;33(10):849-57.

* These authors contributed equally to the manuscript.

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Dankwoord

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Een aantal van jullie heeft inmiddels de promotie achter de rug. Met een aantal van jullie zal ik de samenwerking voortzetten. Veel succes met het afronden van jullie promotietrajecten.

Leden van de Landelijke Werkgroep Epilepsiechirurgie (LWEC). Geweldig om te zien hoe iedereen zich gezamenlijk inspant om vast te stellen of er een operatie mogelijk is. Ik hoop nog lange tijd van de werkgroep deel te kunnen uitmaken.

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Curriculum Vitae

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Monique van Schooneveld werd op 26 juni 1960 geboren in Rotterdam. Ze groeide op in St. Odiliënberg, een dorp in de buurt van Roermond, waar ze haar diploma Atheneum B behaalde aan het Bisschoppelijk College Schöndeln. Na uitloting voor de studie geneeskunde, begon zij met de opleiding tot operatieassistent in het Westeinde Ziekenhuis te Den haag. Vanaf 1980 studeerde ze Pedagogische Wetenschappen aan de Universiteit Utrecht, afstudeerrichting Klinische Pedagogiek. Zij startte in 1986 bij de Sector Neuropsychologie, van het Academisch Ziekenhuis Utrecht (AZU). Bij overgang van de afdeling kinderneurologie van het AZU naar het Wilhelmina Kinderziekenhuis Utrecht (WKZ) in 1989, kwam zij in dienst van het WKZ, waar de Sector Neuropsychologie deel uitmaakt van de afdeling Medische Psychologie en Maatschappelijk werk. Naast haar werkzaamheden in het WKZ, was zij tevens van 1986 tot 1989 project-onderzoeker 'restverschijnselen bij kinderen met een hersenletsel na ongeval', opgezet door BIO revalidatiecentrum. Van 1987 tot 1991 was zij ook als parttime docent verbonden aan de vakgroep Pedagogiek van Hogeschool Katholieke Leergangen Sittard, waar zij onderwijs verzorgde aan MO-A orthopedagogiek in de vakken neuropsychologie, begaafdheidsdiagnostiek, diagnostiek van ontwikkelingsstoornissen en persoonlijkheidsdiagnostiek. Van 1992 tot 2002 is zij ook werkzaam geweest bij Adviesbureau Comenius in De Bilt, adviesbureau voor kinderen met leer- en gedragsproblemen. In 2003 behaalde ze haar postacademische registratie als gezondheidszorgpsycholoog. De vierjarige opleiding tot specialist klinisch neuropsycholoog werd in 2014 succesvol afgerond. Tijdens haar werk als gezondheidszorgpsycholoog en later als klinisch neuropsycholoog in het WKZ, verrichtte ze onderzoek naar de ontwikkeling van kinderen na epilepsiechirurgie. Haar werkzaamheden als klinisch neuropsycholoog bij de Sector Neuropsychologie van het WKZ – neuropsychologische diagnostiek en wetenschappelijk onderzoek bij kinderen met (vermoeden van) cerebrale aandoeningen – zal zij na haar promotie voortzetten. Zij is getrouwd met Ron, ze wonen in Maarssen en ze hebben twee studerende zonen Martijn en Reinier.