Original article

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Correlates of intellectual development before and after hemispherotomy: an analysis of 75 children and adolescents

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ABSTRACT – *Aims*. This study describes the intellectual development of 75 children and adolescents who underwent hemispherotomy. Furthermore, we aimed to reveal predicting factors on pre- and postsurgical development with a focus on the role of aetiology.
Methods. We analysed presurgical and six-month postsurgical developmental and intellectual data of 75 patients (age range: 0.87-19.78 years) and divided them into two groups: a *not severely impaired group* in which outcome of intellectual functioning was reported based on FSIQ score, and a *severely impaired group* (not testable by IQ tests) in which intellectual developmental outcome was described based on developmental quotients instead.
Results. In the *not severely impaired group* (*n* = 31), the preoperative level of intellectual functioning was a strong predictor of postoperative intellectual outcome; for 22/31 (71%) patients, postoperative FSIQ and its subscales were similar to preoperative levels. Improvements were observed for FSIQ in five patients, only for Verbal IQ in one patient and only for Performance IQ in one further patient; significant losses occurred in two patients, only for Performance IQ in both. In the *severely impaired group,* 30/40 (75%) patients showed further development after surgery, nine (23%) patients had the same results as before surgery, and one (2%) patient showed regression. Longer duration of presurgical epilepsy was related to a marginally lower presurgical developmental level, and good seizure outcome was a predictor

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Some of the results were presented on the Annual Meeting of the *Gesellschaft für Epileptologie* in Fürth, Germany in June 2018 (German abstract published in: *Zeitschrift für Epileptologie* 2018; 31, Supp1: 1-44), and have recently been presented during the *Kongress für Kinder- und Jugendmedizin* in Munich, Germany in September 2019 (poster), with publication of the abstract in *Neuropediatrics* (in English: *Neuropediatrics* 2019; 50, S02) and in *Monatsschrift Kinderheilkunde* (in German*: Monatsschrift Kinderheilkunde* 2019; Sonderheft 4).

of better postoperative development. For all patients, early age at seizure onset and early lesion origin correlated with poorer presurgical intellectual development.
Conclusions. Although an entire hemisphere was disconnected, most patients exhibited ongoing development after hemispherotomy or had at least the same preoperative intellectual status; deterioration was rare.

Key words: hemidisconnection, outcome, epilepsy surgery, hemispheric lesions

Hemispheric epilepsies can have severe effects on intellectual development. An earlier seizure onset (*e.g.* Brodtkorb, 1994; Vasconcellos *et al.*, 2001; Freitag and Tuxhorn, 2005; van Schooneveld *et al.*, 2011; Vignoli *et al.*, 2016; Tuchman, 2017; Helmstaedter *et al.*, 2019) as well as longer epilepsy duration (Vendrame *et al.*, 2009; D'Argenzio *et al.*, 2011; van Schooneveld *et al.*, 2011; Honda *et al.*, 2013; Kadish *et al.*, 2019), the latter particularly in patients with severely impaired intellectual functioning, are related to delayed development and lower IQ.

The surgical disconnection of the affected hemisphere (*i.e.* hemispherectomy or hemispherotomy) is an important treatment option for therapy-refractory epilepsies (Vining *et al.*, 1997; Devlin *et al.*, 2003; Shimizu, 2005; Delalande *et al.*, 2007; Marras *et al.*, 2010; Dorfmüller and Delalande, 2013). Seizure freedom can be accomplished in 65-90% of all hemidisconnective surgeries (Daniel *et al.*, 2001; Cross, 2002; Villemure and Daniel, 2006; Griessenauer *et al.*, 2015; Hu *et al.*, 2016). Persisting seizures after hemispheric surgery mostly seem to be linked to aetiology. Poor seizure outcome occurs more frequently in patients with bi-hemispheric structural or EEG pathologies (Greiner *et al.*, 2011; Ciliberto *et al.*, 2012), and in patients with certain brain malformations, in particular hemimegalencephalies and hemispheric cortical dysplasias (Lettori *et al.*, 2008; Bulteau *et al.*, 2013). Seizure freedom is a positive basis for ongoing postoperative development, as seizure freedom and intellectual outcome after epileptic surgery are often highly correlated (*e.g.* Loddenkemper *et al.*, 2007; Griessenauer *et al.*, 2015; Helmstaedter *et al.*, 2019). Regarding variables influencing outcome of intellectual functioning after hemidisconnection, the presurgical intellectual "starting position" turned out to be a strong predictor (Jonas *et al.*, 2004; Battaglia *et al.*, 2006; Marras *et al.*, 2010) as in most patients intellectual functioning remains stable after surgery (Pulsifer *et al.*, 2004; van Schooneveld *et al.*, 2011; Ramantani *et al.*, 2013). Furthermore, an earlier seizure onset has been proclaimed as a predictor for postsurgical intellectual changes (Jonas *et al.*, 2004; Pulsifer *et al.*, 2004; Battaglia *et al.*, 2006; D'Argenzio *et al.*, 2011) and some researchers found correlations between a shorter presurgical epilepsy duration and a higher postsurgical increase in developmental quotients (Jonas *et al.*, 2004; Freitag and Tuxhorn, 2005; Loddenkemper *et al.*, 2007; Honda *et al.*, 2013). On the contrary, Ramantani and colleagues (2013) identified a group of patients with acquired aetiology and superior preoperative development who showed intellectual improvement following late hemidisconnection and longer epilepsy duration. These findings suggest that an interplay between several highly confounded factors, in part, influences intellectual outcome after hemidisconnection.

This study investigated the developmental outcome of a large sample of 75 patients exhibiting a wide distribution of age at surgery and preoperative developmental status. Unlike previous studies (*e.g.* van Schooneveld *et al.*, 2011; Honda *et al.*, 2013), we especially focused on a large group of severely impaired children, hypothesizing that ongoing development after surgery can be achieved even in those patients. In contrast to most earlier studies, we calculated pre- and postsurgical developmental quotients, not only from parental interviews, but also from standardized testing for most patients of this group (83%). A second focus was put on aetiology and, related to this, the "timing" of the brain lesions (*figure 1*). Here, we hypothesized that earlier developing lesions relate to poorer intellectual development. This aspect has, to our knowledge, never been addressed before.

Methods

This study included 75 children and adolescents (46 males) who underwent hemispherotomies at our centre between 1999 and 2016.

Clinical data were collected retrospectively from hospital archives. Postsurgical seizure outcome was classified according to Engel scales (Engel *et al.*, 1993). Standardized developmental and intellectual testing was performed for all patients a few days before and approximately six months (median: 6.4 months; range: 4.9-13.0 months) after surgery. Two different types of psychological measurements were applied: developmental tests and IQ tests. Instruments were selected individually for each patient, according to age, degree of intellectual disability, and state of health at the time of the testing.

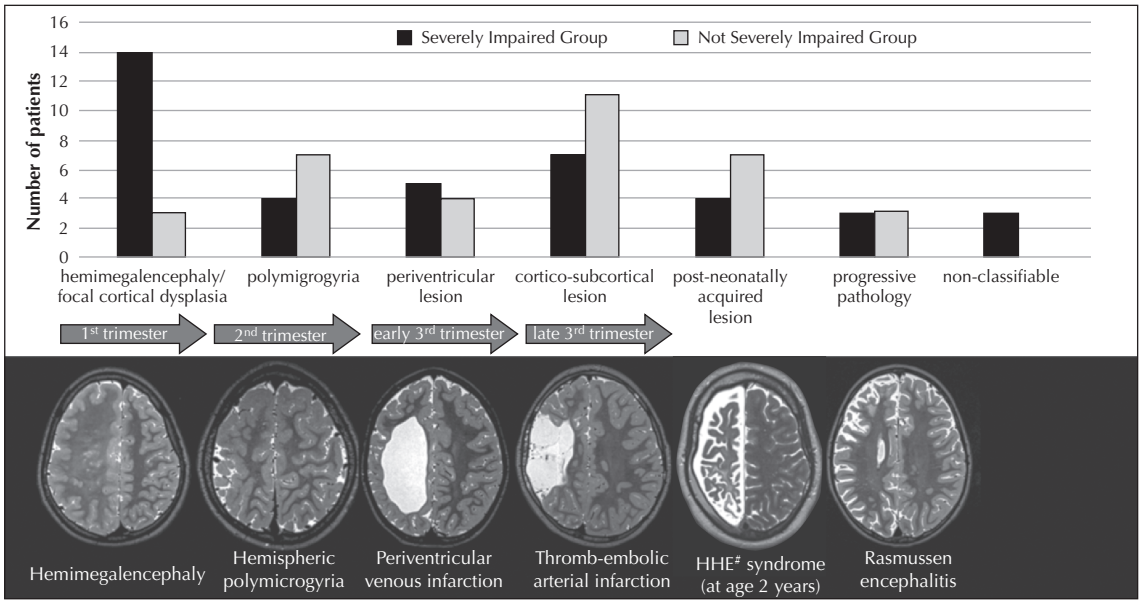

Figure 1. Upper panel: distribution of patients according to lesion; *severely impaired group* (black bars) vs. *not severely impaired group* (grey bars). Lower panel: examples of high-resolution T2-weighted MRI axial images (the abnormal hemisphere is displayed on the left side for each image), arranged in order of "lesion timing" and grade of cognitive impairment. #HHE: hemiconvulsion-hemiplegia-epilepsy.

For all patients who were able to undergo formal IQ testing (31/75; 41%), intellectual functioning was assessed based on age-related IQ measurements: children aged three to five years were examined using the *McCarthy Scales of Children's Abilities* (*MSCA*) (McCarthy, 1972), children and adolescents aged 6 to 16 using the *Hamburg-Wechsler-Intelligenztest für Kinder III* (*HAWIK-III*) (Tewes *et al*., 1999), and adolescents aged 17 and older using the *Wechsler-Intelligenztest für Erwachsene* (*WIE*) (von Aster *et al*., 2006).

Forty-four patients (59%) were not able to participate in regular IQ testing due to young age (< three years; 15/44; 34%) or severely impaired intellectual functions (≥ three years; 29/44; 66%). Here, we examined the developmental status using the *Bayley Scales of Infant Development II* (*BSID-II*) (Bayley, 1993) in 37/44 (84%) patients; instead of developmental indices (because results often ranged far below available test norms), developmental ages were statistically assessed by identifying the age group in which patients scored mean values. Furthermore, in 7/44 (16%) patients whose grade of disability or health condition at the time of the assessment did not allow an evaluable BSID-II execution, the developmental status was assessed by the *communication* scale based on a standardized parental interview - the *Vineland Adaptive Behaviour Scales* (*VABS*) (Sparrow *et al*., 1984). Motor development scales were excluded since outcomes would be negatively influenced by any postoperative motor deterioration. Postsurgical changes in developmental status were calculated from an average presurgical and postsurgical developmental quotient (DQ) of each patient. The average presurgical DQ was defined by $\frac{developmental\_age\_PRE}{real\_age\_PRE}$ and the average postsurgical DQ was defined by $\frac{developmental\_age\_POST - developmental\_age\_PRE}{real\_age\_POST - real\_age\_PRE}$. Outcome after surgery was described as change in developmental quotient $\frac{DQ\,post}{DQ\,pre}$ (CDQ). Hence, a CDQ>0 represented a further development after hemispherotomy, CDQ=0 meant no postoperative changes, and a CDQ<0 indicated postoperative deterioration.

For a quantifiable evaluation, the whole sample was divided into two groups (*table 1*): A *severely impaired group*, comprising all patients with an estimated IQ<40 (reflecting the ICD-10: F70-F73 criteria for severely impaired intellectual abilities) and a *not severely impaired group* including all patients with a measured IQ≥40. For patients aged ≥ three years, this means that those who were able to undergo standard IQ testing were assigned to the *not severely impaired group* (*n*=31), while all others were assigned to the *severely impaired group* (*n*=29). Likewise, for patients aged < three years, those with a DQ>0.5 were assigned to the *not severely impaired group* (*n*=4) and those with a DQ≤0.5 were assigned to the *severely impaired group* (*n*=11). The four patients in the *not severely impaired group* younger than three years were included in the

Table 1. Postsurgical seizure freedom (Engel 1), characteristics of the epilepsy (age at seizure onset, age at surgery, epilepsy duration), and cognitive outcome data, all in medians.

Structural pathology / 'timing' of lesion	**Whole sample (n = 75)**				**Severely impaired group (*n* = 40)**				**Not severely impaired group (*n* = 31)[x]**			
	n / Engel 1	**Age at seizure onset (in years)**	**Age at surgery (in years)**	**Epilepsy duration (in years)**	***n* / Engel**	**DQ_{pre}**	**DQ_{post}**	**CDQ**	**n / Engel 1**	**$FSIQ_{pre}$**	**$FSIQ_{post}$**	**Δ $FSIQ_{post}$ - $FSIQ_{pre}$**
Hemimegalencephaly	5 / 3	.00	2.24	2.04	3 / 1	.23	.15	.50	1 / 1	68	60	-8
Focal cortical dysplasia	12 / 6	.38	4.15	3.38	11 / 5	.20	.37	1.76	1 / 1	55	50	-5
Polymicrogyria	11 / 11	2.00	5.10	2.70	4 / 4	.29	.58	1.86	5 / 5	64	70	1
Periventricular lesion	9 / 7	1.50	7.28	5.04	5 / 4	.19	.40	2.09	4 / 3	48	52	0
Cortico-subcortical lesion*	18 / 16	.80	6.54	4.71	7 / 6	.40	.34	.59	11 / 10	70	72	5
Post-neonatally acquired lesion	11 / 9	2.00	9.52	4.25	4 / 3	.21	.48	1.66	7 / 6	62	68	3
Progressive pathology	6 / 5	3.03	4.27	1.20	3 / 2	.56	.28	1.88	2 / 2	62	63	1
Non-classifiable	3 / 2	1.50	4.97	4.97	3 / 2	.09	.16	.83	-	-	-	-
All	75 / 59	1.00	5.64	3.83	40 / 27	.22	.32	1.60	31 / 28	64	65	2

[x]only patients > 3 years of age included; *pre- or perinatally acquired. n: number of patients; DQ_{pre}, DQ_{post}: developmental quotients pre- and postoperatively; CDQ: DQ_{post} / DQ_{pre}; $FSIQ_{pre}$, $FSIQ_{post}$: full scale intelligence quotients pre- and postoperatively.

whole sample group analyses (*severely* vs *not severely impaired group*), but not in the intra-group analyses of the *not severely impaired group*, as their IQ values were not measured.

Structural pathology groups were classified according to the timing of the lesion (Krägeloh-Mann, 2004):

– hemimegalencephalies and focal cortical dysplasias (FCD) as disorders of neuronal proliferation (accepting that this does probably not hold true for all FCD type 1);
– polymicrogyrias as disorders of cortical organization;
– periventricular lesions as lesions acquired during the "early" third trimester of pregnancy;
– thromb-embolic infarctions as lesions acquired during the "late" third trimester or perinatally;
– post-neonatally acquired (static) lesions;
– and progressive lesions.

Statistical analysis was conducted using SPSS Statistics, Version 24. To detect predictors for pre- and postsurgical (intellectual) developmental, we conducted six multiple linear regression models. As dependent variables, the metric variables *pre- and postsurgical DQ* and *FSIQ*, as well as *CDQ* and *FSIQ change* were included. As independent variables, the metric variables, *age at seizure onset, epilepsy duration, presurgical DQ* and *FSIQ,* and the ordinal variables *aetiology* (from early to late developing lesions, excluding un-classifiable lesions; hemimegalencephalies and FCD were summarized in one group, as they develop approximately at the same time) and *seizure outcome* (Engel Classes 1- 4) were chosen. The variable *age at surgery* was excluded from all analyses because of multicollinearity (*age at surgery x epilepsy duration:* Spearman, r=0.83; $p<0.001$). Furthermore, as the distribution of variables was uneven, non-parametric tests were used for calculations, including Spearman correlations, the Mann-Whitney-U test, Chi^2 tests, and Cochran-Armitage tests for trend. To identify significant changes in FSIQs, a *Reliable Change Index* (RCI) was computed (Christensen and Mendoza, 1986). To detect potentially significant changes in postsurgical scale IQs that might have been masked by analysing FSIQ only, we additionally calculated an RCI for Verbal IQ (VIQ) and for Perceptual IQ (PIQ). For the *severely impaired group*, no RCI was used, as DQs are not standard values. Significance level was set at $p<0.05$.

Results

Median age at surgery was 5.64 years (range: 0.87-19.78 years). Forty-one (55%) patients showed left hemispheric lesions, 31 (41%) right hemispheric lesions, and three (4%) had lesions in both hemispheres; one of the bilaterally lesioned patients received a left hemispherotomy and two had right hemispherotomies. Structural pathologies are presented in *table 1*. Eleven patients had undergone circumscribed epilepsy surgeries prior to their hemispherotomies. Visual fields were evaluated preoperatively whenever possible. Complete or incomplete hemianopias were detected in 27/40 (68%) patients of the *severely* and 20/35 (57%) patients of the *not severely impaired group*, and intact visual fields in 8/40 (20%) patients of the *severely* and 5/35 (14%) of the *not severely impaired group*; the remaining 15 patients either showed insufficient cooperation or their health conditions did not allow perimetry. Postsurgical seizure outcome was classified as Engel Class 1 in 59/75 (79%) patients, Engel Class 2 in 4/75 (5%) patients, Engel Class 3 in 11/75 (15%) patients, and Engel Class 4 in 1/75 (1%) patients.

Regarding all 75 patients, the children in the *severely impaired group* had significantly earlier seizure onsets (median: 0.50 years; range: 0.00-7.50 years) than children in the *not severely impaired group* (median: 3.00 years; range: 0.00-8.00 years; Mann-Whitney, U=313.50, $p<0.001$). Consequently, they also received surgery at earlier ages ($median_{Sev}$: 4.63 years vs $median_{Not}$: 8.39 years; Mann-Whitney, U = 296.00, $p<0.001$), and had had shorter epilepsy durations until surgery ($median_{Sev}$: 3.09 years vs $median_{Not}$: 4.57 years; Mann-Whitney, U=513.00, p=0.05) than children in the *not severely impaired group* (*figure 2*), as variables were dependent (Spearman, $r_{age\ at\ onset\ x\ age\ at\ surgery}$ =0.46, $p<0.001$; $r_{age\ at\ surgery\ x\ epi\ duration}$ =0.80, $p<0.001$). In general, aetiologies did not differ between the groups (Cochran-Armitage test, CA(1)=2.42, p=0.12). However, focusing on hemimegalencephalies and FCD only (very early developing lesions that seem to be linked to worse development and worse seizure outcome compared to later developing lesions), we found these patients nearly exclusively in the *severely impaired group* (14/17 [82%] in the *severely impaired group* vs 3/17 [18%] in the *not severely impaired group*; $Chi^2(1)=7.78$, p=0.01). In addition, they not only showed poorer presurgical development than those with other diagnoses, they also had significantly earlier seizure onsets ($median_{HMG/FCD}$: 0.25 years vs $median_{rest}$: 1.50 years; Mann-Whitney, U=252.00, p=0.002) and a significantly worse postoperative seizure outcome (Cochran-Armitage test, CA(1)=5.15, p=0.02). In general, we found that patients in the *severely impaired group* had significantly worse seizure outcome than patients in the *not severely impaired group* (Cochran-Armitage test, CA(1)=6.68, p=0.01). Furthermore, early "timing" of the lesion correlated with early age at seizure onset (Spearman, r=0.31, p=0.007).

Severely impaired group

Presurgically, the median DQ was 0.22 (range: 0.07-0.63) (*table 1*). A multiple linear regression model (R^2=0.22),

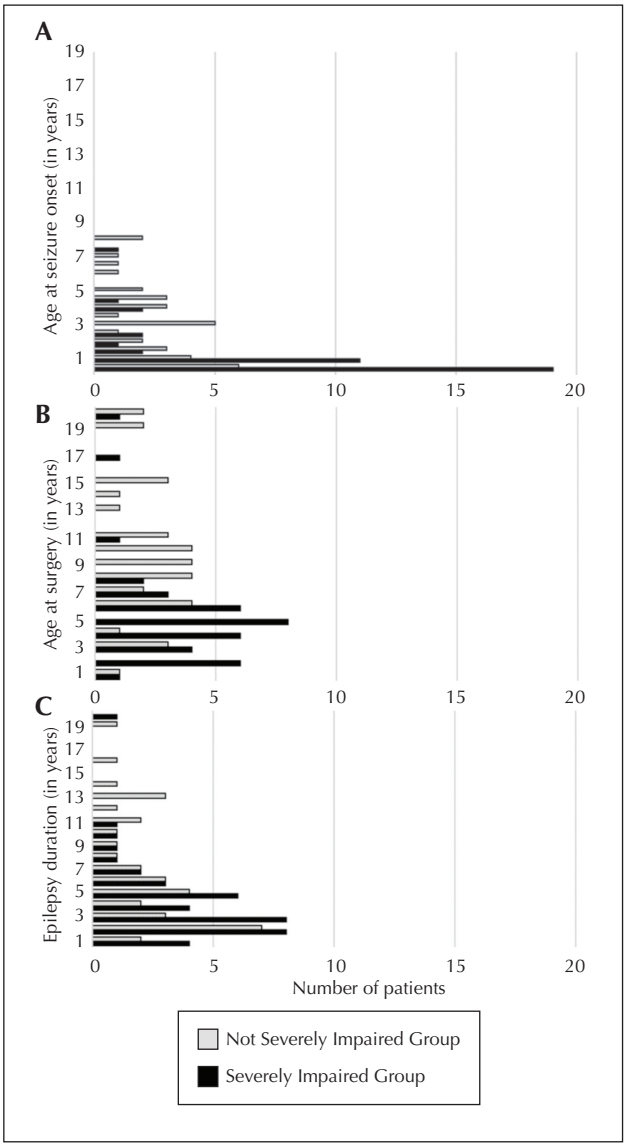

Figure 2. Group differences between the *severely impaired group* (black bars) and the *not severely impaired group* (grey bars) according to age at seizure onset ($median_{Sev}$: 0.50 years vs $median_{Not}$: 3.00 years; U=313.50, $p<0.001$) (A), age at surgery ($median_{Sev}$: 4.63 years vs $median_{Not}$: 8.39 years; U=296.00, $p<0.001$) (B), and epilepsy duration ($median_{Sev}$: 3.09 years vs $median_{Not}$: 4.57 years; U=513.00, $p=0.05$) (C).

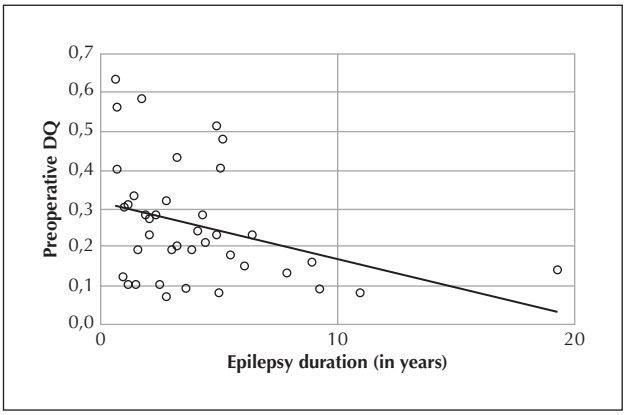

Figure 3. A multiple linear regression model (R^2=0.22, p=0.03) showing *epilepsy duration* as a significant predictor for preoperative intellectual developmental in the *severely impaired group* (b=-0.02, p=0.01).

including the variables *age at seizure onset*, *epilepsy duration*, and *aetiology* as potential influencing factors on *preoperative DQ,* was found to be significant (F=3.39; p=0.03). Shorter *epilepsy duration* was a significant predictor for marginally better development (b=-0.02; t =-2.60; p=0.01) (*table 2, Model 1*) (*figure 3*). Postsurgically, the median DQ had increased to 0.32 (range: -0.68-1.52). A second multiple linear regression model (R^2=0.26) examining the influences of *seizure outcome* and *presurgical DQ* on *postsurgical DQ* was found to be significant (F = 6.04; p=0.004) and identified *seizure outcome* (b=-0.20; t=-2.48; p=0.02) as a significant predictor for *postsurgical DQ* (*table 2, Model 2*). Furthermore, a positive correlation between *presurgical* and *postsurgical DQ* was found (*Spearman*, r=0.37, p=0.02). The median CDQ was 1.60 (range: -7.46-9.37). Twenty-two of 40 (55%) patients in this group showed a higher DQ after surgery than before (CDQ>1), eight (20%) patients showed small improvements (0<DCQ<1), nine (23%) patients showed no postoperative developmental change (CDQ=0), and one (2%) patient showed a developmental loss (CDQ<0). Regarding the effect of ongoing seizure activity after surgery on development, we found further development (CDQ>0) in 24/27 (89%) patients who became seizure-free (Engel Class 1), but only in 6/13 (46%) patients with ongoing seizures (Engel Class >1) (*figure 4*). Therefore, a significant relationship between seizure outcome and CDQ was found (Spearman, r=-0.42, p=0.008). A multiple linear regression model including the variables *age at seizure onset*, *epilepsy duration, aetiology,* and *seizure outcome,* as potential influencing factors on *CDQ,* did not meet the statistical assumption of homoscedasticity (*table 2, Model 3*). Besides seizure outcome, further analyses did not reveal significant correlations between CDQ and any other variable (*age at seizure onset, epilepsy duration* or *aetiology*).

Not severely impaired group

Analysing only the 31/35 (89%) patients older than three years in this group (*i.e.* those with measured IQ values), we found that the preoperative median FSIQ was 64 (range: 42-88) (*table 1*). A multiple linear regression model (R^2=0.11) including *age at*

Table 2. Multiple linear regression models showing significance of model and variables, and regression coefficients (*b*) and confidence intervals [*CI*; 95%].

Model 1: DV: DQ_{pre} (R^2 = .22; F = 3.39; p = .03)		
IV	*b* [*CI*]	*sign.*
Age at onset	-.03 [-.06 - .01]	.08
Epilepsy duration	-.02 [-.03 - -.01]	.01
Etiology	.02 [-.01 - .04]	.08
Model 2: DV: DQ_{post} (R^2 = .26; F = 6.04; p = .004)		
DQ_{pre}	.63 [-.36 – 1.63]	.21
Seizure outcome	-.20 [-.36 - -.04]	.02
Model 3*: DV: CDQ		
Age at onset	-	-
Epilepsy duration	-	-
Aetiology	-	-
Seizure outcome	-	-
Model 4: DV: $FSIQ_{pre}$ (R^2 = .11; F = 1.07; p = .38)		
Age at onset	2.16 [-.45 – 4.77]	.10
Epilepsy duration	-.01 [-1.24 – 1.22]	.99
Aetiology	-.80 [-3.67 – 2.08]	.58
Model 5: DV: $FSIQ_{post}$ (R^2 = .75; F = 41.48; p < .001)		
$FSIQ_{pre}$	.78 [.60 - .96]	<.001
Seizure outcome	-.47 [-5.52 – 4.31]	.84
Model 6: DV: FSIQ change (R^2 = .04; F = .03; p = .88)		
Age at onset	-.07 [-1.49 – 1.34]	.92
Epilepsy duration	-.18 [-.86 - .50]	.59
Aetiology	-.29 [-1.85 – 1.26]	.70
Seizure outcome	.56 [-4.85 – 5.97]	.83

DV: dependent variable; IV: independent variables. *criterion of homoscedasticity was not met.

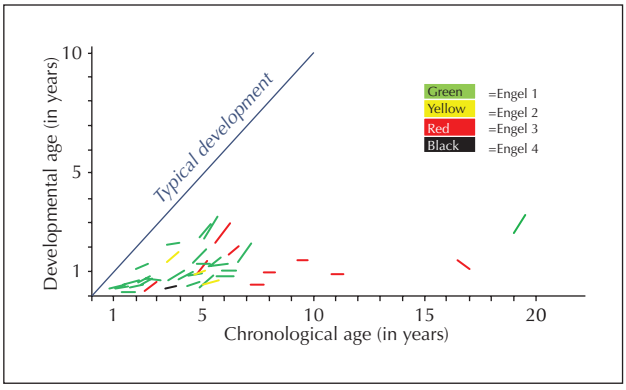

Figure 4. Individual postoperative courses of development for the *severely impaired group* (*n*=40). Each line represents the developmental age of a single patient pre-operation to six months post-operation; different colours indicate different post-operative seizure outcomes.

seizure onset, aetiology, and *epilepsy duration* as potential influencing factors on *preoperative FSIQ* was not significant (F=1.07; p=0.38) (*table 2, Model 4*). The six months postoperative median FSIQ was 65 (range: 42-88) (*table 1*). Regarding postoperative FSIQ, a multiple linear regression model (R^2=0.75) was calculated, including the variables *seizure outcome* and *preoperative FSIQ*. This model was significant (F=41.48; p<0.001) and identified *preoperative FSIQ* as a single influencing factor on *postoperative FSIQ* (b=0.78; t=80; p<0.001) (*table 2, Model 5*) (*figure 5A*). Preoperatively, two (6%) patients had shown no intellectual impairment (FSIQ≥85), 10 (32%) intellectual weaknesses (70≤FSIQ<85), seven (23%) mild intellectual impairment (55≤FSIQ<70), and 12 (39%) moderate impairment (40≤FSIQ<55); postoperatively, two (6%) patients were found with no intellectual impairment, ten (32%) with intellectual weaknesses, and 14 (45%) showed mild, and five (17%) showed moderate intellectual impairment. The median difference between preoperative and postoperative FSIQ ($FSIQ_{post}$-$FSIQ_{pre}$) was +2 IQ points (range: -8-+22). *Reliable Change Indices* (*RCIs*) revealed that 9/31 (29%) patients experienced significant IQ changes: 7/31 (23%) patients showed improvements (FSIQ [*n*=5], only VIQ [*n*=1], only PIQ [*n*=1]) and 2/31 (6%) patients showed significant deteriorations (only PIQ for both) (*table 3*). A multiple linear regression model (R^2=0.04) including *age at seizure onset, epilepsy duration, aetiology*, and *seizure outcome* as potential influencing factors on *postoperative FSIQ change* was not significant (F=0.03; p=0.88) (*table 2, Model 6*). Furthermore, we found no significant correlations between postoperative FSIQ changes and other variables (*age at seizure onset, epilepsy duration, aetiology*, or *seizure outcome*).

Since the subgroup of patients younger than three years in this group (*i.e.* those without measured IQ values) comprised only four subjects, analyses were not performed.

Discussion

The major finding of our study was that, after hemispherotomy, most patients exhibited ongoing development or at least had the same intellectual status as before surgery; deterioration was rare and barely severe. This is consistent with previous findings (van Schooneveld *et al.*, 2011; Ramantani *et al.*, 2013), but based on a larger sample also comprising many patients with severe intellectual impairment, in whom we used precise, standardized measurements to describe postsurgical changes. Furthermore, we were able to demonstrate that the "timing" of the lesion influences early intellectual development.

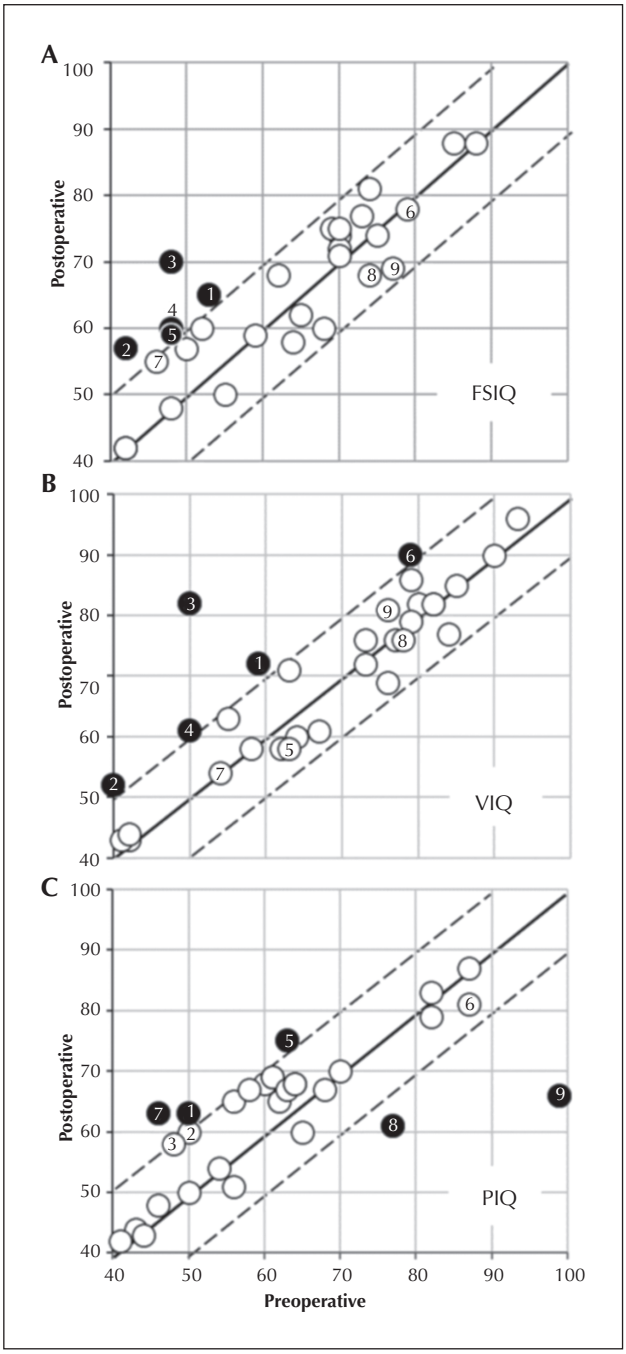

Figure 5. Correlation between pre- and post-operative FSIQ (A), VIQ (B), and PIQ (C) in the *not severely impaired group* (*n*=31). Significant changes (>10 IQ points) are presented as black circles; the numbers indicate individual patients (for cross-comparison). The dashed lines indicate +/- 10 IQ points.

Table 3. Significant differences (postoperative – preoperative) in FSIQ, VIQ, and PIQ, and side of disconnected hemisphere. Patient numbers correspond to those in *figure 5*.

Patient	FSIQ	VIQ	PIQ	Side of HRO
1	+12*	+13*	+13*	L
2	+15*	+12*	+10	R
3	+22*	+32*	+10	L
4	+12*	+11*	+9	R
5	+11*	-5	+12*	L
6	-1	+11*	-6	L
7	+9	0	+17*	R
8	-6	-1	-16*	R
9	-8	+5	-33*	L

HRO: hemispherotomy; R: right; L: left. *significant postoperative change (RCI).

Severely impaired group

This group comprised patients with an estimated IQ<40. Compared with the *not severely impaired group*, we found that this group had an earlier seizure onset (median: 0.50 vs 3.00 years). This relationship between young age at seizure onset and severity of intellectual disability has been reported in many previous investigations (*e.g.* Vascenallos *et al.*, 2001; Cormack *et al.*, 2007; Overwater *et al.*, 2017; Glass *et al.*, 2018). Furthermore, the *severely impaired group* included a higher proportion of patients suffering from structural pathologies arising from disorders of neuronal proliferation, such as hemimegalencephalies and FCD (14 of all 17 [82%] patients with hemimegalencephalies and FCD were found in this group). Here, our data revealed that patients suffering from very early developing lesions were more likely to be found in the *severely impaired group* than in the *not severely impaired group*, and, therefore, show worse intellectual development than patients diagnosed with later developing lesions. These findings confirm former assumptions (Lettori *et al.*, 2008; Honda *et al.*, 2013).

Regarding intellectual outcome after hemispherotomy in severely intellectually impaired patients, few studies have been published so far. A study using developmental scales on 17 severely impaired children found that even children whose early intellectual development was affected drastically due to early onset epilepsies showed positive outcome after hemispherotomy (van Schooneveld *et al.*, 2011). In our larger cohort, we clearly underlined this, with 30/40 (75%) patients showing ongoing development after hemispherotomy, there of 22 with a higher DQ than before surgery. Still, postoperative DQs were, on average, clearly lower than in typically developed peers; nevertheless, the disconnection of one hemisphere did not

further impair intellectual development but allowed an ongoing developmental process after epilepsy-related phases of stagnation and regression. Seizure outcome predicted development after surgery in this group, paralleling findings by others (Freitag and Tuxhorn, 2005; van Schooneveld *et al*., 2011; Honda *et al*., 2013): 24/30 (80%) of all our patients with further development after hemispherotomy were classified as Engel Class I. In contrast, only 3/10 (30%) patients with no postoperative changes or deterioration achieved Engel Class I (Fisher, p=0.006). Lettori (2008), Bulteau (2013), and Honda (2013) and colleagues postulated that patients suffering from disorders of neuronal proliferation, such as hemimegalencephalies or hemispheric FCD, not only show a worse presurgical intellectual development, but additionally show a worse seizure outcome after hemidisconnection than patients with other lesions. This is also true for our *severely impaired group*, as for 9/15 (60%) patients with hemimegalencephalies or FCD, seizure freedom was not achieved. The reasons for the comparatively poor seizure outcome of this patient group are not entirely decoded yet.

Epilepsy duration has also been discussed frequently, related to presurgical intellectual impairment (Basheer *et al*., 2007; Vendrame *et al*., 2009; Overwater *et al*., 2017) and postsurgical intellectual outcome (Freitag and Tuxhorn, 2005; Loddenkemper *et al*., 2007; Honda *et al*., 2013). Consequently, an early surgical intervention has been postulated to provide ongoing developmental processes (Delalande *et al*., 2007; Shurtleff *et al*., 2015; Kadish *et al*., 2019). Our *severely impaired group* data cannot contribute to the assumption that shorter epilepsy duration entails a better intellectual outcome after surgery, but it suggests that epilepsy duration might already influence early childhood development, which means that a longer active epilepsy entails worse intellectual development.

Not severely impaired group

A strength of our study was the availability of FSIQ, VIQ, and PIQ scores for 31 patients, allowing more precise calculations than in other large cohort studies, in which patients were lumped together in "IQ groups", with IQ values calculated and estimated from different IQ and developmental scales (*e.g.* Devlin *et al*., 2003; Ramantani *et al*., 2013). We demonstrated that the overall median FSIQ gain, measured six months after surgery, was small (median: 2 IQ points). This stability in postoperative intellectual abilities is in line with previous investigations (Pulsifer *et al*., 2004; van Schooneveld *et al*., 2011; Althausen *et al*., 2013; Ramantani *et al*., 2013) and fortifies the assumption that postoperative intellectual levels are determined by preoperative levels. Accordingly, preoperative FSIQ was a strong predictor for postoperative FSIQ, both based on our data and previous reports (Jonas *et al*., 2004; Battaglia *et al*., 2006; Marras *et al*., 2010). Several patients, however, showed significant improvements in FSIQ (n=5; 16%), or only in VIQ (n=1; 3%), or only in PIQ (n=1; 3%). Since all these significant improvements exceeded 10 IQ points (2/3 of the IQ standard deviation), we consider them clinically meaningful. Two patients showed significant losses, only in PIQ for both. These two patients both showed intact visual fields preoperatively; hence, it is tempting to speculate that their new hemianopias played a role in this deterioration. On the other hand, this does not seem to be a general rule, since the other three patients with intact visual fields showed stable PIQs despite new hemianopias. The side of hemispherotomy was not connected to changes in FSIQ, VIQ, or PIQ (*table 3*).

In contrast to others, we only identified preoperative IQ as a significant predictor for postoperative IQ. This seems to contradict data of Lettori (2008), D'Argenzio (2011), as well as Ramantani (2013) and co-workers, supporting the notion that age at seizure onset is related to pre- and postoperative IQ. Furthermore, all these studies reported that patients with progressive aetiologies were more likely to have positive outcome and patients with "congenital" aetiologies were less likely to have a positive outcome in intellectual development. This contradiction can be resolved by the comparison between our two groups, which corroborate these findings: patients in the *severely impaired group* showed earlier seizure onsets and earlier developing lesions.

In contrast to the *severely impaired group*, epilepsy duration was not a significant predictor for presurgical FSIQ in the *not severely impaired group*. This is compatible with previous studies on patients whose preoperative intellectual impairment was moderate to mild. Ramantani and colleagues (2013) suggested that older age at surgery and subsequently longer epilepsy duration in such patients reflect less severe seizure history and milder intellectual impairment, enforcing surgical treatment later than in children with catastrophic, early-onset epilepsies. This might also be true for our cohort in the *not severely impaired group*.

Admittedly, our study has several limitations. First, we did not include any long-term data, but only reported a six-month postoperative outcome. This important issue must be addressed in future investigations. Second, the DQ is not a statistical value. Therefore, its postoperative change can be evaluated statistically only on an individual level; furthermore, there was no criteria to indicate clinical meaningfulness. This must be considered in the interpretation of the results. Finally, it remains unclear why some patients with newly acquired hemianopias showed significant losses in PIQ while others did not. This topic should be addressed in future prospective studies.

In conclusion, developmental and intellectual outcome after hemispherotomy was found to be stable in most patients of this study. Early age at seizure onset and early "timing" of the lesion were significantly correlated with poor presurgical intellectual development. In patients with no, mild, or moderate intellectual disabilities, the preoperative intellectual level was a strong predictor for postoperative intellectual outcome. In contrast, in patients with severe or profound intellectual disabilities, good seizure outcome was the best predictor for favourable intellectual development after surgery. Only in these patients was epilepsy duration a predictor for preoperative developmental scores. This suggests that in children suffering from catastrophic, early-onset epilepsies, early surgical interventions that are effective in stopping the epilepsies may prevent further regression in intellectual development. Overall, although an entire hemisphere was disconnected, most patients exhibited ongoing development after hemispherotomy or at least had the same intellectual status as before surgery; deterioration was rare. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What was the intellectual outcome six months after hemispherotomy in general?

(2) What were the strongest predictors for postsurgical development and intellectual functions?

(3) What role does the temporal origin ("timing") of the lesion play in intellectual development?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".