

Cognitive and psychosocial problems in children with epilepsy.

A population-based approach.

by

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2. Terminology and abbreviations.

AEA	Area with epileptic activity
AED	Antiepileptic drug treatment
ANOVA	Univariate analyses of variance
BECT	Benign childhood epilepsy with centro-temporal (Rolandic) spikes
CBCL	Children's Behavior Checklist
CI	Confidence intervals
CNS	Central nervous system
CP	Cerebral palsy
Crypt	Cryptogenic
EEG	Electroencephalography
EF	Executive functions
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4 th Ed. American Psychiatric Association: 2000.
Gen	Generalized
ICM	Incidental memory
ILAE	International League Against Epilepsy
IR	Immediate recall
ITPA	Illinois Test of Psycholinguistic Abilities
IQ	Intelligence Quotient
LR	Localization related
MGD	Mean group difference
MR	Mental retardation
OR	Odds ratio
Raven	Raven Matrices
SNVP	Severe non-verbal problems
SES	Socioeconomic status
SD	Standard deviation
SPSS	Statistical Package of Social Sciences
TRF	Teacher Report Form
VL	Verbal learning
WCST	Wisconsin Card Sorting Test
WF	Word Fluency
WMI	Developmental test of visual-motor integration
WISC-R	Wechsler Intelligence Test for Children- revised
YSR	Youth Self Report

3. General introduction.

Epilepsy is very much a children's disorder (and one of old age). The disorder often starts in childhood years (Forsgren 1997, Blom 1997). Some epilepsy syndromes like BECT are typical for the childhood period and do not continue into adulthood. However, for the most part epilepsy is a chronic condition characterized by repeated occurrence of unprovoked seizures (Hauser *et al* 1991).

Prevalence rates of childhood epilepsy reported from different countries have shown a wide variation with most clustering around 4-6 per 1,000 children (Cowan *et al* 1989). In developing countries epilepsy prevalence rates are frequently higher than in western countries due to factors such as less developed health-care systems, special infections and serious accidents.

An epidemiological approach in research is often used to investigate prevalence, etiology, therapy and prognosis of childhood epilepsy, and may be helpful in planning of health-service and intervention. A considerable proportion of children with epilepsy also have various other disorders such as ADHD, learning problems, psychosocial difficulties, mental retardation, cerebral palsy or other disabilities. The association between epilepsy and mental functions has been a matter of mystification and controversy for centuries. More up to date research has revealed the complexity of the disorder with involvement of neurological, neuropsychological and psychosocial factors (Rutter *et al* 1970, Besag 2002). This has led to a shift to an extended perspective on epilepsy pathogenesis and treatment with inclusion of both neuropsychological and psychosocial aspects.

In children with epilepsy, population-based studies which take these aspects into account, are rare (Besag 2002). The present study addresses these questions in a population-based approach.

3.1. Seizure related factors. Definitions and classifications.

3.1.1. Epilepsies and epileptic syndromes.

Since its presentation (Commission 1989), The International classification system of epilepsies and epileptic syndromes has been in general use in epilepsy research. This system was also used in the present work.

According to the International classification system, epilepsies and epileptic syndromes are classified into three main categories: (1) Localization-related, (2) generalized, and (3) undetermined. Epilepsies within category 1 are classified as idiopathic, symptomatic or cryptogenic cases, whereas those within category 2 are classified as idiopathic, cryptogenic/symptomatic and symptomatic cases. In idiopathic epilepsies no underlying cause can be found to explain the seizures and the onset is frequently in childhood. Symptomatic epilepsies may occur at any age and mental retardation can be present. The etiology is known in such cases. In cryptogenic cases the cause is unclear or hidden, but it is presumed that the epilepsy is symptomatic. Within each of the subgroups mentioned in this section there are several specific, more or less well defined epilepsy types, e.g. benign partial epilepsy of childhood with centrotemporal spikes (Rolandic epilepsy or BECT), childhood absence epilepsy, juvenile myoclonic epilepsy, infantile spasms, Lennox Gastaut syndrome etc.

In clinical practice epilepsies are also frequently divided into two main categories, those with remote symptomatic etiology (known cause) and those without such etiology.

3.1.2. Epileptic seizures.

Since its presentation, The Revised Clinical and Electroencephalographic Classification System of Epileptic Seizures (Commission 1981) has been in general use in epilepsy research. This system was used in the present work. In this system a basic differentiation is made between seizures of focal onset (partial or localization-related seizures) and seizures without focal onset (generalized seizures) (Gastaut 1969).

Partial seizures have clinical or electroencephalographic evidence of local onset (Porter 1988). They arise in specific loci in some neocortical region and carry with them identifiable signatures, either subjective or observational, which may range from disorders of sensation or convulsive movements of a part of the body which may become generalized seizures. (Dreifuss 1987). During *simple partial seizures*, consciousness is preserved and the symptoms can be motoric, sensoric, autonomic or psychic. In *complex partial seizures*, consciousness (responsiveness) is altered (Porter 1988). Such seizures might begin as simple partial with progression that includes impairment of consciousness with automatisms. They may also start with impairment of consciousness. Any activity during the seizures occurs in the form of automatisms (Dreifuss 1987). Complex partial seizures feature discharges from various areas of the limbic system and the temporal lobes (Wolf 1985, Dreifuss 1987, Spiers *et al* 1988, Wieser 1986). *Secondary generalized seizures* are those with partial onset evolving usually to generalized tonic-clonic (grand mal) seizures.

Primary *generalized* seizures are regarded to originate clinically and electroencephalographically at the same time in both hemispheres. *Generalized tonic-clonic seizures* (grand mal) start with a tonic phase evolving to a clonic phase. *Typical absences* start and cease suddenly, whereas *atypical absences* have a slower start and termination and may be accompanied by movements. Other generalized seizure types are *myoclonic, clonic, tonic and atonic seizures*. The exact mechanisms underlying the generation of epileptic activity are not known.

3.1.3. Age at onset.

Childhood epilepsy may start at any age. The highest rate of onset seems to be in the first year of life (Kramer *et al* 1998, Hauser *et al* 1993). There is a general suggestion in the literature that early age of onset and long duration of the epilepsy have a negative influence on the patients' cognitive abilities (Dikmen & Matthews 1977). Early age of onset has also been associated with more psychosocial problems (Dunn & Austin 2004).

3.1.4. Seizure frequency.

Seizure frequency is commonly used to evaluate the activity and severity of the epilepsy and the efficacy of medication in obtaining seizure control. In the literature seizure frequency has been quantified in different ways. In the present work children were divided into three groups: > 12 seizures last year, 1-12 seizures last year, and no seizures last year. In children with more than one seizure type, methods vary in the literature with regard to registration of seizure frequency. In the present study the frequency of the main seizure type was used for this

purpose. We defined the main seizure type as the one that characterized the clinical condition most accurately and was the most important for classification of the epileptic syndrome.

3.1.5. AED treatment.

In addition to seizure frequency, results of AED treatment are used to evaluate the severity of the epilepsy. In the majority of cases AED therapy is initiated when the epilepsy diagnosis is established. Treatment is aimed at enabling the patient to live a normal life and the ideal goal is to achieve complete seizure control with a low dose of a single drug and without side effects (Duncan 1996, Brodie & Kwan 2002). If seizure control is not achieved with the first drug chosen, several other AEDs are at one's disposal. AED`s introduced in the last decades are often referred to as new AED`s. There are indications of fewer cognitive and other negative side effects of the newer AED`s compared to the older ones (Leppik & Baringer 2000). However, advantages and disadvantages have still not been fully demonstrated. Full seizure control is achieved in 65-85 percent of the patients given AED therapy. Some patients with mild, short seizures, rare seizures and/or severe side effects of AED treatment may be better off without medication (Brodie & French 2000, Morton & Pellock 2000).

If AED treatment fails, epilepsy surgery might be an option in some of the difficult cases. According to Brodie & Kwan (2002) epilepsy surgery should be considered after two well-tolerated monotherapy regimes have failed to improve seizure control. In the present study epilepsy surgery was performed in five cases. Vagus nerve stimulation is another possibility in some of the therapy-resistant cases. This option may be tried in intractable, partial onset seizures in patients 12 years of age or older (Schachter & Saper 1998, Uthman 2000).

3.1.6. EEG registrations.

The diagnosis of epilepsy is sometimes difficult to establish, particularly in mild cases or early stages. Diagnostic criteria may also differ from one neurologist to another. In addition to thorough anamnestic information, EEG registrations are of importance in the diagnostic work-up. Prolonged EEG recordings, video-EEG monitoring, invasive EEG registrations and other new techniques have improved the reliability of the diagnosis (Hart 1996).

3.2. Cognitive and neuropsychological aspects of epilepsy.

Cognitive and neuropsychological dysfunctions are frequent in children with epilepsy (Besag 2002). There is evidence that in several cases cognitive functions may already be impaired at the onset of the disease, and that the maturation of cognitive functions in children is susceptible to the adverse influence of epilepsy (Elger *et al* 2004). In several cases structural lesions may also be found. Epilepsy may be part of several brain disorders. The CNS is affected by epileptic seizures themselves, especially those of long duration. Various psychological side effects of AEDs are also frequent in children with epilepsy.

In studies focusing on neuropsychological performance of children with epilepsy, a distinction has been made between idiopathic (causes unknown) and symptomatic cases (causes known). The most common finding has been that neuropsychological impairment is more obvious in cases with known than with unknown etiology (Bulteau *et al* 2000).

In cases with known etiology involving structural brain lesions, cognitive deficit might be regarded as a phenomenon existing together with the epileptic seizures. In several cases the

cognitive deficit might have been present before seizure onset. This still leaves the question of how different kinds of etiology interact with the epileptic process and effects of AED treatment in causing impaired outcome. In cases of idiopathic epilepsy with undetectable brain lesion, seizures themselves and side effects of AEDs may also result in cognitive impairments. Mild cognitive problems occur even in some of the children with BECT (Lindgren *et al* 2004).

In childhood epilepsy several seizure-related characteristics have been reported to be associated with impaired cognitive performance: symptomatic aetiology, early epilepsy onset, non-controllable seizures or high seizure frequency, long duration and severe seizures, and factors related to AED treatment (Bourgeois *et al* 1983, Meador 2002). Atypical absences or minor motor seizures have been found to be frequently associated with cognitive problems in children with epilepsy (Farwell *et al* 1985).

Some researchers claimed that cognitive function in children with epilepsy is skewed towards the lower end (Singhi *et al* 1992). In population-based studies of children with epilepsy, the frequency of mental retardation has been reported to be 24-41 % (Sidenvall, *et al* 1996, Braathen & Theorell 1995, Sillanpaa 1973).

When learning problems are present, children with epilepsy do not appear to demonstrate specific types of learning impairment different from other learning disabled children (Vermeulen *et al* 1994). Some studies of patients with temporal lobe epilepsies have reported hemisphere specific disruption of cognitive skills, while others found no support for focus-related effects (Camfield *et al* 1984). Sturniolo & Galletti (1994) suggested that the relationship between epilepsy and cognitive disorders is indirectly caused by decreased

alertness having a general impact on learning. Impaired attention has been reported in children with epilepsy who demonstrate normal intellectual functioning as well as in those with lowered IQ (Forceville *et al* 1992).

3.3. Psychosocial aspects of epilepsy.

Epilepsy is a heterogeneous disorder with multiple etiologies, seizure types and syndromes, and variable degree of seizure control. Hence there are multiple factors that influence risk of psychopathology in children with epilepsy, such as: demographic, neurological, seizure-related, therapeutic, and psychosocial variables (Dunn & Austin 1999). According to Besag (2004) psychosocial and cognitive functions are, apart from control of seizures, two of the most important factors in determining how well a child with epilepsy progresses towards independence.

3.4. Prevalence and etiology of childhood epilepsy and associated handicaps and/or psychological problems.

The child with additional central nervous system damage is at risk for increased psychopathology. Rutter *et al* (1970) found that 28.6% of children with uncomplicated seizures and 58.3 % of those with seizures and additional neurological damage had psychosocial problems. In comparison the prevalence of psychosocial problems was 6.6% in the general population of children and 11.6% in children with chronic illness not involving the central nervous system. In a recent epidemiological survey of 5-15 year-old children with epilepsy from Great Britain, Davies *et al* (2003) reported remarkably similar prevalence figures. The rate of psychiatric disorders was 37 % in children with epilepsy, 11 % in children

with diabetes mellitus, and 9 % in controls. They found psychosocial disorders in 26.2 % of children with uncomplicated epilepsy and 56 % in children with complicated epilepsy. In a population-based study from Rochester, Minnesota, Hedderick & Buchhalter (2003) found comorbid psychiatric disorders defined by DSM-IV in 51% of children with epilepsy. The figure was reduced to 40% when children with mental retardation and/or pervasive developmental disorder were excluded. Attention deficits and hyperactivity disorder, mood disorder and adjustment disorder were the most common psychiatric diagnoses with a prevalence of 17%, 12%, and 10%, respectively. A study of children with epilepsy and normal intelligence by Ott *et al* (2003) indicated that psychosocial problems were frequently unrecognized or untreated. Psychiatric diagnoses based on DSM-IV criteria were found in 61 % of the children, but only 33 % had treatment for these problems.

Depression is a common, but frequently overlooked problem in children with epilepsy. Ettinger *et al* (1998) found that 26 % of children with epilepsy had symptoms of depression, but none had been identified or treated. Alwash *et al* (2000) found depression in 23 % of adolescents with epilepsy. Oguz *et al* (2002) found depression in 29 % of epileptic children, suicidal ideation was noted in 17 % and more often in adolescents than in children. Children with epilepsy and depression might show other symptoms than adults, such as irritability, withdrawal, somatic concern and sleeping problems (Dunn & Austin 2004).

3.5. Parental factors and SES.

Demographic variables have generally been minimally predictive of the likelihood of psychiatric or psychosocial problems (Dunn & Austin 2004). However, lower socioeconomic

status, defined by either income or caregiver education, have in some studies been associated with psychosocial problems (Austin *et al* 2001, Hermann *et al* 1989).

3.6. Other factors.

Gender has been found to be inconsistent as a predictor of psychological problems in children with epilepsy. Stores (1978) found boys at high risk, while Hoare & Kerley (1991) found no gender difference. Austin *et al* (2000) found girls with epilepsy to have more problems with anxiety whereas boys had more social problems. In a study of children with a first recognized seizure, Austin *et al* (2001) found that boys with prior unrecognized seizures had more problems than girls, whereas a previous study of children with chronic seizures (Austin *et al* 1996) showed that girls with more severe seizures had the most difficulties.

Seizure-related variables have been associated with psychosocial problems in children with epilepsy. Seizure frequency has been shown to be an important predictor of such problems in children with complex partial seizures (Schoenfeld *et al* 1999). In a sample of children with newly onset epilepsy, Austin *et al* (2001) found that children with partial seizures had more psychosocial problems than children with generalized seizures. In an earlier study by Austin *et al* (1992), there was no significant association between seizure type and psychosocial difficulties in children with epilepsy of at least one year's duration. In children with catastrophic epilepsies such as West syndrome or Lennox-Gastaut syndrome, more psychosocial problems as well as considerable cognitive problems are common (Ferrie *et al* 1997).

3.7. Bias in earlier studies.

Most studies on cognitive problems have been done on selected populations rather than epidemiological studies (Besag 2002). According to Besag these studies have added to the understanding of the overall relationship between learning problems and epilepsy. A conclusion to be drawn from these studies is that a high proportion of children with epilepsy have global or specific learning problems.

Studies of psychosocial problems in children with epilepsy have been also been biased and hampered by small sample sizes and failure to consider seizure frequency or seizure severity (Austin *et al* 2002).

4. Aims of the present investigation.

The general aim of the present study was to estimate the character and extent of cognitive, neuropsychological and psychosocial problems in children with epilepsy as compared to controls. Using a population-based controlled study design, we formulated the following research program / questions:

- Description of the neuropaediatric characteristics and IQ of a population-based sample of children with epilepsy.
- Do children with epilepsy more often have non-verbal problems than a sample of control children? If so, which seizure-related factors predict worse or better outcome in this area?

- Do children with epilepsy but without SNVP more often have psychosocial problems than controls? If so, which seizure-related factors predict worse or better outcome in this area?
- Do children with epilepsy but without SNVP more often have EF problems than controls? If so, which seizure-related factors predict worse or better outcome in this area?
- Description of the total problem load and its relationship to seizure-related factors in epilepsy.

5. List of papers.

Paper I.

Waalder PE, Blom BH, Skeidsvoll K, Mykletun A. (2000). Prevalence, Classification and Severity of Epilepsy in Children in Western Norway. *Epilepsia* **41**: 802-810.

Paper II.

Høie B, Mykletun A, Sommerfelt K, Bjørnæs H, Skeidsvoll H, Waaler PE. (2005). Seizure-related factors and non-verbal intelligence in children in Western Norway. *Seizure* **14**: 223-231.

Paper III.

Høie B, Sommerfelt K, Waaler PE , Alsaker FC , Skeidsvoll H, Mykletun A (2006). Psychosocial problems and seizure related factors in children with epilepsy in Western Norway. *Dev Med Child Neurol* **48**: 213-219.

Paper IV.

Høie B, Mykletun A, Skeidsvoll H, Waaler PE, Sommerfelt K (2006) Executive functions and Seizure related factors in children with epilepsy. *Dev Med Child Neurol* **48**:519-25.

During the process of this thesis the name of B. H. Blom has been changed to B. Høie.

6. Methodology.

The methodological approach was selected in order to obtain a comprehensive neuropaediatric and psychological investigation of the children studied. The examination protocol is shown in table 1. The main criteria for selection of psychological methods of child assessment were: 1. They should yield information about a wide range of cognitive, neuropsychological and psychosocial aspects that might have implications for function, treatment and remedy of children with epilepsy. 2. As far as possible they should be valid and standardized tools, available internationally and in Norway. 3. They should not be too time-consuming. 4. They should be suitable for examination of 6-12 year-old children.

6.1. Catchment area.

This study was performed at Haukeland University Hospital in the county of Hordaland, Norway. Hordaland is situated on the south-western coast of Norway and has about 425.000 inhabitants. Approximately 38.600 children borne between 1982-1988 lived in the county during the prevalence period which was from 01.10.94 to 31.03.96 (information obtained from Hordaland County). Hordaland County has 9.7 % of the total Norwegian population and has similar demographic characteristics as Norway as a whole.

6.2. Study population.

The basis for the study were all children with active epilepsy in Hordaland county borne between 01.01.82 and 31.12.88, and residing in the county during the prevalence period. All

general practitioners, specialists in the field, hospitals in the region and the child rehabilitation center in the region were contacted. Haugesund hospital in the neighbor county was also contacted since a few patients from the southern part of Hordaland were known to be regular patients there.

Epilepsy was defined as two or more seizures occurring at least 24 hours apart and unprovoked by any immediate identifiable cause and regardless of AED treatment. Situation related syndromes such as febrile convulsions, isolated seizures and acute symptomatic seizures were excluded. Classification of seizures and epileptic syndromes were performed in accordance with the guidelines set up in the International Classification System (Commission 1989). The total patient population included 198 children with epilepsy.

6.3. Control group.

For each child with epilepsy three control persons of the same gender born within the same month were selected at random by the Norwegian National Birth Register. No limitations were made regarding the selection except that controls should be alive. Theoretically children with epilepsy might be chosen as controls. Other handicaps might also be present. Only one control per child was utilized. If the first selected control did not respond, another of the two left was chosen. All controls were living in Hordaland County at the time of the study. Due to time restrictions only patients were examined with the full WISC-R, whereas only the subtest coding from WISC-R was utilized in the control group. All of the other tests were performed in both study groups.

6.4. Neuropediatric examination.

The children with epilepsy underwent neuropaediatric examination, anamnestic data were collected, the children's hospital records were reviewed, and they had one or several EEG registrations.

6.5. Cognitive and neuropsychological examinations.

WISC-R (Wechsler 1949, Undheim 1978) and Raven Matrices (Raven 1965) were used to evaluate cognitive function. WISC-R was used only in the epilepsy group, while Raven Matrices was utilized in both study groups (Table 1). Although it would have been an advantage to perform WISC-R in both study groups, this was not possible due to time-limitation and since the less time-consuming Raven Matrices could be utilized as a good alternative. IQ tests (WISC-R) have been developed and refined over years so that they have become valid and standardized tools. Raven Matrices function as a robust non-verbal reasoning ability test based on figural test stimuli in the visual modality. Validity coefficients with other intelligence tests are reported to be about .50 -.80 (Sattler 1992).

Executive function (EF) is defined as the ability to maintain a set of appropriate problem-solving strategies for attainment of future goals. EF is considered to be one of the major roles subserved by the frontal cortex. However, opinions differ in the literature with regard to which functions should be included in the EF concept and we therefore tried a broad versus a more narrow definition of EF. In the present study we included 8 items to cover a broad EF definition, whereas only three of the items were included in the narrow EF

definition (paper IV). In our work we included a broad spectrum of tests to investigate EF in the children. The following examination methods were included to cover a broad definition of the EF concept (for a more extensive discussion of a narrow vs a broad EF concept, see chapter 8):

- 1) Visual short time memory from Illinois Test of Psycholinguistic Abilities (ITPA) assigned to assess immediate visual short-term memory, Norwegian translation (Gjessing & Nygaard 1995).
- 2) Visual-motor function using the Developmental Test of Visual-Motor Integration (VMI) (Beery 1989).
- 3) Verbal learning (VL) and immediate recall (IR) were tested by means of 10 unrelated common words adapted from Luria (1966).
- 4) Word fluency test (WF): requiring the child a) to say in 60 seconds as many words as possible starting with a specific letter (s), and b) to name as many animals as possible in another 60 seconds. These tests are sensitive to diffuse reduction in mental efficiency, working memory functions and / or executive functions (Halperin *et al* 1989).
- 5) The Wisconsin Card Sorting Test (WCST) computerized version (Nyman 1996) evaluating the ability to form abstract concepts, deduce abstract categories and to shift and maintain cognitive set. It has been observed to be sensitive to frontal-lobe dysfunction and diffuse brain damage (Robinson *et al* 1980). Seven different scores were obtained: a) number of trials administered, b) total correct responses, c) total errors, d) perseverative responses, e) perseverative errors, f) non-perseverative errors, g) categories completed: failure to maintain set/learning to learn.
- 6) Copying from WISC-R was used to tap visual working memory. The child was given no instruction to remember the task.

7) Incidental memory. The sheet was covered and the child was asked to fill in all numbers he/she remembered under the correct symbols on a new similar sheet allowing 1.5 minutes (Lezak 1995).

6.6. Psychosocial evaluation.

The Achenbach cross informant scales (Achenbach 1991) were utilized to get information about child behavior. Information obtained from mothers, teachers and the children themselves was utilized. Although the Achenbach scales were not designed for diagnosing psychopathology in children with chronic illness, they have been used extensively to assess psychosocial problems in pediatric populations, including children with epilepsy (Miles *et al* 1988, Oostrom *et al* 2001). Several studies have previously questioned the validity and reliability of assessing child behavior by parental report (Goldberg 1990; Najman *et al* 2000). Aman *et al* (1992) pointed out that parents of children with epilepsy may have a tendency to overreact to their child's medical condition and consequently to over-report psychosocial problems. Lack of agreement between maternal and teacher evaluation has also been reported (Sturniolo & Galletti 1994).

The Achenbach scales include 113 questions and make cross informant information comparison possible. Individual scales are summarized in an internalizing and an externalizing summary score and a total problem score (paper III). Some questions deal with school function and are not included in the clinical scales. Information about school function was used in paper IV.

6.7. Depression.

Depression was measured by use of the Birleson Depression Inventory and administered to all children 9 years or older. The inventory consists of 29 questions pertaining to descriptions of the child`s feelings/mood over the past week. The inventory consists of statements to be answered as felt most of the time, sometimes or never (example: I feel like crying/ I am good at things I do) (Birleson *et al* 1987).

6.8. Socioeconomic status (SES).

The socioeconomic and demographic factors were chosen on basis of previous literature (see Sommerfelt 1997). Mothers were invited as informants to answer a questionnaire of parental factors such as paternal and maternal education, whether they held part- time/full-time work, level of work (unskilled, skilled, professional, academic) and income level for both mother and father and for single parent family status. SES was calculated from the mean score from the above mentioned factors as described in the individual papers.

6.9. Examination protocol. Table 1.

Child task: instrument	Name /description	Time used	Examiner/responsible person
Physical examination ¹⁾	Neuropaediatric evaluation	45 minutes	Neuropaediatrician
EEG ¹⁾	EEG recording(s)	30 minutes	Neurophysiologist
Raven Matrices	Non-verbal problem-solving test	30 minutes	Psychologist/ Psychometrist
ITPA	Visual short-term memory	10 minutes	Psychologist/ Psychometrist
WCST	Wisconsin Card Sorting Test	20 minutes	Psychologist/ Psychometrist
REY (VL)	Rey Auditory Learning Test (10 word list)	20 minutes	Psychologist/ Psychometrist
FAS (words on s, animals)	Word Fluency Test	5 minutes	Psychologist/ Psychometrist
WISC-R coding	Wechsler Intelligence Scale-Revised. Coding	5 minutes	Psychologist/ Psychometrist
WISC-R? ¹⁾	Wechsler Intelligence Scale Revised	1.5 hours	Psychologist/ Psychometrist
VMI	Developmental Test of Visual-Motor Integration	20 minutes	Psychologist/ Psychometrist
Raven Matrices	Raven Colored Matrices < 11 years	30 minutes (max)	Psychologist/ Psychometrist
Raven Matrices	Raven Standard Matrices > 11 years	30 minutes (max)	Psychologist/ Psychometrist
Questionnaires:			
Children:			
Birleson	Birleson Depression Inventory Child = or > 9 years	10 minutes	Psychologist/ Psychometrist
YSR (Achenbach)	Youth Self Report Child = or > 11 years	30 minutes	Psychologist/ Psychometrist
Mothers:			
Achenbach	Child Behavior Checklist (CBCL)	30 minutes	Psychologist/ Psychometrist
Social background	SES 30 questions	10 minutes	Psychologist/ Psychometrist
Teachers:			
Achenbach	Teachers Report Form (TRF)	30 minutes	Psychologist/ Psychometrist

¹⁾ Patients only

6.10. Statistical considerations.

Our study included a population-based patient group of reasonable size, a reasonable population, while most psychological studies of children with epilepsy has been based on smaller hospital-based samples (Besag 2002).

However, the population is heterogeneous and for the sake of comparison of seizure related factors, we run into power problems for several subgroups. In several cases, subgroups of the epilepsy population are marginally different (or indifferent) from the control group. Some of these results are probably type 2 errors due to power problems in subgroups.

The reason for performing significance testing in a population, as in this study, has also its relevance in investigating whether findings from this study can be generalized also to a larger population as e.g. the Norwegian population or other comparable populations in developed countries.

Various categorizations of epilepsy: Epilepsy is a heterogeneous disorder, and consequently there are several methods for categorization, such as epilepsy syndromes, seizure types, age at onset, seizure frequency, treatment, knowledge of biological aetiology, etc. There is in the literature a need for clarification of which categorizations are most relevant for studies of medical and psychological outcomes. For example, is epilepsy syndrome of stronger relevance than seizure type, or the opposite? It is problematic to disentangle such effects statistically by means of multivariate regression models or similar methods, since for example seizure type is partly defining epilepsy syndrome, etc.

We have aimed at determining the most significant of the seizure- or epilepsy-related characteristics in relation to psychological functions; is it for example seizure type or epilepsy syndrome. This issue was also addressed by two of the reviewers. There are, however, two reasons why this question cannot be answered; 1) There were too many medical variables and the present patient material did not have the statistical power to permit such analyses. 2) The medical parameters are defined from one another, e.g. epilepsy syndrome is defined from seizure type(s), age of onset, EEG picture etc. However, it is possible to compare the explained variance between e.g. seizure type and epilepsy syndrome in relation to a problem area, and further, to use this information to clarify categorizations of more and less relevance for the problem areas of interest. In our study, across problem areas, epilepsy syndrome was shown to be particularly relevant for the outcomes studied. On the other hand, the EEG picture was not shown to be of any relevance for the outcomes studied.

Cognitive evaluation was performed by both WISC-R and Raven Matrices in the epilepsy population, but only Raven Matrices were used in the control group due to time-limitations. It would have been an advantage having performed WISC-R in both study groups. Raven Matrices are, however, robust non-verbal reasoning tests and validity coefficients are reported to be about 0.50-0.80 (Sattler 1992). We consider Raven Matrices to be a more limited cognitive measure than an IQ test, but we still advocate that Raven Matrices identified the children with the greatest cognitive problems.

The term mental retardation could not be used in the present work since it is defined by means of IQ which was not registered in the control material. Instead we utilized the term severe non-verbal problems to identify children falling at or below Raven 10th percentile. The 10th percentile in this study was equal to being severely mentally retarded, i.e. an IQ at 50 or

below. We performed a regression analysis of scores from 118 children with epilepsy having performed both Raven Matrices and WISC-R (Raven score = $-40.4 + 1.04 \text{ times FSIQ}$). The calculations showed that the 10th percentile of the Raven Matrices equalled an FSIQ = 48.1 which is very close to the definition of severe mental retardation (IQ = or < 50).

Several study questions require multivariate models, as the effects of confounders and multiple risk-factors often are of interest. In these situations, linear and logistic regression models are used for cases with metric and dichotomous dependent variables, respectively. For linear regression analyses, effects were reported as un-standardized (e.g. mean difference between epilepsy- and control group). Further, for logistic regression analyses, effects were reported as odds ratios. An odds ratio is defined as the ratio between the odds in two groups. For example, in the third paper, the odds ratio for having psychosocial problems if having epilepsy was estimated by the following formula: $OR = ((\# \text{ of patients with psycho-social problems}) / (\# \text{ of patients without psycho-social problems})) / ((\# \text{ of controls with psycho-social problems}) / (\# \text{ of controls without psycho-social problems}))$.

Dicotomous versus continuous variables: Most constructs covered as dependent variables in this thesis are – from a psychological perspective – truly of continuous nature. This is, for example, the case for cognitive abilities, EF and psychosocial function. In some places we have dichotomized these constructs, consequently losing variance in these variables. In several cases, a clinical cut-off was defined as below the 10th percentile in the control population. From several perspectives, use of such cut-offs are problematic: (1) There is obviously much variance above the cut-off, that is, within the presumed non-problematic area of any construct, e.g. cognitive abilities, and much of the variance between 10th and 100th percentile could obviously be of clinical relevance. From the statistical point of view, this loss

of clinically relevant variance implies underestimation of effects. (2) Categorization of individuals scoring around the cut-off will be arbitrary, e.g. comparing a score at the 8th versus the 12th percentile. (3) Selection of cut-off is often arbitrary. (4) Employing equal cut-offs across problem areas are based on the presumption that the problem areas are of equal importance, which obviously is not the case. For example, why should the proportion of the general population suffering from EF problems be equal to that suffering from psychosocial problems?

There are several reasons for still using categorical approaches: (1) Using a cut-off identifying a rather small proportion of children with fairly much problems corresponds with the attention of clinicians, who commonly are more interested in children with high problem loads rather than individuals scoring at the 40th or 70th percentile. In this respect, using these cut-offs is a kind of adaptation of research to the common clinical focus and tradition, and also the need for a cut-off between groups who should receive interventions versus those who should not. (2) Group differences between for example children with epilepsy and controls are often easier to communicate using categorical variables rather than continuous; e.g. by reporting differences in prevalences of problems between groups rather than metric regression coefficients.

Use of other statistical methods: Pearson chi-square test was used for testing significance when combining two categorical variables, e.g. CBCL in relation to TRF (paper III). In cases of two by two tables with expected number of cases less than five in at least one cell, Fisher exact test was used, e.g. in paper II (few controls in the SNVP category). Cronbach's coefficient alpha was used to examine internal consistency when combining several metric measures in one composite score, e.g. an EF composite score to cover several

neuropsychological measures of attention, working memory, impulse control etc. A strong coefficient alpha, that is above 0.8, is an empirical argument for applying such a composite score rather than single measures, as these are strongly correlated. However, some details might be lost in the process of making several tests into a summary score.

Independent samples t-test was used for testing equality of means between two samples, e.g. age by study groups. Pearson correlation analysis was used for testing hypotheses of associations between metric variables such as the relationships between CBCL and TRF, CBCL and YRF, and TRF and YRF (Achenbach 1991).

Confounders: Possible confounders must be associated with both the dependent and independent variables to be of any relevance. SES can be regarded as a possible confounder examining the association between having epilepsy or not and any problem area of interest. In the present work, these (and similar) problems were solved by including SES as a covariate in the regression model. In the literature, the SES level has commonly been found to be higher in controls than in children with epilepsy (Austin *et al* 2001, Hermann *et al* 1989). Another confounder example is cognitive function (Raven results) when examining EF function in relation to problem area (paper IV).

Selection of controls: Three controls were selected for each child. Number one on the list was contacted first. 20 percent did not respond to the first contact and then number 2 was contacted. Contact with a number 3 person was never demanded. The procedure might possibly give a bias among controls with a higher tendency to participate in examinations of e.g. children who needed psychological services and / or clever children.

The high answering-rates among patients and the relatively low percentage of internal drop-outs were strengths of the present study. However, as can be seen from variation in answering rates between the different instruments, some responders missed out on parts of the testing procedure due to incidents such as the child being called for EEG registrations, medical examinations, other engagements in and outside the out-patient clinic, and the fact that the families were not able to return another day to finish the testing. In such situations further testing was not possible. However, the internal consistencies as measured by Cronbachs Alpha were satisfactory for all instruments used.

The instruments included in the study were selected according to the aims of the study. In addition to identifying and describing the medical characteristics of children with severe non-verbal problems (SNVP), the study aimed at describing psychosocial and cognitive problems in the rest of the population after exclusion of children with SNVP (papers III and IV). The Achenbach questionnaire consists of questions like “my child fights a lot, my child complains that no one seems to love him/her” etc. These questions demand a certain mental function of the child to be answered. The same can be advocated in measuring cognitive functions.

Ascertainment: The present study was carried out in a country with a relatively stable and homogenous population, and was restricted to a county with only one paediatric department and one EEG laboratory. Review of the EEG files, which has been regarded to be a reliable means of tracing possible cases of epilepsy (Cowan *et al* 1989), was undertaken in our study. From contact with the general practitioners, we found only four children with epilepsy who were unknown to us. We also included five children from Hordaland who were treated at a hospital in a neighbour county. We therefore believe that practically all cases of active

epilepsy were traced in our study. However, in all epidemiological studies of children with epilepsy, some of the mildest cases, especially those with a recent onset, might be overseen.

7. Summary of papers.

Paper I

Prevalence, Classification and Severity of Epilepsy in Children in Western Norway.

Waalder PE, Blom BH, Skeidsvoll K, Mykletun A. (2000). *Epilepsia* **41**: 802-810.

This paper determines prevalence of active epilepsy in school children in Hordaland county, and assesses the usefulness of The International League Against Epilepsy classifications of epilepsies and epileptic syndromes and the corresponding classification of epileptic seizures. Results are presented of neuropaediatric examinations, EEG, and intelligence evaluation (WISC-R). Special emphasis is laid on frequency, additional handicaps and therapeutic problems of severe cases.

Results: Prevalence of active epilepsy was 5.1 per 1000. Main seizure type and epilepsy syndrome could be classified in 98 and 90 % of patients, respectively. Although most epilepsies could be classified, the number of cases in non-specific categories were relatively high. Seizure types/epileptic syndromes were more often localization-related than generalized. Symptomatic etiology was frequent, especially in therapy-resistant cases. 89 % had used or used AEDs, while 13 % had therapy resistant epilepsy. Only 11% of children had never used AEDs and 25% were without present AED treatment.

There were high frequencies of additional neurological deficits, especially of CP and MR. Various combinations of neurological deficits (mental retardation, CP, autistic features, visual deficit, ADHD, auditory deficit) were present in 43% of patients. 40% of the whole epilepsy-population had mental retardation (WISC-R IQ<70).

Conclusion. Prevalence rates for epilepsy was as expected. Most epilepsies could be classified, but number of cases in non-specific categories was relatively high. Neurological comorbidity and mental retardation were common.

Paper II.

Seizure-related factors and non-verbal intelligence in children in Western Norway. Høie B, Mykletun A, Sommerfelt K, Bjørnæs H, Skeidsvoll H, Waaler PE. (2005). *Seizure* **14**: 223-231.

This paper describes the relationship between seizure-related factors, non-verbal intelligence, and socio-economic status (SES) in a population-based sample of children with epilepsy. The investigation included 183 of the 198 children with epilepsy and 126 healthy controls who agreed to participate in psychological studies.

Results: Children with epilepsy were highly over-represented in the lowest Raven percentile group which had severe non-verbal problems (SNVP = 43%), whereas controls were highly over-represented in the higher percentile groups. SNVP were present in only 3% of controls. Presence of SNVP was especially common in children with remote symptomatic epilepsy aetiology, undetermined epilepsy syndromes, myoclonic seizures, early seizure onset, high seizure frequency, and polytherapy. Seizure-related characteristics that were not usually associated with SNVP were idiopathic epilepsies, localisation-related cryptogenic epilepsies, absence and simple partial seizures, and a late onset of epilepsy. Adjusting for SES factors did not significantly change results.

Conclusion: Our population-based study indicated a highly increased risk of SNVP in children with epilepsy.

Paper III.

Psychosocial problems and seizure related factors in children with epilepsy in Western

Norway. Høie B, Sommerfelt K, Waaler P.E, Alsaker FC, Skeidsvoll H, Mykletun A

(2006).*Dev Med Child Neurol.* **48:** 213-219.

In this paper children with SNVP were excluded. The paper describes the influence of seizure-related factors on psychosocial function in the non-retarded part of the population of children (N=117) as compared to controls (N=117).

Results. Psychosocial problems were more common in the epilepsy group (OR = 5-9) and psychosocial problems were significantly related to generalized symptomatic epilepsy, localization related cryptogenic epilepsy, atypical absences, early epilepsy onset and seizure frequency preceding year. There was a high degree of correspondence between mothers' (CBCL) and teachers' (TRF) reports. Both mothers and teachers reported boys with epilepsy to have more problems than girls. In contrast, girls with epilepsy reported more internalization problems as somatic complaints and depression/anxiousness, whereas boys did not (YSR).

Conclusion: Our findings indicated a markedly increased risk of psychosocial problems in children with epilepsy.

Paper IV

Executive functions (EF) and seizure-related factors in children with epilepsy in

Western Norway. Høie B, Mykletun A, Waaler PE, Skeidsvoll H and Sommerfelt K*Dev Med Child Neurol.* Accepted.

The aim of this study was to investigate whether EF measures in addition to non-verbal intelligence measured by Raven matrices might add to our understanding of cognitive functioning and school performance in children with epilepsy. We chose to examine several

cognitive functions which might be included in the EF concept. Children with SNVP were excluded. The study included 117 children with epilepsy and 124 controls.

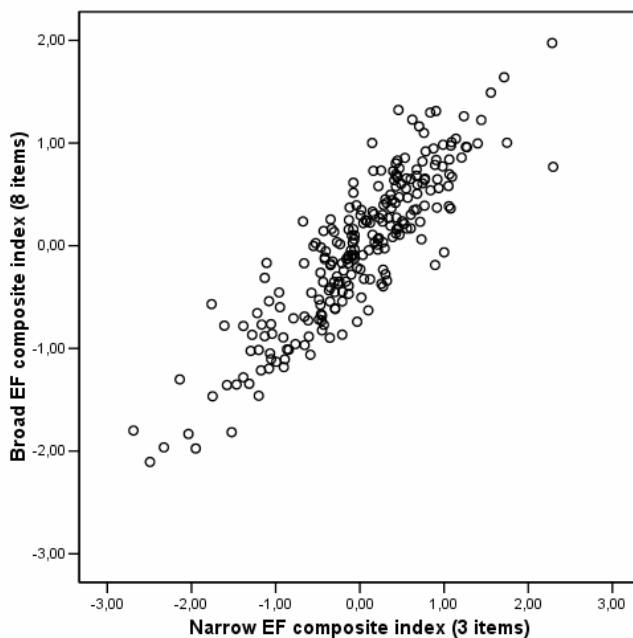
Results. All epilepsy syndromes (except Rolandic epilepsies), an early epilepsy onset, high seizure frequency, and polytherapy with AEDs were associated with decreased EF. Children with epilepsy had more school problems than controls. The school problems could partially be ascribed to cognitive function (Raven) and EF, somewhat less to depression, while SES was of marginal importance. EF and Raven results were only partially overlapping in explaining school problems in children with epilepsy.

Conclusion: Measures of EF contributed to an extended (from Raven) understanding of the school problems in children with epilepsy.

8. Discussion of the EF concept.

Executive function (EF) is usually defined as the ability to maintain a set of appropriate problem-solving strategies for attainment of future goals. EF is considered to be one of the major functions subserved by the frontal cortex. The current view in neuropsychology is that frontal lobes are important for the executive or supervisory aspect of problem solving (Anderson 2002). However, opinions differ in the literature with regard to which functions should be included in the EF concept and we therefore tried a broad versus a more narrow definition of EF. In the present study we included 8 items to cover a broad EF definition, whereas only three of the items were included in the narrow EF definition (paper IV). As demonstrated in the plot diagram (Figure 1), there was a close correspondence between the two EF measures. Pearson correlation between the two measures was strong (.89, $p < .001$).

Figure 1. Plotter chart of scorings according to broad vs narrow EF definition in children with epilepsy (n=110) and controls (n = 106).



In the absence of a gold-standard or consensus in the literature on how to measure EF, we chose to use the broad definition of EF in the following presentation of combined results and total psychological problem load.

9. Combined results and total psychological problem load.

The overlap between behavior, cognition and EF problems was not described in any of the separate papers, and will be presented and discussed in this section. In papers I and II, all children with epilepsy regardless of function were included. In papers III and IV we excluded children with SNVP according to the criteria given in paper II.

9.1. Behavior, cognition and EF problems in patients and controls without SNVP.

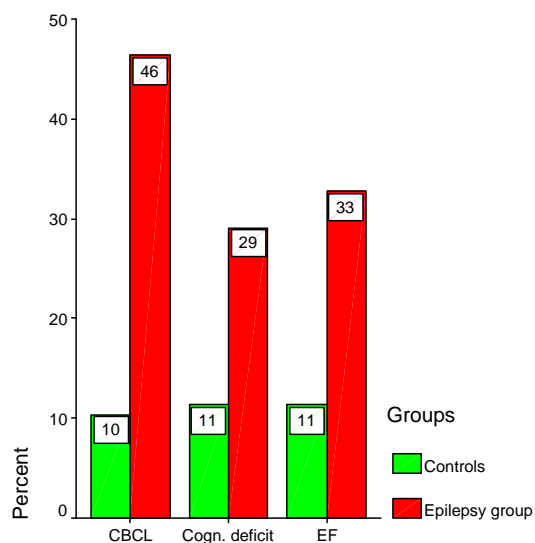
In this section we describe the psychological problem load of children with epilepsy as compared to controls excluding children with SNVP. The following variables were selected for comparison in the combined analyses: *Behavior*: CBCL total problem score or, if missing, TRF total problem score. *Cognition*: Raven Matrices. *EF*: The broad EF index (for explanation see paper IV). In the further presentation, the broad EF index is called EF index.

For each of the variables the 10th percentile for controls was chosen as cut off to define children with problems. For CBCL (or TRF) we identified 12 (10%) of the 117 controls and 55 (47%) of the 117 patients to fall below the cut-off level (paper III). A new Raven 10th percentile cut off score had to be created after exclusion of children with SNVP and this new score turned out to correspond to the Raven 25th percentile as reported in paper II. The procedure identified 13 (11 %) of 122 controls and 37 (31%) of 122 patients to fall below the

25th percentile. This new group was called *children with mild non-verbal problems*. Thirteen (10 %) of 124 controls and 38 (33 %) of 115 patients were identified to fall below the EF index 10th percentile cut off point (paper IV).

Since only children with available data for all of the three outcome measures were included in the new analyses, the number of individuals was somewhat reduced and included 106 controls and 110 patients. The results for girls and boys combined (no significant gender differences were found) are shown in figure 2.

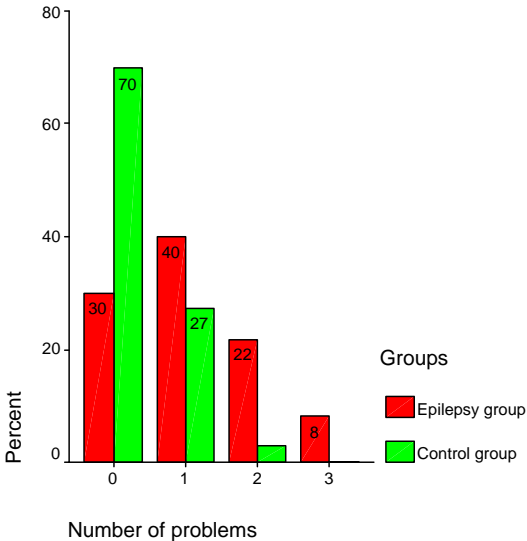
Figure 2. Percentages of patients and controls with problems having scores = or < 10th percentile for controls on CBCL, cognitive function (Raven), and EF (broad definition).



The figure shows that 46 % (n=51) of the patients had behavioural problems, 29 % (n=32) had mild cognitive problems, while 33 % (n=36) had EF problems compared to the 10th percentile cut off points in the control group.

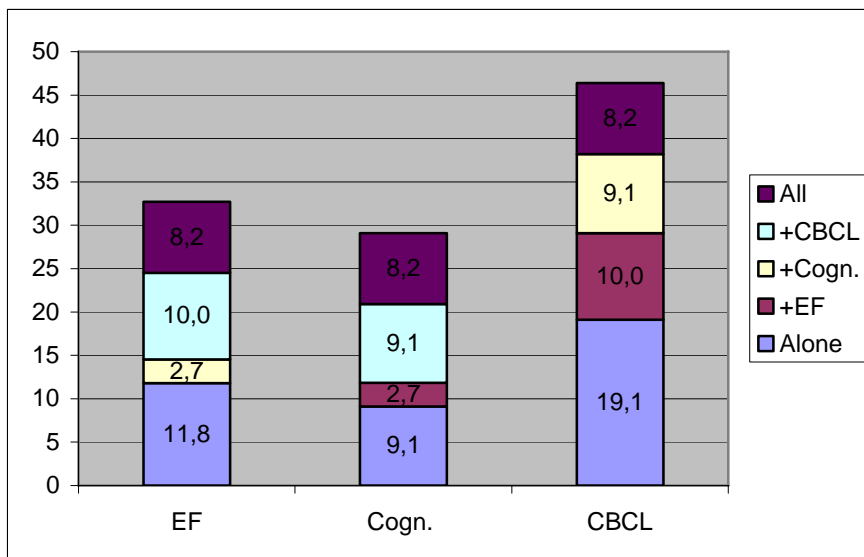
The next step was to investigate problem load (number of areas with problems) in children with epilepsy as compared to controls. As shown in figure 3, more control children than children with epilepsy had no problems (70 % (n=74) versus 30 % (n=33)) while several children with epilepsy had two (22 %, n=24) or even three (8%, n=9) problems, compared to very few controls having two problems at the most.

Figure 3. Percent of children with problems in one, two or three areas.



The next step was to examine the various combinations of problems (Figure 4). The figure

Figure 4. Combinations of problems in epilepsy population.



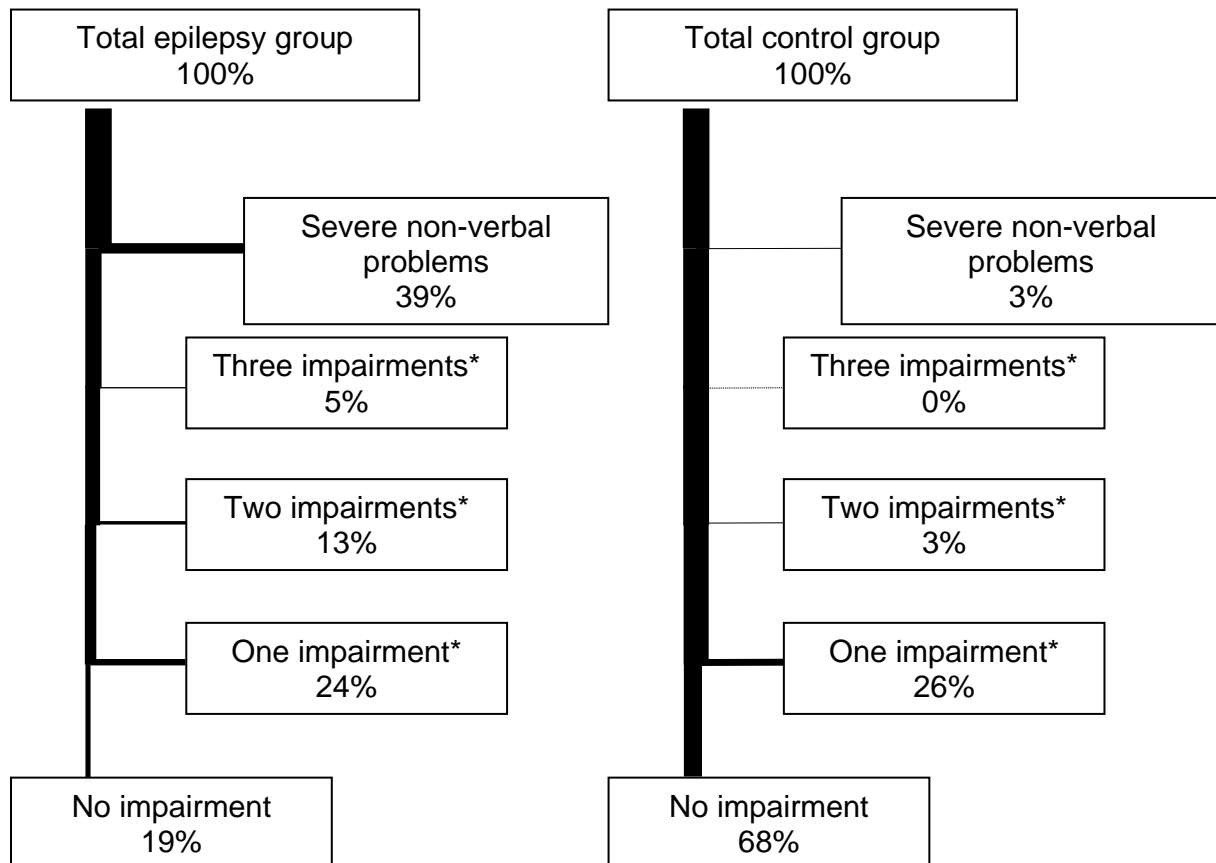
shows that 12 % of the children with epilepsy had problems with EF only, 9 % had mild cognitive problems only, and 19 % had psychosocial problems only. EF problems were present alone or in combination with other problems in 33 % of children. The corresponding figures for mild nonverbal problems and psychosocial problems were 29 % and 47 %, respectively. With one exception various combinations of problems in the same patient were about equally frequent (8 – 10 %). The exception was: the combination of mild nonverbal problems and EF problems (3 %).

9.2. Total cognitive and psychosocial problem load in children with epilepsy.

Figure 5 shows the total cognitive and psychosocial problem load in children with epilepsy as compared to controls. As can be seen from the upper boxes in this figure, all children in the two study groups were included at first. Children with SNVP comprised 39 % (n= 71) of patients and 3 % (n = 4) of controls. The rest of both study groups were categorized with regard to presence or absence of impairments as defined above (mild nonverbal deficits, psychosocial and/or EF problems). As can be seen from the figure, the percentages with no

impairments in children with epilepsy and in controls were 68 % (n = 124) and 19 % (n=35), respectively.

Figure 5. Total cognitive and psychological problem load in children with epilepsy (n = 183) versus controls (n=126).



* Impairments comprise mild non-verbal deficits (Raven), psychosocial problems (CBCL), and EF problems as defined by the 10th percentile in the control group. Psychosocial and EF impairments were assessed only in children without severe non-verbal problems (SNVP).

10. General Discussion.

There are several reasons why it is of fundamental importance to have as precise knowledge as possible about the function of children with epilepsy regarding cognition, behavior and learning difficulties.

1. It can form the basis for improved quality of counseling to individual epilepsy patients.
2. It enhances the planning of optimal health service for children with epilepsy
3. It increases the fundamental knowledge about epilepsy as a marker for brain dysfunction.

The approach of the present study made it possible to describe the psychological problems in an unselected population of children with epilepsy. The study showed that cognitive and psychosocial problems were frequent in children with epilepsy. Of the total population of 183 patients and 126 controls participating in the psychological studies, as many as 39 % of the children with epilepsy had severe non-verbal problems (SNVP) compared to 3 % of the controls. No significant problems in any areas assessed were found in 19 % of children with epilepsy compared to 68 % of controls (figure 5).

In children with epilepsy *without* SNVP, psychosocial, EF and mild nonverbal problems were frequent. In these children (without SNVP), 30 % of the children with epilepsy versus 70 % of the controls were without any of the problems mentioned above (figure 3). Various combinations of problems in the individual child with epilepsy were common. As many as 8 percent of the epilepsy children had problems in all areas assessed, compared to none of the

controls. Psychosocial problems were the most common, followed by EF and mild nonverbal problems (figure 4). To the best of our knowledge, there have been no previous population-based controlled studies addressing a broad range of cognitive and behavioral problems in children with epilepsy.

Psychosocial aspects.

In addition to the challenge of having a chronic disorder, children with epilepsy face difficulties related to having a disorder involving the central nervous system. Our study showed a considerably increased risk of psychosocial problems also among children with epilepsy not having severe non-verbal problems. In their neuropsychiatric studies of children from Isle of Wight, Rutter *et al* (1970) found psychiatric disorders in 28% of those with uncomplicated epilepsies, 38% of children with lesions above the brain stem without epilepsy, and in 58% of children with lesions above the brain stem associated with seizures. In their recent population-based study, Davies *et al* (2003) again emphasized that in children with epilepsy, neurological abnormalities are likely to be a key risk factor for mental health problems. They also reported an under-detection and under-treatment of emotional problems in children with epilepsy. The rates of psychiatric disorders in their study were remarkably similar to those reported 33 years earlier in the Isle of Wight study. According to Davies *et al*, the shortage of relevant research studies in this field seems to reflect clinical practice, where psychiatric diagnoses often are missed in children with epilepsy or, if identified, are considered to be an integral part of the epilepsy and not treated specifically. Ott *et al* (2003) also found, in their studies of children with complex partial seizures or primary generalized epilepsy with absences, that behavioral disorders were often not recognized and not treated. Apart from controlling seizures, attending to behavior and cognitive problems determines how well a child with epilepsy progresses towards independence (Besag 2004).

A series of meta-analyses by Rodenburg *et al* (2005) indicated that children with epilepsy were at increased risk of developing a broad range of psychopathology with somatic problems and attention problems being the most salient symptoms. The analyses indicated that attention problems, social problems and thought problems were more specific to epilepsy in contrast to children with other chronic illnesses such as asthma and diabetes. We found girls themselves to report internalizing problems, somatic concerns and anxiety problems in contrast to boys who did not. Both externalizing and internalizing problems were reported on behalf of both genders by teachers and parents. These observations support a more realistic self-evaluation in girls compared to boys (paper III).

In our study epilepsy syndrome, seizure type, seizure frequency and age of seizure onset were shown to be of significant relevance in relation to psychosocial problems (paper III). A majority of patients in the present study used AED treatment. In clinical practice, such treatment is often suggested to be a cause of behavior problems. In our study there was no significant relationship between children's use of AEDs and psychosocial problems, which was in keeping with recent research suggesting that the majority of children taking AEDs do not experience clinically relevant cognitive or behavioral adverse effects from these medications (Bourgeois 1998). However, Camfield *et al* (2001) reported that the total impact of pediatric epilepsy on psychosocial function was significantly related to seizure frequency and total number of medications taken. Moreover, Bourgeois (1998) pointed out that clinical experience must be used to identify the subgroup of children who remain at risk for significant and clinically relevant cognitive and behavioral adverse effects of AEDs.

Cognitive problems.

Cognitive problems were common among children with epilepsy in the present study. A large percentage of patients had severe non-verbal problems (SNVP). In those without SNVP, mild nonverbal problems and EF problems were also common, as were problems in both areas at the same time. EF and mild nonverbal problems could both explain parts of school problems but were only partially overlapping in doing so (paper IV).

Aldenkamp *et al* (2005) proposed that different epilepsy syndromes are associated with varying degrees of educational underachievement in children with epilepsy. In their measure of educational achievement, intelligence and memory were included. They further suggested that educational underachievement is an indication of a dominant impact of underlying etiology (brain dysfunction or damage). They found that underachievement was especially prominent in patients with localized epilepsies and symptomatic generalized epilepsies. Even having excluded children with severe non-verbal deficits, our study showed that children with localization-related and generalized symptomatic epilepsies struggled with a broad range of problems. In the study by Aldenkamp *et al* (2005) it was found that frequent epileptiform discharges and polytherapy were associated with reduced educational achievement. In our study we found that frequent seizures and early epilepsy onset influenced both the cognitive and the psychosocial function of the children negatively. Early epilepsy onset has also previously been shown to be associated with both cognitive and psychosocial problems (Dunn & Austin 2004).

11. Limitations of the study.

The focus of the work is not new, but several findings are new and can be ascribed to the quality of and broad approach used in the study. The fact that the study was population-based and included a control group made the findings more reliable. The broad approach also allowed us to investigate the relative importance of cognitive and psychosocial problems in the children.

However, the epidemiological approach of the study also had disadvantages. There were few children in several of our subgroups and the approach was therefore not suited for studies of psychological problems in most of the various specific epilepsy syndromes. In this study this would only have been possible for the BECT syndrome. To study the various specific epilepsy syndromes a much larger epidemiological material would have been needed.

The approach of the study has given a picture at one point in time. With regard to future function of the children and prognosis of their epilepsies, a follow-up study would be of great interest.

The study was also limited by the methodology selected for use in our work. In papers III and IV, children with severe non-verbal problems were excluded. The reasons for this were the focus of this part of the study and the fact that the instruments utilized were unsuitable for children with SNVP.

The seizure-related characteristics were interrelated as described in the statistical section.

Within each specific epilepsy syndrome (e.g. BECT, absence epilepsies etc.) there were also

other complicating factors such as heterogeneity between individual patients with regard to type, dosage and combinations of AEDs used, differences in psychological and educational services etc, all influencing the general cognitive and psychosocial function of each child. The present results should be interpreted with these cautions in mind.

12. Conclusions and future prospects.

In addition to their seizure problems *per se* and frequent additional neurological deficits, children with epilepsy run a high risk for psychosocial and cognitive problems. In our population-based study only 19% showed no significant psychological problems, compared to 68 % of the controls.

A high percentage of children with epilepsy had severe cognitive problems. Severe non-verbal problems (SNVP) were especially frequent in children with remote symptomatic epilepsy etiology, myoclonic seizures, early seizure onset, and therapy resistance.

In children with epilepsy and *without* SNVP, both psychosocial, milder non-verbal problems and EF problems were frequent with psychosocial problems as the most common (46%).

Psychological problems in more than one of the areas examined were frequent in children with epilepsy and nearly absent in controls. Both psychosocial and EF problems were significantly associated with epilepsy syndrome, age of epilepsy onset and seizure frequency.

In this study children with Rolandic epilepsies (BECT) did not have significantly more psychological problems than controls.

Girls with epilepsy reported more psychosocial problems than boys did, while mothers and teachers reported more of such problems in boys than in girls. These observations might indicate a need for specific investigations and treatment of psychosocial problems in boys as well as in girls with epilepsy, and may also indicate that girls are more realistic in their self-evaluation.

Most of the children with epilepsy need an individual assessment by an interdisciplinary team that is familiar with the complexity of the psychological problems encountered in several cases. Since emotional problems are common, interventions in this area should be addressed at an early stage. The high frequency of learning, cognitive and neuropsychological problems indicate a need of an individual assessment and educational plan for most patients. The fact that the disease for the most part is chronic indicates a requirement for early intervention and follow-up programs for psychological problems that meets the individual needs of children with epilepsy.

In addition to studies of prognosis of the seizure problems, there is a need for epidemiological follow-up studies of psychological and educational problems in children with epilepsy.

Epilepsy constitutes a heavy burden for most of the children and their families. Resilience factors should be addressed in future research and evaluation procedures should be developed to optimize successful habilitation programs.

13. References.

- Achenbach TM (1991). Integrative Guide for the 1991 CBCL/4-18 YSR, and TRF Profiles. Burlington VT: University of Vermont Department of Psychiatry
- Aldenkamp AP, Weber B, Overweg-Plandsoen WC, Reijns R & Van Mill S (2005). Educational underachievement in children with epilepsy: a model to predict the effects of epilepsy on educational achievement. *J Child Neurol* **20**: 175-180.
- Alwash RH, Hussein MJ & Matloub FF (2000). Symptoms of anxiety and depression among adolescents with seizures in Irbid, Northern Jordan. *Seizure* **9**: 412-416.
- Aman MG, Werry JS & Turbott SH (1992). Behavior of children with seizures. Comparison with norms and effect of seizure types. *J Nerv Ment Dis* **180**: 124-129.
- Anderson P (2002). Assessment and development of executive function (EF) during childhood. *Neuropsychol Dev Cogn C Child Neuropsychol* **8**: 71-82.
- Austin JK, Risinger MW & Beckett LA (1992). Correlates of behavior problems in children with epilepsy. *Epilepsia* **33**: 1115-1122.
- Austin JK, Huster GA, Dunn DW & Risinger MW (1996). Adolescents with active or inactive epilepsy or asthma: a comparison of quality of life. *Epilepsia* **37**: 1228-1238.
- Austin JK, Dunn DW & Huster GA (2000). Childhood epilepsy and asthma: changes in behavior problems related to gender and change in condition severity. *Epilepsia* **41**: 615-623.
- Austin JK, Harezlak J, Dunn DW, Huster GA, Rose DF & Ambrosius WT (2001). Behavioral problems in children before first recognized seizure. *Pediatrics* **107**: 115-122.
- Austin JK, Dunn DW, Caffrey HM, Perkins SM, Harezlak J & Rose DF (2002). Recurrent seizures and behavioral problems in children with first recognized seizures: a prospective study. *Epilepsia* **43**: 1564-1573.
- Beery KE (1989). The VMI administration, scoring and teaching manual. 3rd edition. Cleveland: Modern Curriculum Press.
- Besag FM (2002). Childhood epilepsy in relation to mental handicap and behavioural disorders. *J Child Psychol Psychiatry* **43**: 103-131. Review.
- Besag FMC (2004). Behavioral aspects of pediatric epilepsy syndromes. *Epilepsy Behav* **5**: (Suppl 1) S3-13. Review.
- Birleson P, Hudson I, Buchanan DG & Wolff S (1987). Clinical evaluation of a self-rating scale for depressive disorder in childhood (Depression Self-Rating Scale) *J Child Psychol Psychiatry* **28**: 43-60.
- Blom S (1997). Epilepsivård. Inte bara en fråga om anfallsreducering. (Epilepsy care. Not only a question of reducing seizures. In Swedish). *Läkartidningen* **94**: 1869-1870.

- Bourgeois BFD, Prenskey AL, Palkes HS, Talent BK & Busch SG (1983). Intelligence in epilepsy: a prospective study in children. *Ann Neurol* **14**: 438-444.
- Bourgeois BF (1998). Antiepileptic drugs, learning, and behavior in childhood epilepsy. *Epilepsia* **39**: 913-921. Review.
- Braathen G & Theorell K (1995). A general hospital population of childhood epilepsy. *Acta Paediatr Scand* **84**: 1143-1146.
- Brodie MJ & French JA (2000). Management of epilepsy in adolescents and adults. *Lancet* **356**: 323-329. Review.
- Brodie MJ & Kwan P (2002). Staged approach to epilepsy management. *Neurology* **58**: (8 Suppl 5): S2-8.
- Bulteau C, Jambaque I, Viguier D, Kieffer V, Dellatolas G & Dulac O (2000). Epileptic syndromes and school placement: a study of 251 children. *Dev Med Child Neurol* **42**: 319-327.
- Camfield PR, Gates R, Ronen G, Camfield C, Ferguson A & MacDonald GW (1984). Comparison of cognitive ability, personality profile and school success in epileptic children with pure right versus left temporal lobe EEG foci. *Ann Neurol* **15**: 122-126.
- Camfield C, Breau L & Camfield P (2001). Impact of pediatric epilepsy on the family: a new scale for clinical and research use. *Epilepsia* **42**: 104-112.
- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for Revised Clinical and Electroencephalographic Classification of Epilepsies and Epileptic Seizures. *Epilepsia* (1981) **22**: 489-501.
- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for Revised International Classification of Epilepsies and Epileptic Syndromes. *Epilepsia* (1989) **30**: 389-399.
- Cowan LD, Bodensteiner JB, Leviton A & Doherty L (1989). Prevalence of epilepsies in children and adolescents. *Epilepsia* **30**: 94-106.
- Davies S, Heyman I & Goodman R (2003). A population survey of mental health problems in children with epilepsy. *Dev Med Child Neurol* **45**: 292-295.
- Dikmen S & Matthews CG (1977). Effect of major motor seizures upon cognitive-intellectual functions in adults. *Epilepsia* **18**: 21-29.
- Dreifuss FE (1987). Epileptic seizures and syndromes. In: Dam M, Johannessen SI, Nilsson B and Sillanpaa M (eds) *Epilepsy: Progress in treatment*. Chichester: John Wiley and Sons; pp 17-25.
- Duncan JS (1996). Principles of treatment of patients with chronic active epilepsy. In: Shorvon S, Fish D, Dreifuss F, Thomas D (eds). *The treatment of epilepsy*. Oxford: Blackwell Science Ltd; pp 177-190.

- Dunn DW & Austin JK (1999). Behavioral issues in pediatric epilepsy. *Neurology* **53**:(5 Suppl 2) S 96-100.
- Dunn DW & Austin JK (2004). Differential diagnosis and treatment of psychiatric disorders in children and adolescents with epilepsy. *Epilepsy Behav* **5**: (suppl 3) S10-S17.
- Elger CE, Helmstaedter C & Kurthen M (2004). Chronic epilepsy and cognition. *Lancet Neurology* **3**: 663-672. Review.
- Ettinger AB, Weisbrot DM, Nolan EE, Gavow KD, Vitale SA, Andriola MR, Lenn NJ, Novak GP & Hermann BP (1998). Symptoms of depression and anxiety in pediatric epilepsy patients. *Epilepsia* **39**: 595-599.
- Farwell JR, Dodrill CB & Batzel LW (1985). Neuropsychological abilities of children with epilepsy. *Epilepsia* **26**: 395-400.
- Ferrie CD, Madigan C, Tilling K, Maisey MN, Marsden PK, Robinson RO (1997). Adaptive and maladaptive behaviour in children with epileptic encephalopathies: correlations with cerebral glucose metabolism. *Dev Med Child Neurol* **39**: 558-595.
- Forceville EJM, Dekker MJA, Aldenkamp AP, Alpherts WCJ & Schelvis AJ (1992). Subtest profiles of the WISC-R and WAIS in mentally retarded patients with epilepsy. *J Intellect Disabil Res* **36**: 45-59.
- Forsgren L (1997). Epilepsi drabbar särskilt små barn och gamla. (Epidemiology of epilepsy. Epilepsy primarily affects small children and the elderly). In Swedish. *Läkartidningen* **94**:1899-1902.
- Gastaut H (1969). Classifications of the epilepsies. Proposal for an International Classification. *Epilepsia* **10**: (suppl) 14-21.
- Gjessing HJ & Nygaard HD (1995). ITPA. *Illinois test of psycholinguistic abilities: Håndbok med instruksjoner og normer. Norsk utgave*. Oslo: Skolepsykologi-Materiellservice.
- Goldberg WA (1990). Marital Quality, parental personality and spousal agreement about perceptions and expectations for children. *Merill Palmer Quarterly* **36**: 531-556.
- Halperin JM, Healey JM, Zeitchik E, Ludman WL, & Weinstein L (1989). Developmental aspects of linguistic and mnemonic abilities in normal children. *J Clin Exp Neuropsychol* **11**: 518 -528.
- Hart YM (1996). Principles of Treatment of Newly Diagnosed patients. In: Shorvon S, Fish D, Dreifuss F, Thomas D (eds). *The treatment of epilepsy*. Oxford Blackwell Science Ltd. pp. 169-176.
- Hauser WA, Annegers JF & Kurland LT (1991). Prevalence of Epilepsy in Rochester, Minnesota: 1940-1980. *Epilepsia* **32**: 429-445.

- Hauser WA, Annegers JF & Kurland LT (1993). Incidence of Epilepsy and Unprovoked Seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* **34**: 453-468.
- Hedderick E & Buchhalter JR (2003). Comorbidity of childhood-onset epilepsy and psychiatric and behavioral disorders: a population-based study. *Ann Neurol* **54**: (suppl 7) p.115.
- Hermann BP, Whitman S & Dell J (1989). Correlates of behavior problems and social competence in children with epilepsy aged 6-11. In: BP Hermann and M Seidenberg, editors, *Childhood epilepsies: neuropsychological, psychosocial and intervention aspects*. Wiley, New York pp 143-157.
- Hoare P & Kerley S (1991). Psychosocial adjustment of children with chronic epilepsy and their families. *Dev Med Child Neurol* **33**: 201-215.
- Kramer U, Nevo Y, Neufeld MY, Fatal A, Leitner Y & Harel S (1998). Epidemiology of epilepsy in childhood: a cohort of 440 consecutive patients. *Pediatr Neurol* **18**: 46-50.
- Leppik IE & Baringer JR (2000). Selecting treatment in patients with epilepsy. *Hospital practice*. 15: 35-42, 45-47 Discussion 51-52.
- Lezak MD (1995). *Neuropsychological Assessment*. Third Ed. New York: Oxford University Press, pp. 463-464.
- Lindgren Å, Kihlgren M, Melin L, Croona C, Lundberg S & Eeg-Olofsson O (2004). Development of cognitive functions in children with Rolandic epilepsy. *Epilepsy Behav* **5**: 903-910.
- Luria AR (1966). *Higher cortical functions in man*. New York: Basic Books.
- Meador, KJ (2002). Cognitive outcomes and predictive factors in epilepsy *Neurology* **58**: (suppl 5): S 21-S 26.
- Miles MV, Tennison MB & Greenwood RS (1988). Assessment of antiepileptic drug effects on child behavior using the Child Behavior Checklist. *J Epilepsy* **1**: 209-213.
- Morton LD & Pellock JM (2000). Overview of childhood epilepsy and epileptic syndromes and advances in therapy. *Curr Pharm Des* **6**: 879-900.
- Najman JM, Williams GM, Nikles J, Spence S, BorW, O`Callaghan M, Le Brocque R & Andersen MJ (2000). Mothers' mental illness and child behavior problems: cause-effect associations or observation bias? *J Am Acad Child Adolesc Psychiatry* **39**: 592-602.
- Nyman H (1996). Wisconsin Card Sorting Test. Svensk utgave. Stockholm: Psykologforlaget.
- Oguz A, Kurul S & Didrik E (2002). Relationship of epilepsy-related factors to anxiety and depression scores in epileptic children. *J Child Neurol* **17**: 37-40.
- Ott D, Siddarth P, Gurbani S, Koh S, Tournay A, Shields WD & Caplan R (2003). Behavioral disorders in pediatric epilepsy: unmet psychiatric need. *Epilepsia* **44**: 591-597.

- Ostrom KJ, Schouten A, Kruitwagen CL, Peters AC & Jennekens-Schinkel A (2001). Epilepsy-related ambiguity in rating the child behavior checklist and the teacher's report form. *Epileptic Disord* **3**: 39-45.
- Porter RJ (1988). Classification of epileptic seizures. Part three. In Laidlaw J, Richens A, Osley J (eds): *A textbook of epilepsy*. Edinburgh: Churchill Livingstone.
- Raven JC (1965). *Progressive Matrices*. London: H.K. Lewis and Co.
- Robinson AL, Heaton RK, Lehman RA & Stilson DW (1980). The utility of Wisconsin Card Sorting Test in detecting and localizing frontal lobe lesions. *J Consult Clin Psychol* **48**: 605-614.
- Rodenburg R, Stams GJ, Meijer AM, Aldenkamp AP & Dekovic M (2005). Psychopathology in children with epilepsy: A meta- analysis. *J Pediatr Psychol* **30**: 453-468.
- Rutter M, Graham P & Yule W (1970). *A neuropsychiatric study in childhood*. *Clinics in Developmental Medicine Nos. 35/36*. Philadelphia: Lippincott.
- Sattler, JM (1992). Assessment of intelligence and infant development with specialized measures. In: JM Sattler *Assessment of children*, 3rd edition. JM Sattler Publisher Inc., La Mesa, CA, USA: pp 294-327.
- Schachter SC & Saper CB (1998). Vagus nerve stimulation. *Epilepsia* **39**: 677-686.
- Schoenfeld J, Seidenberg M, Woodard A, Hecox K, Inglese C, Mack K & Hermann B (1999). Neuropsychological and behavioral status of children with complex partial seizures. *Dev Med Child Neurol* **41**: 724-731.
- Sidenvall R, Forsgren L & Heijbel J (1996). Prevalence and characteristics of epilepsy in children in Northern Sweden. *Seizure* **5**: 139-146.
- Sillanpaa M (1973). Medico-social prognosis of children with epilepsy. Epidemiological study and analysis of 245 patients. *Acta Paediatr Scand* (suppl 273): 3-104.
- Singhi PH, Bansal U, Singhi S & Pershad D (1992). Determinants of IQ profile in children with idiopathic generalized epilepsy. *Epilepsia* **33**: 1106-1114.
- Sommerfelt K. Preschool neurodevelopment in non-handicapped children with birth weight less than 2000 g. Doctoral dissertation, Department of pediatrics and Department of Biological and Medical Psychology. University of Bergen 1997.
- Spiers PA, Schomer DL, Blume HW & Mesulam MM (1988). Temporolimbic epilepsy and behavior. In: Mesulam MH (ed) *Principles of Behavioral Neurology*. Philadelphia: FA Davis Company.
- Stores G (1978). School children with epilepsy at risk for learning and behaviour problems. *Dev Med Child Neurol* **20**: 502-508.

Sturniolo MG & Galletti F (1994). Idiopathic epilepsy and school achievement. *Arch Dis Child* **70**: 424-428.

Undheim JO (1978). Håndbok for Wechsler Intelligence Scale for Children-revised (Wechsler1974). Trondheim: Norsk psykologforening.

Uthman BM (2000). Vagus nerve stimulation for seizures. *Arch Med Res* **31**: 300-303.

Vermeulen J, Kortstee SWAT, Alpherts WCJ & Aldenkamp AP (1994). Cognitive performance in learning disabled children with and without epilepsy. *Seizure* **3**: 13-21.

Wechsler D (1949). Wechsler Intelligence Scale for Children-revised. New York: The Psychological Corporation.

Wieser HG (1986). Psychomotor seizures of hippocampal-amygdalar origin. In Pedley TA and Meldrum BS (eds) *Recent Advances in Epilepsy*. Edinburgh: Churchill-Livingstone.

Wolf P (1985). The classification of seizures and the epilepsies. In Porter RJ and Morselli PL (eds) *The Epilepsies*. London: Butterworths.