



Psychopathology, psychosocial functioning, and IQ before and after epilepsy surgery in children with drug-resistant epilepsy

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ARTICLE INFO

Article history:

Received 27 August 2008

Revised 3 October 2008

Accepted 31 October 2008

Available online 19 November 2008

Keywords:

Epilepsy surgery

Children

Treatment outcome

Psychopathology

Children's global assessment scale

Cognition

Attention deficit hyperactivity disorder

Pervasive developmental disorder

Autism

ABSTRACT

This is a prospective study of a consecutive series of children undergoing epilepsy surgery. The main aims were to evaluate the heterogeneity with respect to psychopathology and IQ, and to use a global assessment scale (Children's Global Assessment Scale [CGAS]) to evaluate psychosocial functioning. Clinical neuropsychiatric and neuropsychological assessments were made at baseline and at the 2-year follow-up in 24 patients, and changes were analyzed at an individual level. Psychiatric disorders (mainly attention deficit hyperactivity disorder and/or autism spectrum disorders) were found in 17 of 24 at some point. All except one child with psychiatric diagnoses before surgery still had at least one diagnosis at follow-up. Intellectual ability remained stable in the majority of cases, both in individuals with and in individuals without mental retardation. The CGAS illustrated the consequences of the extensive comorbidity in this cohort. The behavioral problems had been undiagnosed despite parental concern in many cases, indicating an unrecognized need for services for children with drug-resistant epilepsy.

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1. Introduction

Medically intractable epilepsy is a neurological condition with a significant impact on the affected child and her or his family. The aim of epilepsy surgery is usually to cure the patient of drug-resistant seizures, but in children with catastrophic epilepsy, the aim may also be to reduce seizure frequency or seizure severity to prevent cognitive and behavioral deterioration [1]. Outcome with respect to seizure control after epilepsy surgery is well documented, as are cognitive effects. The general cognitive level often remains stable at a group level [2–4]. The histopathological diagnoses, the localization of the lesion, and the surgical procedure have implications for outcome. Better seizure outcome after surgery is reported in patients with vascular malformations and tumors, and worse outcome is reported in patients with malformations of cortical development (MCDs) and gliosis [5]. Hemispherectomies carry the best prognosis, followed by temporal lobe resections (60–80% seizure free) [6].

Outcome with respect to psychopathology and behavior in children has received more attention only recently. Reports of behav-

ioral outcome after surgery have often relied on anecdotal information or retrospective analyses of medical data [7]. Neuropsychological assessment before and after surgery is an accepted tool for quality and outcome control, but is not equivalent to neuropsychiatric assessment, and the two complement each other. There are positive reports on postsurgical developmental and behavioral outcome in children with drug-resistant epilepsy [1,8,9], but there are also less favorable reports [10].

Children with severe epilepsy who are candidates for epilepsy surgery constitute a heterogeneous group. Neurodevelopmental disorders such as mental retardation (MR), pervasive developmental disorders (PDDs)—including autistic disorder, Asperger syndrome, and PDD not otherwise specified (NOS)—and attention deficit hyperactivity disorder (ADHD) are common [11]. Intellectual functioning may range from superior to profound MR.

The PDDs, which occur in 0.5–1% of children in the general population, are characterized by severe reciprocal social and communication difficulties in combination with repetitive behavior, and are documented in 19–38% of pediatric candidates for resective surgery [10,12]. There are some follow-up studies on the outcome of epilepsy surgery in children with PDD, and in most cases, there appear to be no or minor effects concerning the core deficits in social interaction, communication, and rigid or repetitive behaviors,

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but in some cases associated behavioral problems improve [10,13,14].

ADHD, one of the disruptive behavior disorders, is the most common behavioral disorder of childhood. It affects 3–5% of school-aged children [15,16] and is four to five times more frequent in children with epilepsy [17,18]. In McLellan and colleagues' study [10] on children undergoing temporal lobe resections, 27% had ADHD. Oppositional defiant disorder (ODD), another disruptive behavior disorder, often comorbid with ADHD, consists of repetitive and persistent oppositional and disobedient behaviors directed toward authority figures. The prevalence of ODD is less well established.

The efficacy of an intervention can be established on the basis of symptomatic improvement, but this is not always the same as functional improvement. Global assessment of psychosocial functioning has been used in intervention studies as a clinically meaningful measure incorporating several aspects of functioning [19]. Global assessment scales, such as the Children's Global Assessment Scale (CGAS), have been used in studies not only of psychiatric disorders, but also of physical disorders [20–23].

The main aims of this prospective 2-year follow-up study were (1) to evaluate the complexity and heterogeneity with respect to psychopathology and IQ in a pediatric epilepsy surgery series, and (2) to use a global assessment scale for the evaluation of psychosocial functioning. We wanted to examine the spectrum of clinical neuropsychiatric disorders (including their degree of overlap and comorbidity) and establish the rate of psychiatric disorders before and after surgery. A secondary aim was to examine whether questionnaires given to parents could identify the psychiatric disorders in children with drug-resistant epilepsy.

2. Methods

2.1. Subjects

Twenty-five children and adolescents (15 boys, 10 girls) consecutively operated on for drug-resistant epilepsy at Sahlgrenska University Hospital in Sweden between 2002 and May 2006 were assessed before epilepsy surgery and at follow-up 2 years after surgery. Children who underwent callosotomy were excluded, as were children referred to our center from other Nordic countries, as the greater part of their presurgical assessments had been done in their home countries.

Fifteen children had epilepsy onset before 5 years of age; the median age at epilepsy onset was 4.0 (Q_1 : 2.6, Q_3 : 8.6, range: 0–17.7) years. Median duration of epilepsy was 6.9 (Q_1 : 2.7, Q_3 : 9.5, range: 0.3–18.9) years, and median age at surgery was 13.4 (Q_1 : 9.3, Q_3 : 16.3, range: 4.2–19.4) years. One girl with no psychopathology and of average intelligence died from sudden unexpected death 22 months after surgery. She had been seizure free after a temporal lobe resection on the right side at age 14 (histopathological diagnosis: gliosis).

Table 1 lists the baseline characteristics of the remaining 24 cases.

Two subjects had cerebral palsy (Nos. 1 and 18) and two had tuberous sclerosis (Nos. 12 and 24). Sixteen had at least daily seizures. The surgical location was temporal in nine, frontal in eight, parietal in two, and occipital in two. In three subjects there were disconnections of hypothalamic hamartomas. The histopathological diagnoses were lesions ($n=5$), cortical malformations ($n=6$), cortical malformations in combination with gliosis ($n=6$), gliosis ($n=2$), tuberous sclerosis ($n=2$), and hypothalamic hamartomas ($n=3$). Lesions encompassed two gangliogliomas, one astrocytoma, and two dysembryoplastic neuroepithelial tumors (DNETs); cortical malformations included both major malforma-

tions and microdysgenesis [24]; and gliosis included both atrophic–gliotic lesions and mesial sclerosis. Three cases (Nos. 11, 12, and 21) were reoperated during the follow-up period, and outcome was assessed 2 years after the second operation; the histopathological diagnoses were the same except in one case (No. 21) (see Table 1). No major surgical complications were noted. Two-year seizure outcome was categorized as class 1, seizure free ($n=7$); class 2, not seizure free but >75% reduction in seizure frequency ($n=7$); class 3, 50–75% reduction in seizure frequency ($n=5$); and class 4, <50% reduction in seizure frequency ($n=5$). No child was taking psychotropic medications at baseline, but at follow-up one child (No. 1) was being treated with methylphenidate and another (No. 24) with risperidone.

2.2. Procedures

2.2.1. The assessment of psychopathology

All patients underwent clinical neuropsychiatric assessments by the first author before and 2 years after epilepsy surgery. The neuropsychiatric assessment included an in-depth clinical interview covering, in a systematic fashion, family and school functioning, symptoms of MR, learning disorders, communication disorders, PDD, attention deficit and disruptive behavior disorders, tic disorders, separation anxiety disorder, obsessive–compulsive disorder, and depression. The assessment of children with PDD also included further multidisciplinary workup using the Diagnostic Interview for Social and Communication Disorders (DISCO) [25] and the Autism Diagnostic Observation Schedule–Generic (ADOS-G) [26]. Psychopathology was diagnosed according to DSM-IV criteria [15], but subjects diagnosed with PDD-NOS fulfilled at least five DSM-IV criteria for autistic disorder with or without first symptoms before the age of 3. ADHD co-occurring with PDD and/or MR was also diagnosed. ADHD was divided into the predominantly inattentive type-impulsive (ADHD-I), predominantly hyperactive-impulsive type (ADHD-H), and combined type (ADHD-C). Disruptive behavior disorder not otherwise specified (DBD-NOS) was diagnosed in subjects with a behavioral disturbance characterized by rage attacks, lability, and disinhibition significantly interfering with functioning.

Behaviors reported as troublesome by the parents' at the baseline semistructured neuropsychiatric interview were discussed again at follow-up, as were new problematic behaviors, and the parents' perception of possible change in behavior was classified by the first author as positive, no change, or negative.

2.2.1.1. *Questionnaires included in the neuropsychiatric assessment.* The Strengths and Difficulties Questionnaire (SDQ). The SDQ is a parent and teacher screening questionnaire on the adjustment and psychopathology of 3- to 16-year-olds [27]. The response alternatives consist of 25 statements in the domains Emotional Symptoms, Conduct Problems, Hyperactivity/Inattention, Peer Relationship Problems, and Prosocial Behavior. Parents are asked to disagree (0), agree to some extent (1), or agree (2). The sum score of 20 items of all domains except Prosocial Behavior generates a Total Difficulties score with a range of 0 to 40. A score of at least 14 on the Swedish version of the SDQ is considered abnormal [28].

The Conners' Brief Parent Rating Scale (BPRS). Conners' BPRS is a 10-item attention deficit hyperactivity questionnaire that was constructed from Conners' Parent Rating Scale [29,30]. The scale yields a total sum score of 0 to 30, and scores above 10 indicate possible ADHD.

The Autism Spectrum Screening Questionnaire (ASSQ). The ASSQ (previously known as the Asperger Syndrome and High-Functioning Autism Screening Questionnaire) is a 27-item parent and teacher questionnaire [31] that yields a total score ranging from 0 to 54. A score >15 indicates a possible PDD in children 6–17 years old [32,33].

Table 1
Baseline characteristics of the individuals in the study (n = 24)

ID	IQ category ^a	Age at surgery (years)	Epilepsy duration (years)	Sex	DSM-IV diagnoses ^b	Baseline seizure frequency (per month)	Surgical procedure/ side ^c	Histopathological diagnosis	Seizure outcome class ^d
1	A	5.4	1.0	F	PDD-NOS, ADHD-C, DBD-NOS	5	FLR/L	Giosis	3
2	A	9.5	6.5	M	ADHD-C, ODD	12	TLR/L	Cortical malformation, gliosis	1
3	A	9.5	5.5	F	0	11	PLR/R	Cortical malformation	2
4	A	12.8	0.3	M	0	450	OLR/R	Lesion	1
5	A	12.9	8.8	F	0	25	FLR/R	Cortical malformation	2
6	A	14.8	7.2	F	0	60	FLR/L	Lesion	2
7	A	16.6	9.1	F	0	50	TLR/R	Lesion	1
8	Near A	4.2	2.0	F	0	15	TLR/L	Cortical malformation	1
9	Near A	7.7	3.6	M	0	98	FLR/R	Cortical malformation	3
10	Near A	11.2	4.5	M	0	9	OLR/R	Cortical malformation, gliosis	1
11	Near A	12.1	2.0	F	Mixed receptive/ expressive language disorder	25	1st op: TLR/L 2nd op: TLR/L	1st op: lesion 2nd op: lesion	Reop <2 years: 3
12	Near A	14.2	2.2	M	ADHD-I, DBD-NOS	60	1st op: PLR/L 2nd op: PLR/L	1st op: tuberous sclerosis 2nd op: tuberous sclerosis	Reop <2 years: 4
13	Near A	17.4	13.9	M	ADHD-I	40	TLR/L	Cortical malformation, gliosis	2
14	Near A	17.6	0.4	F	0	38	TLR/L	Lesion	2
15	Near A	19.4	18.9	M	PDD-NOS	62	Open disconnection/R	Hypothalamic hamartoma	4
16	MildMR	6.3	3.2	F	PDD-NOS, ADHD-C, DBD-NOS	100	FLR/L	Cortical malformation, gliosis	4
17	ModMR	8.2	8.2	M	Autistic disorder, ODD	182	Open disconnection	Hypothalamic hamartoma	4
18	ModMR	13.4	9.9	M	Autistic disorder	17	TLR/R	Cortical malformation, gliosis	1
19	ModMR	14.6	9.1	M	0	10	FLR/R	Cortical malformation	2
20	ModMR	16.0	14.8	M	ADHD-I, ODD	345	FLR/R	Cortical malformation, gliosis	3
21	ModMR	16.7	6.9	M	ADHD-I	450	1st op: TLR/L 2nd op: POLR/L	1st op: gliosis 2nd op: cortical malformation, gliosis	Reop <2 years: 4
22	ModMR	18.0	14.0	M	ADHD-C, DBD-NOS	90	FLR/R	Cortical malformation	1
23	SMR	15.7	15.7	M	PDD-NOS, ADHD-I, DBD-NOS	280	Endoscopic disconnection/L	Hypothalamic hamartoma	3
24	PMR	9.1	9.0	M	Autistic disorder, DBD-NOS	300	TLR/L	Tuberous sclerosis	2

^a A, IQ >84; Near A, IQ 70–84; MildMR, IQ 50–69; ModMR, IQ 35–49; SMR, IQ 20–34; PMR, IQ <20.

^b PDD-NOS, pervasive developmental disorder not otherwise specified; ADHD-C, attention deficit hyperactivity disorder—combined type; ADHD-I, attention deficit hyperactivity disorder—inattentive type; DBD-NOS, disruptive behavior disorder not otherwise specified; ODD, oppositional defiant disorder.

^c TLR, temporal lobe resection; FLR, frontal lobe resection; PLR, parietal lobe resection; OLR, occipital lobe resection; POLR, parieto-occipital lobe resection.

^d Class 1, seizure free; class 2, not seizure free but >75% reduction in seizure frequency; class 3, 50–75% reduction in seizure frequency; class 4, <50% reduction in seizure frequency; Reop <2 years, reoperated within 2 years of first operation; outcome 2 years after last operation.

Parents of children with mental ages below 3 years (two boys with PDD) were not given the SDQ or ASSQ. Before surgery, all parents returned Conners' BPRS, 19 returned the SDQ, and 20 returned the ASSQ. At follow-up, all parents returned Conners' BPRS, and 22 returned the SDQ and ASSQ.

2.2.2. The assessment of psychosocial functioning

General psychosocial functioning was assessed by the first author using the CGAS. The CGAS is a single global scale with 10 verbally defined hierarchical levels of functioning. It is used to rate the general functioning of children 4–16 years old and generates a score from 1 to 100 on a hypothetical continuum of mental health/illness [34]. This scale was later expanded to include the age range 0–23 years [19]. A score >70 indicates good functioning or only a mildly abnormal psychosocial situation; a score of 70–61, some difficulty in a single area, but generally functioning pretty well; a score of 60–51, variable functioning with sporadic difficulties in several but not all social areas; a score of 50–41, a moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area; a score of 40–31, major impairment of functioning in several areas and inability to function in

one of these areas; a score of 30–21, inability to function in almost all areas or serious impairment in communication; a score of 20–11 means gross impairment in all forms of communication; and a score ≤10 indicates a need for constant supervision (24-hour care).

To check interrater agreement in the CGAS assessments, the first rater created 49 case histories, describing the 25 cases preoperatively and postoperatively (one child lost to follow-up), which were given to an experienced child psychiatrist (S.S.) for scoring. The second rater was blind to information about diagnoses, and the case histories were randomly ordered. There was total interrater agreement on children with good psychosocial functioning (CGAS >70). Regarding the direction of change in the CGAS at follow-up (improvement, no change, or worsening), the two raters agreed completely in 79% of the cases. The disagreement concerned three cases where the first rater assessed improvements, i.e. higher CGAS scores of 5 to 10, while the second rater scored no change. In another two cases, the first rater scored no change in CGAS scores and the second rater assessed improvements of 4 or 5 CGAS scores. The final classification was based on the assessments made by the first rater who had met and examined the children.

2.2.3. The assessment of IQ

Intelligence or mental age was neuropsychologically (G.V.) assessed within 1 year before surgery treatment and 2 years afterward in all subjects. Children's level of functioning and mental age, rather than the chronological age, were taken into consideration when choosing the method for assessment of intelligence or development. The Swedish versions of Griffiths' Developmental Scales [35], the Wechsler Preschool and Primary Scale of Intelligence—Revised (WPPSI-R) [36], the Wechsler Intelligence Scale for Children—Third Edition (WISC-III) [37], or the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) [38] were used. One boy (No. 22) had incomplete IQ results and was excluded from analyses concerning change in cognitive ability after surgery. In subjects with severe and profound MR, the developmental quotient (DQ) equivalent to IQ was reported.

2.3. Statistical methods

The median and the quartiles Q_1 and Q_3 were used to describe the data. Possible changes in an individual's paired data were evaluated by means of cross-tables or scatterplots when suitable. Possible difference in proportions between groups was analyzed, and the 95% confidence interval (CI) for the difference in proportions according to Wilson [39] was calculated. A 95% CI not covering a zero difference is a sign of statistical significant difference in proportions, $P < 0.05$.

3. Results

Table 2 illustrates the results concerning psychopathology, intellectual abilities, and psychosocial functioning at baseline and 2 years after surgery.

3.1. Psychopathology

Psychopathology was diagnosed in 14 of 24 subjects at the pre-surgical assessment (Table 2), and in 9 of them, there was more than one diagnosis. Seven children were diagnosed with PDD. ADHD was diagnosed in nine, three of whom had PDD. Of the cases with ADHD, four had the combined type and five the predominantly inattentive type. ODD was diagnosed in three, and DBD-NOS in six children with PDD, ADHD, or both. No child had emotional disorder, tic disorder, or obsessive-compulsive disorder. One child had a mixed receptive-expressive language disorder, with Full Scale IQ in the near-average range, but a Verbal IQ of 66 and Performance IQ of 91.

Before referral to our center for assessment by the epilepsy surgery team, 4 of 24 children had been assessed psychiatrically and diagnosed with PDD (Nos. 17, 18, and 24) or ADHD (No. 13).

At the neuropsychiatric follow-up assessment 2 years after surgery (Table 2), a total of 16 children had psychopathology. In 11 of 16 there was more than one diagnosis. Seven children still had PDD. ADHD was diagnosed in eight, two of whom had the combined type and six the predominantly inattentive type. There were two children who no longer had ADHD-C, and one child who no longer had ADHD-I, but there were two new cases of ADHD-I. ODD was found in three, one of whom had ADHD-I, one PDD, and one depression. DBD-NOS remained, except in one child with autistic disorder who no longer had rage attacks interfering with functioning. Emotional disorders were present in five children in the form of separation anxiety disorder in two and depressive disorder not otherwise specified in three. In two boys the depression was characterized by passivity, increased sleepiness, and aloofness, in contrast with the girl, who was dysphoric and very irritable, and who acted out. One child still had mixed receptive-expressive language disorder.

Table 2
Psychopathology, IQ category, and psychosocial functioning before and 2 years after epilepsy surgery

DSM-IV diagnosis ^a	ID	IQ category ^b		CGAS		Seizure outcome class ^c	Behavioral change ^d
		Preop	Postop	Preop	Postop		
Autistic disorder							
Preop							
Postop							
Autistic disorder	18	ModMR	ModMR	35	61	1	Positive
Autistic disorder, ODD	17	ModMR	ModMR	20	30	4	Positive
Autistic disorder, DBD-NOS	24	PMR	PMR	5	5	2	Positive
PDD-NOS	15	Near A	Near A	48	50	4	Positive
PDD-NOS, ADHD-C, DBD-NOS	1	A	Mild MR	20	25	3	Positive
PDD-NOS, ADHD-C, DBD-NOS	16	Mild MR	Mod MR	40	17	4	Negative
PDD-NOS, ADHD-I, DBD-NOS	23	SMR	SMR	15	20	3	Positive
ADHD-C, ODD	2	A	A	61	95	1	Positive
ADHD-I, DBD-NOS	12	Near A	Near A	67	52	4	Negative
ADHD-I	13	Near A	A	61	45	2	Negative
ADHD-I, ODD	20	ModMR	ModMR	57	47	3	Negative
ADHD-I	21	ModMR	ModMR	65	65	4	No change
ADHD-C, DBD-NOS	22	ModMR	ModMR	45	50	1	Positive
Mixed receptive/ expressive language disorder	11	Near A	Near A	62	62	3	No change
0	14	Near A	A	80	60	2	Negative
0	8	Near A	Near A	85	85	1	Positive
0	7	A	A	72	91	1	Positive
0	3	A	Near A	82	60	2	Negative
0	4	A	A	95	95	1	No change
0	5	A	A	82	90	2	Positive
0	6	A	A	90	91	2	Positive
0	10	Near A	Near A	70	70	1	No change
0	9	Near A	Mild MR	79	65	3	Negative
0	19	ModMR	Mild MR	60	51	2	Negative

^a ADHD-I, attention deficit hyperactivity disorder—inattentive type; ADHD-C, attention deficit hyperactivity disorder—combined type; ODD, oppositional defiant disorder; DBD-NOS, disruptive behavior disorder not otherwise specified; PDD-NOS, pervasive developmental disorder not otherwise specified.

^b A, IQ >84; Near A, IQ 70–84; Mild MR, IQ 50–69; ModMR, IQ 35–49; SMR, IQ 20–34; PMR, IQ <20.

^c Class 1, seizure free; class 2, not seizure free but more than 75% reduction in seizure frequency; class 3, 50–75% reduction in seizure frequency; class 4, <50% reduction in seizure frequency.

^d According to the reports from parents during the neuropsychiatric interview.

In all, a diagnosis of a psychiatric disorder had been made in 17 of 24 children at the pre- or postoperative assessment, and a total of 13 had PDD, ADHD, or both. Among the children with preoperative psychopathology, one was without a diagnosis after surgery. Of the 10 children without a preoperative diagnosis, seven still had no psychiatric diagnosis at follow-up.

The questionnaires did not identify all children in our series with psychopathology according to the DSM-IV. At the preoperative assessment, 5 of 14 children with a psychiatric diagnosis reached the SDQ cutoff score for psychopathology, and 5 of 16 children did so at the 2-year follow-up. The cutoff score for ADHD according to Conners' BPRS was reached by seven of nine children with ADHD preoperatively and three of eight postoperatively. The ASSQ cutoff for PDD was reached by three of five children with PDD preoperatively and two of five postoperatively.

According to the neuropsychiatric interview with parents, there was a positive behavioral change in 12, there was no change in 4, and there was a negative change in 8 children at the 2-year follow-up (Table 2). A parental perception of a negative behavioral change was noted in 8 of 17 non-seizure-free children and in none of the seizure-free children ($P < 0.05$, 95% CI 6–69%).

3.2. Psychosocial functioning

Eight patients had CGAS scores above 70, indicating good functioning or only mildly abnormal psychosocial functioning, at the presurgical assessment, and six at follow-up (Table 2). Subjects with PDD had CGAS scores in the range 5–48 before surgery, in contrast to the children without PDD who had CGAS scores in the range 45–95.

In 16 of 24 there were improvements or no change in psychosocial functioning 2 years after surgery. Among the seven seizure-free subjects, none had worsened psychosocial functioning. The individual changes in psychosocial functioning (CGAS) are illustrated in Fig. 1.

An improvement of the CGAS score of ≥ 20 was noted for two subjects who became seizure free (Nos. 2 and 18 in Table 2). A decrease in the CGAS score of ≥ 20 was noted in three

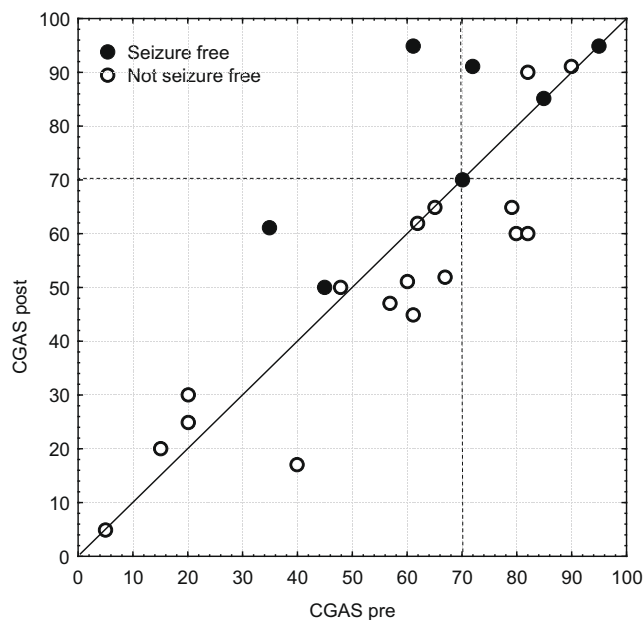


Fig. 1. Psychosocial functioning, as assessed with the CGAS, before surgery (x axis) and 2 years after surgery (y axis), for each subject ($n = 24$). Seizure free children ($n = 7$) are represented by the filled dots.

subjects (Nos. 3, 14, and 16): one girl with PDD-NOS, ADHD-C, DBD-NOS, and mild MR who had a cognitive decline and no seizure reduction after surgery; and two girls with normal psychosocial functioning before surgery, but with emotional disorders postoperatively, one with depression and ODD, and one with separation anxiety disorder and ADHD-I. Their seizure frequency was reduced by more than 75%, but they were not seizure free.

Agreement was observed between parents' perception of a negative behavioral change and a decrease of 9 to 23 CGAS scores (Table 2), as well as between no perceived behavioral change and unchanged CGAS scores. Parents' perception of a positive behavioral change was reflected as no or usually only a minor improvement in CGAS. The parents of children with PDD reported a positive behavioral change, except in one case (No. 16).

3.3. IQ

Seven children had average intelligence (IQ > 84), eight had near-average intelligence (IQ in the range 70–84), and nine had below-average intelligence (IQ < 70) with functional impairment, that is, MR (Table 2). At follow-up, 7 had an IQ > 84 , 6 had an IQ of 70–84, and 11 had MR. The individual changes in IQ in 23 children are illustrated in Fig. 2.

No change or < 8 points of change in IQ was noted in 17 of 23 children at follow-up, and in 5 children there was a decrease in IQ of ≥ 10 points. Three had a cognitive deterioration of more than 20 IQ points (Nos. 1, 9, 16); they had undergone surgical procedures in the frontal lobe, their seizure outcome class was 3 or 4, and two of them had PDD. One gained 11 IQ points (No. 19).

In Table 3, children with IQ < 70 are compared with children with IQ ≥ 70 . Baseline psychopathology was more common in the group with IQ < 70 . IQ remained stable in the majority of cases both in individuals with and in individuals without MR.

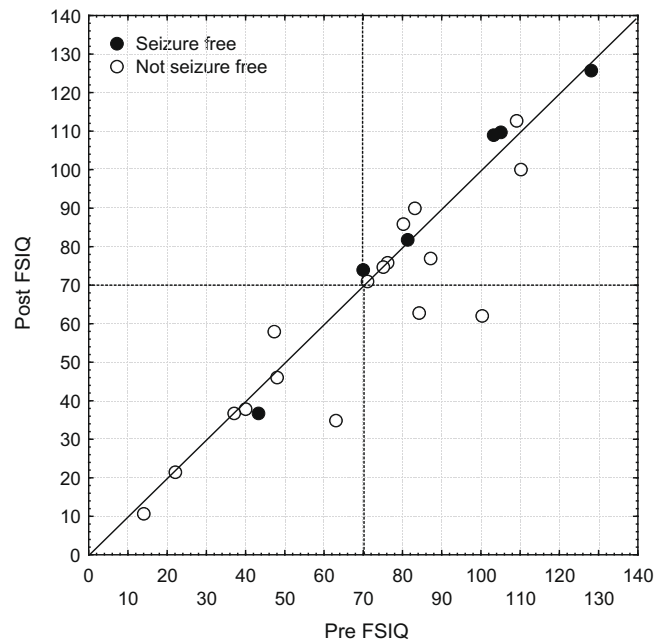


Fig. 2. Intellectual ability before surgery (x axis) and 2 years after surgery (y axis), for each subject ($n = 23$). Seizure-free children ($n = 6$) are represented by the filled dots. Median IQ at the presurgical assessment was 76 (Q₁: 47, Q₃: 100, range: 14–128). At the 2-year follow-up, median IQ was 74 (Q₁: 38, Q₃: 90, range: 11–126).

Table 3
Comparison of children with IQ <70 and IQ ≥70 at baseline

	IQ < 70 (n = 9)	IQ ≥ 70 (n = 15)
Preoperative psychopathology	8	6
Seizure outcome		
Seizure free	2	5
>75% reduction in seizure frequency or seizure freedom	4	10
Negative change >10 points in CGAS scores at follow-up	1	5
Negative intellectual change ≥10 IQ points at follow-up	1	4

4. Discussion

This is a prospective study of a consecutive case series of children with medically intractable epilepsy of different etiologies who have undergone different surgical procedures. It differs from a prospective controlled study where the aim is to test a hypothesis and in samples from populations. In our study, all children eligible for a 2-year follow-up were evaluated. The value of the study is the multivariate follow-up of outcomes; each child was compared with him- or herself and diagnoses were based on clinical neuropsychiatric examination and neuropsychological assessment. One aim of the descriptive study was to evaluate the complexity of these children. Such an evaluation is important if one wants to shed light on the fact that the outcome in this group is very heterogeneous and involves various variables, which this study shows. The conclusion that epilepsy surgery was the cause of the observed outcomes cannot be drawn without an appropriate comparison group. This is an ethical dilemma in outcome studies concerning pediatric epilepsy surgery. The heterogeneity of pediatric epilepsy surgery candidates is much greater than that of adults; recurrent seizures may represent a considerable risk for intellectual decline in children, whereas intellectual functioning seems to be less vulnerable in adults [40]. Only one epilepsy surgery study using a comparison group in the form of candidates accepted for surgery (in adults) has ever been published [41]. To date, among the pediatric epilepsy surgery studies on outcome using control groups [9,42–44], the comparison groups comprised children with drug-resistant epilepsy who could not be accepted for epilepsy surgery.

There have been very few prospective studies examining the impact of epilepsy surgery on psychopathology in children [10,14]. In the largest study on 60 children undergoing temporal lobe resections, 83% had a diagnosis at some point and a high rate of psychiatric comorbidity [10]. This was very similar to our finding of psychopathology in 71% and comorbidity in the majority of the children at the pre- or 2-year postoperative assessment. The proportion of affected children was not smaller 2 years after surgery, which is in line with McLellan and colleagues' study [10].

It has been shown that PDD is common in individuals with MR [45], and more common in individuals with severe MR than in those with mild MR [46]. Almost one-third of the children in our study had PDD, a frequency within the range of two previous studies addressing the rate of autism in pediatric candidates for epilepsy surgery [10,12]. We found a high comorbidity of MR and ADHD in PDD. In McLellan and colleagues' study, MR was significantly associated with PDD, and among the 16 children with ADHD in that study, 9 also had PDD. The fact that the parents of all children with PDD but one in our series reported positive behavioral effects at follow-up, but the children still had severe impairments in psychosocial functioning, illustrates the pervasiveness of PDD. The DSM-IV definition of the diagnostic category PDD-NOS is very broad, which makes comparison of results from different studies and interventions problematic. We chose to define PDD-NOS very stringently with the intent of not including uncertain cases. Three

additional cases had autistic traits. Multicenter studies are needed to accumulate a sufficiently large number of cases to study the effects of epilepsy surgery on children with PDD.

In children without epilepsy, ADHD is most often of the combined type, but in children with epilepsy, the inattentive type seems to be at least as common as the combined type [17]. In our series, ADHD-I was more common than ADHD-C. It has been suggested that children with epilepsy and ADHD-C are more likely to have truly independent comorbid conditions, and those with ADHD-I and epilepsy have comorbidity in which the inattention and epilepsy are both related to a common central nervous system disturbance [47]. However, in our small series, two boys with ADHD-C no longer had ADHD at follow-up. They were both seizure free after surgery.

In McLellan and colleagues' study [10], the majority of children with emotional disorders developed these disorders postoperatively, as in our study. Depressive disorder was diagnosed in three non-seizure-free teenagers at follow-up. Symptoms of depression in children with epilepsy are often underrecognized and more common than in children without epilepsy [48].

A secondary aim in this study was to examine whether questionnaires given to parents could identify the psychiatric disorders in children with drug-resistant epilepsy. The questionnaires were not used to assess behavioral outcome. We would not have identified all the children with psychopathology if we had used only the SDQ, Conners' BPRS, and ASSQ questionnaires. The children who reached the cutoff scores on the SDQ and ASSQ all had CGAS scores <70, and with one exception this was also true for Conners' BPRS. Another parental questionnaire, the Childhood Behavior Checklist (CBCL) [49], has been used to document behavioral outcome after epilepsy surgery [9,42,43], and efforts have been made to create more epilepsy-specific questionnaires not only for adults, but also for children, such as the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) [50]. There is not yet a Swedish translation of this questionnaire. According to our results, the neuropsychiatric clinical evaluation, history taking, and use of agreed diagnostic criteria, such as those from DSM-IV, in combination with the neuropsychological assessment, are still the most important assessment tools for psychopathology.

This is the first study using the CGAS to examine outcome with respect to psychosocial functioning after epilepsy surgery. The CGAS is not a measure of epilepsy-specific impact; it reflects impairments and disabilities in social interaction, communication, and behavior. The global assessment scale revealed psychosocial dysfunction in the majority of cases in our study. In most cases there was improvement or no change in psychosocial functioning at follow-up. In three of the eight cases with a change for the worse, this was caused by depression, and their deterioration in psychosocial functioning would probably be reversible with appropriate interventions. Children with PDD had the lowest scores before surgery. Although parents of six of seven children with PDD described a positive change in behavior after surgery, the CGAS scores remained quite stable in five of these cases. The CGAS revealed the consequences of the extensive comorbidity in this cohort, and could be used to illustrate the complexity of children with severe epilepsy and psychopathology.

IQ remained stable at a group level as shown in previous studies [2–4]. This was true also for a majority of individual cases both with and without MR. Our study suggests that a small positive behavioral change may be considered very positive by parents with a severely impaired child, even if it does not change the psychosocial functioning level or cognitive abilities, and a negative behavioral change may affect the psychosocial functioning level very much in a child without MR. Psychiatric disorders were more common in children with below-average intelligence and in children not rendered seizure free by surgery. Parents of children who did

not become seizure free perceived a negative behavioral change significantly more often than parents of seizure-free children.

It is known that behavioral and emotional problems often go undiagnosed in individuals with epilepsy, even if these problems may be more burdensome than the epilepsy [51–54]. Among our subjects, only four had been assessed psychiatrically before referral to our center. Recognizing and addressing behavioral issues constitute the crucial first step in treatment. Even if the cause is multifactorial [55], the interventions are built on parental awareness of the child's impairment, and include behavioral modification, rehabilitation, and, in some cases, medication.

5. Conclusion

The diagnosis of drug-resistant epilepsy is seldom the only diagnosis in a child who is being considered as a candidate for epilepsy surgery. A neurodevelopmental disorder and/or a psychiatric disorder was diagnosed in 17 of 24 children at the pre- or postsurgical assessment in our series, and contributed in a major way to the psychosocial dysfunction in affected children. The proportion of affected children was not smaller 2 years after surgery. The need for parental counseling and interventions must be met. Further prospective studies that examine the impact of epilepsy surgery on psychopathology and psychosocial functioning in children are necessary. The goal of achieving better seizure control after epilepsy surgery is a realistic one, whereas the goal of improving the psychosocial situation is unrealistic in children with psychopathology unless parents and children are offered effective interventions.

Ethical approval

The study was approved by the Medical Ethical Committee of Gothenburg University.

Acknowledgments

We are grateful to the following persons at Sahlgrenska University Hospital: Thomas Ahlsén, psychologist, and Ulrika Johansson, special teacher, at the Child Neuropsychiatry Clinic, for ADOS-G evaluations; the Epilepsy Surgery team, especially Birgitta Olovson, nurse and coordinator, and Professor Paul Uvebrant. We thank Professor Elisabeth Svensson, Department of Statistics, Örebro University, Sweden, for comments and discussions. The study was supported by grants from the Margarethahemmet Foundation, the Linnéa and Josef Carlsson Foundation, GlaxoSmithKline, and the Swedish Science Council (Grant 2006-3449 to C.G.).

References

- Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. *Epilepsia* 2005;46:561–7.
- Adams CBT, Beardsworth ED, Oxbury SM, Oxbury JM, Fenwick PBC. Temporal lobectomy in 44 children: outcome and neuropsychological follow-up. *J Epilepsy* 1990;3:157–68.
- Björnæs H, Engberg Stabell K, Heminghyt E, Røste G, Bakke S. Resective surgery for intractable focal epilepsy in patients with low IQ: predictors for seizure control and outcome with respect to seizures and neuropsychological and psychosocial functioning. *Epilepsia* 2004;45:131–9.
- Szabo CA, Wyllie E, Stanford LD, et al. Neuropsychological effect of temporal lobe resection in preadolescent children with epilepsy. *Epilepsia* 1998;39:814–9.
- Zentner J, Hufnagel A, Wolf HK, et al. Surgical treatment of temporal lobe epilepsy: clinical, radiological, and histopathological findings in 178 patients. *J Neurol Neurosurg Psychiatry* 1995;58:666–73.
- Maton B, Jayakar P, Resnick T, Morrison G, Ragheb J, Duchowny M. Surgery for medically intractable temporal lobe epilepsy during early life. *Epilepsia* 2008;49:80–7.
- Williams J, Griebel M, Sharp G, Boop F. Cognition and behaviour after temporal lobectomy in pediatric patients with intractable epilepsy. *Pediatr Neurol* 1998;19:189–94.
- Asarnow RF, LoPresti C, Guthrie D, et al. Developmental outcomes in children receiving resection surgery for medically intractable infantile spasms. *Dev Med Child Neurol* 1997;39:430–40.
- Lendt M, Helmstaedter C, Kuczaty S, Schramm J, Elger CE. Behavioural disorders in children with epilepsy: early improvements after surgery. *J Neurol Neurosurg Psychiatry* 2000;69:739–44.
- McLellan A, Davies S, Heyman I, et al. Psychopathology in children with epilepsy before and after temporal lobe resection. *Dev Med Child Neurol* 2005;47:666–72.
- Besag F. Childhood epilepsy in relation to mental handicap and behavioural disorders. *J Child Psychol Psychiatry* 2002;43:103–31.
- Taylor D, Neville B, Cross H. Autistic spectrum disorders in epilepsy surgery candidates. *Eur Child Adolesc Psychiatry* 1999;8:189–92.
- Danielsson S, Rydenhag B, Uvebrant P, Nordborg C, Olsson I. Temporal lobe resections in children with epilepsy: neuropsychiatric status in relation to neuropathology and seizure outcome. *Epilepsy Behav* 2002;3:76–81.
- Szabo CA, Wyllie E, Dolske M, Stanford LD, Kotagal P, Comair YG. Epilepsy surgery in children with pervasive developmental disorder. *Pediatr Neurol* 1999;20:349–53.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Assoc.; 1994.
- Kadesjö B, Gillberg C. Attention deficit and clumsiness in Swedish 7-year-old children. *Dev Med Child Neurol* 1998;40:796–804.
- Dunn D, Austin JK, Harezlak J, Ambrosius WT. ADHD and epilepsy in childhood. *Dev Med Child Neurol* 2003;45:50–4.
- Dunn D, Kronenberger W. Childhood epilepsy, attention problems and ADHD: review and practical considerations. *Semin Pediatr Neurol* 2006;12:222–8.
- Schorre BE, Vandvik IH. Global assessment of psychosocial functioning in child and adolescent psychiatry: a review of three unidimensional scales (CGAS, GAF, GAPD). *Eur Child Adolesc Psychiatry* 2004;13:273–86.
- Danielsson S, Viggelid G, Gillberg C, Olsson I. Lack of effects of vagus nerve stimulation on drug-resistant epilepsy in eight pediatric patients with autism spectrum disorders: a prospective 2-year follow-up study. *Epilepsy Behav* 2008;12:298–304.
- Diseth T, Emblem R. Somatic function, mental health, and psychosocial adjustment of adolescents with anorectal anomalies. *J Pediatr Surg* 1996;31:638–43.
- Diseth T, Bjordal R, Schultz A, Stange M, Emblem R. Somatic function, mental health and psychosocial functioning in 22 adolescents with bladder exstrophy and epispadias. *J Urol* 1998;159:1684–90.
- Spurkland I, Bjornstad PG, Lindberg H, Seem E. Mental health and psychosocial functioning in adolescents with congenital heart disease: a comparison between adolescents born with severe heart defect and atrial septal defect. *Acta Paediatr* 1993;82:71–6.
- Nordborg C, Sourander P, Silfvenius H, Blom S, Zetterlund B. Mild cortical dysplasia in patients with intractable partial seizures: a histological study. In: Wolf P, Dam M, Janz D, Dreifuss FE, editors. *Advances in epileptology*. New York: Raven Press; 1987. p. 29–33.
- Wing L, Leekam S, Libby S, Gould J, Larcombe M. The diagnostic interview for social and communication disorders: background, inter-rater reliability and clinical use. *J Child Psychol Psychiatry* 2002;43:307–25.
- Lord C, Risi S, Lambrecht L, et al. The autism diagnostic observation schedule—generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* 2000;30:205–23.
- Goodman R. Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry* 2001;40:1337–45.
- Malmberg M, Rydell A-M, Smedje H. Validity of the Swedish version of the strengths and difficulties questionnaire (SDQ-Swe). *Nord J Psychiatry* 2003;57:357–63.
- Conners CK. The Conners Rating Scales: Use in clinical assessment, treatment planning and research. In: Maruish M, editor. *Use of psychological testing for treatment planning and outcome assessment*. Hillsdale, NJ: Erlbaum; 1994.
- Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 1998;26:257–68.
- Ehlers S, Gillberg C. The epidemiology of Asperger syndrome: a total population study. *J Child Psychol Psychiatry* 1993;34:1327–50.
- Ehlers S, Gillberg C, Wing L. A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. *J Autism Dev Disord* 1999;29:129–41.
- Posserud MB, Lundervold AJ, Gillberg C. Autistic features in a total population of 7–9-year-old children assessed by the ASSQ (Autism Spectrum Screening Questionnaire). *J Child Psychol Psychiatry* 2006;47:167–75.
- Shaffer D, Gould MS, Brasic J, Ambrosini P, Fisher P, Bird H, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry* 1983;40:1228–31.
- Alin-Akerman B, Norberg L. Griffiths' Developmental Scales [Griffiths' utvecklingskala I o. II, Swedish version]. Stockholm: Psykologiförlaget AB; 1991.
- Wechsler D. Wechsler preschool and primary scale of intelligence—revised (WPPSI-R Swedish version). Stockholm: Psykologiförlaget AB; 1999.
- Wechsler D. Wechsler Intelligence Scale for Children. (WISC-III Swedish version). Stockholm: Psykologiförlaget AB; 1999.
- Wechsler D. Wechsler Adult Intelligence Scale—Revised (WAIS-R Swedish version). Stockholm: Psykologiförlaget AB; 2003.
- Newcombe RG, Altman DG. Proportions and their differences. In: Altman DG, Machin D, Bryant TN, Gardner MJ, editors. *Statistics with confidence*. Bristol: BMJ Books; 2000. p. 45–57.

- [40] Bjørnaes H, Stabell K, Henriksen O, Løyning Y. The effects of refractory epilepsy on intellectual functioning in children and adults: a longitudinal study. *Seizure* 2001;10:250–9.
- [41] Wiebe S, Blume WT, Girvin JP, Eliasziw M. For the effectiveness and efficiency of surgery for temporal lobe epilepsy study group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001;345:311–8.
- [42] Smith ML, Elliott IM, Lach L. Cognitive, psychosocial, and family function one year after pediatric epilepsy surgery. *Epilepsia* 2004;45:650–60.
- [43] Elliott IM, Lach L, Kadis DS, Smith ML. Psychosocial outcomes in children two years after epilepsy surgery: has anything changed? *Epilepsia* 2008;49:634–41.
- [44] Mikati MA, Rahi AC, Shamseddine A, Mroueh S, Shoeib H, Comair Y. Marked benefits in physical activity and well-being, but not in functioning domains, 2 years after successful epilepsy surgery in children. *Epilepsy Behav* 2008;12:145–9.
- [45] Shah A, Holmes N, Wing L. Prevalence of autism and related conditions in adults in a mental handicap hospital. *Appl Res Ment Retard* 1982;3:303–17.
- [46] De Bildt A, Sytema S, Kraijer D, Minderaa R. Prevalence of pervasive developmental disorders in children and adolescents with mental retardation. *J Child Psychol Psychiatry* 2005;46:275–86.
- [47] Noeker M, Haverkamp F. Neuropsychological deficiencies as a mediator between CNS dysfunction and inattentive behaviour in childhood epilepsy. *Dev Med Child Neurol* 2003;45:717–8.
- [48] Dunn D, Austin JK, Huster GA. Symptoms of depression in adolescents with epilepsy. *J Am Acad Child Adolesc Psychiatry* 1999;38:1132–8.
- [49] Achenbach TM. Manual for the Child Behavior Checklist/4–18 and 1991 profile. Burlington: Department of Psychiatry, University of Vermont;1991.
- [50] Sabaz M, Cairns DR, Lawson JA, Nheu N, Bleasel AF, Bye AM. Validation of a new quality of life measure for children with epilepsy. *Epilepsia* 2000;41:765–74.
- [51] Devinsky O. Psychiatric comorbidity in patients with epilepsy: implications for diagnosis and treatment. *Epilepsy Behav* 2003;4:S2–S10.
- [52] Kanner A. When did neurologists and psychiatrists stop talking to each other? *Epilepsy Behav* 2003;4:597–601.
- [53] Ott D, Siddarth P, Gurbani S, et al. Behavioral disorders in pediatric epilepsy: unmet psychiatric need. *Epilepsia* 2003;44:591–7.
- [54] Steffenburg S, Gillberg C, Steffenburg U. Psychiatric disorders in children and adolescents with active epilepsy and mental retardation. *Arch Neurol* 1996;53:904–12.
- [55] Austin J, Caplan R. Behavioral and psychiatric comorbidities in pediatric epilepsy: toward an integrative model. *Epilepsia* 2007;48:1639–52.