EPILEPSY AND CHILDHOOD AUTISM

with special reference to neuropsychiatric aspects
on surgical interventions for medically intractable epilepsy

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To Stefan
Simon, Hannah, Michael and Julia

THE BLIND MEN
AND THE ELEPHANT

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

The First approach'd the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"

The Second, feeling of the tusk,
Cried, -"Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

The Third approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," quoth he, "the Elephant
Is very like a snake!"

The Fourth reached out his eager hand,
And felt about the knee.
"What most this wondrous beast is like
Is mighty plain," quoth he,
'"Tis clear enough the Elephant
Is very like a tree!"

The Fifth, who chanced to touch the ear,
Said: "E'en the blindest man
Can tell what this resembles most;
Deny the fact who can,
This marvel of an Elephant
Is very like a fan!"

The Sixth no sooner had begun
About the beast to grope,
Then, seizing on the swinging tail
That fell within his scope,
"I see," quoth he, "the Elephant
Is very like a rope!"

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!

JG Saxe (1816-1887), from a hindoo fable

ABSTRACT

Epilepsy is much more common in individuals with autism than in the general population. The extent to which epilepsy influences the outcome of autism is poorly understood. Many children with medically intractable epilepsy have neurodevelopmental disorders, including autism. The objective of this study was to gain further insight into the co-occurrence of epilepsy and autism.

In a population-based follow-up study of 120 individuals with autism diagnosed in childhood, 108 were reassessed at ages 17-40 years. The majority had autism and mental retardation (MR). The carers of 42/43 with a history of epilepsy were interviewed, and medical charts were reviewed. Epilepsy onset was most common in the first years of life but also occurred in adults. Partial seizures dominated and seizure frequency had a great impact on the individuals' lives. Epilepsy remitted in 16%. Severe MR and autism were significantly associated with epilepsy, especially in females. The cognitive level and the adaptive behaviour level were significantly lower in the epilepsy group than in the non-epilepsy group.

The medical charts of 16 children undergoing temporal lobe resections were reviewed and the histopathological specimens were re-evaluated. Psychopathology was found in 12. Five had autism before and after surgery, one of whom became seizure free, and in three there was a positive behavioural change. Malformations of cortical development were associated with worse seizure outcome and were more common in children with psychopathology.

A neuropsychiatric examination and assessments of psychosocial functioning and IQ were performed at baseline and at 2-year follow-up to assess individual outcome in *(i)* 25 children undergoing epilepsy surgery, and in *(ii)* eight children with autism and intractable epilepsy treated with vagus nerve stimulation (VNS).
In study *(i)* psychopathology (mainly autism and ADHD) was present in 17 of the children at some point and contributed in a major way to the psychosocial dysfunction in affected children. Among the children with preoperative psychopathology, one was without a diagnosis after surgery. The IQ level before surgery predicted the IQ level after surgery in most cases. Seven had autism before and after surgery, and the parents reported a positive behavioural change in six. Psychosocial functioning was mainly stable in autism, except in one child who became seizure free and improved in psychosocial functioning and in one child who deteriorated.
In study *(ii)* no one had a reduced seizure frequency after two years of VNS, autism remained and changes concerning intellectual abilities and psychosocial functioning were minor in most subjects. The parents of three children reported a positive change in social interactive abilities, and those of one child reported a negative change.

In conclusion, the follow-up study of young adults with autism showed high rates of epilepsy, poor prognosis, and low remission rates. Neuropsychiatric disorders were common at baseline and two years after epilepsy surgery. A diagnosis of autism in children with intractable epilepsy remained after surgical intervention. Symptomatic improvement is not always the same as functional improvement. The main aim of epilepsy surgery is seizure control, regardless of whether or not there is co-existing psychopathology.

Key words: epilepsy, autism, epilepsy surgery, VNS, children, treatment outcome, psychopathology, cognition
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LIST OF PAPERS

This study is based on the following papers:

I. Danielsson S, Gillberg IC, Billstedt E, Gillberg C, Olsson I. Epilepsy in young adults with autism: a prospective population-based follow-up study of 120 individuals diagnosed in childhood. *Epilepsia 2005;46:918-23.*

II. 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.*

III. Danielsson S, Viggedal G, Steffenburg S, Rydenhag B, Gillberg C, Olsson I. Psychopathology, psychosocial functioning and IQ in children with drug-resistant epilepsy before and after epilepsy surgery. *Epilepsy Behav; in press.*

IV. Danielsson S, Viggedal 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.*

ABBREVIATIONS

ABC	Autistic Behavior Checklist
AD	Autistic Disorder
ADI-R	Autism Diagnostic Interview-Revised
ALC	Autistic-like Condition
APA	American Psychiatric Association
AED	Antiepileptic Drug
ADOS	Autism Diagnostic Observation Schedule
ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-C	ADHD, Combined type
ADHD-H	ADHD, predominantly Hyperactive-Impulsive type
ADHD-I	ADHD, predominantly Inattentive type
ASSQ	Autism Spectrum Screening Questionnaire
BPRS	Brief Parent Rating Scale
CBCL	Childhood Behavior Checklist
CGAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impressions-Improvement scale
CI	Confidence Interval
CNS	Central Nervous System
CP	Cerebral Palsy
CSWS	Continuous Spike-and-Wave during Sleep
CT	Computerized Tomography
DBD	Disruptive Behaviour Disorders
DISCO	Diagnostic Interview for Social and Communication Disorders
DQ	Developmental Quotient
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
FSIQ	Full Scale IQ
HH	Hypothalamic Hamartoma
ICD	International Classification of Diseases
ILAE	International League Against Epilepsy
IQ	Intelligence Quotient
MCD	Malformations of Cortical Development
MMR	Mild Mental Retardation (IQ 50-69)
MR	Mental Retardation (IQ<70)
MRI	Magnetic Resonance Imaging
fMRI	Functional Magnetic Resonance Imaging
NOS	Not Otherwise Specified
ODD	Oppositional Defiant Disorder
PDD	Pervasive Developmental Disorder
QOLCE	Quality of Life in Childhood Epilepsy Questionnaire
SDQ	Strengths and Difficulties Questionnaire
SMR	Severe Mental Retardation (IQ<50)
TLR	Temporal Lobe Resection
VNS	Vagus Nerve Stimulation
WHO	World Health Organization

INTRODUCTION

Autism is one of the neurodevelopmental disorders, as are eg mental retardation (MR), speech and language disorders and cerebral palsy (CP). They are heterogeneous conditions but have in common the long-term effects of delay and disability, caused by damage to the neurological processes responsible for developmental functioning. Neurodevelopmental disorders can be caused by many different underlying disorders and pathological processes. The neuropsychiatric disorders are closely related to the neurodevelopmental disorders and can be agreed on and communicated to others by reference to criteria such as those of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association (APA) 1994) or the International Classification of Diseases (ICD) (World Health Organization (WHO) 1993). Taylor has pointed out that diagnostic schedules bring a certain level of understanding for clinical purposes and can suggest certain courses of action, but that our diagnostic categories are weak with which to do science (Taylor 2003). If a "medical" diagnosis is made very early in a child with a neurodevelopmental disorder, such as "epilepsy" or "tuberous sclerosis", this medical or aetiological diagnosis will often take precedence and the child will not be referred for further examinations. Psychopathology is more common in children with epilepsy than in the general population, but often remains undiagnosed (Rutter et al. 1970; Davies et al. 2003).

Neurodevelopmental disorders often occur together, but our knowledge of the exact prevalence and public health implications is often hindered by a lack of population-based surveillance data (Kirby 2002), as well as by changes over time in definitions and classifications. The extent to which epilepsy influences the outcome of autism is poorly understood. This thesis focuses on the relationship between autism and epilepsy from two perspectives: epilepsy in individuals with autism, and autism and other neuropsychiatric disorders in children who go through surgical interventions for medically intractable epilepsy.

BACKGROUND

Epilepsy

Epilepsy is defined as two or more epileptic seizures, unprovoked by any immediate identifiable cause (the International League Against Epilepsy (ILAE), 1997) and excludes seizures that are only neonatal. A new definition has been proposed and is debated (Fisher et al. 2005). The prevalence is 0.5-1% in the childhood population and the aetiology is unknown in 55-75% of cases (Cowan 2002). An epileptic seizure is a transient clinical event that results from abnormal activity of synchronized, more or less extensive populations of cerebral neurons and this abnormal activity results in paroxysmal disorganization of one or several brain functions (Aicardi 1998). Epilepsy is classified according to seizure type and syndrome (ILAE 1981 and 1989). The current classification system is debated (Loddenkemper et al. 2005; Engel 2006). A diagnosis of epilepsy is typically based on the history from witnesses in combination with the results from EEG and more seldom from video-EEG recordings.

Epilepsy and intellectual ability

The severity of mental retardation (MR) in terms of IQ exerts a major influence on development and adjustment, and the presence of any major physical disability in MR has substantial bearing on outcome (O'Brien 2001). Epilepsy is a common disorder among

individuals with MR (Steffenburg et al. 1995). In European population-based studies about one out of five with MR has epilepsy (Forsgren et al. 1990), and 31 % of children with epilepsy have MR (Sillanpää 1992). According to the DSM-IV (APA 1994) the criteria for MR are:

A. Significantly sub average intellectual functioning: an IQ of approximately 70 or below on an individually administered IQ-test (for infants, a clinical judgement of significantly sub average intellectual functioning).
B. Concurrent deficits or impairments in present adaptive functioning (i.e., the person's effectiveness in meeting the standards expected for his or her cultural group) in at least two of the following areas: communication, self-care, home-living, social/interpersonal skills, use of community resources, self-direction, functional academic skills, work, leisure, health, and safety.
C. The onset is before 18 years.

There are different degrees of severity: mild MR (IQ 50-55 to approximately 70), moderate MR (IQ 35-40 to 50-55), severe MR (IQ 20-25 to 35-40) and profound MR (IQ <20-25). In research, MR is often divided into only two different degrees of severity: mild MR (MMR) (IQ 50-69) and severe MR (SMR) (IQ<50).

At least one out of ten children with MMR (Hagberg et al. 1981) will have epilepsy, and among those with SMR, approximately one out of three (Gustavsson et al. 1977). An earlier age of onset of seizures is associated with poorer cognitive function (Hermann et al. 2008). Recurrent seizures may represent a considerable risk for intellectual decline in children (Bjørnaes et al. 2001; Freitag & Tuxhorn 2005).

Epilepsy and psychopathology

In an often quoted neuropsychiatric study in childhood, Rutter and co-workers reported that 7% of children in the general population had psychopathology compared with 12% of children with physical, non-neurological disorders, 29% of children with uncomplicated epilepsy, and 58% of children with structural brain anomalies (Rutter et al. 1970). Thirty years later another population-based study reported strikingly similar results (Davies et al. 2003). In a recent critical review, studies identifying factors associated with behavioural and psychiatric co-morbidities in paediatric epilepsy were placed in two categories: illness-related variables and psychosocial variables (Austin & Caplan 2007). Concerning the illness-related variables (seizure frequency and control; type of epilepsy; age of onset; duration of epilepsy and antiepileptic drugs (AEDs)) the authors stressed that these variables are associated with co-morbid cognitive and linguistic deficits, which in turn contribute to behaviour difficulties, especially in children with MR, intractable epilepsy and early onset epilepsy. As regards psychosocial variables it was concluded that greater family stress, fewer family adaptive resources, more negative perceptions about epilepsy, more negative parent-child interactions, and poorer family adjustment were associated with more child behaviour problems.

Older studies suggested that the type of epilepsy and left lateralization of epileptiform activity were associated with more severe behavioural disturbances (Rutter et al. 1970; Lindsay et al. 1979). More recent studies indicate, however, that there is no association between type of seizure disorder and type of psychopathology in children with epilepsy and normal IQ, and that children with temporal lobe epilepsy do not have more disturbances except psychosis (Caplan & Austin 2000). The most often reported psychiatric disorders in children with epilepsy are disruptive behaviour disorders (DBD), (attention-deficit/hyperactivity disorder (ADHD), oppositional

defiant disorder (ODD) and conduct disorder) and emotional disorders (depression and anxiety) which are found in about one fourth to one third (Dunn & Austin 2008). The DSM-IV discriminates three subtypes of ADHD: the predominantly inattentive type (ADHD-I), the predominantly hyperactive-impulsive type (ADHD-H) and the combined type (ADHD-C). Co-morbidity is common with eg emotional disorders and ODD. In children without epilepsy ADHD is more common in boys and most often of the combined type. In children with epilepsy the inattentive type seems to be as common as the hyperactive-impulsive type, and at least as common in girls as in boys (Dunn et al. 2003). Autism is often co-occurrent with epilepsy in children with MR. In a population-based study on children with MR and active epilepsy, a psychiatric diagnosis was found in 59%, the majority having autism (38%) (Steffenburg et al. 1996).

Prognosis

The prognosis of seizure disorders varies widely. Childhood onset epilepsy often remits. In a population-based study by Camfield et al. (1993), 55% of childhood epilepsy cases remitted. Predictors of remission have been shown to be the occurrence of only one type of seizure, normal mental and neurological development and the absence of a detectable cause (Brorson & Wranne 1987). There is an increased mortality in epilepsy at all ages, with the highest mortality rates in cohorts of persons with MR and intractable epilepsy (Sperling et al.1999). Although the majority of patients with epilepsy in childhood will be free of seizures as adults, there is still an increased risk for social and educational problems, as well as an increased risk of premature death (Sillanpää et al. 1998).

Intractable epilepsy

About 20-30% of children with epilepsy still have seizures in spite of medication. The figures vary, because the definitions of intractability differ (Huttenlocher 1994). Medical intractability can be defined as a situation where a person continues to have seizures despite accurate epilepsy diagnosis and appropriately selected and dosed AEDs. Strong predictors for intractability are other signs of neurodeficits such as MR. In comparison to children with epilepsy and MMR, additional disabilities such as CP, visual impairment, communication and behavioural problems are more common in children with SMR and epilepsy, as are intractable seizures (Airaksinen et al. 2000).

The catastrophic epilepsy disorders begin in children younger than 5 years, are difficult to control and are strongly associated with MR. A child with intractable epilepsy may have additional impairments due to the underlying brain dysfunction (also causing epilepsy) or due to epilepsy induced dysfunction. Hermann & Seidenberg (1995) presented the concept that an epileptogenic cortex may adversely affect the extratemporal regions that mediate executive function abilities, thereby resulting in performance deficits, including neuropsychiatric co-morbidities. In the group of children with drug-resistant epilepsy not eligible for epilepsy surgery there are many with severe cognitive impairments and other disabilities (Besag 2002; Devinsky 2003).

Treatment

Treatment of intractable epilepsy is multiprofessional and includes pharmacological treatment, in some cases epilepsy surgery and - if epilepsy surgery is not possible - ketogenic diet or vagus nerve stimulation (VNS).

Epilepsy surgery

Epilepsy surgery may be considered in children and adults with partial seizures or generalized seizures that are caused by a localizable cortical abnormality. The pre-operative evaluation aims at analyzing potential benefits and risks of the procedure and is therefore comprehensive and multidisciplinary. History taking and neurological examination, video-EEG with surface electrodes and structural magnetic resonance imaging (MRI) are used to establish the presence of a zone of cortical abnormality. Sometimes additional investigations may be required in case of discordant findings, or if the seizure focus is close to functionally important cortex. Additional investigations may include positron emission tomography (PET)/single-photon emission computed tomography (SPECT), functional MRI (fMRI), magnetoencephalography (MEG) and video-EEG monitoring using subdural or depth-electrodes. Virtually all epilepsy surgery centres include a comprehensive neuropsychological assessment before and after surgery. This assessment can provide information about areas of brain dysfunction and relate it to the epileptogenic area, it can identify the risks to speech and other functions related to surgery and evaluate cognitive outcome. A neuropsychiatric assessment should be included but is not routine at all centres.

There are two main types of surgical procedures for epilepsy – resective and disconnective procedures; a resective procedure aims at removing the region causing seizures, while the disconnective procedure is used to limit the spread of seizure activity.

Histopathological findings

The most common histopathological findings reported after temporal lobe resections (TLR) are hippocampal sclerosis, tumours (often specific low-grade tumours), vascular malformations and malformations of cortical development (MCD) (Zentner et al. 1995). Pathology in 50 preschool children undergoing different epilepsy surgery procedures, showed focal cortical dysplasia (a kind of MCD) in 44%, tumours in 26% and mixed in 30 % (encephalitis, hypoxic-ischemic damage, tuberous sclerosis, hippocampal sclerosis with microdysgenesis and hemimegalencephaly) (Freitag & Tuxhorn 2005).

Major MCD are usually classified according to distinct macroscopical patterns, whereas minor malformations such as microdysgenesis are classified according to specific microscopical features (Mischel et al. 1995; Nordborg et al. 1999), for which different investigators have used different diagnostic criteria. Focal dysplasia of the cerebral cortex in epilepsy surgery candidates was described by Taylor et al. in 1971. It has been difficult to achieve a uniform terminology and there is an on-going debate (Palmini et al. 2004). Dual or multiple aetiology is not always reported in epilepsy surgery series (Vinters et al. 1993). Patients are often classified according to the main histopathological or neuroradiological feature in predetermined groups. Eriksson et al. (1999), however, presented all the histopathological diagnoses in 139 children and adults from the Gothenburg epilepsy surgery series 1987-95. MCD and atrophic-gliotic lesions were the most common findings; MCD were found in 56% of the children, and in 23% of the adults.

Outcome

Resective surgery means taking away dysfunctional brain tissue, but to rule out that the procedure creates or aggravates a dysfunction, epilepsy candidates are carefully monitored before and after surgery. In an editorial commentary Taylor et al. pointed out that new measures of outcome are needed and that different outcome categories can be outlined based on the probability of success (Taylor et al. 1997). Most surgical procedures aim at seizure freedom especially in patients with defined lesions. However, in children with catastrophic epilepsy, the aim may be to reduce seizures in order to prevent an intellectual and behavioural decline. Better seizure outcome after surgery is reported in patients with vascular malformations and tumours, and worse outcome in patients with MCD and gliosis (Zentner et al. 1995). Not only the histopathological diagnosis, but also the localization of the lesion and the surgical procedure have implications for outcome. Hemispherectomies and TLR carry the best prognosis with 43-79% and 58-78% seizure free children, respectively (Spencer & Huh 2008). Complex partial seizures of temporal lobe origin are the most common type of intractable seizures in adults and have the most successful outcome after surgical treatment. The results are reported to be equally good in some paediatric series, which include only selected patients without MR (Wyllie et al. 1998; Mohamed et al. 2001). Temporal lobe epilepsy is responsible for less than one third of surgical resections in children and most paediatric series also include extratemporal and multilobar resections. There are several studies reporting good results of TLRs, but fewer studies evaluating the effects of extratemporal resections (Sinclair et al. 2004).

The only randomized controlled trial of surgery for intractable temporal lobe epilepsy in candidates older than 16 years without MR showed that surgery is superior to prolonged medical therapy, concerning freedom from seizures and better quality of life (Wiebe et al. 2001). In the adult population it has until recently been assumed that patients with MR are bad candidates for epilepsy surgery. The belief is that their neurodeficit means that the epileptogenic zone is not localized enough for resection, or that a resection will result in worsened cognitive dysfunction. This has been challenged by Bjørnæs (2004), showing a good seizure outcome after resective surgery in adult patients with focal epilepsy and IQ<70, provided that the operation was done relatively shortly after the onset of epilepsy. The possibility of surgical treatment of medically intractable epilepsy in individuals with MR should be considered. In a recent follow-up study on resective epilepsy surgery in Sweden 1990 to 1999, 72 out of 448 patients (including children) had IQ<70. IQ was shown to be an independent predictor of seizure freedom: 22% in the IQ<50 group, 37% in the IQ50-69 compared with 61% in the IQ≥ 70 group (Malmgren et al. 2008). When seizure outcome was related to histopathological diagnoses, the lesional cases had the best outcome across all three groups.

Stability concerning IQ is the main postoperative result at group level in most studies on cognitive effects of temporal lobe epilepsy surgery in adults (Engman et al. 2001; Baxendale 2008) and in children (Adams et al. 1990; Szabo et al. 1998), but there is individual heterogeneity. In pre-school children a catch-up development may occur, but only in seizure free patients (Freitag & Tuxhorn 2005). Intractable seizures seem to have more serious cognitive consequences in children than in adults and this has been suggested to depend on the vulnerability of intellectual abilities during the rapid development in childhood (Bjørnæs et al. 2001). Development is partly based on the continuous experiences of the child, including normal options for learning and interacting.

Little is known about the effects of epilepsy surgery on psychiatric disorders in children, although psychopathology is common in epilepsy surgery candidates (Taylor et al. 1999; McLellan et al. 2005). The largest published follow-up study addressing effects on

psychopathology in children undergoing TLRs for intractable epilepsy is a case-note review of performed neuropsychiatric assessments at baseline and at least one year after surgery 1992-1998 in the Epilepsy Surgery Programme at Great Ormond Street Hospital for Children in London (McLellan et al. 2005). Reports of behavioural outcome after surgery often rely on neuropsychological observations, parental questionnaires or anecdotal information without clinical neuropsychiatric assessment before surgical intervention. There are positive reports on the developmental and behavioural outcome after epilepsy surgery in children (Asarnow et al. 1997; Lendt et al. 2000; Freitag & Tuxhorn 2005), but there are also less favourable reports (McLellan et al. 2005; Mikati et al. 2008; Elliott et al. 2008).

Vagus nerve stimulation (VNS)
VNS is a palliative approach when epilepsy surgery is not possible (Wheless & Maggio 2002). A pulse generator is implanted below the left clavicle, electrodes are tunnelled to the left cervical vagus nerve and the stimulator settings are externally programmed. There are some major issues to be considered (Schachter 2002); there are no precise indications and we do not know the exact mechanism of action or optimal stimulation parameters. There are costs and, even though minor, surgical risks involved. More than 50 % seizure reduction is reported in 45% to 53% of children in the two largest series (Helmers et al. 2001; Murphy et al. 2003). Duration of reported outcome varies. Most studies on VNS effects are retrospective and there are no randomized controlled studies in children. There have been reports on positive effects on quality of life and behaviour with VNS, both in patients with improved seizure situation and in those without (Lundgren et al. 1998; Valencia et al. 2001; Hallböök et al. 2005). In a prospective study on 16 children there were positive effects on behaviour and some other quality of life parameters independent of seizure control at 6-month follow-up, but these effects did not persist at follow-up two years later (Aldenkamp et al. 2001 and 2002).

Autism

The definitions of autism, or pervasive developmental disorder (PDD) according to the DSM-IV (APA 1994) or the ICD-10 (WHO 1993), include impairment and disability in three broad areas: social reciprocal interaction abilities, reciprocal communicative abilities, and behaviour, including a narrow range of stereotypic behaviours, activities and interests. In this thesis the term “autism” will be used synonymously with PDD. The term “autism spectrum disorders” is synonymous with the term PDD and includes the diagnoses autistic disorder (AD), Rett syndrome, disintegrative disorder, Asperger syndrome and PDD not otherwise specified (PDD-NOS), roughly equivalent to the terms “atypical autism” and “autistic-like conditions” (ALC). The ICD-10 and DSM-IV definitions of AD (Table 1) are conceptually identical and facilitate research and clinical services (Volkmar et al.1994).

There is a debate regarding the delineation of PDD-NOS (DSM-IV) and atypical autism (ICD-10), since these diagnoses do not have operationalized diagnostic criteria making it difficult to compare data across research groups. Buitelaar et al. have suggested a scoring rule based on a short set of seven ICD-10/DSM-IV criteria with a cut-off of at three items and one social interaction item set as mandatory (Buitelaar et al. 1999). Gillberg has suggested that at least four of the 12 DSM-IV criteria for AD should be met for a diagnosis of atypical autism/PDD-NOS, including two criteria for qualitative impairment in social interaction (Billstedt et al. 2005).
Since the criteria for PDD diagnoses are descriptive, the importance of a multidisciplinary assessment must be stressed. Combining information from multiple sources is essential. Diagnostic decision-making is straightforward if the clinical impression is consistent with the

results from standardized methods of collecting information with eg the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing et al. 2002) or the Autism Diagnostic Interview-Revised (ADI-R) (Rutter et al. 2003) in combination with a semistructured observation, like the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 2000), (Risi et al. 2006).

Table 1. The diagnostic criteria for autistic disorder according to the DSM-IV

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

1. **qualitative impairment in social interaction, as manifested by at least two of the following:**
   a. marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
   b. failure to develop peer relationships appropriate to developmental level
   c. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
   d. lack of social or emotional reciprocity
2. **qualitative impairments in communication as manifested by at least one of the following:**
   a. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
   b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
   c. stereotyped and repetitive use of language or idiosyncratic language
   d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
3. **restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:**
   a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
   b. apparently inflexible adherence to specific, nonfunctional routines or rituals
   c. stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
   d. persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Developmental abnormalities are present from the first years of life in the majority of cases, but about one third of parents of children diagnosed with AD report that their child first seemed to develop normally, but then had a loss of already acquired language and social skills in the second or third year of life, ie an autistic regression. The regression is rarely documented except by parents' reports, so it may be disputed (Rapin 1995). Recent data suggest that most of these children also demonstrate previous, subtle developmental delays of social and communicative behaviours (Rogers 2004). It is not until the function in question fails to materialize or materializes imperfectly that a neurodevelopmental disorder is apparent (Taylor 2003).

A recent paper describes the high prevalence of co-morbid psychiatric disorders (specific phobia, obsessive compulsive disorder and ADHD) in children with autism and points out that there are treatments to be offered (Leyfer et al. 2006).

The prevalence of MR is higher in autism than in the general population, especially in AD (Gillberg 1995; Rapin 1999). In a population-based study on autism in preschool children the prevalence of MR was 29.8%; in children with AD 66.7%, PDD-NOS 12% and in Asperger syndrome 0 (Chakrabarti & Fombonne 2005). On the other hand, population-based studies have shown neuropsychiatric disorders in 40% of children with MR (Einfeld & Tonge 1996; Strømme & Diseth 2000). Autism is much more common in individuals with an intellectual impairment: approximately one out of ten with MMR, and one out of three with SMR have autism (Nordin & Gillberg 1996, de Bildt et al. 2005)

Aetiology

Autism has a multitude of different aetiologies. There is strong evidence supporting a neurobiological basis (Volkmar & Pauls 2003). Twin and family studies suggest that most cases of autism arise because of a combination of genetic factors (Bailey et al. 1995; Acosta & Pearl 2003). Macrocephaly, acceleration followed by deceleration of brain growth, increased neuronal packaging in the limbic system, decreased neuronal cell size particularly in the amygdale, and a decreased number of Purkinje cells in the cerebellum, are but some of the neuropathological findings that have been replicated in autism. Hughes has pointed out the finding of underconnectivity in the brain in autism; both MRI and fMRI studies have shown thinning of the corpus callosum and reduced connectivity in the frontal and temporal fusiform areas, among other regions (Hughes 2007). Minicolumnar pathology in the prefrontal cortex and within the middle temporal gyrus has been found, and it has been suggested to be the result of a different circuitry or spatial morphologic features in the brains of individuals with autism (Casanova et al. 2002). Mirror neurons are cells around the sulcus centralis in the frontal and parietal lobes that are active not only during one's own performance, but also when observing someone or something else. They are thought to be essential for empathy and considered deficient in autism, explaining the difficulty in understanding and predicting the behaviour or emotions of others - and maybe also the impaired imitation ability - often seen in autism (see review by Oberman & Ramachandran 2007).

In 12-35 % of subjects with autism, an underlying medical disorder can be identified (Gillberg & Coleman 1996; Kielinen et al. 2004). Associated medical conditions in autism are chromosomal abnormalities, neurocutaneous disorders (eg tuberous sclerosis), Rett syndrome, fetal valproate syndrome, Möbius syndrome, central nervous system (CNS) infections and some metabolic disorders. MR is often part of the clinical picture. Studies of congenital anomalies associated with autism have shown that there seem to be critical periods during embryogenesis (Arndt et al. 2005; Johansson et al. 2006). It has been suggested that studies on autism aetiology and brain morphology should be limited to children with "essential" autism, excluding children with "complex" autism, ie children with microcephaly and/or abnormal physical features. This would allow analysis of a more uniform population and probably the group with "essential" autism is the more heritable subgroup (Miles et al. 2005). Ongoing research into the relationship between neurophysiology, neuroanatomy, neurochemistry, and genetic factors is likely to increase our understanding of the complex aetiology of autism.

Epidemiology

Higher awareness and changed diagnostic criteria have altered the concept that autism is rare (Wing 2002). The prevalence rate of AD is 0.1-0.2%, while the prevalence rate of PDD is considerably higher, 0.5-1%. AD is three to four times more common in males than in females. The sex ratio is lower among cases with SMR and higher in those with normal IQ (Gillberg 1995).

Prognosis

Follow-up studies of children with AD show variable outcome, but a majority of individuals have a low social functioning ability in adulthood, few live independently or are capable of employment and the autistic symptoms most often persist throughout life (von Knorring & Hägglöf 1993; Billstedt et al. 2005). Positive prognostic factors are the ability to use verbal communicative language in preschool years and a relatively higher IQ level (Lotter 1974; Nordin & Gillberg 1998), maybe at least IQ>70 (Howlin et al. 2004). Conversely, coexisting conditions, such as SMR and epilepsy, are considered negative prognostic factors (Nordin & Gillberg 1998). For the individual child diagnosed with autism, a cautious approach needs to be taken when discussing prognosis with the parents and the individual. The ability to function adequately in adult life may depend as much on interventions and support from the family, employment and social services as on basic intelligence (Howlin et al. 2004).

Epilepsy and autism

Epileptiform EEG abnormalities in autism

The reported rate of epileptiform EEG abnormalities in children with autism without epilepsy has ranged from 6-61%, with the lowest rates if only routine EEG is used and the highest rates with 24-hour ambulatory EEG (Chez et al. 2006). Studies have shown that a history of autistic regression versus non-regression does not predict the presence of EEG epileptiform activity (Tuchman & Rapin 1997; Hrdlicka et al. 2004; Chez et al. 2006). There are studies showing normalization of EEGs with valproic acid treatment in children with autism (Chez et al. 2006), but no studies showing if future epilepsy can be prevented by treatment, or if there is a positive influence on the core symptoms and prognosis of autism. It has not been satisfactorily shown that treating subclinical epileptic spikes in this population improves behaviour. Possible side effects from AEDs - somatic, cognitive and behavioural - must be considered, as there are few studies on treatment and long-term effects on groups with MR with or without autism (Kerr & Bowley 2001). There are preliminary studies showing that some AEDs may have positive psychotropic effects in a subgroup of children with autism (Martino & Tuchman 2001). One must be aware that AD, Asperger syndrome and autistic-like conditions are behaviourally defined diagnoses, in contrast to the epileptic encephalopathies, eg infantile spasms, Landau Kleffner syndrome or the syndrome of continuous spike-and-wave during sleep (CSWS). These diagnoses are based on specific EEG findings together with clinical symptoms and signs and affect both previously healthy children and children with neurodevelopmental disorders. The acquired functional deficits, including cognitive and/or language regression, seen in these children are potentially reversible and treatable as they are presumed to be caused by epileptiform activity.

Epilepsy in autism

Epilepsy is more common in people with autism, with or without MR, than in the general population (Volkmar & Nelson 1990; Gillberg 1991; Tuchman 2000; Tuchman & Rapin 2002), more recent studies suggesting that about one third of individuals with autism will develop epilepsy (Tuchman, 2000). Kielinen et al. found epilepsy in 18% of children with autism (2004). In a study of 100 males with Asperger syndrome presenting at a specialist unit, four had epilepsy (Cederlund & Gillberg 2004).

According to Tuchman (2004), it is reasonable to hypothesize that many autistic symptoms represent underlying dysfunction in overlapping structures in the CNS, as well as dysfunction in

neurochemical systems, and that abnormalities in these systems may be responsible for the higher rates of epilepsy in this population. Tuberous sclerosis is one established cause of autism and epilepsy and it has been used as a model for testing theories of the brain basis of autism (Bolton et al. 2002). Individuals with tuberous sclerosis are at a very high risk of developing autism, if the onset of seizures is within the first three years of life, and when temporal tubers are present and associated with temporal lobe epileptiform discharges. There is a co-morbidity of epilepsy, autism and MR (Shah et al. 1982; Olsson et al. 1988; Volkmar & Nelson 1990; Steffenburg et al. 1996; Steffenburg et al. 2003). Literature reports sometimes seem to be contradictory due to differences in methods regarding cognitive level, aetiology, age, diagnostic criteria for autism and epilepsy, and duration of follow-up.

Autism in epilepsy

There are few studies on the prevalence of autism in individuals with epilepsy, but autism and ADHD are probably the two most common neuropsychiatric disorders in children with epilepsy (Besag 2002), especially if the epilepsy is drug-resistant. Davies et al. found autism in 16% of children with epilepsy and neurodeficits, but in none with uncomplicated epilepsy (Davies et al. 2003). In a population-based study of children with MR and active epilepsy, autism was found in 38% (Steffenburg et al. 1996). In a retrospective descriptive study from a rehabilitation and epilepsy unit only 48/573 (8%) children with epilepsy had autism, but the group with mental decline, 86/573 (15%), had been excluded from assessment considering autism **(**Boel 2004). In a tertiary epilepsy clinic the prevalence of autism was 32% in children, when screened with an autism screening questionnaire (Clarke et al. 2005). Among children with therapy resistant epilepsy being assessed before resective epilepsy surgery, autism was diagnosed in 19-38% of subjects (Taylor et al.1999; McLellan et al. 2005).

Treatment and interventions for epilepsy and autism

The assessment procedure leading to the diagnosis of autism will explain the individual's sometimes seemingly illogical or odd behaviour and painful lack of social reciprocity. It will often be a turning point in the lives of these families. The individual and his or her family can find information and learn from professionals, from other parents in support groups and from the experiences of high functioning individuals with autism. A diagnosis makes it possible to get access to the services for the disabled. It will also be possible to strive for a more autism-friendly environment at home and at preschool, school or at work. The medical work-up will lead to the aetiology in some cases. The risk for future siblings or children can be discussed on the basis of the knowledge evolving from the genetic studies on autism. Early diagnosis is of importance, since interventions during pre-school years seem to result in a better adaptive behaviour level at school age (Eikeseth 2008). In a review paper on the current treatment options in autism, the author concluded that there is not *one* single treatment that is declared efficacious based on well-controlled studies, but based on current knowledge behavioural techniques and structured teaching based on visual cues are the most effective interventions (Francis 2005). When behavioural problems fail to improve by appropriate behavioural and educational approaches, medication can be used to facilitate management and to improve symptoms. Pharmacological interventions are important in epilepsy, sleep disturbance and in coexisting neuropsychiatric disorders, such as ADHD, depression or obsessive-compulsive disorder.

Apart from AEDs, the treatment of epilepsy includes education and support to parents, teachers and to the person with epilepsy. It is essential to understand that treatment should be individualized and to take into consideration the individual's co-morbidities and concomitant medications. The treatment goals are to achieve seizure control, optimal physical, behavioural and cognitive function using the simplest possible AED regimen. It has been shown that

individuals with autism can participate in prolonged EEG monitoring (Chez et al. 2006). There is a great challenge meeting the needs of persons with both epilepsy and autism. Since their communication abilities are often very limited or special, they often need to have a spokesman. Side effects have to be addressed carefully, as regards cognition and behaviour.

Prognosis in epilepsy and autism

In epilepsy, abnormal mental and neurological development is a negative prognostic factor, as is epilepsy for the outcome in autism (Gillberg & Steffenburg 1987; Kobayashi & Murata 1998). Given that SMR and epilepsy so often occur together, it is difficult to separate the prognostic effects in autism of epilepsy and SMR, respectively. There are few studies addressing the long term prognosis of seizure disorders in children with autism (Kobayashi & Murata 1998; Mouridsen et al. 1999), and no previous population-based study. In a retrospective follow-up study from a referral centre of 130 patients (aged 18-35 years) with autism, remission of epilepsy was seen in four out of 33 subjects (Hara 2007).

Epilepsy surgery and autism

Until recently there have been very few prospective follow-up studies of epilepsy surgery in cases with autism where the effect on the core symptoms of autism is reported, and there are no reports with age-matched non-operated controls. Partial recovery of social and language regression was reported in two children with focal epilepsy after surgical treatment (Neville et al.1997), and there are some more case studies (Hoon & Reiss 1992; Gillberg et al. 1996; Perez-Jimenez et al. 2003). Szabo et al. reported neurological, neuropsychological and psychiatric outcome after epilepsy surgery in five children with autism (Szabo et al. 1999). McLellan et al. have followed the largest cohort (n=60) of children undergoing TLRs, including 23 with autism (McLellan et al. 2005). Discussing epilepsy surgery and the effects on autistic symptoms is a completely different matter from surgical treatment of autistic regression in cases with epileptiform activity but without clinical seizures. In most countries surgery for autistic regression is not performed. There are published reports though (Patil & Andrews 1998; Lewine et al.1999; Nass et al. 1999), but some are considered controversial and ethical concerns have been raised (Kanner 2000; Tharp 2004; Tuchman 2004). In cases with autism without medically intractable epilepsy and/or specific epileptic encephalopathies there are no data at the present time to support the use of surgical intervention.

VNS and autism

Studies based on the VNS Outcome Registry Data (Cyberonics, Inc., Houston, TX, USA) with voluntarily submitted data suggest that VNS may lead to improvements concerning alertness, verbal communication, memory, school/professional achievement, mood, postictal state and seizure clustering in individuals with autism (Park 2003; Warwick et al. 2007). There is a case report of a patient with Asperger syndrome and high seizure frequency successfully treated with VNS and followed for six months (Warwick et al. 2007). There is one prospective study (Rychlicki et al. 2006) and some retrospective studies on clinical case series including small numbers of children with autism treated with VNS for intractable epilepsy (Murphy et al. 2000; Parain et al. 2001; Nagarajan et al. 2002; Alexopoulos et al. 2006). These studies have not included neuropsychiatric assessments and there are few detailed descriptions concerning what exactly is implied by “a positive change” reported in some individuals with autism.

AIMS

The purpose of this study was to gain further insight into the co-occurrence of autism and epilepsy, by focusing on the one hand on epilepsy in autism in a long-term perspective, and on the other hand on autism and other neuropsychiatric disorders in children who go through surgical interventions for medically intractable epilepsy. There has previously not been a population-based long-term follow-up study looking at epilepsy in autism, and there are few studies investigating the effects of epilepsy surgery on psychopathology, including autism, in children.

More specifically, the aims were:

- To study the frequency, characteristics and outcome of epilepsy in a population-based series of children with autism growing up (study I);

- To investigate differences in intellectual and adaptive level between young adults with autism and epilepsy, and young adults with autism without epilepsy (study I);

- To assess psychopathology, including autism, in children with medically intractable epilepsy, undergoing epilepsy surgery, and to assess possible behavioural change after surgery (studies II and III);

- To relate psychopathology and histopathology to seizure outcome after temporal lobe epilepsy surgery in children (study II);

- To assess outcome concerning psychopathology, IQ and psychosocial functioning two years after epilepsy surgery in children (study III);

- To investigate the effect of VNS on seizures, behaviour, IQ and psychosocial functioning in children with autism and intractable epilepsy (study IV).

METHODS

Study I: Epilepsy in autism – a long-term follow-up study

Study group

The study group is described in Figure 1. In 2000 to 2001, a population-based follow-up study was performed of 120 individuals with childhood autism born 1962-1984 (Billstedt et al. 2005). The recruited subjects came from three population-based studies of autism performed in the 1980s (Gillberg 1984, Gillberg & Steffenburg 1986, Gillberg et al. 1991). In the original studies there were 78 children with AD and 42 with PDD-NOS (here referred to as ALC), 47% had SMR, 35% MMR and 18% did not have MR. At follow-up 108 individuals could be assessed.

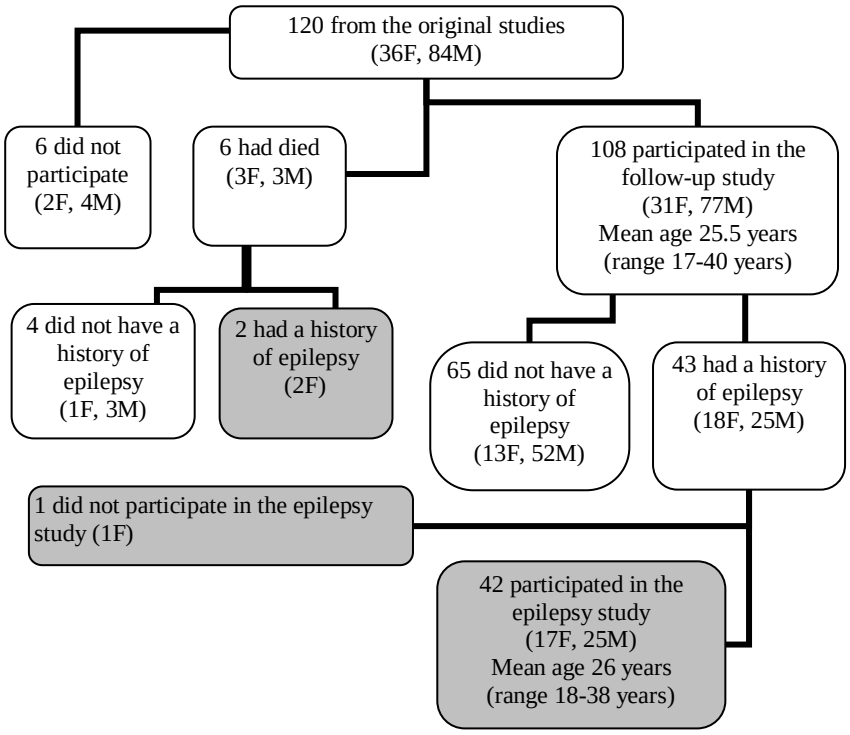

Figure 1. Subjects in study I.

The assessments included a psychiatric/medical assessment and a neuropsychological evaluation with the Wechsler Scales and/or the Vineland Adaptive Behaviour Scale (Sparrow et al. 1984) and the DISCO (Wing et al. 2002). The results have been reported elsewhere (Billstedt et al. 2005). The male to female ratio was 2.5:1. Ninety-two (85%) met DSM-IV criteria for AD, 15 (14%) for PDD-NOS (here referred to as ALC, defined as at least four or more of the 12, but not full DSM-IV diagnostic criteria for AD) and one individual did no longer meet full criteria for AD or ALC at follow-up. SMR was present in 77/108 (71%), MMR in 25 (23%) and 6 (6%) did not have MR. The adaptive level was below the four year age equivalent level in 59% of the cases.

We do not have information concerning epilepsy in the six individuals who did not participate. Among the six who had died before follow-up we know that two had epilepsy. Both were girls with epilepsy onset during the first year of life and they are included when we present age at epilepsy onset in the cohort.

Forty-three out of 108 had a history of epilepsy. The parents of one woman with active epilepsy declined participation in the epilepsy study. When group comparisons between the epilepsy and non-epilepsy groups are made in the following, this case will be included in the epilepsy group. Forty-two individuals with epilepsy participated in the epilepsy study.

Methods

Parents or carers were interviewed according to a systematically applied protocol. The individuals participated at a median age of 25 years (Q_1, 21; Q_3, 33, range 18 – 38 years) after consent from a parent or a close relative. All interviews were made by the author by telephone or in person at their place or at the clinic. Data extracted from the interviews concerned: seizure semiology, age at onset, the occurrence of status epilepticus, seizure frequency, duration and course of epilepsy, use of antiepileptic and psychotropic drugs, and medical services supplied. The medical records from child and adult medical and psychiatric assessments were not reviewed until after the structured interview had been analyzed, in order to avoid influence by the previous interpretations and investigations. Neuroimaging had been performed in 33/42 (10 both computerized tomography (CT) and MRI; 23 only CT). Results from at least one interictal EEG recording were available for all cases but one.

The seizure semiology and EEG findings were thoroughly discussed with an experienced child neurologist and seizure types were classified into four main categories (ILAE 1981):

1. *The partial seizure group* included simple partial and complex partial seizures with or without secondarily generalized seizures. If there was a history of obvious focal semiology preceding a generalized seizure it was classified as partial, or if the seizure with or without impaired consciousness was associated with focal motor signs, autonomic symptoms or automatisms.

2. *The generalized seizure group* included primarily generalized epilepsies.

3. *The mixed partial and generalized seizure group*.

4. *The unclassified group* included cases with insufficient descriptions of seizure semiology, mainly due to the difficulty to differ an epileptic seizure from behaviour in some subjects with SMR and autism.

Studies II-IV: Autism and other neuropsychiatric disorders in children and adolescents with medically intractable epilepsy in the epilepsy surgery programme at Sahlgrenska University Hospital

Study groups

Baseline data of the three studies are shown in Table 2.

Table 2. Baseline data of children with intractable epilepsy

	Study II n=16	Study III n=25	Study IV n=8
Type of intervention	Temporal lobe resection	Resective surgery or disconnection of HH	VNS
Male:female	7:9	15:10	7:1
Median age at epilepsy onset (years)	3.2 (range 0.1-10.0)	4.0 (range 0.0-17.7)	2.8 (range 0.2-9.0)
Median age at intervention (years)	10.0 (range 3.5-19.0)	13.4 (range 4.2-19.4)	13.3 (range 5.7-18.6)
Median epilepsy duration (years)	5.5 (range 1.0-16.5)	6.9 (range 0.3-18.9)	9.2 (range 4.2-16.2)
IQ≥70	8	16	1
IQ 50-69	4	1	1
IQ < 50	4	8	6
Neurodevelopmental disorders besides intractable epilepsy with or without psychopathology	**8**	**10**	**8**
MR only	7	8	6
MR + CP	1	1	1
CP only	0	1	1
Aetiological diagnosis			
Tuberous sclerosis	1	2	1
HH	0	3	1
Angelman syndrome	0	0	1
Viral encephalitis	1	0	0

Abbreviations: MR, mental retardation; CP, cerebral palsy; VNS, vagus nerve stimulation; HH, hypothalamic hamartoma.

Study II: Sixteen patients in a consecutive series undergoing TLRs between 1995 and 1998. The 2-year outcome data could be assessed in 13 patients. Three were re-operated and two years had not passed since the last operation at the time of the study.

Study III: Twenty-five patients consecutively operated with resections or disconnections between 2002 and May 2006. Children undergoing callosotomies were excluded, as were those referred to our centre from other Nordic countries. Three were re-operated during the study period and the follow-up assessment was made two years after the second operation. The surgical location was temporal in ten, frontal in eight, parietal in two, and occipital in two. In three subjects there were disconnections of hypothalamic hamartomas. The 2-year outcome data was assessed in all but one girl, who died from sudden unexpected death 22 months after surgery.

Study IV: Eight consecutive patients with autism who started VNS treatment between 2001 and March 2005. One had previously been through epilepsy surgery. In one boy the VNS treatment was stopped after six months due to deterioration of behaviour and increased seizure frequency. Seven patients were followed up after two years treatment with VNS.

Methods

All patients had been assessed in the epilepsy surgery programme with investigations aiming at finding the epileptogenic focus. As part of the pre-operative work-up there were neuropsychological (Studies II-IV) and neuropsychiatric (Studies III-IV) assessments, which were repeated at the 2-year follow-up. The overall seizure frequency was defined as the mean total seizure frequency per month during a period of three months before the assessment. The 2-year seizure outcome was expressed as class 1, seizure free; class 2, not seizure free but more than 75% reduction of seizure frequency; class 3, 50-75% reduction of seizure frequency and class 4, less than 50% reduction of seizure frequency.

If epilepsy surgery was not an alternative, treatment with VNS was offered (Study IV). The Neuro Cybernetic Prosthesis (NCP) System from Cyberonics Inc. was implanted by a neurosurgeon. Stimulation parameters were adjusted by a child neurologist according to standard practice. The stimulus intensity was increased stepwise to the highest tolerated level. In one patient rapid cycling (seven seconds on, 12 seconds off) was used after one year. No other stimulation strategies were tried. AEDs were left unchanged unless increased seizures or adverse effects made changes necessary.

The neuropsychiatric and neuropsychological assessments

The methods are summarized in Table 3, and described in more detail below.

Assessment of psychopathology and behaviour (Studies II, III and IV)

The retrospective assessment of psychopathology (Study II)

The medical records from the neurological and psychological evaluations preoperatively and two years postoperatively were reviewed and data indicating neuropsychiatric symptoms were summarized. Eight children (50%) had been assessed by a child psychiatrist at some point and diagnosed as having a disorder according to the DSM-IV (APA 1994). For the remaining children the main behavioural problems were described, if they were limiting the child's function in at least two situations, ie at home, at school or at visits to the child neurologist or to the neuropsychologist as reported in the medical records. In these eight cases we do not know for certain if the children with inattention and activity control problems fulfilled the actual criteria for ADHD according to the DSM-IV.

The prospective assessment of psychopathology (Studies III and IV)

All patients had clinical neuropsychiatric assessments by the author before and two years after the surgical intervention. It 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 behaviour disorders, tic disorders, separation anxiety disorder, obsessive compulsive disorder and depression. Psychopathology was diagnosed according to DSM-IV criteria (APA 1994). Subjects diagnosed with PDD-NOS fulfilled at least five DSM-IV criteria for AD with or without first symptoms before the age of three years. ADHD co-occurring with PDD and/or MR was diagnosed. Disruptive behaviour disorder not otherwise specified (DBD-NOS) was diagnosed in subjects with a behavioural

disturbance characterized by rage attacks, lability and disinhibition significantly interfering with functioning. The assessment of children with autism included further multidisciplinary work-up using the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing et al. 2002), the Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord et al. 2000) and in-depth discussions concerning which of the descriptive criteria of the DSM-IV that were met and suggestions about interventions and information to the families.

Table 3. N**europsychiatric and neuropsychological methods**

	Study II n=16	Study III n=25	Study IV n=8
Diagnostic criteria	DSM-IV (n=8)	DSM-IV	DSM-IV
Neuropsychiatric assessment before and two years after intervention	Chart review	Neuropsychiatric examination	Neuropsychiatric examination
		DISCO and ADOS-G (n=7)	DISCO and ADOS-G
Questionnaires to parents	Conners BPRS	Conners BPRS SDQ, ASSQ	ABC
Assessment of behavioural change	Reports from parents and professionals	Parental perception	CGI-I
Assessment of psychosocial functioning		CGAS	CGAS
Assessment of intellectual ability	Wechsler scales Griffiths developmental scales	Wechsler scales Griffiths developmental scales	Wechsler scales Griffiths developmental scales

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; BPRS, Brief Parent Rating Scale; CGAS, Children's Global Assessment Scale; SDQ, Strengths and Difficulties Questionnaire; ASSQ, Autism Spectrum Screening Questionnaire; DISCO, Diagnostic Interview for Social and Communication Disorders; ADOS-G, Autism Diagnostic Observation Schedule-Generic; ABC, Autistic Behavior Checklist; CGI-I , Clinical Global Impressions-Improvement scale

Questionnaires

- The Conners Brief Parent Rating Scale (BPRS) (Studies II and III)

The Conners BPRS is a 10-item attention-deficit-hyperactivity questionnaire that was constructed from the Conners Parent Rating Scale (Conners 1994, Conners et al. 1998). The scale yields a total sum score of 0 to 30, and scores above 10 indicate possible ADHD.

- The Strengths and Difficulties Questionnaire (SDQ) (Study III)

The SDQ is a parent and teacher screening questionnaire of the adjustment and psychopathology of 3-16-year-olds (Goodman 2001). The response alternatives consist of 25 statements concerning emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviour. 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 behaviour 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 (Malmberg et al. 2003).

- The Autism Spectrum Screening Questionnaire (ASSQ) (Study III)
The ASSQ (previously known as the *the Asperger syndrome and High-Functioning Autism Screening Questionnaire)* is a 27-item parent and teacher questionnaire (Ehlers & Gillberg 1993) that yields a total score ranging from 0 to 54. A score above 15 indicates a possible PDD in children 6-17 years old (Ehlers et al. 1999, Posserud et al. 2006).

- Autistic Behaviour Checklist (ABC) (Study IV)
The ABC is a well-established instrument measuring levels of autistic behaviour in individuals with severe disabilities. A total score above 67 indicates autism, and scores above 53 indicate "suspected autism" (Krug et al. 1980).

Parents were asked to return the questionnaires before and two years after surgery, but four chose not to do so in Study II. In Study III, parents of children with mental ages below three years (two boys with PDD), were not given the SDQ or the ASSQ; 19 parents returned the SDQ and 20 the ASSQ preoperatively. At follow-up 22 returned the SDQ and the ASSQ.

Assessment of behavioural change (Studies II, III and IV)
The 2-year behavioural outcome in Study II was based on reports from parents combined with the observations of the child neurologist and neuropsychologist and on changes in Conners BPRS scores. In Study III it was based on the parental perceptions concerning behavioural change two years after surgery, and was classified by the author as *positive, no change* or *negative*. The Clinical Global Impressions-Improvement scale (CGI-I) was used in Study IV. It is a clinician-rated instrument for scoring global improvement. The scale ranges from 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse to 7 = very much worse (Hollander et al. 2001).

Assessment of psychosocial functioning (Studies III and IV)
The general psychosocial functioning was assessed by the author using the Children's Global Assessment Scale (CGAS). The CGAS is a single global scale with 10 verbally defined hierarchical levels of functioning (see Appendix). It is used to rate the general functioning of children under the age of 18 years and enables scoring from 1 to 100 on a hypothetical continuum of mental health/illness (Shaffer et al. 1983). A score above 70 indicates good functioning or only a mildly abnormal psychosocial situation; 70-61, some difficulty in a single area, but generally functioning pretty well; 60-51, variable functioning with sporadic difficulties in several but not all social areas; 50–41, a moderate degree of interference in functioning in most social areas or a severe impairment of functioning in one area; 40-31, major impairment of functioning in several areas and inability to function in one of these areas; 30-21, inability to function in almost all areas or serious impairment in communication; 20-11 gross impairment in all forms of communication; a score below 10 a need for constant supervision (24-hour care).

To check interrater agreement in the CGAS assessments in Study III, the first rater created 49 case histories, describing the 25 cases pre- and postoperatively (one child died before follow-up), which were given to an experienced child psychiatrist for scoring. The second rater was blind to information about diagnoses, and the case histories were randomly ordered. A total inter-rater agreement was found regarding 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 a range of 4-10 CGAS scores in five cases. The final classification was based on the assessments made by the first rater who had met and examined the children.

Assessment of intellectual ability (Studies II, III and IV)
Intelligence or mental age was assessed within one year before the surgical intervention and two years after in all the individuals. At the neuropsychological examination the 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 the Griffiths Developmental Scales (Alin-Åkerman & Norberg 1991) or the Wechsler scales were used (Wechsler 1999a, Wechsler 1999b, Wechsler 2003). In subjects with severe and profound MR the developmental quotient (DQ) equivalent to IQ was reported.

Assessment of histopathological diagnosis (Studies II and III)
The specimens obtained at resection in Study II were re-evaluated by a neuropathologist blinded regarding seizure outcome and psychopathology. All histopathological abnormalities were recorded. In Study III the results were taken from the medical records.

Statistical methods

For comparisons of proportions across groups the Chi squared test was used and in the event of small numbers Fisher's exact test was used. Mann-Whitney test was used for non-parametric comparison of data from two independent groups. (Study I)

The median and the quartiles Q_1 and Q_3 were used to describe the data. Possible changes in the individual's paired data were evaluated by means of cross tables or scatter plots when suitable. Possible difference in proportions between groups was analyzed and the 95% confidence interval (CI) for the difference in proportions according to Wilson was calculated (Newcombe & Altman 2000). A 95% CI not covering a zero difference is a sign of statistical significant difference in proportions, $p<0.05$. (Study III)

Ethics

The designs of studies I, III and IV were approved by the Ethical Committee at the Medical faculty at the University of Gothenburg. The retrospective Study II was considered part of a quality control and evaluation of the assessment procedure and outcome measures.

RESULTS

Study I: Epilepsy in autism – a long-term follow-up study

Overall frequency of epilepsy and epilepsy onset (n=120)

At least 45/120 individuals (38%) with AD or ALC had epilepsy. Median age at onset was 5.5 years (Q_1, 1.25; Q_3, 11.5, range 1 month to 32 years). Figure 2 shows the age at onset of epilepsy in the 45 individuals.

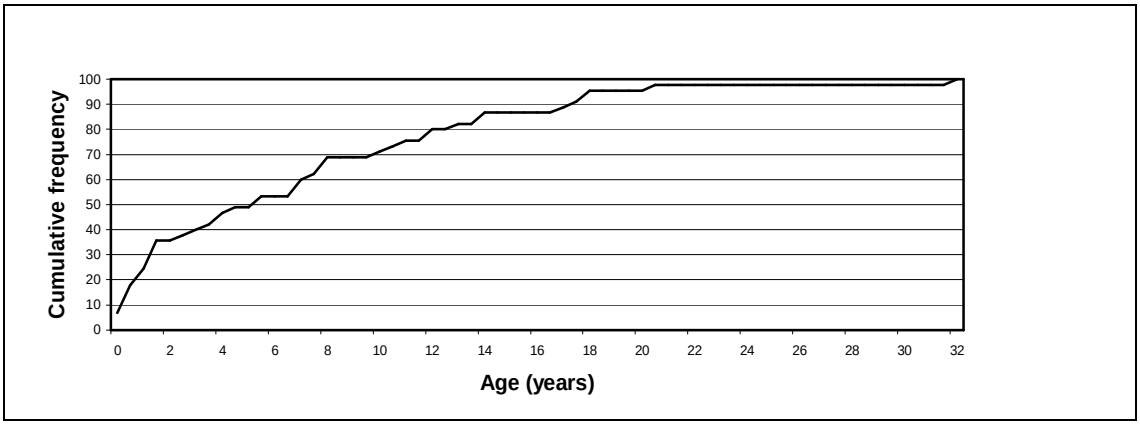

Figure 2. Age at onset of epilepsy in 45 individuals with autism and epilepsy.

Twenty-seven out of 45 had SMR as children and 18 had MMR or average/near average cognitive ability. The median age at epilepsy onset in the 27 with SMR was 3.5 years, compared to 7.2 years in those without SMR, a statistically non-significant difference.

Comparison between the epilepsy and non-epilepsy groups at follow-up

There were 43 with epilepsy and 65 without (Table 4). In those with SMR at follow-up, 48% (37/77) had a history of epilepsy, in those with MMR 20% (5/25) and in those without MR 17% (1/6). Epilepsy was more common in females, 58% (18/31) versus 32% (25/77) in males ($p=0.01$; 95% CI 6% to 46%) and SMR was significantly more common in the epilepsy group than in the non-epilepsy group ($p<0.01$; 95% CI 8% to 40%). The adaptive behaviour level was lower than the four year age equivalent level significantly more often in the epilepsy group compared to the non-epilepsy group ($p<0.05$; 95% CI 3% to 39%). The adaptive behaviour level was below that of a one-year-old in 11/108 cases (eight females, three males). Of these, eight had epilepsy (19% of the epilepsy group) and three did not (5% of the non-epilepsy group) ($p<0.01$; 95% CI 1% to 27%).

Table 4. Gender, frequency of associated medical conditions, PDD-diagnoses, cognitive and adaptive levels in the epilepsy and non-epilepsy groups

.	*Cases with epilepsy (n=43)*	*Cases without epilepsy (n=65)*
Gender		
Male	25 (58%)	52 (80%)
Female	18 (42%)	13 (20%)
Male: female ratio	1.4:1	4.0:1
Associated medical condition	10 (23%)	13 (20%)
AD or ALC at follow-up[1]		
AD	40 (93%)	52 (80%)
ALC	3 (7%)	12 (18%)
Cognitive level		
SMR	37 (86%) *	40 (62%)
MMR	5 (12%)	20 (31%)
Not MR	1 (2%)	5 (8%)
Adaptive level		
<4 year age equivalent level	31 (72%) **	33 (51%)

[1]At follow-up one individual (without epilepsy) did not have AD or ALC.
*p < 0.01; subjects with epilepsy versus those without
**p < 0.05; subjects with epilepsy versus those without

Severe MR, epilepsy and gender

Twenty-four out of 48 individuals with SMR as children had a history of epilepsy at follow-up. Twelve out of the 15 females with SMR (80%) had a history of epilepsy, compared to 12/33 males (36%), a statistically significant difference ($p<0.05$; 95% CI 18% to 70%). Seventy-seven out of 108 adults had SMR. Almost all had AD, 97% of the 37 with epilepsy and 95% of the 40 without. Among those with epilepsy there were almost as many males as females (1.2:1), whereas there were almost six times more males than females in the non-epilepsy group (5.7:1). Epilepsy was more common in females with SMR, 17/23 (74%), than in males, 20/54 (37%) ($p<0.05$; 95% CI 15% to 59%). There were no statistically significant differences concerning the low adaptive behaviour level or the frequency of childhood SMR in the SMR and epilepsy and SMR and non-epilepsy groups.

Characteristics of epilepsy in autism (n=42)

Seizure type at onset was partial in 23, generalized in 10, mixed partial and generalized in six and unclassified in three. Three individuals had undergone epilepsy surgery as children, and two of them were seizure free with AED treatment as adults. There was no change in seizure type during the follow-up time or before remission in 86% of the cases. Hospitalization due to status epilepticus was reported in 16/42 cases (38%), and five of these had repeated episodes. Severe trauma secondary to epileptic seizures had occurred in 11/42 cases (26%), eg near drowning, fractures or head trauma. Out of the 38 with epilepsy onset before age 18 years, six (16%) had remission of epilepsy, defined as no seizures or medication for more than five years. Two additional cases were seizure free with AED treatment.

Active epilepsy

At follow-up 34/42 (81%) had active epilepsy, defined as one or more epileptic seizures in the 5-year period before the study, regardless of AED treatment. The majority, 25/34 (73%), had partial seizures alone or in combination with generalized seizures. Seizure frequency was more than one seizure per year in 24/34 (71%). Seventeen of these had more than one seizure every month. Antiepileptic monotherapy was used in 19 cases and a combination of two AEDs in ten. Three were on three or more AEDs and two had none. Psychotropic drugs (antipsychotics, antidepressants and/or lithium) were used in 16/34. Intractable epilepsy, defined as more than one seizure every week, was seen in 11. Six of them had contact with a neurologist once or twice a year. In three cases only two different types of AEDs in monotherapy had ever been tried out. There were no significant differences comparing the intractable and the non-intractable groups concerning age at epilepsy onset, gender, cognitive level or seizure types. Among those with active epilepsy 13/34 (38%) respondents said epilepsy had the greatest impact on the person's daily life as an adult, more frequently in those with intractable epilepsy (9/11) than among those without (4/23), ($p<0.001$; 95% CI 39% to 91%). In the latter subgroup, autism and/or MR were most burdensome.

Studies II-IV: Autism and other neuropsychiatric disorders in children and adolescents with medically intractable epilepsy in an epilepsy surgery programme

Study II

Data on the 16 children and adolescents treated surgically for temporal lobe epilepsy is shown in Table 5. Twelve out of 16 had psychopathology, most often DBD and/or autism. All the children with autism had MR, and three had problems with hyperactivity. The behavioural change postoperatively was assessed in 13 out of 16 children. The remaining three (no 6, 9, 13) were re-operated and two years had not passed since the last operation at the time of the study, but we now know that one of them was seizure free two years after the re-operation (no 13), and two were class 3 (no 6 and 9). In 11/13 there was a positive or no behavioural change. No child rendered seizure free deteriorated in behaviour. One out of five children with autism became seizure free. The parents of the children with autism reported a positive behavioural change in three children (calmer, less aggressive), no change in one and there were more symptoms of autism in one boy. The parents of the children with attention deficits and/or hyperactivity noted that their children could concentrate better and/or were less hyperactive after surgery. Most patients had more than one histopathological diagnosis. Ten out of 12 children or adolescents with psychiatric problems and seven out of eight children with MR had MCD. No child with normal cognitive function and behaviour had MCD.

Table 5. Data on 16 children and adolescents followed up two years after TLR

Pat no	Sex	Cognitive status	Psychiatric diagnosis/ behaviour	Seizure frequency (per month) at baseline	Histopathological diagnosis	Seizure outcome (class)	Behavioural change
Children with autism							
1*	F	SMR	AD, hyperactivity	50	Microdysgenesis, gliosis	1	Positive
2*	F	MMR	AD, hyperactivity	40	Microdysgenesis, gliosis	2	Positive
3*	F	MMR	Asperger syndrome, hyperactivity	170	Postinflammatory lesions, cortical dysplasia, gliosis	4	No change
4*	F	SMR	AD	200	Tuberous sclerosis	3	Positive
5*	M	SMR	AD	100	1st op and 2nd op: focal cortical dysplasia, gliosis	3	Negative
Children with attention deficits with or without hyperactivity							
6*	M	MMR	ADHD, DCD	750	1st op: microdysgenesis, gliosis 2nd op: microdysgenesis, gliosis	Reop	Reop
7*	M	No MR	ADHD, DCD	8	Ganglioglioma	1	Positive
8	F	MMR	Inattention, hyperactivity	110	Gliosis	1	Positive
9	M	No MR	Inattention, hyperactivity	300	1st op: microdysgenesis, gliosis 2nd op: microdysgenesis, gliosis	Reop	Reop
10	F	SMR	Inattention, hyperactivity	235	Microdysgenesis, gliosis	2	Positive
Children with other psychiatric problems							
11	M	No MR	Impulsiveness, aggressiveness	15	DNET, microdysgenesis	1	Positive
12*	F	No MR	Depressive disorder	90	Oligodendroglioma and microdysgenesis	1	Positive
Children with no psychopathology							
13	M	No MR	-	30	1st op: DNET, 2nd op: DNET	Reop	Reop
14	F	No MR	-	15	Mesial sclerosis	2	Negative
15	F	No MR	-	50	Oligoastrocytoma, gliosis	1	No change
16	M	No MR	-	15	Ganglioglioma	1	No change

Abbreviations: Pat no, patient number; F, female; M, male; AD, autistic disorder; ADHD, attention-deficit/ hyperactivity disorder; DCD, developmental coordination disorder; DNET, dysembryoplastic neuro-epithelial tumour; Reop, re-operated, not followed up two years after last operation; class 1, seizure free; class 2, not seizure free but more than 75% reduction of seizure frequency; class 3, 50-75% reduction of seizure frequency; class 4, less than 50% reduction of seizure frequency.

* Assessed and diagnosed by a child psychiatrist

Study III

Table 6 shows the main results regarding psychopathology, IQ, psychosocial functioning and seizure outcome.

Three cases (no 11, 12, 21) had been re-operated during the follow-up period and outcome was assessed two years after the second operation. The histopathological diagnoses were lesions (two gangliogliomas, one astrocytoma and two dysembryoplastic neuroepithelial tumours (DNET)) (n=5), MCD (n=6), MCD in combination with gliosis (n=6), gliosis (n=2), tuberous sclerosis (n=2) and hypothalamic hamartomas (n=3).

Psychopathology

Psychopathology was diagnosed in 14/24 subjects at the pre-surgical assessment, and in nine of them there was more than one diagnosis. Seven children were diagnosed with autism. ADHD was diagnosed in nine, three of whom had autism. Four out of 24 children had been assessed psychiatrically and diagnosed with autism (no 17, 18, 24) or ADHD (no 13) before referral to the epilepsy surgery team. At the neuropsychiatric assessment two years after surgery, a total of 16 children had psychopathology. In 11/16 there was more than one diagnosis. Seven children still had autism. In all, a diagnosis of a psychiatric disorder had been made in 17/24 children at the pre- or postoperative assessments and a total of 13 had autism, ADHD or both. At follow-up there were five new cases with emotional disorders and two new cases with ADHD-I. Among the children with pre-operative psychopathology, one was without a diagnosis after surgery. Seven of the 10 children without a pre-operative diagnosis still had no psychiatric diagnosis at follow-up.

Questionnaires

At the pre-operative assessment five out of 14 children with a psychiatric diagnosis reached the SDQ cut-off score for psychopathology, and five out of 16 children at the 2-year follow-up. The cut-off score for ADHD according to the Conners BPRS was reached in seven out of nine children with ADHD pre-operatively and in three out of eight post-operatively. The ASSQ cut-off for autism was reached in three children pre-operatively and in two post-operatively among the five out of seven children with autism whose parents were given the questionnaire.

Behavioural outcome

According to the neuropsychiatric interview with parents, 12 children had a positive, four had none and eight had a negative behavioural change at the 2-year follow-up. A parental perception of a negative behavioural change was found in eight out of 17 not seizure free children and in none of the seizure free children ($p<0.05$; 95% CI 6% to 69%).

Table 6. Psychopathology, IQ, psychosocial functioning and seizure outcome

DSM-IV diagnoses at baseline	DSM-IV diagnoses at follow-up	ID	IQ at baseline	IQ at follow-up	CGAS at baseline	CGAS at follow-up	Seizure out-come (class)	Behavioural change*
Autistic disorder	PDD-NOS, separation anxiety disorder	18	ModMR	ModMR	35	61	1	Positive
Autistic disorder, ODD	Autistic disorder, ODD	17	ModMR	ModMR	20	30	4	Positive
Autistic disorder, DBD-NOS	Autistic disorder, DBD-NOS	24	PMR	PMR	5	5	2	Positive
PDD-NOS	PDD-NOS	15	Near A	Near A	48	50	4	Positive
PDD-NOS, ADHD-C, DBD-NOS	Autistic disorder, ADHD-C	1	A	MMR	20	25	3	Positive
PDD-NOS, ADHD-C, DBD-NOS	Autistic disorder, ADHD-C, DBD-NOS	16	MMR	Mod MR	40	17	4	Negative
PDD-NOS, ADHD-I, DBD-NOS	PDD-NOS, DBD-NOS	23	Severe MR	Severe MR	15	20	3	Positive
ADHD-C, ODD	0	2	A	A	61	95	1	Positive
ADHD-I, DBD-NOS	ADHD-I, depressive disorder	12	Near A	Near A	67	52	4	Negative
ADHD-I	ADHD-I, DBD-NOS	13	Near A	A	61	45	2	Negative
ADHD-I, ODD	ADHD-I, ODD, depressive disorder	20	ModMR	ModMR	57	47	3	Negative
ADHD-I	ADHD-I	21	ModMR	Mod MR	65	65	4	No change
ADHD-C, DBD-NOS	DBD-NOS	22	ModMR	ModMR	45	50	1	Positive
Mixed receptive/ expressive language disorder	Mixed receptive/ expressive language disorder	11	Near A	Near A	62	62	3	No change
0	ODD, depressive disorder	14	Near A	A	80	60	2	Negative
0	0	8	Near A	Near A	85	85	1	Positive
0	0	7	A	A	72	91	1	Positive
0	ADHD-I, separation anxiety disorder	3	A	Near A	82	60	2	Negative
0	0	4	A	A	95	95	1	No change
0	0	5	A	A	82	90	2	Positive
0	0	6	A	A	90	91	2	Positive
0	0	10	Near A	Near A	70	70	1	No change
0	ADHD-I	9	Near A	MMR	79	65	3	Negative
0	0	19	ModMR	MMR	60	51	2	Negative

Abbreviations: ADHD-I, attention-deficit/hyperactivity disorder – inattentive type; ADHD-C, attention-deficit/hyperactivity disorder-combined type; ODD, oppositional defiant disorder; DBD-NOS, disruptive behaviour disorder not otherwise specified; PDD-NOS, pervasive developmental disorder not otherwise specified; A, IQ>84; Near A, IQ 70-84; MMR, IQ 50-69; ModMR, IQ 35-49; Severe MR, IQ 20-34; PMR, IQ<20; CGAS, Children's Global Assessment Scale; class 1, seizure free; class 2, not seizure free but more than 75% reduction of seizure frequency; class 3, 50-75% reduction of seizure frequency; class 4, less than 50% reduction of seizure frequency.
*According to the reports from parents during the neuropsychiatric interview.

Psychosocial functioning

Eight patients had CGAS scores above 70 at the pre-surgical assessment, and six at follow-up (Table 6). Subjects with autism had CGAS scores in the range 5 to 48 before surgery and those without autism in the range 45 to 95 (Figure 3). In 16 out of 24 there were improvements or no change in psychosocial functioning two years after surgery. Among the seven seizure free subjects no one had a worsened psychosocial functioning. The individual changes in psychosocial functioning (CGAS) are illustrated in Figure 3.

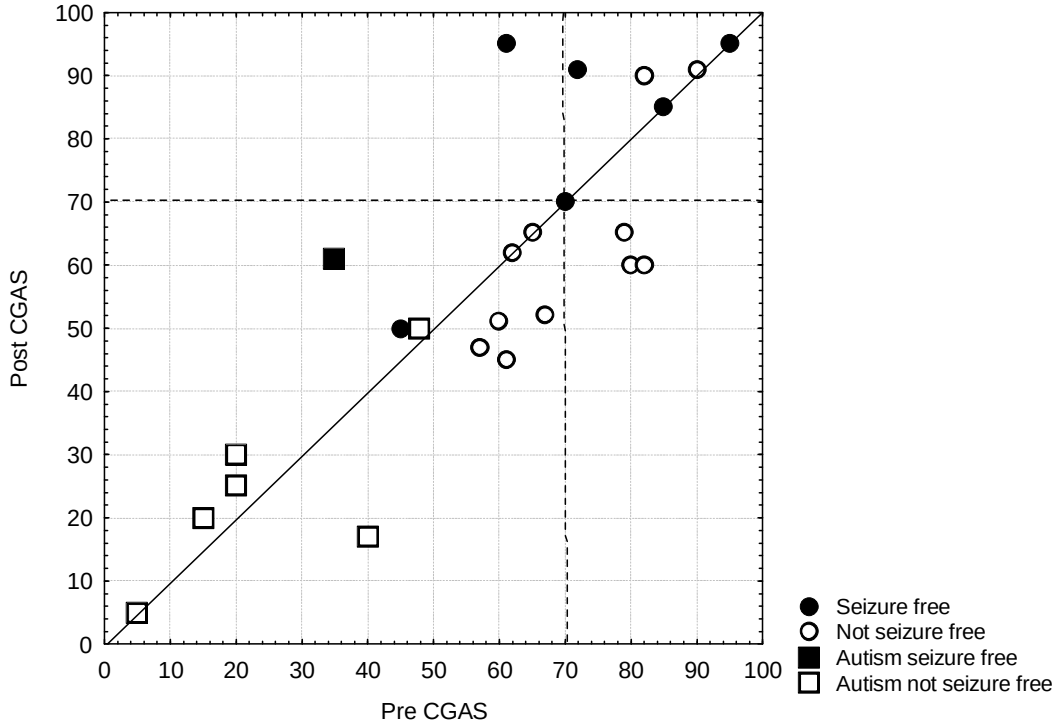

Figure 3. The psychosocial functioning classified according to the CGAS before surgery on the x-axis and two years after surgery on the y-axis for each subject (n=24).

CGAS improvement of 20 or more was seen in two individuals (no 2, 18), who became seizure free, one of whom had autism. CGAS deterioration of 20 or more was seen in three subjects (no 3, 14, 16) (Table 6): one girl with autism and MMR who had an intellectual decline and no seizure reduction after surgery. The other two girls had normal psychosocial functioning before surgery, but had emotional disorders postoperatively - one with depressive disorder and ODD, and one with separation anxiety disorder and ADHD-I. They had their seizure frequency reduced by more than 75%, but were not seizure free.

An agreement was found between parents' perception of a negative behavioural change and a decrease in CGAS of 9 to 23 scores. There was also an agreement between parents' perceived "no change" and unchanged CGAS scores. A positive behavioural change, as perceived by the parents, was reflected as none or, in most subjects, a minor increase in CGAS scores. The parents of children with autism reported a positive behavioural change, except in one case.

Intellectual ability

The individual changes in full scale IQ (FSIQ) in 23 children are illustrated in Figure 4. The majority, 17/23, had no change or less than eight points change in IQ. IQ remained stable in the majority of cases both in individuals with and without MR. Five children had a decrease of 10 or more IQ points. Three had a deterioration of more than 20 IQ points (no 1, 9, 16); they had undergone surgical procedures in the frontal lobe, had seizure outcome class 3 or 4 and two of them had autism. One gained 11 IQ points (no 19).

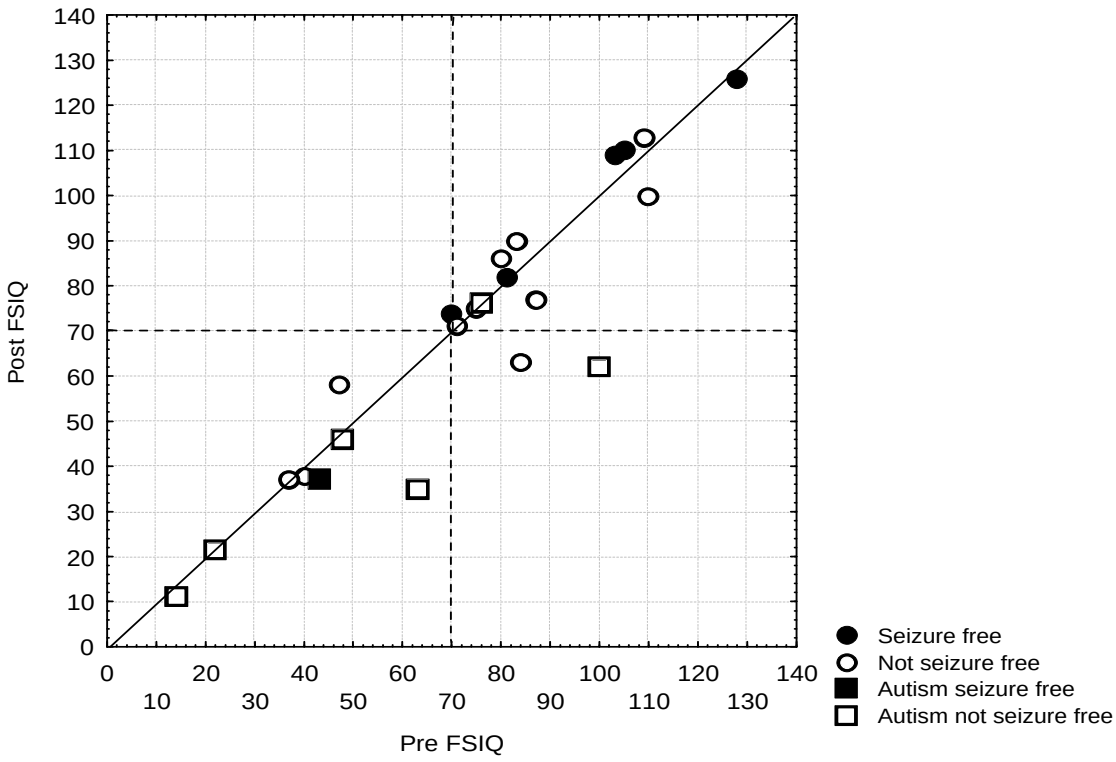

Figure 4. The FSIQ before surgery on the x-axis and two years after surgery on the y-axis for each subject (n=23). Median IQ at the presurgical assessment was 76 (Q_1 47; Q_3 100, range 14 to 128). At the 2-year follow-up median IQ was 74 (Q_1 38; Q_3 90, range 11 to 126).

Baseline psychopathology was more common in the nine children with IQ<70, than in the 15 children with average or near average intellectual ability ($p<0.05$; 95% CI 17% to 81%).

Group differences concerning seizure outcome (Studies II, III)

Table 7 shows data from the 2-year follow-up of the 40 operated individuals in Studies II and III, comparing the group rendered seizure free (n=15) with the not seizure free group (n=25). There was a significant difference of proportion of tumours in the seizure free group (53%) compared to the non seizure free group (12%) ($p<0.05$; 95% CI 13% to 69%), while the other differences in proportions considering autism, IQ<70 or psychopathology were not statistically significant.

Table 7. Group differences concerning seizure outcome (Studies II, III)

	All subjects in studies II and III (n=40)	Seizure free (n=15)	Not seizure free (n=25)
Female gender	18 (45%)	6 (40%)	12 (48%)
Male gender	22 (55%)	9 (60%)	13 (52%)
Autism	12 (30%)	2 (13%)	10 (40%)
IQ<70	17 (42%)	4 (27%)	13 (52%)
Psychopathology	26 (65%)	8 (53%)	18 (72%)
Tumours	11 (28%)	8 (53%)*	3 (12%)

*p<0.05

Study IV

There was no change in seizure frequency at the 2-year follow-up in the seven patients with autism who continued the VNS treatment for intractable epilepsy. No complications were reported and only mild adverse effects in two subjects (intermittent hoarseness). In five the AED regimen was unchanged at follow-up compared to baseline. One had started on a ketogenic diet (no 1 in Table 8).

The neuropsychiatric findings are shown in Table 8. Four patients had ADHD in addition to autism. Attention span and/or ability to remain seated when appropriate were positively affected at follow-up, but not to the extent that the diagnoses were changed. The clinical baseline autism diagnoses were unchanged at follow-up, as were the DISCO-algorithm diagnoses. The subjects in our study all had pervasive impairments, reflected in the very low CGAS scores. After two years of VNS treatment three subjects had a positive change (no 1, 2, 4) in the quality of social interactive abilities and one had a negative change (no 6) compared to baseline. The changes were minor in all but one (no 2), and did not affect the overall ability to participate in daily life. The boy with a negative change did not interact and was mostly indifferent to everyone also at baseline (no 6). Before VNS three had profound, two severe, one moderate, one mild MR and one had average intelligence. No one improved in IQ/DQ points compared to baseline, and only one had a discrete improvement of mental age (no 7). One lost >20 IQ/DQ points (no 1), and another two lost ten or more during the two years with continuing seizures (no 4, 5).

Table 8. Neuropsychiatric findings and psychosocial functioning before and after two years of VNS

ID	DSM-IV diagnoses at baseline	ABC score before	ABC score after VNS	ADOS score before	ADOS score after VNS	CGAS score before	CGAS score after VNS	CGI-I score	Comments on behavioural change at follow-up
1	Autistic disorder, MMR	73	53	22	16	11	18	3	Social interaction with other children possible if guided by adult
2	Autistic disorder, ADHD, PMR	68	86	16	15	1	10	2	Less negative to others´ efforts to make contact Attention span for chosen activity up to 15 minutes instead of zero Utters some sounds with meaning if you know him very well More alert
3	Autistic disorder, ADHD, severe MR	70	-	15	-	4	-	-	Discontinued VNS treatment
4	Atypical autism, ADHD, severe MR	49	37	19	21	21	30	3	May initiate contact with others Can engage for a minute in something someone else suggests instead of not doing so Less easily distracted
5	Autistic disorder, ModMR	72	66	13	13	15	15	4	None
6	Autistic disorder, PMR	77	72	20	20	5	1	6	More passive and aloof More repetitive activities
7	Atypical autism, ADHD, PMR	82	78	7	4	7	7	4	Sometimes sits, but is continually restless, instead of having an inability to remain seated No change in attention span
8	Asperger Syndrome	8	8	15	14	50	45	4	None

Abbreviations: ADHD, attention deficit hyperactivity disorder; ABC, Autistic Behavior Checklist; ADOS, Autism Diagnostic Observation Schedule; CGAS, Children's Global Assessment Scale; CGI-I, Clinical Global Impressions-Improvement scale; PMR, profound MR (IQ<20); severe MR (IQ 20-34); ModMR, moderate MR (IQ 35-49); MMR, mild MR (IQ 50-70).

Seizure outcome and behavioural outcome in Studies II-IV

Table 9 summarizes the 2-year outcome in all children with medically intractable epilepsy (n= 47) in studies II-IV: seizure freedom (class 1) and behavioural outcome in children with MR (n=23), psychopathology (n=33) and autism (n=19), respectively. It also shows the high co-occurrence of MR and ADHD in children with medically intractable epilepsy and autism: MR was present in 16 children with autism, and ADHD in nine.

Table 9. A summary of the 2-year outcome in Studies II-IV

	Study II **n=16**	***Study III*** **n=24**	***Study IV*** **n=7**
Seizure outcome			
-class 1	8	7	0
-class 2	3	7	0
-class 3	4	5	0
-class 4	1	5	7
Positive or unchanged behavioural outcome	**11** [a]	**16**	**6**
Subjects with MR at baseline	**8**	**9**	**6**
-and seizure outcome class 1	2	2	0
-and seizure outcome class 1 or 2	4	4	0
-positive or unchanged behavioural outcome	6 [a]	6	5
Subjects with psychopathology at baseline	**12**	**14**	**7**
-and MR	8	8	6
-and seizure outcome class 1	5	3	0
-and seizure outcome class 1 or 2	7	5	0
-positive or unchanged behavioural outcome	9 [a]	10	6
Subjects with autism at baseline	**5**	**7**	**7**
- and MR	5	5	6
-and ADHD	3	3	3
-and seizure outcome class 1	1	1	0
-and seizure outcome class 1 or 2	2	2	0
-positive or unchanged behavioural outcome	4	6	6
Autistic disorder	4	3	4
PDD-NOS	0	4	2
Asperger syndrome	1	0	1

[a] In study II there is missing data on behaviour at 2-year follow-up in three children due to re-operation: one child without MR or psycho-pathology, one child with MR and psychopathology and one child with psychopathology without MR.

DISCUSSION

General discussion of main findings

Epilepsy in autism (Study I)

Strengths and limitations

The study is the first population-based cross-sectional study of adults with autism and epilepsy performed to date. It is also a prospective longitudinal and retrospective cohort study of children with autism, where the exposure is epilepsy and we study the history of epilepsy in autism. The rate of attrition was low, and the cohort was considered representative of autism in children as diagnosed at the time of the original studies (Gillberg 1984; Steffenburg & Gillberg 1986; Gillberg et al. 1991). The cohort does not include subjects with Asperger syndrome and only about one in five had IQ>70 when they were children. Therefore the results cannot be generalized to apply to all individuals with autism as it is defined today. Further, in cases with SMR and epilepsy, autism may have been underdiagnosed in the original population-based autism diagnostic studies, since it was shown in a later epidemiological study on children with MR and active epilepsy born during the same era in Gothenburg (Steffenburg et al. 1996) that there were previously unknown cases of AD. A prospective study specifically on epilepsy in autism could have given more details on the classification of epilepsy and aetiological diagnosis with repeat EEGs and at least one MRI.

The high rate of epilepsy in autism and epilepsy characteristics

The occurrence of epilepsy up to ages 18 to 38 years in this population-based cohort was at least 38%. The reported rate of epilepsy in autism has varied from 7-42% and has been highest in studies including adolescents and young adults with SMR (Olsson et al. 1988; Volkmar & Nelson 1990; Tuchman et al. 1991; Mouridsen et al. 1999; Pavone et al. 2004). The atypically low rate of 7% was reported in children with autism without SMR or a known associated medical condition (Pavone et al. 2004). In a retrospective follow-up study on a clinical series of 130 individuals 18-35 years old diagnosed with autism in childhood and without a known associated medical condition epilepsy was found in 25% (Hara 2007).

Data from the present study indicate that the risk for epilepsy is highest in the first years of life and decreases from puberty and onwards. One third had epilepsy onset before age two years. However, four subjects had seizure onset after the age of 18 years and since the median age in our cohort was 25 years, our figures on epilepsy occurrence in adults with autism must be seen as a minimum. The bimodal distribution of epilepsy onset with a peak in both the toddler and adolescent periods (Volkmar & Nelson 1990) was not replicated. Rossi et al. (2000) found that two thirds of 18 cases with AD and MR had epilepsy onset after age 12 years, whereas the corresponding rate here was about one in four. In contrast with Rossi, we have not excluded cases of AD with congenital or acquired encephalopathy, which might explain the difference. Also, ours is a population-based sample which has not been the case in previous studies of epilepsy in autism.

Generalized seizures are considered to be the most frequent seizure type in children or equally frequent as partial seizures in the general population (Sidenvall et al. 1996). However, the most common seizure type in adults is partial seizures, accounting for 60% (Forsgren 1990). It has previously been shown that a majority of cases with epilepsy in autism have partial seizures. In the study by Olsson et al. (1988), three quarters of all children with autism and epilepsy had

partial seizures only or in combination with other seizure types, as did three quarters of adults with active epilepsy in our study. The clinical symptoms of seizures and information from medical records were used for the classification. We had to rely on the history from parents and assistants, since we did not have access to video-EEG or ictal EEG recordings, except in those who previously had presurgical assessments. Subclassification of seizures as simple or complex partial could not be done. People with autism and MR can only very rarely report on somatosensory, special-sensory or affective seizure symptoms. Another problem is that a focal brain lesion may be the epileptogenic lesion triggering the seizure event, despite the lack of focal seizure symptoms, due to rapid generalization. Interictal EEGs were used to support the clinical classification, but classification of seizures was not possible in a few cases. This is not surprising, considering that it is hard even for close relatives or for professionals to assess what constitutes an epileptic seizure and what is a marked lack of awareness of the existence and intentions of others in some individuals with autism.

Seizure frequency was more than once a year in two thirds in our study, similar to Forsgren's study on the prevalence of epilepsy in MR (Forsgren et al. 1990). Among the one third of adults with active epilepsy who had more than one seizure every week, there was some concern that the individuals did not have truly medically intractable epilepsy. Some had only tried a very limited number of AEDs and five did not have regular contact with a neurologist, despite the fact that epilepsy had the greatest impact on the person's daily life as an adult, and was considered to be even more burdensome than MR or autism. Patients who do not achieve adequate seizure control with older AEDs deserve a trial with newer AEDs. For individuals with medically intractable epilepsy, the treatment approach must be multiprofessional and the possibility of epilepsy surgery should be considered.

The combination of autism, MR and epilepsy is an indicator of severe brain dysfunction and in 23% an associated medical condition was documented in our study. MRI is the neuroimaging method to be preferred in an aetiological diagnosis of epilepsy, but this had only been performed in one fourth in our series. With the improved MRI techniques of today many of them may have turned out to have MCD.

Childhood onset epilepsy often remits, but less often in cases with more than one type of seizure, abnormal mental and neurological development or with a detectable cause (Brorson & Wranne 1987). An early response to AED is the single best predictor of remission (Sillanpää et al. 1998). The rate of epilepsy remission in a population-based cohort of children with autism growing up has not previously been described. In our study it was only 16 %, and probably reflects the underlying brain dysfunction.

SMR and female gender as risk factors for epilepsy in autism

Epilepsy is more common in SMR than in MMR or no MR (Forsgren et al. 1990; Tuchman et al. 1991; Steffenburg et al. 1995). Many studies on the epidemiology of epilepsy and MR have previously lacked data about autism, but now the concept of autism spectrum disorders has developed and there is a growing awareness and knowledge about autism among specialists and the general public alike (Wing & Potter 2002). Almost half the group with SMR and autism in our sample had epilepsy by early adult life, whereas epilepsy in MMR occurred in 20%. The incidence of epilepsy is slightly higher in males than in females (Christensen et al. 2005). Epilepsy was significantly more common in females with autism than in males in our study, which has been observed previously (Volkmar & Nelson 1990; Tuchman et al. 1991; Elia et al. 1995). Females are less likely to have autism without more severe brain dysfunction (Volkmar & Nelson 1990; Elia et al. 1995). Women with autism and SMR significantly more often had

epilepsy compared to men with the same diagnoses in our study. A recent meta-analysis concluded that the risk for epilepsy in autism is a function of severity of intellectual disability and suggested that autism associated with epilepsy is a subgroup of autism distinguished by its male to female ratio (Amiet et al. 2008).

Epilepsy as a negative prognostic factor for outcome in autism

Epilepsy is considered to be a negative prognostic factor for the outcome of autism (Kobayashi & Murata 1998; Nordin & Gillberg 1998), as was shown in our study. Billstedt et al. (2005) described the outcome of the whole study population (n=108) as very poor in 57% (no ability to lead any kind of independent existence and no clear verbal or non-verbal communication), and poor in another 21% (no independent social progress but some clear verbal or non-verbal communication). The group of adults with autism and epilepsy in our study had significantly more often SMR and a very low adaptive level compared to adults with autism and no epilepsy. Given that SMR is often a co-morbid feature it is difficult to separate the prognostic effects on autism of epilepsy and SMR respectively. Aicardi has pointed out that the disturbance resulting from epilepsy tends to multiply the disability rather than simply add to other difficulties in individuals with neurodevelopmental disorders (Aicardi 1998).

Autism in medically intractable epilepsy (Studies II-IV)

Strengths and limitations

Studies II-IV are case series reports with small numbers, but a strength is that they are descriptive studies of consecutive cases. The subjects in study II and III represent a subgroup of children with medically intractable epilepsy referred to and operated at an epilepsy surgery centre with a population-based referral system. It differs from a prospective controlled study where the aim is to test a hypothesis and the groups consist of samples from populations. Studies III and IV are prospective evaluation studies performed on all children eligible for a 2-year follow-up. The value of the studies is the multivariate follow-up of outcomes; each child was compared to itself and diagnoses were based on in-depth clinical neuropsychiatric examinations and neuropsychological assessments. One aim of study III was to evaluate the complexity of these children's problems. 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. Conclusive comments concerning epilepsy surgery being the cause of observed outcomes cannot be made without an appropriate comparison group. This is a dilemma in outcome studies concerning paediatric epilepsy surgery; the heterogeneity in paediatric epilepsy surgery candidates is much greater than in adults and recurrent seizures may represent a considerable risk for intellectual decline in children, while intellectual functioning seem to be less vulnerable in adults (Bjørnæs et al. 2001). Only one epilepsy surgery study using a comparison group in the form of accepted candidates for surgery (in adults) has been published (Wiebe et al. 2001). When assessing the seizure outcome after surgery in our studies, only changes in seizure frequency has been reported, and not changes in seizure severity. Even if seizure frequency is reduced or unaltered, the seizure types may change for the better or the worse. Study II is a retrospective study on psychopathology conducted when neuropsychiatric evaluations pre- and postoperatively were not part of the epilepsy surgery programme in Sweden. It can be looked upon as a pilot study leading on to the prospective studies III and IV. We have used up-to-date measures and criteria for case definitions. We chose to define PDD-NOS very stringently in order not to include uncertain cases. Although the DSM-IV criteria for neuropsychiatric disorders are not validated for use in children with intractable epilepsy, the ILAE commission on psychobiology of epilepsy recommends that co-morbid psychopathology should be classified using conventional criteria (Krishnamoorthy et al. 2007).

The high frequency of neuropsychiatric disorders in epilepsy surgery candidates

The largest published follow-up study addressing effects on psychopathology in children undergoing epilepsy surgery is a case-note review of performed neuropsychiatric assessments before and after TLRs (McLellan et al. 2005). A psychiatric disorder at some point was found in that study in 50/60 children (83%) and our corresponding numbers were 12/16 (75%) in children undergoing TLRs and 17/24 (71%) in children undergoing different surgical procedures for epilepsy. Just as in McLellan's study the most common neuropsychiatric disorders were autism and DBD and there was a high rate of psychiatric co-morbidity. The neurodevelopmental disorders described in the first part of the DSM-IV start at an early age and often occur together. This is also true in the general population of children (Kadesjö & Gillberg 2001), and not just in epilepsy surgery candidates. Psychiatric disorders were more common in children with IQ<70. Epilepsy is more frequent and often more difficult to treat in children with MR, and children with MR are at higher risk of psychopathology (Strømme & Diseth 2000).

The proportion of affected children was not smaller two years after surgery, which is in line with McLellan's study. In study III, the neuropsychiatric disorders completely resolved post-operatively in one child, and in three children without psychopathology pre-operatively, neuropsychiatric disorders evolved post-operatively.

ADHD tends often to be of the combined type in children without epilepsy, but in children with epilepsy the inattentive type seems to be at least as common as the combined type (Dunn et al. 2003). In Study III, 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 co-morbid conditions and those with ADHD-I and epilepsy have a co-morbidity in which the inattention and epilepsy are both related to a common central nervous system disturbance (Noeker & Haverkamp 2003). 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's study (2005) the majority of children with emotional disorders developed these postoperatively, consistent with the findings in our study. Depressive disorder was diagnosed in three not seizure free teenagers at follow up in Study III. Symptoms of depression in children with epilepsy are often under-recognized and more common than in children without epilepsy (Dunn et al. 1999).

In several outcome studies, data on behaviour is drawn from questionnaires. The questionnaires were not used to assess behavioural outcome in studies III and IV. We would not have identified all the children with psychopathology if we had only used the parental questionnaires SDQ, Conners BPRS and the ASSQ. Another parental questionnaire, the Childhood Behavior Checklist (CBCL) (Achenbach 1991), has been used to document behavioural outcome after epilepsy surgery (Smith et al. 2004; Elliott et al. 2008; Gleissner at al. 2008). Efforts have also been made to create more epilepsy-specific questionnaires not only in adults, but also in children, including the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) (Sabaz et al. 2000). There is not yet a Swedish translation of this questionnaire.

There have been three papers on behavioural outcome after epilepsy surgery using the CBCL and control groups for studying behavioural outcome. Compared to the control groups, Lendt et al. showed an improvement of behavioural problems in the operated group three months after surgery (2000), while Smith and Elliott et al. showed no changes in psychosocial functioning within the first year, but significant effects on the social competence and social problem subscale

scores after two years (2004 and 2008). The comparison groups in these studies consisted of children with drug-resistant epilepsy who could not be accepted for epilepsy surgery and the children were not neuropsychiatrically assessed. Based on our results, we would advocate neuropsychiatric assessments comparing and describing psychopathology before and after surgery rather than relying on group analyses of questionnaires, and to treat data as dependent before and after intervention.

In Study III psychiatric disorders were more common in children not rendered seizure free by surgery, and the parents of children who did not become seizure free perceived a negative behavioural change significantly more often than the parents of seizure free children. A small positive behavioural change may be considered very positive in a severely impaired child, even if it does not change the global functioning level or cognitive abilities, and a negative behavioural change may affect the psychosocial functioning level very much in a child with average or near average intellectual ability. This should be taken into consideration at the pre-operative counselling.

The low rate of previously neuropsychiatrically assessed children with intractable epilepsy despite behavioural difficulties (Study III)

Only four out of the 25 individuals in this group had been assessed psychiatrically before referral to our centre. It is known that behavioural and emotional problems often go undiagnosed in individuals with epilepsy, even if these problems may be the most burdensome (Steffenburg et al. 1996; Devinsky 2003; Kanner 2003; Ott et al. 2003). To recognize and address the behavioural issues is a crucial first step to treatment irrespective of seizure frequency. Even if the cause is multifactorial (Austin & Caplan 2007), the interventions are built on parental awareness of the child's impairment, and may include behavioural modification, rehabilitation and in some cases medication.

Autism and epilepsy surgery (Study II, III)

Almost one third of the epilepsy surgery candidates had autism, a frequency within the range of two previous studies (Taylor et al. 1999; McLellan et al. 2005). We found a high co-morbidity of MR and ADHD in autism and medically intractable epilepsy. In McLellan's study MR was significantly associated with autism; only 22% of cases with autism did not have MR compared with 73% of children without autism, and among the 16 children with ADHD, nine had also autism. It has been shown that autism is common in individuals with MR and epilepsy (Steffenburg et al. 1996), and more common in individuals with SMR than in MMR (de Bildt et al. 2005).

The lack of effect of surgical resections for epilepsy concerning the core symptoms of autism is in line with the studies by Szabo et al. (1999) and McLellan et al. (2005). In McLellan´s study 21/23 with autism still had autism at follow-up. They were described as improved (n=11), no change (n=7) and deteriorated (n=3); 43% of children with autism were seizure free after surgery, compared to 70% of children without autism, a statistically non-significant difference. In the prospective study by Szabo et al. on five children with autism, four had TLRs and one had a temporo-parieto-occipital resection. Two years after surgery all children still had autism and developmental delay, but one child showed substantial improvement on all measures, despite persistent seizures. Four children were seizure free: two demonstrated mild improvement, one no improvement and one decline. The proportion of affected children was not smaller two years after surgery in our studies. Even if there was no change in PDD-diagnosis in most of the 12 individuals with autism in Studies II-III and only two became seizure free and another two had >75% reduction of seizure frequency, parents perceived improvements in behaviour after

surgery in ten children. The fact that the parents of six out of seven children with autism in study III reported positive behavioural effects at follow-up, but five out of six still had severe impairments in psychosocial functioning is an illustration of the pervasiveness of autism.

The stability of intellectual ability after surgery in children with or without MR (study III)
IQ remained stable at a group level as shown by others (Adams et al. 1990; Szabo et al. 1998). This was true also for a majority of individual cases with or without MR. Epilepsy and AEDs can cause a state-dependant learning disability that must be distinguished from MR, because it is potentially reversible (Besag 2001). It is only in exceptional cases that the cognitive impairment is an effect of epileptiform EEG discharges; on the other hand these discharges seem to have an additional mild negative effect concerning the mental processes *alertness* and *mental speed* (Aldenkamp & Arends 2004).

Histopathology, psychopathology and seizure outcome
The histopathological findings were indicative of developmental anomalies of the brain in 10/12 subjects with medically intractable epilepsy and pre-operative behavioural problems and/or psychiatric diagnoses in Study II. The fact that eight had MR in addition to the seizure disorder may indicate a more diffuse pathological process. In all, eight out of 16 (50%) became seizure free in Study II. Post-operative seizure outcome is related to histopathological diagnosis. In the Cleveland Clinic paediatric series (n=136) seizure free outcome was present in 82% after surgery due to tumour, versus 52% in MCD (Wyllie et al. 1998). In a review by Sisodiya (2000), approximately 40% of cases with a histopathological diagnosis of MCD were rendered seizure free after surgery. Using volumetric MRI data, extralesional volumetric abnormality of gray and subcortical matter has been demonstrated in patients with MCD and epilepsy, indicating the existence of extensive structural disorganization outside visually identified focal lesions (Sisodiya et al. 1995). MCD are being recognized as one of the causes of epilepsy, MR, autism and other neurodevelopmental disorders (Taylor et al. 1971; Purpura et al. 1982; Humphreys et al. 1990; Piven et al. 1990; Meencke & Veith 1992; Kuzniecky et al. 1994; Casanova et al. 2002; Palmini et al. 2004). Even with high-resolution MRI, MCD may remain undetected and may only be histologically found after epilepsy surgery (Raymond et al. 1995). The pathogenetic relevance of microdysgenesis in epilepsy has been a matter of controversy for many years. However, Nordborg et al. (1999) reported that patients with intractable seizures with the histopathological finding of microdysgenesis closely resemble those with major malformations in several clinical aspects. They had significantly more often MR and had a significantly lower age at seizure onset than the patients without parenchymal malformations.

In the study by McLellan et al. (2005), MCD were reported in 15/60 cases, much less often than in our study. They did not find a correlation between neuropsychiatric status and seizure outcome except when comparing children with the same histopathological finding of hippocampal sclerosis (33 cases: 12 with autism and 21 without) where the seizure outcome was significantly better in cases without autism than in those with autism. Except for the difference in proportion of tumours in the seizure free group compared to the non seizure free group in Studies II and III, the other differences in proportions considering autism, IQ<70 or psychopathology were not statistically significant.

Psychopathology and psychosocial dysfunction (Study III-IV)

These are the first studies using CGAS to examine outcome considering psychosocial functioning after epilepsy surgery and VNS treatment respectively. CGAS is not a measure of epilepsy-specific impact; it reflects impairments and disabilities in social interaction, communication and behaviour. The global assessment scale revealed psychosocial dysfunction in the majority of cases in our studies. Cases with autism had the lowest scores before surgery and the scores remained quite stable in most cases. The CGAS could be used to illustrate the problem panorama in children with severe epilepsy and psychopathology. The scale has an advantage compared with the CGI-I or parents' perception of behavioural change, in that the total situation of the patient is evaluated and not just particular symptoms. The Vineland Adaptive Behaviour Scales (Sparrow et al. 1984) could also be used in future studies on outcome of epilepsy surgery for a general assessment of adaptive behaviour, concerning communication skills, socialisation, daily living skills and motor skills. The scales have been used in two population-based follow-up studies on autism – one in children with previous infantile spasms (Saemundsen et al. 2007), and the other one in the cohort used in Study I (Billstedt et al. 2005).

Autism and VNS

Since there have been reports on positive effects on quality of life and behaviour with VNS, both in patients with improved seizure situation and in those without (Lundgren et al. 1998; Valencia et al. 2001; Hallböök et al. 2005), it was important to study possible VNS effects on psychopathology in our patients with autism and to report the results, even if no-one achieved seizure control. Our disappointing results concerning seizure control may reflect the severe underlying encephalopathy in our subjects, the more long-standing severe epilepsy and/or the difficulty in our group to tolerate higher stimulation parameters (Aldenkamp et al. 2002; Majoie et al. 2005; Alexopoulos et al. 2006; Rychlicki et al. 2006). The use of a combination of many AEDs is often unavoidable in children with intractable epilepsy not eligible for epilepsy surgery, with a high risk for cognitive and behavioural side effects. The side effects of VNS are considered to be minor, and there are no known negative interactions with AEDs. VNS may facilitate a reduction in AED treatment, but there are studies reporting a failure to do so (Murphy et al. 2003; Alexopoulos et al. 2006). Our low rate of complications and type of side effects reported are in line with previous reports (Labar 2000).

Studies based on the VNS Outcome Registry Data (Cyberonics, Inc., Houston, TX, USA) suggest that chronic VNS may lead to improvements in autism (Park 2003; Warwick et al. 2007). The registry has weaknesses - biases in selection, assessment and voluntary reporting of subjects. The patients analyzed do not necessarily represent all patients in the registry with autism, and the criteria used for the reported diagnosis are not known. In a few mostly retrospective follow-up series with VNS treated children, one to nine children diagnosed with autism have been included (Murphy et al. 2000; Parain et al. 2001; Nagarajan et al. 2002; Alexopoulos et al. 2006; Rychlicki et al. 2006; Warwick et al. 2007). It is hard to draw conclusions about the behavioural effects on children with autism from these reports, since it is not known if and how all children in the series have been neuropsychiatrically assessed. In the paper by Murphy et al. (2000) disruptive behaviours are described to have disappeared, but this does not necessarily mean that the overall situation, concerning ability to participate in social interaction, need for supervision or core communication symptoms of autism have changed. When core symptoms of autism do change, eg in a child with autism who earlier did not make social approaches actively but now does so, it is of course positive for that child and gives him/her opportunities to develop. However, this might lead to an increased need for constant supervision, as well as to major changes in the approach needed at school and/or at home.

The hypothesis from our study is that in children with autism without effects on seizure control, the behavioural effects concerning the core symptoms of autism are minor, if any. Increased alertness has been reported in some children treated with VNS (Lundgren et al. 1998; Helmers et al. 2001; Hallböök et al. 2005; Majoie et al. 2005). Since alertness is the prerequisite for sustained, focused and divided attention this might be the reason for the improvement concerning attention span and/or ability to remain seated when appropriate in the three children with ADHD and autism in our study.

There are few studies on cognitive effects of VNS in children. No patient in our series improved in IQ/DQ scores over time. The developmental arrest or mental decline probably reflects an ongoing adverse influence caused by seizures on cognitive development. VNS was considered not to influence cognitive level or quality of life measurements unfavourably after two years of treatment in one prospective study of 19 children (Majoie et al. 2005). In another prospective study on 16 children there were no differences in cognitive functioning before and after nine months' treatment with VNS for most children; 2/15 improved and one deteriorated. In the four children with SMR there were no improvements (Hallböök et al. 2005).

Practical implications of findings

The findings that almost one third of adults with childhood autism and MR had active epilepsy and that the majority of children with autism, MR and epilepsy will become adults with the same diagnoses and with a low adaptive level in daily life, should be heeded by health administrators when planning resources. The study raises the question whether individuals with autism, MR and epilepsy are optimally taken care of by the medical system. Adults with autism and MR are severely impaired, but epilepsy with frequent seizures will aggravate their situation further. Also, onset of epilepsy may occur in adulthood. A big issue is the need for education concerning epilepsy in the "autism-friendly" environment and for education about the needs of a person with autism in the "epilepsy-friendly" environment. It is a delicate balance to investigate comprehensively enough for the best possible care and to respect the aloofness of some individuals with autism and not put these individuals into stressful situations. On the other hand, such respect must never be an excuse for not investigating, diagnosing and treating epilepsy in people with autism and MR.

The high frequency of neuropsychiatric disorders in children with drug-resistant epilepsy makes comprehensive and structured diagnostic practice concerning psychopathology in this group important and necessary. Even in children with intractable epilepsy there are potentially treatable co-morbid disorders and diagnosis is the first step to interventions and support. Early diagnosis and interventions for autism seem to affect the future adaptive level in a positive way, and there is no reason to think that this does not apply to preschool children with the combination of epilepsy and autism. For many parents or assistants, the behavioural and cognitive impairments become linked with the epilepsy. They might therefore set hopes that a surgical intervention for epilepsy per se will improve the whole situation. It should be part of the neuropsychiatric pre-operative assessment to discuss realistic goals, and it cannot yet be stated that there is a clear relationship between seizure outcome and behavioural effects. A goal of achieving better seizure control after epilepsy surgery is a realistic one, whereas a goal of improving the psychosocial situation in children with co-morbid psychopathology is unrealistic unless effective interventions are offered. Trying to rate the overall psychosocial functioning is mandatory if one wants to

better understand the complexity of the impairments and disabilities in children with autism and epilepsy. Symptoms change more quickly than functioning.

The studies further suggest that we need more precise background data concerning cognitive level, psychopathology and psychosocial functioning to be able to discuss outcome of epilepsy surgery in future studies. Questionnaires, observational schedules for autism and validated structured interviews are not adapted to children with on-going severe epilepsy or gradual mental decline. Such instruments are never sufficient as the only source of data on which to base a diagnosis, but together they can add valuable information that is comparable from one clinic to another. However, the clinical neuropsychiatric evaluation, history taking and use of agreed diagnostic criteria, in combination with the neuropsychological assessment, are still the most important tools that can be used assessing psychopathology. Studies need to be descriptive and every child needs to be compared to itself.

Multicenter studies are necessary to accumulate a sufficiently large number of cases to study effects of epilepsy surgery on children with autism. The results to date suggest that families should be made aware of the fact that behavioural symptoms in children with focal epileptogenic lesions and autism may or may not improve after epilepsy surgery. This makes it important to diagnose autism before surgery; otherwise parents' expectations may be too high.

Finally the study hopefully leads to increased awareness of individuals with both epilepsy and autism, so that optimal support and interventions can be provided and planned for through the collaboration between psychiatry and neurology.

CONCLUSIONS

In a community based sample of individuals with autism followed from childhood through to adult age it was shown that more than one third had epilepsy and that the remission rate of epilepsy was low. Epilepsy onset was most often in the first years of life, but also occurred in adults. Seizure frequency had a great impact on the individuals' lives. Partial seizures were the dominating seizure type. SMR and autism were significantly associated with epilepsy, especially in females. Epilepsy was a negative prognostic factor concerning cognitive and adaptive outcome. In two consecutive case series of children with drug-resistant epilepsy undergoing epilepsy surgery neuropsychiatric disorders were common at baseline and two years after intervention. Only few children had been assessed concerning the behavioural difficulties before referral to the epilepsy surgery team. A neuropsychiatric disorder contributed on a large scale to the psychosocial dysfunction in children with medically intractable epilepsy. The parents of children who did not become seizure free perceived a negative behavioural change significantly more often than the parents of seizure free children. The IQ level before surgery predicted the IQ level after surgery in most cases. Almost one third had autism, in combination with MR in most cases, and with ADHD in half of the cases. A diagnosis of autism remained after surgery. In a consecutive case series of children with severe epilepsy and autism treated with VNS, changes concerning behaviour, intellectual abilities and psychosocial functioning were minor when there was no reduction of seizure frequency. Further studies are needed to assess outcome regarding psychopathology and psychosocial functioning after epilepsy surgery and VNS treatment.

SAMMANFATTNING PÅ SVENSKA

De flesta barn med epilepsi blir anfallsfria med läkemedelsbehandling och epilepsin är övergående. Epilepsi hos barn med utvecklingsrelaterad funktionsnedsättning, t ex autism, är mer svårbehandlad. Den här avhandlingen handlar dels om epilepsi hos individer med autism, dels om neuropsykiatriska funktionsnedsättningar hos barn med så svårbehandlad epilepsi att epilepsikirurgi är ett alternativ.

Målsättningen med studien var att öka kunskapen kring samsjukligheten mellan autism och epilepsi. I en långtidsuppföljande delstudie på vuxna med autism var syftet att beskriva förekomsten av epilepsi och hur ofta epilepsin är övergående samt att jämföra hur individer med respektive utan epilepsi mår och har utvecklats. I de tre övriga delstudierna har olika aspekter på neuropsykiatriska funktionsnedsättningar, framför allt autism, studerats hos barn med svårbehandlad epilepsi som genomgår epilepsikirurgi eller får behandling med vagusnervstimulering (VNS).

I en populationsbaserad uppföljningsstudie av 120 individer diagnostiserade med autism i barndomen, kunde 108 bedömas på nytt i 17-40-årsåldern. Som vuxna hade majoriteten utvecklingsstörning och alla utom en hade fortfarande autism. Av de 43 som hade eller hade haft epilepsi, intervjuades närstående till 42 och en analys gjordes av journaler från barn- och vuxensjukvården (Studie I). I delstudierna av autism och andra neuropsykiatriska funktionsnedsättningar hos barn med svårbehandlad epilepsi, studerades två konsekutiva serier av barn som genomgick epilepsikirurgi på Sahlgrenska Universitetssjukhuset i Göteborg: en retrospektiv journalstudie av 16 barn som genomgick temporallobsresektion mellan 1995 och 1998 (Studie II) och en prospektiv studie på 25 barn som genomgick epilepsikirurgi mellan 2002 och maj 2006 (Studie III). I det fjärde delarbetet redovisas en prospektiv studie på 8 barn med autism vars epilepsi inte var operabel och som fick behandling med VNS. I de prospektiva studierna gjordes en klinisk neuropsykiatrisk bedömning och diagnostisering enligt vedertagna diagnoskriterier, en bedömning av psykosocial funktionsnivå och en neuropsykologisk bedömning av begåvningsnivå före och två år efter interventionen (Studie III och IV).

Vuxna med autism och utvecklingsstörning hade en uttalad funktionsnedsättning och ca 1/3 hade epilepsi. Av dessa 43 hade 1/3 haft epilepsidebut före 2 års ålder, men insjuknande förekom även upp i vuxen ålder. Epilepsin var övergående under uppväxten hos sex individer. Partiella anfall med eller utan sekundär generalisering var den dominerande anfallstypen, och 1/3 med aktiv epilepsi hade fler än ett anfall varje vecka. Riskfaktorer för epilepsi var kvinnligt kön och IQ<50. När vuxna med epilepsi jämfördes med dem utan epilepsi var både begåvningsnivån och funktionsnivån lägre i gruppen med epilepsi.

I den retrospektiva studien av temporallobsopererade barn hade 12 av 16 barn neuropsykiatrisk funktionsnedsättning. Fem hade autism före och efter operationen, varav en blev anfallsfri, och i tre fall noterades en positiv beteendeförändring vid uppföljningen. Missbildning av hjärnbarken var associerad med sämre utfall avseende anfallsfrihet och var vanligare hos barnen med psykopatologi. I den prospektiva studien av opererade barn hade 17 av 24 uppföljda barn psykopatologi före eller efter operationen eller både och. Fyra av barnen hade bedömts av läkare avseende beteendesymtomen före den epilepsikirurgiska utredningen. Begåvningsnivån var stabil efter operationen i de flesta fall, även hos barn med utvecklingsstörning. 13 barn hade autism, ADHD eller bägge. Sju hade autism före och efter operationen, varav en blev anfallsfri. I sex fall upplevde föräldrarna en positiv beteendeförändring, men barnens låga psykosociala

funktionsnivå var i fem fall av dessa väsentligen stabil. Barnen med autism som behandlades med VNS fick ingen anfallslindring, och behandlingen fick avslutas hos en pga försämrat beteende. Hos de sju som kunde följas upp efter två års behandling noterades ingen positiv förändring avseende intellektuell utveckling eller psykosocial funktionsnivå och oförändrad autism-diagnos, men positiv förändring av vissa beteendesymtom hos tre och negativ förändring hos en.

Slutsats

En tredjedel av individerna med autism i barndomen och utvecklingsstörning fick under uppväxten epilepsi. IQ<50 och kvinnligt kön var riskfaktorer. Epilepsin var varaktig i majoriteten av fallen, svårbehandlad hos 1/3 och en negativ prognosfaktor avseende IQ och funktionsnivå. Närstående upplevde att svårbehandlad epilepsi var mer betungande än både autism och utvecklingsstörning hos dessa individer. Barn med svårbehandlad epilepsi som genomgick epilepsikirurgi var en heterogen grupp, där mer än två tredjedelar hade neuropsykiatriska diagnoser – oftast autism och/eller ADHD – som bidrog till en låg psykosocial funktionsnivå. Beteendeproblemen hade i de flesta fall inte diagnostiserats tidigare vilket kan tala för ett otillräckligt tillsett behov hos barn med svårbehandlad epilepsi. Förekomsten av psykopatologi var högre hos barn som hade en samtidig utvecklingsstörning och hos barn som inte blev anfallsfria. Autism, liksom utvecklingsstörning, fanns kvar efter epilepsikirurgi, men anfallsfrihet tycktes kunna påverka den psykosociala funktionsnivån positivt i vissa fall vilket behöver studeras ytterligare. Behandling med VNS som inte resulterar i anfallsreduktion tycktes inte påverka kognitiv eller psykosocial funktionsnivå hos barn med svårbemästrad epilepsi och autism, men fler prospektiva studier behövs. Att aktivt sträva efter en så optimal anfallssituation som möjligt är minst lika angeläget hos dessa individer som hos individer utan autism.

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APPENDIX

The Children's Global Assessment Scale (CGAS) (Shaffer et al. 1983)

100-91
Superior functioning in all areas (at home, at school and with peers), involved in a range or activities and has many interests (eg, has hobbies or participates in extracurricular activities or belongs to an organized group such as Scouts, etc). Likable, confident, "everyday" worries never get out of hand. Doing well in school, no symptoms.

90-81
Good functioning in all areas. Secure in family, school and with peers. There may be transient difficulties and "everyday" worries that occasionally get out of hand (eg mild anxiety associated with an important exam, occasional "blow ups" with siblings, parents or peers).

80-71
No more than slight impairment in functioning at home, at school, or with peers. Some disturbance of behaviour or emotional distress may be present in response to life stresses (eg, parental separations, deaths, births of a sib) but these are brief and interference with functioning is transient. Such children are only minimally disturbing to others and are not considered deviant by those who know them.

70-61
Some difficulty in a single area, but generally functioning pretty well, (eg, sporadic or isolated antisocial acts, such as occasionally playing hooky or petty theft; consistent minor difficulties with school work, mood changes of brief duration; fears and anxieties which do not lead to gross avoidance behaviour; self doubts). Has some meaningful interpersonal relationships. Most people who do not know the child well would not consider him/her deviant but those who do know him/her well might express concern.

60-51
Variable functioning with sporadic difficulties or symptoms in several but not all social areas. Disturbance would be apparent to those who encounter the child in a dysfunctional setting or time but not those who see the child in other settings.

50-41
Moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area, such as might result from, for example, suicidal preoccupations and ruminations, school refusal and other forms of anxiety, obsessive rituals, major conversion symptoms, frequent anxiety attacks, frequent episodes of aggressive or other antisocial behaviour with some preservation of meaningful social relationships.

40-31
Major impairment in functioning in several areas and unable to function in one of these areas, ie, disturbed at home, at school, with peers, or in the society at large, eg, persistent aggression without clear instigation; markedly withdrawn and isolated behaviour due to either mood or thought disturbance, suicidal attempts with clear lethal intent. Such children are likely to require special schooling and/or hospitalization or withdrawal from school (but this is not a sufficient criterion for inclusion in this category).

30-21
Unable to function in almost all areas, eg, stays at home, in ward or in bed all day without taking part in social activities OR severe impairment in reality testing OR serious impairment in communication (eg, sometimes incoherent or inappropriate).

20-11
Needs considerable supervision to prevent hurting other or self, eg, frequently violent, repeated suicide attempts OR to maintain personal hygiene OR gross impairment in all forms of communication, eg, severe abnormalities in verbal and gestural communication, marked social aloofness, stupor, etc.

10-1
Needs constant supervision (24-hour care) due to severely aggressive or self-destructive behaviour or gross impairment in reality testing, communication, cognition, affect, or personal hygiene.

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