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Surgical versus medical treatment for severe epilepsy: consequences for intellectual functioning in children and adults. A follow-up study

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We compared the effects of medical and combined surgical and medical treatment of refractory epilepsy on intellectual functioning in a group of children ($n = 13$) and a group of adults ($n = 15$).

The patients were tested with the age-appropriate versions of Wechsler's intelligence scales twice prior to and once after epilepsy surgery. There were no significant differences between the groups in preoperative epilepsy-related variables, including age at onset. The IQ scores were submitted to two-way analyses of variance (ANOVA). We also evaluated individual changes in IQ scores.

Adult patients maintained stable levels of performance after drug treatment as well as following surgery, while children declined in Full Scale IQ after both kinds of treatment. Children also declined in Performance IQ, but not in Verbal IQ after drug treatment, and in Verbal IQ, but not in Performance IQ after surgery. Three of six children who underwent a significant decline in Full Scale IQ before surgery did not show any further decline postoperatively.

We have proposed a developmental model to account for the different findings in children and adults, and conclude tentatively that refractory, long-standing epilepsy may interfere with intellectual development both during drug treatment and following combined surgical and medical treatment in children, while the impact of long-standing refractory epilepsy of similar severity as in children is not strong enough to reduce intellectual performance in adults, irrespective of treatment modality.

Key words: refractory epilepsy; treatment; intelligence; children; adults.

INTRODUCTION

Drug treatment has been the principal therapy for epileptic seizures since the introduction of bromide in 1857. Drugs have proven to be very effective. At present about 80% of patients with epilepsy will obtain seizure control on medication[1]. These results are usually achieved without serious adverse effects on cognition, particularly if the seizures are controlled with one drug and blood serum levels are within the recommended range[2]. However, about 20% of patients with epilepsy continue to have seizures despite drug treatment[3]. The combined effect of seizures and the use of one or more antiepileptic drugs (AEDs) raise concerns about intellectual functioning. Several recent follow-up studies of patients with medically intractable epilepsy indicate that the risk for intellectual decline may be considerable in children[4–8], while most adult patients seem to maintain a relatively stable IQ[7, 9, 10]. Since the seizure disorders in different studies are not described in comparable units, however, one may argue that the children studied may have had a more severe epilepsy than the adults. A common measure of seizure severity would be warranted in order to clarify this issue.

Resective surgery aimed at eliminating epileptic seizures has proven to be a good alternative to drug treatment in carefully selected patients with

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medically refractory epilepsy. Approximately two thirds of surgically treated patients become seizure free, and in addition about 25% experience a worthwhile improvement[11].

Although seizure control is the primary goal of surgical treatment, a beneficial effect on cognitive functioning is supposed to occur, particularly in children[12, 13]. Indeed, some surgically treated patients have experienced considerable intellectual improvements[14]. In general, however, the postoperative changes in intellectual functioning in adults appear to be modest. Apart from a moderate decline in memory functions, particularly after left temporal lobe surgery, adult patients most often seem to maintain stable test results[15–17]. The relatively few studies performed in children do not indicate significant postoperative changes in mean Full Scale IQ scores[18–20]. Westerveld *et al.*[21] however, found a significant postoperative increase in Performance IQ in children who underwent left temporal lobe surgery. Furthermore, it has been suggested that patients who decline in intellectual functioning during preoperative drug treatment, may have the potential for a reversal of the negative trend after surgery[22–24]. Such a positive effect has been reported in patients treated with hemispherectomy[25], but it is not clear whether a similar result can be expected following focal resections. We are aware of only one case study addressing this question[26]. This study reported a postoperative improvement in Verbal IQ in a child treated with left temporal lobectomy who went through a deterioration in academic achievement preoperatively.

In the present study, we wanted to compare the longitudinal effects of refractory seizures on intelligence in children and adults over a period of drug treatment and following surgery. Previous studies assessing the effects on cognitive functioning of these two kinds of treatment have compared patients under consideration for surgery with patients who were not surgical candidates[10, 27]. Such comparisons may be of limited value, since these groups may differ in variables with relevance for cognitive functions, for example seizure frequency[28, 29] or distribution of epileptogenic tissue[30, 31]. The design adopted in the present study circumvents such difficulties by employing repeated assessments of the same patients during presurgical drug treatment and after surgery. This design also permits direct comparisons between groups on epilepsy-related variables. There appears to be no previously published study of this kind.

PATIENTS AND METHODS

Thirty-nine patients who had been tested twice before and once after resective epilepsy surgery with age-appropriate versions of Wechsler's intelligence scales, were considered for the study. The selection was done retrospectively. At the first assessment most patients had an epilepsy which was not as yet recognised as drug resistant, while some of them were in an early phase of the preoperative work-up. Thirteen patients were children (<18 years) when surgery was performed, 15 were adults (≥18 years) at the first assessment. Eleven patients were children at the first assessment and adults at surgery. Because we wanted to compare the effects of two types of treatment in a group of paediatric patients to those in a group of adults, these eleven patients were not included in the study.

In a previous study[32] we described the changes in IQ scores in 34 children and adults over several years with antiepileptic drug treatment for refractory seizure disorders. The patients in the present study comprise a sub-sample of this group who have subsequently been treated surgically and completed our standard follow-up assessment 2 years after surgery.

Surgical procedures

Twenty-four patients were treated by anterior temporal lobectomy including the foremost part of the hippocampus in 19 cases. One adult patient underwent a selective amygdalohippocampectomy and another a temporo-occipital resection. Among the children, one had a frontal lobe resection and another had multilobar (temporoparietal) resections.

Epileptic seizures

For each patient the number and types of seizures during the month preceding the two preoperative test occasions were registered based either on the patients' or the parents' seizure calendars, or on records made by the staff. Severity of the seizure activity in the two groups was assessed by three experienced epileptologists, who blindly and independently rated each patient's seizure records. Both seizure frequency and seizures types were evaluated. Seizure activity prior to Test 1 was rated using a graded five-point Likert scale ranging from 0, 'no seizures', to 4, 'very severe seizure disorder'. The individual changes in seizure severity during the preoperative test–retest interval were also rated, using a seven-graded scale ranging from −3 'much worse' to +3 'much better'. The inter-rater reliability was satisfactory in both ratings (Kendall coefficient of concordance 0.89, $P < 0.001$ and 0.94, $P < 0.001$, respectively). The rating procedures are further described in Bjørnæs *et al.*[32] Postoperative seizure control was classified in accordance with the suggestions made by Engel[33] and coded in

Arabic figures, with class IV a, b and c assigned the values 4, 5, and 6, respectively.

EEG

Each patient's EEG records prior to the preoperative test occasions were blindly rated by a senior neurophysiologist. Ratings considered degree and distribution of pathology and included assessment of background activity, focal slowing, sharp waves, and spike and wave activity. A graded 5 point Likert scale was used. Changes in EEG pathology from Test 1 to Test 2 were rated according to a 7 point scale ranging from −3, 'much worse' to +3, 'much better'. At Test 3, EEG background activity, focal slow waves, and epileptiform activity were evaluated separately using 5 point scales.

Antiepileptic drugs (AEDs)

During the preoperative test–retest period all patients were treated with AEDs. Thirteen of the adults and nine of the children had changes in the types of drugs received in this period, but without obtaining seizure control. Nine patients were on drug monotherapy at Test 1, 14 at Test 2 and 14 at Test 3. Three patients were without antiepileptic drugs at Test 1, none at Test 2, and 1 at Test 3. These patients were not excluded from the study because they all had received drugs for a substantial period of time pre- and post-operatively.

Test versions

The patients were tested with the age appropriate Norwegian versions of the Wechsler Intelligence Scales. Seven of the children were tested three times with the Wechsler Intelligence Scales for Children-Revised (WISC-R)[34], while six children were first tested with the WISC-R and later with the Wechsler Adult Intelligence Scale (WAIS)[35]. The adults were tested three times with the WAIS. Standardisation of both versions was done simultaneously in Norway, and the norm tables are assumed to be reasonably equivalent[36]. All IQ scores were therefore included irrespective of the version of the test used.

The interval between Test 1 and Test 2 was 4.3 years on average. The average time elapsed from Test 2 to surgery was 2.5 months, and Test 3 was performed on average 2.1 years after surgery.

Test scores

Because the focus of interest was the long-term effects of treatment on level of intelligence rather than cognitive profiles, only summary IQ scores were considered (i.e. Verbal, Performance, and Full Scale IQ scores).

Test–retest effects

Practice effects, i.e. a gain in IQ scores upon retesting, are demonstrated in normal adults[37] as well as in normal children[38]. Such changes are also seen in groups of patients with epilepsy on stable drug treatment[39]. However, test–retest gains seem to be either absent[40] or negligible[41] in patients with frequent epileptic seizures. In accordance with these previous studies, we did not anticipate substantial practice effects in the present study, because our patients had severe refractory seizures, and because test–retest intervals were relatively long[42]. Besides, potential practice effects would probably be present in both groups, and not compromise comparisons between groups.

Another possible confounding factor in the study of cognitive change is regression toward the mean[43]. This statistical artefact significantly influences the results if initial test scores are significantly inversely correlated to the measures of change[44]. This was not the case in the present study. Thus, no corrections for regression effects were considered necessary.

Individual changes

In addition to average changes in IQ scores based on the group data, we wanted to study individual changes. But because all patients underwent active drug treatment with changes in types, number, or dosages of AEDs, we could not isolate error variance from the treatment effects. Consequently, individual changes had to be described in arbitrarily chosen values, as previously done in the studies by Bourgeois *et al.*[45] and Gilliam *et al.*[46] In accordance with these studies, IQ scores equal to or greater than ±10 points were deemed presumably reliable individual changes.

Statistical methods

Categorical data were analysed using the Chi-square test wherever the requirements for this test were met. The Fisher exact test was used in 2 × 2 contingency tables with few patients. Ordinal-scale data and continuous data with large differences between the groups with respect to error variance were compared among groups using the median test. Where appropriate, continuous demographic variables were analysed by Student's *t*-test for independent samples. Verbal, Performance, and Full Scale IQ scores were

separately submitted to repeated-measures analyses of variance, with group as independent variable and test occasion as repeated-measures factor. *Post hoc* tests were performed using Duncan's multiple range test. *P*-values less than 0.05 in two-tailed tests were considered statistically significant. The statistical analyses were run with Statistica for Windows[47].

RESULTS

Demographic and seizure-related variables

At Test 1, the children were on average 10.2 years of age, and the adults were 24.6. When surgery was performed, the children and adults were on average 14.0 and 29.6 years of age, respectively (Table 1). The adults had had their epilepsy significantly longer than the children at both preoperative test occasions (median 5.5 and 9.3 years in the children, 12.7 and 18.8 years in the adults, respectively).

However, there were no significant differences between children and adults with respect to epilepsy-related variables such as aetiology, age at onset of seizures, number of generalised tonic–clonic and complex partial seizures prior to the test occasions, laterality or location of the epileptic focus, EEG pathology and seizure severity prior to Test 1, nor in preoperative changes in EEG pathology and seizure severity. Furthermore, we found no significant differences between the groups in postoperative seizure control or EEG pathology. The preoperative test–retest interval, and the postoperative follow-up interval did not differ between groups. In short, differences between the groups were primarily related to age.

IQ scores

Mean IQ scores at the three test sessions are shown in Table 2. The analysis of variance revealed no

Table 2: Mean IQ scores and standard deviations.

	Test 1	Test 2	Test 3
VIQ			
Children	89.7 (18.4)	84.9 (20.6)	76.0 (18.0)
Adults	81.9 (17.7)	84.8 (19.2)	85.8 (18.6)
PIQ			
Children	93.7 (15.7)	87.4 (17.1)	86.6 (19.6)
Adults	76.1 (20.2)	82.7 (18.5)	81.9 (23.1)
FSIQ			
Children	90.5 (17.1)	84.3 (19.8)	78.6 (18.9)
Adults	77.6 (19.2)	82.5 (19.0)	83.5 (18.8)

Abbreviations: VIQ, Verbal IQ; PIQ, Performance IQ; FSIQ, Full Scale IQ.

Table 1: Demographic and epilepsy-related variables.

	Children (n = 13)	Adults (n = 15)	P
Sex, m/f	8/5	9/6	NS[a]
Etiology: cryptogenic/symptomatic	9/4	9/6	NS[b]
Laterality of epileptic focus: left/right	7/6	7/8	NS[a]
Age at seizure onset (years), median (qr)	5.0 (5.0)	10.0 (13.0)	NS[c]
Duration of epilepsy at Test 1 (years), median (qr)	5.5 (5.2)	12.7 (11.6)	<0.01[c]
Age at Test 1 (years), mean (SD)	10.2 (2.7)	254.6 (4.7)	
CPS/month at Test 1, median (qr)	11.0 (69.0)	9.0 (15.0)	NS[c]
GTC/month at Test 1, median (qr)	0.0 (0.0)	0.1 (2.0)	NS[c]
Seizure severity at Test 1, median (qr)	3.0 (2.0)	2.3 (1.3)	NS[c]
EEG pathology at Test 1, median (qr)	2.0 (2.0)	2.0 (1.0)	NS[c]
Time Test 1–Test 2 (years), mean (SD)	3.5 (2.7)	5.0 (3.8)	NS[d]
Duration of epilepsy at Test 2 (years), median (qr)	9.3 (6.3)	18.8 (15.9)	<0.01[c]
CPS/month at Test 2, median (qr)	20.0 (81.0)	9.0 (10.0)	NS[c]
GTC/month at Test 2, median (qr)	0.0 (3.0)	0.1 (4.0)	NS[c]
Change in EEG-pathology Test 1–Test 2, median (qr)	−2.0 (2.0)	0.0 (1.0)	NS[c]
Change in seizure severity Test 1–Test 2, median (qr)	1.0 (6.0)	1.0 (9.0)	NS[c]
Age at operation (years), mean (SD)	14.0 (2.6)	29.7 (5.4)	
Temporal/extratemporal resections	11/2	14/1	NS[b]
Time op to Test 3 (years), median (qr)	2.1 (0.2)	2.0 (0.1)	NS[c]
Postoperative seizure control, median (qr)	2.0 (3.0)	3.0 (3.0)	NS[c]
EEG pathology at Test 3 (postoperative)			
Background activity, median (qr)	0.0 (1.0)	0.0 (1.0)	NS[c]
Focal slow activity, median (qr)	1.0 (0.0)	1.0 (1.0)	NS[c]
Epileptiform activity, median (qr)	0.0 (1.0)	0.0 (1.0)	NS[c]

Abbreviations: m, male; f, female; crypt, cryptogenic; symp, symptomatic; SD, standard deviation; CPS, complex partial seizures; GTC, generalized tonic–clonic seizures; qr, quartile range; op, operation; EEG, electroencephalogram; NS, not significant.
[a] Chi-square test; [b] Fisher exact; [c] Median test; [d] *t*-test for independent samples.

Table 3: Individual changes in IQ scores (number of patients experiencing gains, losses or stable IQ scores).

	Verbal IQ			Performance IQ			Full Scale IQ		
	Gains	Stable	Losses	Gains	Stable	Losses	Gains	Stable	Losses
Drug treatment									
Children	1	7	5	1	7	5	1	6	6
Adults	4	11	0	5	10	0	3	12	0
Drugs + surgical treatment									
Children	0	7	6	3	6	4	1	7	5
Adults	2	12	1	3	9	3	1	13	1

significant group effects, but a significant effect of test occasion was found in Verbal IQ scores, mainly due to the appreciable decline in the children's scores ($F(2, 52) = 3.3$, $P < 0.05$). Moreover, significant interaction effects between groups and test sessions were found in Verbal IQ ($F(2, 52) = 9.4$, $P < 0.001$), Performance IQ ($F(2, 52) = 4.4$, $P < 0.05$), and Full Scale IQ ($F(2, 52) = 9.8$, $P < 0.001$), showing that the descending trend in IQ scores in the children was significantly different from the ascending trend in the adults.

Post hoc tests of within-group changes showed a statistically significant decline in FSIQ scores from Test 1 to Test 2 in the children ($P < 0.05$). In addition, there was a significant decline in Verbal IQ scores in the children from Test 2 to Test 3 ($P < 0.01$). In the adults, there were no significant changes in any of the IQ scores between Test 1 and 2, nor between Test 2 and 3. Between-group comparisons showed no significant differences in Verbal, Performance and Full Scale IQ scores at any of the test sessions.

Individual changes

When comparing the effects on intelligence of drug treatment versus combined treatment with drugs and surgery in terms of individual changes, we found no substantial differences in any of the IQ scores. For example, six patients (21%) declined by 10 or more points in Full Scale IQ scores after drug treatment (Table 3), four patients (14%) experienced gains, while 18 patients (64%) had no substantial change in their scores. After surgery, six patients (21%) declined in FSIQ, two (7%) showed gains, while 20 (71%) maintained a stable performance. Similar results were found in Verbal and Performance IQ scores.

The six patients who experienced a drop in FSIQ scores of 10 or more points during drug treatment were all children (46%). None in the adult group showed a comparable decline. One child and three adults increased their FSIQ scores. With the results shown in Table 3 arranged in a 2×2 contingency table with the categories 'stable' and 'gains' collapsed, these differences between the groups achieved statistical significance ($P < 0.01$, Fisher exact test). The differences between the groups in Verbal and Performance IQ scores were also significant (P-values < 0.05). These results indicate that the risk for a significant decline in Verbal, Performance, and Full Scale IQ scores during the period with drug treatment was greater in the paediatric than the adult group. After surgery, similar analyses showed that significantly more children than adults declined in Verbal IQ ($P < 0.03$), but not in Performance or Full Scale IQ (P-values > 0.05).

Analyses of the number of patients experiencing *gains* in IQ scores revealed no significant differences between the groups after drug treatment or after surgery (all P-values > 0.1, the category 'gains' vs. the categories 'stable' and 'losses' collapsed, Table 3). Thus, the likelihood of an increase in IQ scores was not different for children and adults.

Of the six children who declined in Full Scale IQ before surgery, the downward trend was reversed after surgery in three. All of these children became seizure free (Engel class I)[33]. However, the downward trend persisted in three children. Two of these patients had no reduction in seizure frequency 2 years after surgery (Engel class IVb)[33]. One, however, was seizure free.

DISCUSSION

The present results show that there was no mean decline in IQ in the sample of adult patients during the preoperative period (5 years on average) with drug treatment, despite a refractory seizure disorder which was sufficiently severe to warrant surgical treatment. They also maintained a relatively stable level of intellectual functioning at the assessment 2 years after surgical treatment. These results are in agreement with several longitudinal studies of intelligence in adult patients with refractory epilepsy treated either with antiepileptic drugs[7, 9, 10, 39], or with the combination of drugs and surgery[7, 10, 48].

Recurrent refractory seizures in children, on the other hand, seem to have a negative impact on intelligence. In the present study, serial testing during drug treatment over the average preoperative period of 3.5 years showed a significant mean decline in Full Scale

IQ. These results are in line with the findings in previous follow-up studies of children with refractory epileptic seizures[4–6, 49]. After surgery, however, there was no significant decline in Performance or Full Scale IQ, although a decline was seen in Verbal IQ scores. A greater risk for decline in Verbal than Performance IQ following epilepsy surgery has also been found in some previous studies in adult patients[50, 51].

We found no indications that the children had more severe seizure conditions or more progressive courses than the adults preoperatively, nor did we find differences between the groups with respect to postoperative variables with potential effect on intelligence, namely seizure control and EEG (Table 1). It should be noted, however, that findings concerning the role played by postoperative seizure control for cognitive functioning are equivocal. Leonard[51], for example, found that adult patients with good seizure control performed better than those with poor seizure control on a variety of cognitive measures including tests of intelligence, and Lieb *et al.*[41] reported impairment in Full Scale IQ in 63 % of adult patients with poor postoperative seizure relief. On the other hand, in a study of Westerveld *et al.*[21] seizure relief was not significantly predictive of postoperative change in IQ scores in children. One recent study have shown that the postoperative EEG may have predictive value for cognitive functioning[52].

Even though several follow-up studies have described a decline in IQ scores in children with refractory epilepsy, the way the changes progress is not well known. The issue was addressed in a study by Neyens *et al.*[8] who administered intelligence tests three times with approximately 6 months test–retest intervals to children with epilepsy. They found a relatively decline in children with epilepsy compared to controls, and this decline was greater in children with a recent onset of seizures than in those who had a longer duration of epilepsy. The investigators interpreted the results to partly support a cascadic model for intellectual deterioration. According to this model children with epilepsy are supposed to show a process of mental deterioration shortly after the onset of epilepsy. The results in our sample of children with medically refractory seizures do not fit well into this model. There were no significant correlations between duration of epilepsy at Test 1 and changes in IQ scores from Test 1 to Test 2 (P-values > 0.7). Inspection of the scatterplots revealed one extreme outlier, a child who increased the Verbal, Performance and Full Scale IQ scores by 31, 18, and 29 points, respectively. Even with this case removed, the correlations were not significant (P-values > 0.8). On the other hand, with the outlier removed from the data set a significant negative correlation was obtained between the duration of the preoperative test–retest interval and changes in Verbal IQ scores ($P < 0.02$), and close to significant correlations with Full Scale IQ scores ($P < 0.06$) (Fig. 1). As our sample of children had had their epilepsy for more than 5 years on average at the first assessment, these results suggest that changes in intelligence may follow an approximately linear trend for several years. One explanation of the differences between the study by Neyens *et al.*[8] and the present one may be related to differences in the severity of the seizure disorder, as six of the 11 children in the former study responded well to drug treatment and were seizure free at the end of the follow-up period, while this was not the case preoperatively in any of our children.

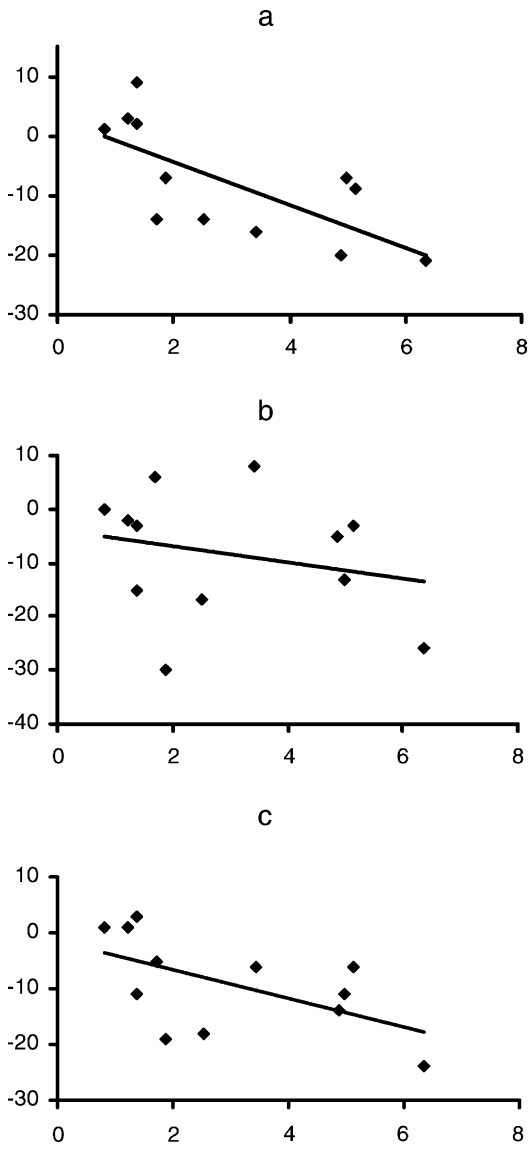

Fig. 1: Changes in Verbal (*a*); Performance (*b*); and Full Scale (*c*) IQ scores with different peroperative test–retest intervals (years) in children.

Since the present data suggest that changes in IQ scores may follow a linear course, pre- and postoperative follow-up intervals of the same length would be

preferable. This was, however, not possible to secure as the selection of patients was done retrospectively. The preoperative test–retest interval was 4 years and the postoperative follow-up interval was 2.1 years, on average. To take these differences into consideration we adjusted the individual IQ scores at Test 1 in all patients *as if* the pre- and postoperative test–retest intervals were equal, using linear interpolation. If IQ1, IQ2, and IQ3 were IQ scores at Test 1, Test 2 and Test 3, respectively, the new (recomputed) IQ score at Test 1 was: $IQ1new = IQ2 - ((IQ2 - IQ1/(T2 - T1)) \times (T3 - T2))$ where T1, T2 and T3 were points of time of the respective test sessions. A similar analysis of variance as performed above with these adjusted IQ scores at Test 1 gave essentially the same results: no group effects, a significant test effect for Verbal IQ ($F(2, 52) = 5.0$, $P < 0.02$) and significant interaction effects in Verbal IQ ($F(2, 52) = 12.8$, $P < 0.001$), Performance IQ ($F(2, 52) = 5.4$, $P < 0.01$) and Full Scale IQ ($F(2, 52) = 12.9$, $P < 0.001$). Two alterations occurred, however, in the *post hoc* test results: The preoperative decline in Performance IQ and the postoperative decline in Full Scale IQ became significant in the children (both P-values < 0.05).

The joint conclusions to be drawn from these two analyses are that Verbal, Performance, and Full Scale IQ scores follow significantly different courses in children and adults. In children, IQ scores from serial testing show a decline, while adults maintain IQ scores at a stable level. Furthermore, children may be more at risk for a decline in Performance than Verbal IQ during drug treatment, while the situation seems to be the other way round following surgery. As Verbal and Performance subscales are all entered into the calculation of Full Scale IQ scores, both kinds of treatment pose a risk for decline in general intelligence in the children.

Individual changes

Drug treatment versus surgery

The proportions of patients undergoing changes in IQ scores equal to or greater than 10 points were largely the same during drug treatment and following surgery (Table 3). About 40% of the children declined both pre- and postoperatively, while most adults obtained stable results. Only one patient in each group experienced a gain in Full Scale IQ scores. These findings illustrate that the prospects for a substantial improvement in intellectual functioning following surgery may be modest even in seizure free patients ($n = 12$), in line with previous findings in children[21] and in adults[15, 16]. Drug withdrawal would probably not make any great difference[53, 54].

Effects of surgery on preoperative cognitive decline

This question have been addressed in a case study by Jambaqué *et al*.[26], who found a postoperative increase in Verbal IQ following left temporal lobectomy in a child who had gone through a preoperative deterioration in academic achievement. To our knowledge, this is the only previous report of a reversal of a preoperative decline in functioning subsequent to a focal resection. In a study of intellectual change in children treated by lesionectomy Bourgeois *et al*.[52] found indices of a progressive preoperative cognitive deterioration in 18%, and a postoperative improvement in 25% of children who became seizure free. Unfortunately, the postoperative outcome in the children who declined preoperatively was not reported separately. In the present study, we found no further decline in three of six children who had experienced a significant preoperative drop in Full Scale IQ. These three children were all seizure free 2 years after surgery (Engel class Ia). All of them had been treated with temporal lobectomy, one left and two right. Two of the three children who continued to decline had no reduction in seizure frequency after surgery (class IVb). They were both treated with temporal lobectomy, one left and one right. The third child who declined was seizure free, but had gone through a multilobar resection in the left hemisphere, and was the only one who developed a permanent postoperative neurological deficit. The present results thus lend some support to the supposition that epilepsy surgery may arrest an ongoing preoperative intellectual deterioration in patients who become seizure free.

A developmental model

Changes in IQ scores may have different implications in children and adults. We have previously proposed a developmental model to account for the different courses in intellectual functioning in the two groups[32]. Refractory epilepsy seems to retard the intellectual development in many of our children, which is reflected in a diminishing IQ, while the impact of recurrent seizures is not severe enough to reduce intellectual functioning substantially in adults, at least not adults with relatively early onset of seizures.

Methodological considerations

Ideally, the comparison of medical and surgical treatment should be done prospectively in controlled clinical trials with patients who are randomised either to a prolongation of medical treatment before surgery, or to immediate surgery. This also would

make it possible to secure pre- and postoperative observation periods of equal length. Such an approach was chosen in a recent study by Wiebe *et al.*[55] who randomly assigned patients to surgery or treatment with antiepileptic drugs for 1 year. Effects on seizures and quality of life were considered. The investigators concluded that surgery is clearly superior to drug treatment with respect to both outcome measures. However, this approach is controversial, because of the risks inherent in the diagnosis of medically intractable seizures[56, 57].

The retrospective approach chosen in the present study, although avoiding ethical concerns and problems with respect to differences between surgical and non-surgical groups of patients, may limit the generalisability of findings. As the patients had been referred to the epilepsy centre several years prior to the preoperative evaluation, they might have had a more serious epilepsy than is usually found in the population of surgical candidates. This may be one reason why children in the present study as a group had a poorer prognosis with respect to pre- to post-postoperative intellectual changes than reported in previous studies[19, 58, 59]. The findings by Austin *et al.*[60] that children with high as opposed to low initial seizure severity continued to obtain low scores in academic achievement despite improvement in the seizure condition, support this view.

Another prognostic factor for postoperative change in cognitive functioning in which our group of children seems to differ from many previous studies is the preoperative duration of epilepsy[19, 46, 52, 61]. Meyer *et al.*[61] clearly demonstrated that the chance for a positive postoperative change was inversely related to the preoperative duration of epilepsy. Inspection of their data shows that the risk for a negative change is drastically increased when preoperative duration of epilepsy exceeds 7 years. This may be another reason why so many children in the present study experienced a drop in postoperative IQ, since the duration of epilepsy when surgery was performed was 9 years on average.

A comparison between the patients selected for the present study and the remaining 132 surgical candidates at the time of the preoperative assessment showed that the selected patients had a significantly earlier age at onset of seizures (7.4 vs. 11.5 years, $t = 2.2$, $P < 0.05$, *t*-test for independent samples) and were younger than the remaining patients (22.2 vs. 29.4 years, $t = 3.2$, $P < 0.01$). On the other hand, duration of epilepsy, Verbal, Performance, and Full Scale IQ scores did not vary significantly between groups (all *P*-values > 0.4). Thus, our results may apply mainly to relatively young surgical candidates with early onset of refractory seizures, and, presumably, a relatively severe seizure condition.

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REFERENCES

1. Duncan, J. S. Principles of treatment of patients with chronic active epilepsy. In: *The Treatment of Epilepsy* (Eds S. Shorvon, F. Dreifuss, D. Fish and D. Thomas). Oxford, Blackwell, 1996: pp. 177–190.
2. Meador, K. J. Cognitive side effects of antiepileptic drugs. *The Canadian Journal of Neurological Sciences* 1994; **21**: 12–16.
3. Hopkins, A. and Shorvon, S. Definitions and epidemiology of epilepsy. In: *Epilepsy*, 2nd Edition (Eds A. Hopkins, S. Shorvon and G. Cascino). London, Chapman and Hall, 1995: pp. 1–24.
4. Lindsay, J., Ounsted, C. and Richards, P. Long-term outcome in children with temporal lobe seizures. V. Indications and contra-indications for neurosurgery. *Developmental Medicine and Child Neurology* 1984; **26**: 25–32.
5. Kotagal, P., Rothner, D., Erenberg, G., Cruse, R. P. and Wyllie, E. Complex partial seizures of childhood onset. A 5-year follow-up study. *Archives of Neurology* 1987; **44**: 1177–1180.
6. Czochanska, J., Langner-Tyszka, B., Losiowski, Z. and Schmidt-Sidor, B. Children who develop epilepsy in the first year of life: a prospective study. *Developmental Medicine and Child Neurology* 1994; **36**: 344–350.
7. Holmes, M. D., Dodrill, C. B., Wilkus, R. J., Ojemann, L. M. and Ojemann, G. A. Is partial epilepsy progressive? Ten-year follow-up of EEG and neuropsychological changes in adults with partial seizures. *Epilepsia* 1998; **39**: 1189–1193.
8. Neyens, L. G., Aldenkamp, A. P. and Meinardi, H. M. Prospective follow-up of intellectual development in children with a recent onset of epilepsy. *Epilepsy Research* 1999; **34**: 85–90.
9. Kalska, H. Cognitive changes in epilepsy. A 10-year follow-up. *The Finnish Society of Sciences and Letters* 1991.
10. Selwa, L. M., Berent, S., Giordano, B., Henry, T. R., Buchtel, H. A. and Ross, D. A. Serial cognitive testing in temporal lobe epilepsy: longitudinal changes with medical and surgical therapies. *Epilepsia* 1994; **35**: 743–749.
11. Engel Jr, J., Van Ness, P. C., Rasmussen, T. B. and Ojemann, L. M. Outcome with respect to epileptic seizures. In: *Surgical Treatment of the Epilepsies*, 2nd Edition (Ed. J. Engel Jr). New York, Raven Press, 1993: pp. 609–621.
12. Sperling, M. R. Who should consider epilepsy surgery? Medical failure in the treatment of epilepsy. In: *The Surgical Management of Epilepsy* (Eds A. R. Wyler and B. P. Hermann). Boston, Butterworth, 1994: pp. 26–31.
13. Duchowny, M. S., Harvey, S., Sperling, M. R., Williamson, P. D. Indications and criteria for surgical intervention. In: *Epilepsy: a Comprehensive Textbook* (Eds J. Engel Jr and T. A. Pedley). Philadelphia, Lippincott, 1997: pp. 1677–1685.
14. Chelune, G. J., Naugle, R. I., Luders, H., Sedlak, J. and Awad, I. A. Individual change after epilepsy surgery: practice effects and base-rate information. *Neuropsychology* 1993; **7**: 41–52.
15. Hermann, B. P. and Wyler, A. R. Neuropsychological outcome of anterior temporal lobectomy. *Journal of Epilepsy* 1988; **1**: 327–334.

16. Phillips, N. A. and McGlone, J. Grouped data do not tell the whole story: Individual analysis of cognitive change after temporal lobectomy. *Journal of Clinical and Experimental Neuropsychology* 1995; **17**: 713–724.
17. Seidenberg, M., Hermann, B., Wyler, A. R., Davies, K., Cohan, F. C. and Leveroni, C. Neuropsychological outcome following anterior temporal lobectomy in patients with and without the syndrome of mesial temporal lobe epilepsy. *Neuropsychology* 1998; **12**: 303–316.
18. Oxbury, S. M., Creswell, C. S., Oxbury, J. M. and Adams, C. B. T. Neuropsychological outcome after temporal lobe epilepsy surgery in children under 16 years of age: 5-year follow-up. *Epilepsia* 1996; **37** (Suppl. 5): 183.
19. Szabo, C. A., Wyllie, E., Stanford, L. D. *et al.* Neuropsychological effect of temporal lobe resection in preadolescent children with epilepsy. *Epilepsia* 1998; **39**: 814–819.
20. Knight, E. S., Oxbury, J. M., Oxbury, S. M. and Middleton, J. A. Cognitive development in children under 12 years of age after temporal lobe epilepsy surgery (TLES) for dysembryoplastic neuroepithelial tumor (DNET). *Epilepsia* 1998; **39** (Suppl. 6): 172.
21. Westerveld, M., Sass, K. J., Chelune, G. J. *et al.* Temporal lobectomy in children: cognitive outcome. *Journal of Neurosurgery* 2000; **92**: 24–30.
22. Løyning, Y. Selection of patients for surgery. In: *Paediatric Epilepsy* (Eds M. Sillanpää, S. I. Johannessen, G. Blennow and M. Dam). Petersfield, Wrightson Biomedical Publishing Ltd, 1990: pp. 295–310.
23. Shields, W. D., Duchowny, M. S. and Holmes, G. L. Surgically remediable syndromes of infancy and early childhood. In: *Surgical Treatment of the Epilepsies*, 2nd Edition (Ed. J. Engel Jr). New York, Raven Press, 1993: pp. 35–48.
24. Huttenlocher, P. R. When does childhood epilepsy become intractable? Indications and contraindications for epilepsy surgery in children. *Seminars in Pediatric Neurology* 1994; **1**: 118–126.
25. Lindsay, J., Ounsted, C. and Richards, P. Hemispherectomy for childhood epilepsy: a 36-year study. *Developmental Medicine and Child Neurology* 1987; **29**: 592–600.
26. Jambaqué, I., Pinard, J. M., Dulac, O. and Ponsot, G. Neuropsychologie et chirurgie de l'épilepsie chez l'enfant. *Approche neuropsychologique des apprentissages chez l'enfant* 1992; **4**: 9–14.
27. Guldvog, B., Løyning, Y., Hauglie-Hanssen, E., Flood, S. and Bjørnæs, H. Surgical versus medical treatment for epilepsy. I. Outcome related to survival, seizures, and neurologic deficit. *Epilepsia* 1991; **32**: 375–388.
28. Dikmen, S. and Matthews, C. G. Effect of major motor seizure frequency upon cognitive-intellectual functions in adults. *Epilepsia* 1977; **18**: 21–29.
29. Farwell, J. R., Dodrill, C. B. and Batzel, L. W. Neuropsychological abilities of children with epilepsy. *Epilepsia* 1985; **36**: 395–400.
30. Kløve, H. and Fitzhugh, K. B. The relationship of differential EEG patterns to the distribution of Wechsler–Bellevue scores in a chronic epileptic population. *Journal of Clinical Psychology* 1962; **18**: 334–337.
31. Dodrill, C. B. and Wilkus, J. Relationships between intelligence and electroencephalographic epileptiform activity in adult epileptics. *Neurology* 1976; **26**: 525–531.
32. Bjørnæs, H., Stabell, K., Henriksen, O. and Løyning, Y. The effects of refractory epilepsy on intellectual functioning in children and adults. A longitudinal study. *Seizure* 2001; **10**: 250–259.
33. Engel Jr, J. Outcome with respect to seizures. In: *Surgical Treatment of the Epilepsies* (Ed. J. Engel Jr). New York, Raven Press, 1987: pp. 553–571.
34. Wechsler, D. *Manual for the Wechsler Intelligence Scale for Children-Revised*. New York, The Psychological Corporation, 1974. Norwegian translation and standardisation by J. O. Undheim, 1978.
35. Wechsler, D. *Manual for the Wechsler Adult Intelligence Scale*. New York, The Psychological Corporation, 1955. Norwegian translation and standardisation by H. Engvik, O. Hjerkinn and S. Seim, 1978.
36. Flynn, J. R. The mean IQ of Americans: massive gains 1932 to 1978. *Psychological Bulletin* 1984; **95**: 29–51.
37. Matarazzo, J. D., Carmody, T. P. and Jacobs, L. D. Test–retest reliability and stability of the WAIS: a literature review with implications for clinical practice. *Journal of Clinical Neuropsychology* 1980; **2**: 89–105.
38. Wechsler, D. *Manual for the Wechsler Intelligence Scale for Children-Revised*. New York, The Psychological Corporation, 1974.
39. Dodrill, C. B. and Wilensky, A. J. Neuropsychological abilities before and after 5 years of stable antiepileptic drug therapy. *Epilepsia* 1992; **33**: 327–334.
40. Rausch, R., Henry, T. R., Ary, C. M., Engel Jr, J. and Mazziotta, J. Asymmetric interictal glucose hypometabolism and cognitive performance in epileptic patients. *Archives of Neurology* 1994; **51**: 139–144.
41. Lieb, J. P., Rausch, R., Engel Jr, J., Brown, W. J. and Crandall, P. H. Changes in intelligence following temporal lobectomy: relationship to EEG activity, seizure relief, and pathology. *Epilepsia* 1982; **23**: 1–13.
42. Catron, D. W. and Thompson, C. C. Test–retest gains in WAIS scores after four retest intervals. *Journal of Clinical Psychology* 1979; **35**: 352–357.
43. Nesselroade, J. R., Stigler, S. M. and Baltes, P. B. Regression toward the mean and the study of change. *Psychological Bulletin* 1980; **88**: 622–637.
44. Hermann, B. P., Wyler, A. R., VanderZwagg, R. *et al.* Predictors of neuropsychological change following anterior temporal lobectomy: role of regression toward the mean. *Journal of Epilepsy* 1991; **4**: 139–148.
45. Bourgeois, B. F. D., Prensky, A. L., Palkes, H. S., Talent, B. K. and Busch, S. G. Intelligence in epilepsy: a prospective study in children. *Annuals of Neurology* 1983; **14**: 438–444.
46. Gilliam, F., Wyllie, E., Kashden, J. *et al.* Epilepsy surgery outcome: comprehensive assessment in children. *Neurology* 1997; **48**: 1368–1374.
47. *Statistica for Windows*. StatSoft, Inc., Tulsa, USA, 2000.
48. Alpherts, W. C., Vermeulen, J., Franken, M., Aldenkamp, A. P. and van Veelen, C. W. No adverse effects on intelligence 6 years after surgery for epilepsy. *Nederlands Tijdschrift voor Geneeskunde* 1999; **143**: 251–254 [Article in Dutch].
49. Rodin, E. A., Schmaltz, S. and Twitty, G. Intellectual functioning of patients with childhood-onset epilepsy. *Developmental Medicine and Child Neurology* 1986; **28:** 25–33.
50. Ivnik, R. J., Sharbrough, F. W. and Laws Jr, E. R. Effects of anterior temporal lobectomy on cognitive function. *Journal of Clinical Psychology* 1987; **43**: 128–137.
51. Leonard, G. Temporal lobe surgery for epilepsy: neuropsychological variables related to surgical outcome. *The Canadian Journal of Neurological Sciences* 1991; **18**: 593–597.
52. Bourgeois, M., Sainte-Rose, C., Lellouch-Tubiana, A. *et al.* Surgery of epilepsy associated with focal lesions in childhood. *Journal of Neurosurgery* 1999; **90**: 833–842.
53. Chen, Y., Chi Chow, J. and Lee, I. Comparison the cognitive effect of anti-epileptic drugs in seizure-free children with epilepsy before and after drug withdrawal. *Epilepsy Research* 2001; **44**: 65–70.
54. Aldenkamp, A. P., Alpherts, W. C., Blennow, G. *et al.* Withdrawal of antiepileptic medication in children—effects on cognitive function: the Multicenter Holmfrid Study. *Neurology* 1993; **43**: 1861–1862.

55. Wiebe, S., Blume, W. T., Girvin, J. P. and Eliasziw, M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *The New England Journal of Medicine* 2001; **345**: 311–318.
56. Nakken, K. O. Medical risks in intractable epilepsy. In: *Intractable Epilepsy* (Eds S. I. Johannessen, L. Gram, M. Sillanpää and T. Tomson). Petersfield, UK, Wrightson Biomedical Publishing Ltd, 1995: pp. 171–182.
57. Sillanpää, M., Jalava, M., Kaleva, O. and Shinnar, S. Long-term prognosis of seizures with onset in childhood. *Epilepsia* 1998; **39**: 744–748.
58. Oxbury, S. M., Creswell, C. S., Oxbury, J. M. and Adams, C. B. T. Neuropsychological outcome after temporal lobe epilepsy surgery in children under 16 years of age: 5 year follow-up. *Epilepsia* 1996; **37** (Suppl. 5): S183.
59. Williams, J., Griebel, M. L., Sharp, G. B. and Boop, F. A. Cognition and behavior after temporal lobectomy in pediatric patients with intractable epilepsy. *Pediatric Neurology* 1998; **19**: 189–194.
60. Austin, J. K., Huberty, T. J., Huster, G. A. and Dunn, D. W. Does academic achievement in children with epilepsy change over time? *Developmental Medicine and Child Neurology* 1999; **41**: 473–479.
61. Meyer, F. B., Marsh, W. R., Laws Jr, E. R. and Sharbrough, F. W. Temporal lobectomy in children with epilepsy. *Journal of Neurosurgery* 1986; **64**: 371–376.