

Paper II



Seizure-related factors and non-verbal intelligence in children with epilepsy

A population-based study from Western Norway

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KEYWORDS

Epilepsy;
Epidemiology;
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Children

Summary

Purpose: To study the relationship between seizure-related factors, non-verbal intelligence, and socio-economic status (SES) in a population-based sample of children with epilepsy.

Methods: The latest ILAE International classifications of epileptic seizures and syndromes were used to classify seizure types and epileptic syndromes in all 6–12 year old children ($N = 198$) with epilepsy in Hordaland County, Norway. The children had neuropsychiatric and EEG examinations. Of the 198 patients, demographic characteristics were collected on 183 who participated in psychological studies including Raven matrices. 126 healthy controls underwent the same testing. Severe non-verbal problems (SNVP) were defined as a Raven score at or <10th percentile.

Results: Children with epilepsy were highly over-represented in the lowest Raven percentile group, whereas controls were highly over-represented in the higher percentile groups. SNVP were present in 43% of children with epilepsy and 3% of controls. These problems were especially common in children with remote symptomatic epilepsy aetiology, undetermined epilepsy syndromes, myoclonic seizures, early seizure debut, high seizure frequency and in children with polytherapy. Seizure-related characteristics that were not usually associated with SNVP were idiopathic epilepsies, localization related (LR) cryptogenic epilepsies, absence and simple partial seizures, and a late debut of epilepsy. Adjusting for socio-economic status factors did not significantly change results.

Conclusions: In childhood epilepsy various seizure-related factors, but not SES factors, were associated with the presence or absence of SNVP. Such deficits may

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be especially common in children with remote symptomatic epilepsy aetiology and in complex and therapy resistant epilepsies. Low frequencies of SNVP may be found in children with idiopathic and LR cryptogenic epilepsy syndromes, simple partial or absence seizures and a late epilepsy debut. Our study contributes to an overall picture of cognitive function and its relation to central seizure characteristics in a childhood epilepsy population and can be useful for the follow-up team in developing therapy strategies that meet the individual needs of the child with epilepsy.

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Introduction

Numerous studies of selected groups of children with epilepsy have demonstrated an association between epilepsy and cognitive deficits.^{1–6} Some studies indicated that intelligence scores of children with epilepsy are in the normal range, tending to cluster towards the lower end, especially in symptomatic epilepsy.^{7–11} According to Smith¹² and Meador¹³ the majority of children with epilepsy show no cognitive impairment. In population-based studies of children with epilepsy, the frequency of mental retardation has been reported to be 24–41%.^{14–19} Bourgeois et al.⁹ argued that in childhood epilepsy, being a heterogeneous disorder, the reported average IQ scores are largely results of the samples studied.

In childhood epilepsy several seizure-related characteristics have been reported to be associated with impaired cognitive performance: non-controllable seizures or high seizure frequency, long duration and severe seizures, symptomatic aetiology, early onset of epilepsy and treatment related factors.^{9,13} Atypical absences and other minor-motor seizures have also been found to be frequently associated with cognitive problems.⁸

There are several methodological problems when assessing the relationship between epilepsy and intellectual performance. Typical examples are inconsistencies in diagnosis and classification of epileptic syndromes, variability in classification of seizure types and other seizure-related factors, and insufficient use of control groups. In addition, potential confounding by socio-economic status (SES) factors has rarely been assessed and few studies have been population-based.

We have previously studied prevalence and medical aspects of childhood epilepsy in Western Norway.¹⁹ In that study intelligence was assessed using WISC-R in patients, but control children without epilepsy were not included. Mental retardation (MR) defined as IQ < 70 was found in 39% of children. In the present study, the focus was not the frequency of MR, but whether various seizure-related characteristics are associated with increased frequency of cognitive problems. A robust measure of cognition, non-verbal reasoning

ability was assessed. To ensure a reliable estimate of the frequency of such cognitive problems, a population-based, controlled study design was chosen.

Methods

Population

The study population, including medical characteristics, has been previously described.¹⁹ The study was conducted in Hordaland County in Western Norway. As of January 1, 1995, the county had 416,184 inhabitants (9.6% of the Norwegian population); 38,593 were born between January 1, 1982 and December 31, 1988 (information from Hordaland County Office 1995). Demographic characteristics of the county, such as average income and proportion of rural versus urban residence are similar to those of Norway as a whole. In Norway there are relatively small differences in socio-economic conditions and public access to health services.

Case ascertainment

The only paediatric department in Hordaland County is situated at The University Hospital of Bergen. Nearly all children with active epilepsy in the county are treated and controlled by neuro-pediatricians working in this department. The only EEG laboratory in the county is also situated at The University Hospital. Children in Hordaland who have experienced at least two epileptic seizures are generally referred for EEG registration and a neuropediatric examination. The following case identification methods were used: (a) review of hospital files of all patients aged 6–12 years with seizure disorders who had been examined in the paediatric department, (b) review of EEG files of all children in the specified age group registered at the EEG laboratory within the last 5 years, and (c) contact with the county's general practitioners, department of child psychiatry, special institutions for disabled children, and other hospitals in Hordaland and neighbouring counties.

Inclusion and exclusion criteria

Included in the study were all children ($N = 198$) born between January 1 1982 and December 31 1988 who had active epilepsy, and resided in Hordaland during the prevalence period, which was from October 1, 1994 to March 31, 1996. Of the 198 children, 15 patients refused testing by Raven matrices. Prevalence of epilepsy per 1000 children between 6 and 12 years of age was calculated for January 1, 1995. Exclusion criteria were: (a) single or isolated seizures (one or more epileptic seizures occurring within a 24 h period), (b) febrile seizures, (c) other provoked seizures occurring in close temporal association with an acute systemic condition, a metabolic or toxic influence or in association with an acute central nervous disorder, e.g. infection, trauma or haemorrhage, and (d) cases that appeared to be non-epileptic events, e.g. syncope, sleep disorders, migraine or pseudoseizures (behaviour disorders).

Controls

One hundred and twenty six healthy controls from Hordaland County matched for sex and age with the study children were randomly selected from The Norwegian Birth Registry. Mean age of the 183 patients and the 126 controls was 10.7 years (S.D.: 2.1) and 10.9 years (S.D.: 2.2), respectively ($p = .48$). The controls were only given psychological examinations.

Definitions

An epileptic seizure was defined as a clinical manifestation, within the last 4 years, presumed to result from an abnormal and excessive discharge of a set of neurones in the brain. Epilepsy was defined as two or more seizures occurring at least 24 h apart, unprovoked by any immediate identifiable cause, and regardless of antiepileptic drug (AED) treatment. The epilepsy was defined as active if at least one of the seizures had occurred during the last 4 years.

Epileptic seizures and epileptic syndromes were classified according to the international classification system of The International League Against Epilepsy (ILAE).^{20,21} Classification of seizures was based on seizure descriptions and EEG, including video-EEG recordings when available. For children with more than one seizure type, seizure frequency was categorised by the most frequent seizure type within the last year. Main seizure type was defined as the one that most accurately described the clinical condition and was most important for classification of the epileptic syndrome. The term remote symptomatic

aetiology was reserved for epilepsy with an obvious etiological factor which might be regarded as responsible for the brain dysfunction, such as: cerebral malformation, chromosome aberration, congenital syndrome, CNS infection or haemorrhage, serious perinatal complications, acute infantile encephalopathy, cerebral tumours, traffic accident injury, cerebral palsy, and progressive encephalopathy.

Children with a Raven score equal to or less than the 10th percentile according to published normative data for Raven matrices were defined as having severe non-verbal problems (SNVP). Children who were not testable due to obvious MR ($N = 44$) were also defined the same way. These children had one of the following characteristics: no language, a combination of CP and severe MR, or severe cognitive problems (testing had to be discontinued).

Psychological examinations

Epilepsy patients and controls were tested with Raven Coloured Matrices (for children less than 11 years old) or Raven Standard Matrices (for children 11 years old or more).²² Raven matrices is 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 0.50–0.80.^{23,24}

For practical reasons, 21 patients were not tested with the Raven matrices. In these cases test results from the Wechsler Intelligence Scale-Revised (WISC-R)²⁴ were available. The performance scores were transformed to Raven scores by use of a regression model estimated from test results of the 118 children with epilepsy who were given both WISC-R and Raven tests.

Medical examinations

Children with epilepsy were examined by a neuro-pediatrician, usually one of the authors (P.E.W.). Collected data included demographic information, aetiology of epilepsy, epilepsy syndrome classification, age of onset of seizures, main seizure type, seizure frequency last year, and treatment. The children underwent one or several EEG registrations. All EEG registrations were examined by one of the authors (H.S.). Six brain areas were evaluated with regards to past and/or present epileptogenic activity (AEA): frontal right and left, middle right and left, and posterior right and left areas. Epileptogenic activity (spikes and slow waves) was regarded as present in an area if it had been observed in at least one EEG registration. Further details concerning medical examinations have been published previously.¹⁹

Assessment of demographic characteristics

A clinical child psychologist (B.H.B.) interviewed all participating children and their parents. A trained test technician tested one third of the children with epilepsy and two thirds of the control group, the rest were tested by the psychologist. While the children were tested, their mothers were asked questions about educational level, work, and income. SES was assessed by using a summary score based on income level, present occupation, and educational level (Cronbach's $\alpha = .63$). For two parent households, the SES score was calculated as the mean score for both parents. All families were categorised as low, average or high SES.

Statistical methods

Statistical analyses were performed using the SPSS 10.0.²⁵ Difference in prevalence of SNVP between the epilepsy group and the controls was calculated using logistic regression analyses, and expressed as odds ratio (Fig. 1). The prevalence of SNVP in the control group was 3.2% ($N = 4/126$) and Fishers exact test was used to test hypotheses of higher prevalences of cognitive deficits than 3.2% within each medical subgroup of the epilepsy population (Tables 1 and 2). In Tables 1 and 2 all prevalences of SNVP are given with 95% confidence intervals.

Ethics

The study was approved by the Norwegian Data Inspectorate and by the Regional Committee on

Medical Research Ethics. Written informed consent was obtained from all parents in both study groups.

Results

Raven scores of children with epilepsy and controls are given in Fig. 1. The number of children with SNVP was 79 (43%) in the epilepsy group and 4 (3%) in the control group ($OR = 21.5$, $p < .001$). Adjusting for SES did not affect these results. The SES variable, was therefore, excluded in further analyses. Children with epilepsy were highly over-represented in the lower Raven percentiles, while controls were highly over-represented in the higher percentiles. Twelve percent of the epilepsy group versus 40% of the controls received the highest Raven scores.

The relationships between various seizure-related characteristics and SNVP are shown in Tables 1 and 2. Numbers and percentages of children with epilepsy and SNVP within each category of epilepsy related medical characteristics were compared to the proportion of children with SNVP in the control group. The majority of seizure-related characteristics were associated with significantly increased frequency of SNVP. The highest frequency (80%) was found in children with remote symptomatic epilepsy aetiology. SNVP were also frequent (65–78%) in children with undetermined epilepsy syndromes, myoclonic seizures, a small subgroup with various seizure types, early onset of epilepsy, high seizure frequency and in children with polytherapy (Table 1).

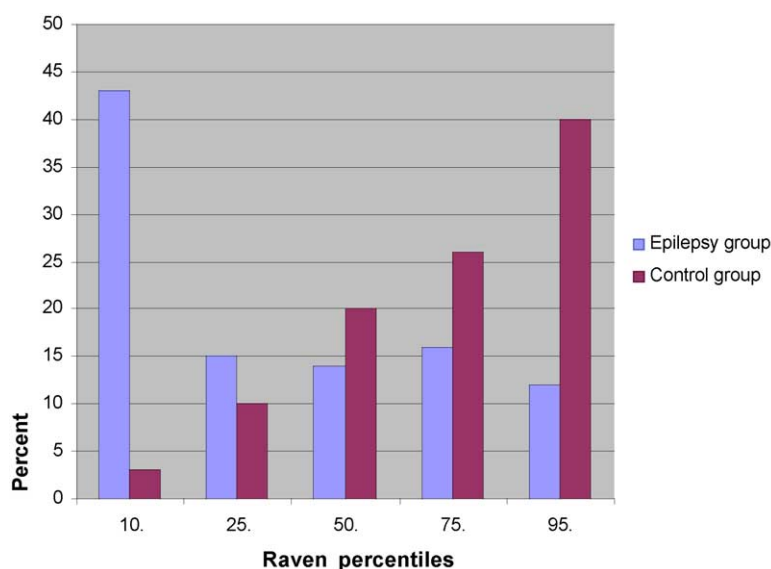


Figure 1 Cognitive function (Raven scores) in 183 children with epilepsy and 126 control children. Children with epilepsy who were not testable due to obvious mental retardation ($N = 44$), were placed in the 10th percentile category.

Table 1 Seizure-related factors and severe non-verbal cognitive deficits (low Raven scores) in 183 children with epilepsy.

Seizure-related factor	Number in epilepsy group	Severe non-verbal cognitive deficit present		Significance ^a
		N	% (95% CI)	
Remote symptomatic aetiology				
Not present	137	41	30 (22–38)	<.001
Present	46	37	80 (69–92)	<.001
Epileptic syndrome				
LR idiopathic	30	2	7 (–2–16)	.325
LR symptomatic	42	26	62 (47–77)	<.001
LR cryptogenic	25	5	20 (4–36)	.007
Gen. idiopathic	20	3	15 (–1–31)	.054
Gen. crypt. or sympt.	24	14	58 (39–78)	<.001
Gen. symptomatic	23	14	61 (41–81)	<.001
Undetermined	19	14	74 (54–93)	<.001
Main seizure type				
Simple partial	21	4	19 (2–36)	.015
Complex partial	56	24	43 (30–56)	<.001
Secondary generalized	27	11	41 (22–59)	<.001
Absences	15	2	13 (–4–31)	.124
Atypical absences	24	13	54 (34–74)	<.001
Myoclonic	9	7	78 (51–105)	<.001
Tonic–clonic	24	12	50 (30–70)	<.001
Other ^b	7	5	71 (38–105)	<.001
Age at epilepsy debut				
0–1 years	52	37	71 (59–83)	<.001
2–3 years	33	11	33 (17–49)	<.001
4–5 years	30	10	33 (16–50)	<.001
6–7 years	29	13	45 (27–63)	<.001
8–9 years	28	5	18 (4–32)	.011
10+ years	11	2	18 (–5–41)	.074
Seizure frequency last year				
None	50	11	22 (11–33)	<.001
1–12 seizures per year	55	16	29 (17–41)	<.001
>12 seizures per year	78	51	65 (55–76)	<.001
AED treatment last year				
None	45	18	40 (26–54)	<.001
One drug	108	39	36 (27–45)	<.001
Two or three drugs	30	21	70 (54–86)	<.001
AED treatment past and/or present				
None	20	6	30 (10–50)	<.001
One drug	64	21	33 (21–44)	<.001
Two drugs	47	13	28 (15–40)	<.001
Three or more drugs	52	38	73 (61–85)	<.001

CI: confidence intervals; LR: localization related; Gen: generalised; Crypt: cryptogenic; AED: antiepileptic drug.

^a Fisher exact test, patients vs. the 126 controls.

^b Tonic ($n = 2$), atonic ($n = 1$), infantile spasms ($n = 1$), not classifiable ($n = 3$).

The lowest percentages (7–15%) of SNVP were observed in children with localization related (LR) idiopathic epilepsies (in the present material only represented by cases with benign childhood epilepsy with centro-temporal spikes, BECT), generalised idiopathic epilepsies, and absence seizures. In these

groups the frequency of SNVP was not significantly different from controls.

Relatively low frequencies (18–33%) of SNVP were found in children with absence of remote symptomatic epilepsy aetiology, LR cryptogenic epilepsy, simple partial seizures, onset of epilepsy 2–5

Table 2 Areas of brain with epileptogenic activity (AEA) and severe non-verbal cognitive deficits (low Raven scores) in children with epilepsy.

	Number in epilepsy group ^a	Severe non-verbal cognitive deficit present		Significance ^c
		N	% (95% CI) ^b	
AEA^d				
Frontal right	95	49	52 (42–62)	.001
Frontal left	83	44	53 (42–64)	.001
Middle right	124	58	47 (38–56)	.001
Middle left	119	56	47 (38–56)	.001
Posterior right	105	47	45 (35–54)	.001
Posterior left	92	47	51 (41–61)	.001
Number of AEA				
No areas	23	9	39 (19–59)	.001
One area	34	7	21 (7–34)	.002
Two to five areas	53	24	45 (32–59)	.001
Generalized	72	37	51 ^e (40–63)	.001

^a N = 182. One child refused EEG registration.

^b CI: confidence interval.

^c Fisher exact test.

^d Not mutually exclusive.

^e Increased to 61% if typical absences were excluded.

years old and 8 years of age or later, seizure freedom or low seizure frequency last year, or never having taken more than two AED's.

Table 2 shows the relationship between areas of epileptogenic EEG activity and SNVP in children with epilepsy. In all AEA subgroups, SNVP were significantly more frequent than in the 126 control children.

Discussion

In the present study a high frequency of SNVP was found among children with epilepsy (43%) compared to controls (3%). To our knowledge, the frequency of severe non-verbal problems in children with epilepsy has not been studied in a population-based sample of children. We found that remote symptomatic aetiology was combined with an exceptionally high frequency of SNVP (80%). The frequent combination of definable organic brain disorder and epilepsy has been well-established in previous studies.^{14–18,26} It should be noted, however, that in the present study SNVP also occurred in 41 children (30%) without remote symptomatic epilepsy aetiology.

In our study, all symptomatic epilepsy syndrome groups showed high frequencies of children with SNVP (58–62%). This is in accordance with previous studies.^{5,9} In a hospital-based study, Bulteau et al.²⁷ found that children with symptomatic or cryptogenic generalised epilepsies or undetermined epileptic syndromes had lower mean IQ scores than

children with idiopathic generalised epilepsy or with LR epilepsies. The present high frequency of SNVP (74%) in the 19 children with undetermined epilepsy syndromes might be caused by the complicated and extensive nature of the disorder in many of these cases.

We found a relatively low frequency (20%) of SNVP in children with LR cryptogenic epilepsies. To our knowledge this observation has not been reported previously. However, taxonomic problems might complicate this picture. In the proposed new scheme for people with epileptic seizures and with epilepsy,²⁸ the term “probably symptomatic epilepsy syndrome”, used to define syndromes that are believed to be symptomatic, but where no aetiology has been identified, will replace the term cryptogenic epilepsy. With the rapid development of clinical epileptology many cases, which today are grouped as cryptogenic, will, in the future, be regarded as symptomatic cases. The present low frequencies of SNVP in children with LR idiopathic epilepsies (in our study BECT cases only) and idiopathic generalised epilepsy syndromes might be expected.^{29,30} However, even in these groups, less severe cognitive problems occur.^{31–33}

In our study, evaluation of the relationship between seizure type and frequency of SNVP was made difficult by the fact that, over the years, about one fourth of the patients had experienced only one seizure type, whereas about one third had more complicated patterns with three to 10 different types of seizures.¹⁹ Use of main seizure type as a seizure variable disclosed a low frequency of SNVP in

patients with simple partial and absence seizures, reflecting the above mentioned benign course of BECT and idiopathic generalised epilepsy syndromes. Conversely, we found that SNVP occurred in 50–78% of children with myoclonic, atypical absence and tonic–clonic seizures. Previously, high frequency of cognitive problems has been found in children with atypical absences and minor-motor seizures.⁸ High frequency of major motor seizures combined with early onset and long duration of the epilepsy has been reported to give a substantially increased probability of severe cognitive–adaptive dysfunction.³⁴ Schoenfeld et al.³⁵ reported significant impairment of cognitive function in children with complex partial seizures. Tonic–clonic, myoclonic, atypical absence, and complex partial seizures were most common in Swedish children with severe MR and epilepsy.²⁶ The present results were in accordance with these earlier findings.

Early onset of epilepsy has been regarded as an unfavourable factor in childhood epilepsy.^{5,27,36} The present study showed that an epilepsy debut before 10 years of age was associated with a significantly increased occurrence of SNVP, the highest risk being when seizure onset was before 2 years of age. Other authors have reported similar results.^{36,37} This may be because those with an early epilepsy debut are more likely to have a more severe structurally abnormal brain. An alternative might be that those with early debut may have seizures and epileptic activity during a longer time period and this in itself may be detrimental to cognitive function.

In epilepsy research, response to therapy is frequently evaluated by means of information about seizure frequency and use of AEDs. Children with high seizure frequency and polytherapy are usually regarded as suffering from therapy resistant epilepsies. The combination of therapy resistance, mental retardation and other neurological disabilities has been reported to be frequent in children with epilepsy.^{15,16,18,19} In the present study SNVP were common in children with frequent seizures. A lower mean IQ in children with frequent seizures has also been previously demonstrated.²⁷ Improved seizure control may result in improvement of patients' cognitive functions. In a prospective study of adult epileptic patients, Kalska³⁸ reported an improvement of time-limited visuo-spatial reasoning to be related to low seizure frequency at a 10 years' follow-up.

In our study AED polytherapy was found to be associated with a high risk of SNVP. This result was in accordance with recent research indicating that children who require treatment that combines several AEDs have more extensive cognitive difficulties than patients who receive monotherapy.^{27,35} This may be explained either by a more difficult epilepsy

with a higher associated frequency of cognitive impairments in these cases or by side effects of the AEDs used.

In most epidemiological studies of childhood epilepsy, results of EEG investigations have not been separately analysed. In the present study, only 21% of children with epilepsy had one AEA affected, which might reflect several BECT patients to be in the group. Otherwise the present EEG results, concerning both localization of epileptic activity in the brain and number of areas affected, did not disclose groups with especially high or low frequencies of SNVP.

SES variables were not found to be confounding results in the present study. The relatively homogeneous population in the Scandinavian countries could explain this observation. Furthermore, the cognitive deficits were frequently profound, making associations with SES less likely.³⁹

Epilepsy is caused by a functional aberration of the brain where structural lesions may also be found in several cases. The central nervous system (CNS) is frequently affected by the seizures themselves and by AED-treatment. There is also an increased risk of cognitive dysfunctions between seizures. The causes of cognitive problems in epilepsy are multiple, some related to structural brain damage or early onset of epilepsy. In cases where patients have mental retardation this is often caused by the same brain lesion that led to epilepsy.⁴⁰

In epidemiological epilepsy research there are problems of classification in some epilepsy cases. In the future such difficulties may be less common with advances in neurodiagnostic technology, new insights into fundamental neuronal mechanisms of epilepsy, rapid developments in molecular genetics, and by introduction of the proposed new classification system of epileptic seizures and syndromes²⁸ mentioned above. However, even within well-defined epilepsy syndromes the clinical picture may vary considerably between individual patients.

The various seizure-related variables used in the present study were partly overlapping. Therefore, as in other similar research, their individual effects cannot be precisely estimated.⁴¹ However, we may still conclude that in children with epilepsy SNVP frequently occur together with remote symptomatic aetiology, symptomatic or undetermined epilepsy syndromes, myoclonic seizures, high seizure frequency and polytherapy.

Epilepsy is caused by functional aberration in the central nervous system where structural lesions may also be found. Epileptic seizures themselves as well as antiepileptic drugs, affect the CNS. Cognitive problems in children with epilepsy may have several causes. Ongoing epileptic activity, especially when

early onset, may disturb cognitive function. Alternatively, structural brain damage may cause both epilepsy and cognitive problems.

The population of Norway is regarded as stable and homogeneous. The present study was restricted to a county with only one paediatric department and only one EEG laboratory. In this county, children with possible epilepsy are usually referred to a neuropediatrician or at least an EEG registration. By contacting general practitioners we found that only four children had fallen outside this system. We, therefore, believe that all children with active epilepsy, including mild cases, were traced in this study. This conclusion was supported by the prevalence of childhood epilepsy in the present material (5.1 per 1000), which was in accordance with recent studies from developed countries.^{14–17}

Conclusions

Psychological studies of children with epilepsy have, for the major part, been based on investigations in hospital based patient materials. Our study was population-based controlled and contributes to the following:

1. It gives an overall picture of non-verbal cognitive functions and their relationship to seizure-related characteristics and SES factors in childhood epilepsy.
2. Various seizure-related characteristics, but not SES factors, are associated with presence or absence of SNVP in children with epilepsy in developed countries.
3. Children with epilepsy were highly over-represented in the lowest Raven percentile group whereas controls were highly over-represented in the higher percentile groups.
4. High frequencies of SNVP may be found in children with remote symptomatic aetiology, undetermined epilepsy syndromes, myoclonic seizures, early epilepsy debut, and therapy resistant epilepsies.
5. Low frequencies of SNVP may be found in children with BECT, LR cryptogenic and generalised idiopathic epilepsy syndromes, simple partial seizures, and a late epilepsy debut.
6. EEG results were not related to especially high or low frequencies of SNVP.

The present study shows the importance of focusing not only on antiepileptic drug treatment to achieve seizure reduction, but to acknowledge very frequent cognitive dysfunctions in these children. To achieve this, we believe that a multidisciplinary

approach focusing on a specific child's weaknesses and strengths is mandatory. Knowledge about the risks associated with specific seizure-related factors may help the health professionals to foresee and plan optimal follow-up strategies. Furthermore, it is of utmost importance to help parents and teachers achieve a realistic acceptance of the child's cognitive abilities.

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