Original article

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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.

Key words: children, epilepsy, hemispherectomy, mental development, intelligence

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In terms of seizure reduction, the outcome of hemispherectomy is favourable for children regardless of their age (for a review, see Spencer and Huh, 2008).
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 (Samargia and Kimberly, 2009). However, subtle change may be concealed for a number of reasons. The age range of children within studies 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 (Anastasi, 1988). 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 assumed values of MDI or IQ, *e.g.* 23 and 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 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 1A* for children assessed with developmental scales and in *table 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 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.

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 (Engel *et al.*, 1993). 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) (van der Meulen and Smrkovský, 1983; van der Meulen *et al.*, 2003). 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) (Vander

Table 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)	Hemisphe-rectomy (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; Isch: ischaemia; M: male; PC: porencephalic cyst; Pt: patient; Prog: progressive; RAS: Rasmussen encephalitis; SWS: Sturge-Weber syndrome.

Steene and Bos, 1997), Wechsler Intelligence Scales for Children-Revised (WISC-RN) (van Haassen *et al*., 1986), McCarthy Developmental Scales (MOS 2½-8½) (van der Meulen and Smrkovský, 1986) and the Kaufman Assessment Battery for Children (GOS 2½-4½) (Neutel *et al*., 1996). 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 (SPSS Inc, 2007). Spearman's rank correlation coefficient was used to analyse the association between the time of assessment and MA, MDD and full-scale intelligence quotient (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 (1988).

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 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 1*). MA and time of

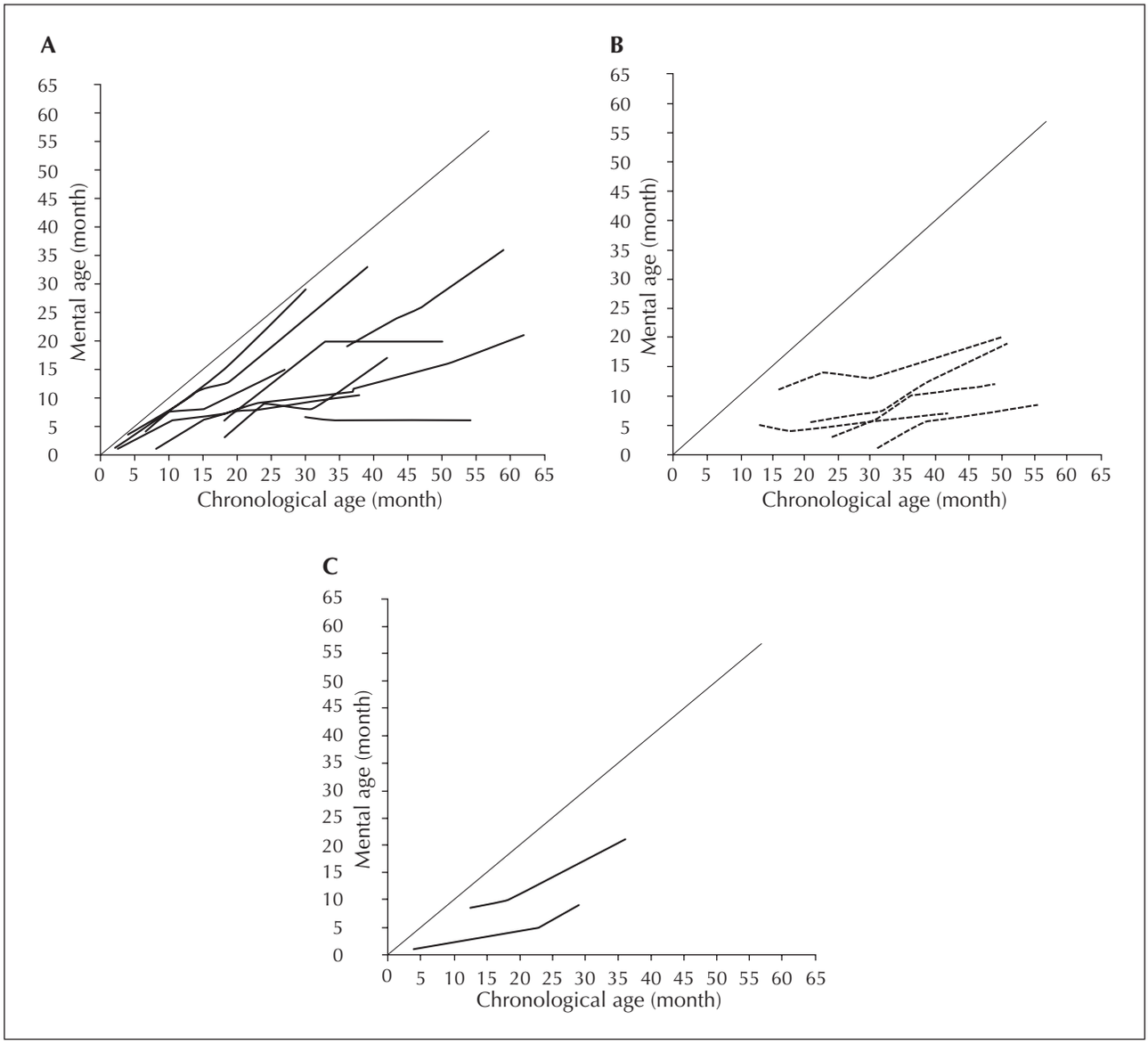

Figure 1. Mental development expressed as mental age before and 24 months after hemispherectomy. The initial point of each graph corresponds to the initial assessment prior to hemispherectomy. **A**) Infants and preschoolers with developmental pathology (n=10). **B**) Infants and preschoolers with acquired pathology (n=5). **C**) Infants and preschoolers with progressive pathology (n=2).

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 correlations 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.

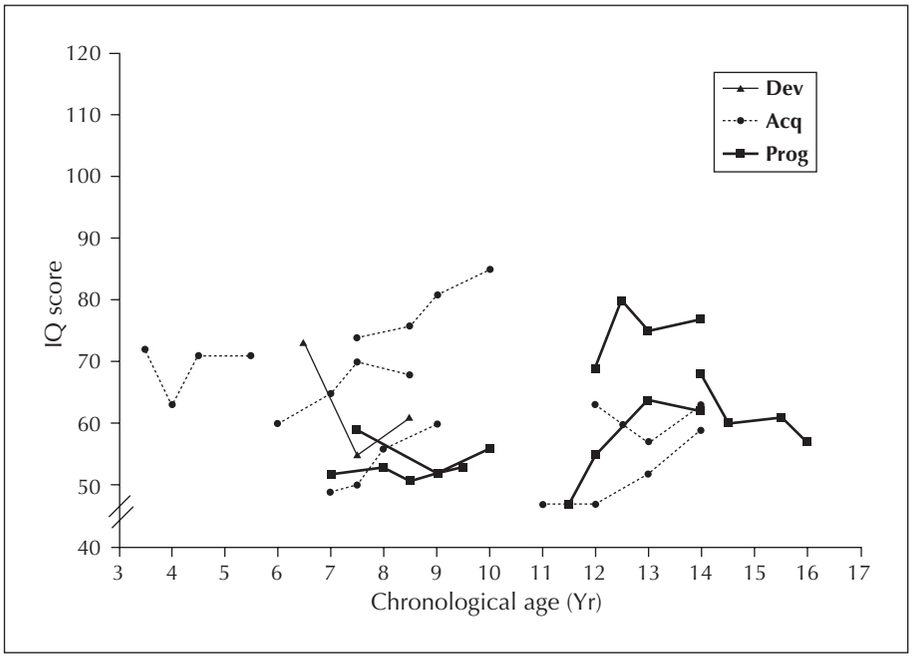

Figure 2. Intelligence expressed as Full Scale Intelligent Quotient (FSIQ) before and 24 months after hemispherectomy. The initial point of each graph corresponds to the initial assessment prior to hemispherectomy. Patients with developmental (Dev), acquired (Acq) and progressive (Prog) pathology are presented separately, as indicated.

Children assessed with intelligence scales
(table 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.

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 (mean FSIQ=64.3; sd=9.3) were compared *(figure 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.

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, 2009). 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 (Devlin *et al*., 2003; Pulsifer *et al*., 2004; Lettori *et al*., 2008) 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 (Vasconcellos *et al*., 2001; Cormack *et al*., 2007). 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 (Basheer *et al*., 2007; Jonas *et al*., 2004) 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 (van Empelen *et al*., 2004).

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 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 (2005).

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 (Pulsifer *et al*., 2004). 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 (1981) 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 (Duval *et al*., 2008).

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 (Devlin *et al*., 2003; Lettori *et al*., 2008; Pulsifer *et al*., 2004; Vining *et al*., 1997). 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 (Jaspers *et al*., 2010), 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 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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Disclosure.

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