Original article

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The consequences of idiopathic partial epilepsies in relation to neuro-psychological functioning: a closer look at the associated mathematical disability

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ABSTRACT – Although the seizure prognosis is mostly favorable in idiopathic partial epilepsies, there is some empirical evidence showing that subtle neuropsychological impairments, with a consequent risk of academic underachievement, are not rare. We investigated neuropsychological functioning including attention, memory, visuomotor ability, and executive functioning with a closer look at the associated mathematical ability in patients with idiopathic partial epilepsies. A battery of age-appropriate, neuropsychological and mathematics achievement tests was administered to 30 participants with idiopathic partial epilepsy [13 children with benign epilepsy with centrotemporal spikes (BECTS), 17 children with idiopathic childhood occipital epilepsies (ICOE)], and to 30 healthy participants matched for age, sex, handedness, and socioeconomic status. Results did not support any impairment in overall neuropsychological functioning in participants with idiopathic partial epilepsies, whereas, isolated deficits did exist. The mean performance of the IPE group was significantly lower than the control group in six out of 12, neuropsychological measures: drawing ($p < 0.01$), digit span ($p < 0.05$), verbal learning ($p < 0.01$), object assembly ($p < 0.01$), similarities ($p < 0.05$), and vocabulary ($p < 0.001$). Results suggested that one should be cautious regarding neuropsychological and academic prognosis in the so-called benign idiopathic partial epilepsies of childhood.

Key words: rolandic epilepsy, BECTS, Gastaut occipital epilepsy, Panayiotopoulos syndrome, mathematics achievement, cognitive functioning, neuropsychology

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Idiopathic partial epilepsy (IPE) includes epileptic syndromes with a considerably high incidence of remission such as benign epilepsy with centrotemporal spikes (BECTS), and idiopathic childhood occipital epilepsies (ICOE) (Panayiotopoulos 2002, Engel 2001).

BECTS is the most common type of partial motor epilepsy in childhood (Beaussart 1972, Cavazzutti 1980), where the absence of interictal neurological and mental dysfunctions is included in the diagnostIdiopathic partial epilepsy ()ic criteria (Commission on Classification and Terminology of the International League Against Epilepsy 1989). ICOE, with two distinct clinical types: early onset benign childhood occipital epilepsy (Panayiotopoulos type), or, "early-onset benign occipital seizure susceptibility syndrome" (Panayiotopoulos 1999a, 1999b), and late onset childhood occipital epilepsy (Gastaut type) (Panayiotopoulos 2002, Engel 2001), is not as homogeneous in its clinical presentations and prognosis as BECTS (Guerrini *et al.* 1993). Specifically, the prognosis in the Gastaut type is still uncertain compared to Panayiotopoulos type. However, what is certain is that atypical evolutions to more severe forms of epilepsy, and to severe impairments in neuropsychological functioning in BECTS and two clinical types of ICOE, are very rare (Panayiotopoulos 2002). Idiopathic photosensitive occipital lobe epilepsy (IPOE), previously considered as part of the Gastaut type of ICOE, is classified as a new syndrome of reflex epilepsy according to the ILAE Task Force on Classification and Terminology (Engel 2001), however its boundaries and prognosis are still uncertain (Panayiotopoulos 2002).

The long-term medical and psychosocial prognosis of BECTS is excellent, with essentially most children entering long-term remission by mid-adolescence (Lerman 1992, Wirrell 1998); however, some impairment of visuomotor coordination (Heijbel and Bohman 1975), impulsivity, hyperactivity, academic underachievement, learning difficulties, attention problems, and auditory-verbal or visuospatial deficits (Massa *et al.* 2001) were reported.

Cognitive and behavioral problems resulting from IPE are correlated with atypical clinical forms and their atypical evolution (Panayiotopoulos 1999a, 1999b, Verrotti *et al.* 2002), together with atypical EEG features such as the persistence of a prolonged slow focus and a strong activation of spike and waves during sleep (Massa *et al.* 2001), and frequent occurrence of continuous spike-waves during slow sleep-like patterns (Deonna 2000, Massa *et al.* 2001). However, subtle intellectual impairment (Fois *et al.* 1988, D'Alessandro *et al.* 1990), or isolated neuropsychological problems (Gülgönen *et al.* 2000, Gündüz *et al.* 1999, Verrotti *et al.* 2002) are found. Furthermore, a variety of minor disturbances in behavior and fine-motor control have been observed in association with rolandic spike foci with or without seizures (Van der Meij *et al.* 1992, Yung *et al.* 2000).

Earlier studies also document academic underachievement in children with IPE, despite the fact that these children have normal intellectual functioning (Bourgeois *et al.* 1983, Seidenberg *et al.* 1986). In a recent longitudinal study, Bailet and colleagues (2000) found that children with IPE had high rates of grade retention, and placement in special education compared to their with sibling controls. We investigated the risks in children with IPE for impairments in overall neuropsychological functioning as well as discrete functions such as intelligence, attention, memory, visuomotor ability, and executive functioning. Mathematics achievement was also investigated to find out whether an association exists between discrete neuropsychological deficits and mathematical ability in children with IPE compared to healthy children and children with BECTS and ICOE.

Methods

Participants

The IPE group consisted of 21 male and nine female children, ranging in age from seven to 15 years (10.8 years ± 2.06). Ninety percent were right-handed; socioeconomic status (SES; parental educational and occupational levels) varied from high (n = 4), to medium (n = 20), to low (n = 6). Participants were recruited from a pool of patients at the University of Istanbul, Cerrahpaşa Medical Faculty, Department of Neurology, Division of Child Neurology. The IPE group included 13 children with BECTS, six children with Panayiotopoulos type of ICOE, eight children with the Gastaut type of ICOE, and three children with IPOE. There were no significant demographic differences between subgroups of IPE. All but two children were receiving antiepileptic monotherapy, such as carbamazepine (10 to 20 mg/kg/day), sodium valproate (20 to 30 mg/kg/day), or vigabatrine (50 mg/kg/day).

Neuropsychological test results of nine children from the ICOE group were reported previously, as part of another study (Gülgönen *et al.* 2000). All participants were selected according to the criteria in the relevant literature

Abbreviations:
IPE : *idiopathic partial epilepsies*
BECTS : *benign epilepsy with centrotemporal spikes*
ICOE : *idiopathic childhood occipital epilepsies*
IPOE : *idiopathic photosensitive occipital lobe epilepsy*
SES : *socioeconomic status*
WISC-R : *Wechsler intelligence scale for children-revised*
WRAML : *wide range assessment of memory and learning*
WRAVMA : *wide range assessment of visuomotor abilities*
COWAT : *controlled oral word association test*
WRAT-III : *wide range achievement test-III*

(Engel 2001, Genton and Guerrini 1994, Panayiotoupoulos 2002). Each child had had several EEGs obtained at times following diagnosis. EEG results, therefore, were not obtained at the time of neuropsychological testing. EEG characteristics of the children with BECTS included epileptogenic foci with right (n = 4), left (n = 3), bilateral R>L (n = 1), bilateral L>R (n = 2) and variable (n = 3) hemispheric involvement. Focal paroxysmal discharges in the EEGs of the ICOE group displayed right (n = 5), left (n = 1), bilateral and symmetrical (n = 1), bilateral R>L (n = 4), bilateral L>R (n = 1) and variable (n = 2) placement.

EEG features of children with BECTS had epileptiform discharges only in the centro-temporal regions. Children with ICOE included focal epileptiform discharges in the parieto-occipital and/or occipital regions, with additional foci in the centrotemporal regions in ten.

Twenty-six children had been seizure-free for the two months prior to assessment. All had normal neurological examination. No neuroimaging abnormality was found in 28 participants for whom neuroimaging information was available (19 cranial MRI, 9 cranial CT). *Table 1* summarizes the characteristics of the IPE group.

A control group of thirty healthy children, matched for chronological age (10.8 years ± 2.05), sex (70% male), handedness (90% right-handed) and SES [high (n = 2), medium (n = 21), low (n = 7)], was recruited from one of the public schools in the Istanbul metropolitan area. Additional selection criteria for the control group included: no history of epilepsy, or other neurological disorder, febrile seizures, mental retardation, psychiatric disorders, learning disability or other developmental disabilities among the control children or their families.

Table 1. Characteristics of the IPE Group.

Patients	Type of IPE	Age-at-onset	Age in years; months	Treatment	Handedness	Sex	SES	EEG focus
1	P-t	3	7; 2	CBZ	R	F	Middle	Bi R>L PO+Bi CT
2	P-t	5	9; 4	CBZ	R	M	Middle	V O+L CT
3	P-t	5	9; 5	CBZ	R	F	Middle	L O
4	P-t	8	10; 3	CBZ	R	M	Low	R PO+R CT
5	P-t	12	12; 4	-	R	M	Middle	R O+ R CT
6	P-t	8	13; 5	CBZ	R	M	Middle	Bi R>L O+Bi R>L T
7	G-t	4	7	VPA	L	M	Low	R O
8	G-t	8	9; 10	CBZ	R	M	Middle	Bi R>L O+Bi CT
9	G-t	8	9; 7	VPA	R	F	Middle	V O+R CT
10	G-t	9	10; 9	VPA	R	M	Middle	Bi R>L O+L CT
11	G-t	4	10; 3	VPA	R	F	Low	R O+R CT
12	G-t	5	12	CBZ	R	F	Low	Bi L>R PO+L CT
13	G-t	10	13; 5	CBZ	R	M	Low	Bi PO
14	G-t	11	15	VGB	R	M	High	R PO
15	IPOE	7	9; 5	-	R	M	High	Bi PO
16	IPOE	10	11; 10	VPA	L	M	Middle	R PO
17	IPOE	7	14; 3	CBZ	R	M	Middle	R O
18	BECTS	5	8; 1	VPA	R	M	Middle	V CT
19	BECTS	8	8; 6	CBZ	R	M	High	L CT
20	BECTS	8	9; 3	CBZ	R	F	Low	R CT
21	BECTS	8	9; 4	CBZ	R	F	Middle	Bi R>L CT
22	BECTS	8	10; 5	CBZ	R	M	Middle	Bi L>R CT
23	BECTS	10	10; 9	CBZ	R	M	High	Bi L>R CT
24	BECTS	7	11; 7	VPA	R	M	Middle	R CT
25	BECTS	6	11; 3	CBZ	R	F	Middle	V CT
26	BECTS	8	11; 5	CBZ	R	F	Middle	R CT
27	BECTS	7	12; 1	CBZ	R	M	Middle	R CT
28	BECTS	10	13; 8	CBZ	R	M	Middle	V CT
29	BECTS	8	13; 9	CBZ	R	M	Middle	L CT
30	BECTS	9	9; 9	CBZ	R	M	Middle	L CT

P-t: early onset benign childhood occipital epilepsy (Panayiotopoulos type); **G-t**: late onset childhood occipital epilepsy (Gastaut type); **IPOE**: idiopathic photosensitive occipital lobe epilepsy; **BECTS**: benign epilepsy with centrotemporal spikes; **CBZ**: carbamazepine; **VPA**: valproate; **VGB**: vigabatrine; **R**: right; **L**: left; **F**: female; **M**: male; **Bi**: bilateral; **PO**: parieto-occipital; **O**: occipital; **CT**: centro-temporal; **R>L**: right dominant; **L>R**: left dominant; **V**: variable (bilateral independent foci).

Table 2. Means and standard deviations (in parentheses), and F-values on test domains for IPE group and the control group.

		IPE Group (n = 30)	Control Group (n = 30)	
Domains	Sub-tests	M (SD)	M (SD)	F-Values
I. Visual modality				
A. Attention	Finger windows (WRAML)	8.60 (2.90)	9.17 (2.57)	0.64
B. Memory	Design memory (WRAML)	8.73 (3.02)	9.83 (2.65)	2.25
	Visual learning (WRAML)	8.66 (3.27)	9.43 (2.68)	0.98
C. Visual motor	Drawing (WRAVMA)	12.83 (2.88)	15.07 (2.42)	10.58**
II. Verbal modality				
A. Attention	Digit span (WISC-R)	9.26 (2.30)	10.80 (2.47)	
6.19*				
B. Memory	Story memory (WRAML)	8.46 (3.05)	8.93 (2.74)	0.39
	Verbal learning (WRAML)	11.00 (2.70)	12.90 (2.48)	
8.08**				
C. Language	COWAT	9.56 (2.62)	10.46 (3.02)	1.46
III. Intelligence				
A. Visual	Block design *executive* (WISC-R)	11.80 (2.99)	13.03 (3.05)	2.49
	Object assembly *executive* (WISC-R)	10.90 (2.47)	12.76 (2.63)	8.02**
B. Verbal	Similarities *executive* (WISC-R)	10.50 (1.85)	11.80 (2.16)	6.28*
	Vocabulary *language* (WISC-R)	8.17 (2.42)	11.20 (2.54)	22.40**
IV. Maths achievement	WRAT III	101.67 (15.05)	113.23 (15.11)	8.83**

Scores are mean and standard deviations of scaled scores for sub-tests of neuropsychological functioning, and standard scores for maths achievement. F-values representing significance between IPE and control groups. *$p < 0.05$; ** $p < 0.01$.
WISC-R (Wechsler Intelligence Scale for Children-Revised, WRAML (Wide Range Assessment of Memory and Learning), WRAVMA (Wide Range Assessment of Visual-Motor Abilities), COWAT (Controlled Oral Word Association Test). WRAT III; Wide Range Achievement Test III- arithmetic subtest.
Domain of Performance IQ: (Object Assembly & Block Design).
Domain of Verbal IQ: (Similarities & Vocabulary).

Procedure

Parents of all children were interviewed to obtain relevant consent and demographic and medical information. A battery of age-appropriate, neuropsychological tests and one achievement test in mathematics were individually administered to children with IPE in the Neuropsychology Laboratory of the Cerrahpaşa Medical Faculty, Department of Neurology, Division of Child Neurology. Healthy children were assessed in a similar setting at the public school in Istanbul. Tests were chosen on the basis of their appropriateness for Turkish school children. The testing took approximately two hours.

Assessment

The neuropsychological tests were selected to measure functioning in six domains: intelligence, attention, memory and learning, visuomotor, language, and executive functioning with visual and verbal tests for each domain. *table 2* summarizes neuropsychological tests and associated functional domains including visual and verbal modalities.

Neuropsychological tests included the short form of the Turkish version of the Wechsler intelligence scale for children-revised (WISC-R): similarities, digit span, vocabulary, object assembly and block design plus a prorated full scale IQ score (Wechsler 1974, Rourke and Finlayson 1978, Sattler 1992); the wide range assessment of memory and learning (WRAML): story memory, design memory, finger windows, visual learning, verbal learning subtests (Sheslow and Adams 1990); the drawing subtest of the wide range assessment of visuomotor abilities (WRAVMA) (Adams and Sheslow 1995) and the Controlled Oral Word Association Test (COWAT) (Spreen and Strauss 1991). The neuropsychological tests were translated into Turkish by graduate students of Boğaziçi University, Istanbul with the assistance and review of a practicing clinical neuropsychologist from the community.

The arithmetic subtest of the wide range achievement test-III (WRAT-III) (Spreen and Strauss 1991) was used to measure mathematics achievement, and to identify the types of mathematical errors occurring. The test is designed to measure the skills that are needed to do arithmetic. The arithmetic subtest consists of an oral arithmetic component for children aged 7 or younger, a written arithmetic component for children aged 8 and older. Overall, children were asked to count, read number symbols, solve oral problems and perform written computations. Scores are age corrected standard scores and represent

arithmetic abilities. Careful observation of the individual responses, along with error analysis, may provide important implications for identification of and intervention for any mathematics difficulties (Knopp, 2004).

Data analyses

Data were analyzed using the statistical packages for social sciences (SPSS-version 13.0). The significance level was set at 0.05, unless otherwise indicated. All measures of neuropsychological functioning were presented as means and standard deviations. The significances of group mean differences in neuropsychological functioning for each test were evaluated by analysis of variance (ANOVA).

Results

The results for the IPE and control children in the neuropsychological tests, intelligence and mathematics achievement are shown in *table 2*. On the neuropsychological tests, the mean performance of the IPE group was significantly lower than the control group for three out of eight of the individual measures: drawing [$F = 10.58$, $p < 0.01$]; digit span [$F = 6.19$, $p < 0.05$]; and verbal learning [$F = 8.08$, $p < 0.01$]. In addition, on the WISC-R, children with IPE performed significantly worse than the control group on the object assembly [$F = 8.02$, $p < 0.01$], similarities [$F = 6.28$, $p < 0.05$] and vocabulary [$F = 22.4$, $p < 0.001$] subtests. Achievement in mathematics in the IPE group was significantly lower than that in the control group [$F = 8.83$, $p < 0.01$]. Based on the written errors of the participants on the arithmetic subtest of the WRAT-III, three categories of errors are identified based on the clinical sample of the Boğaziçi University Center for Psychological Research and Services; spatial errors, operational errors and errors of memory. Two types of spatial errors were observed: a) mis-alignment of numbers in columns or subtracting the minuend from subtrahend; and b) poorly formed writing of numbers or poor use of space given the computation, two types of operational errors were identified: a) mis-reading of a mathematical sign; and b) missing or adding a step to the calculation (*e.g.*, 75+8 = 163). The third category included errors of memory (*e.g.*, failure to remember a particular number fact). The results of the Mann-Whitney U test however, revealed no significant differences between the IPE group and the control group in the types of mathematical errors made.

Further analyses were performed between subgroups of IPE, despite some overlapping clinical and laboratory features, to explore differences in neuropsychological functioning including intelligence and achievement in mathematics. No significant differences were found in the neuropsychological functions between the ICOE (IPOE group has not been included) and BECTS groups. ICOE participants with bilateral EEG discharges (n = 8) did not differ from those with unilateral discharges (n = 6).

Discussion

Idiopathic partial epilepsies are more suitable for investigating aspects such as the centrotemporal area in rolandic epilepsy (Elger *et al.* 2004). Hence, these patients are expected to have deficits in the cognitive functions controlled by the respective areas of the brain. Furthermore, the seizure symptomatology is mild in these syndromes, and seizures are responsive to treatment when indicated usually with a single drug. Indeed, IPEs are considered to be benign as regards the overall clinical outcome; however, there has been growing evidence showing isolated neuropsychological and/or academic deficits in these children. A series of 220 patients with benign epilepsy with occipital paroxysms (BEOP) revealed psychomotor/cognitive deficits in 14% of them (Van der Meij *et al.* 1992).

Investigators have reported cognitive decline and attention disorders (De Saint-Martin *et al.* 2001); language delay and regression (Deonna *et al.* 2000); problems in memory, visual perception, verbal fluency and fine motor skills (Weglage *et al.* 1997, Croona *et al.* 1999); some motor and language deficits (Gündüz *et al.* 1999); and problems in attention, memory and intellectual functioning (Gülgönen *et al.* 2000); mild intellectual disability with behavioral problems, and with specific learning disabilities (Yung *et al.* 2000) as well as some deterioration in intellectual abilities, including the diagnosis of mild mental retardation (Caraballo *et al.* 2001).

The present study supported the presence of several isolated deficits in neuropsychological functioning among children with IPE rather than a generalized impairment in all areas of neuropsychological functioning. The performance of children with IPE on the tests of drawing ability, verbal learning, visuospatial synthesis, abstract verbal reasoning, and vocabulary, were poorer than controls. Children with IPE however, did not differ significantly from the control group as regards visual attention, visual learning and memory, memory for contextual verbal material (stories), verbal fluency, or visual analysis. In general, it might be concluded that IPE apparently had a relatively greater negative influence upon some verbal skills (vocabulary subtest of the WISC-R and verbal learning), as compared with visual skills although there was no significant difference between groups as regards another set of tests which involved verbal processing such as story memory and verbal fluency. This finding is consistent with previously observed language dysfunction and associated school failures among Turkish children with benign idiopathic partial epilepsies (Gündüz *et al.* 1999, Gülgönen *et al.* 2000). Indeed, BECTS may lead to impairment relatively specific to oral language such as dysfluency, or difficulties in word

finding and naming and/or specific difficulties in written language (Deonna *et al.* 1993, Deonna, 2000). Even though the patients were in remission (Monjauze *et al.* 2005), they might also show difficulties in non-verbal skills such as in the area of visuospatial and/or attentional skills (Deonna, 2000).

In order to interpret the results, it is necessary to consider the function of each assessment tool in our study. Drawing (WRAVMA-drawing), as reflecting integration of visual and motor abilities, putting puzzles together (object assembly) requiring visuospatial synthesis, and abstract verbal reasoning (similarities) tests would require high levels of integration. Furthermore, rote verbal learning (*e.g.*, verbal learning), requires the individual to organize new information for effective learning and recall, as opposed to information presented in context (story memory). Finally, block design, a measure of visuospatial analysis, and object assembly, a measure of visuospatial synthesis, both require normal executive functions (such as speed of visuomotor organization), as well as normal visual acuity and manual dexterity as prerequisites.

At this point, it is also important to make the distinction between the cognitive deficits or learning problems that can be ascribed to a localized epileptic dysfunction such as might occur in the case of foci in the perisylvian region and more specific abilities such as verbal expression, from those which are mostly due to involvement of more general abilities such as sustained attention, processing efficiency, response inhibition and planning such as might occur in the case of more diffuse involvement of the brain (Deonna, 2000).

Findings can be best interpreted in view of a neuroconstructivist approach (Karmiloff-Smith 1998), which accepts domain-specific cognitive modules and conceives of them as emerging through a developmental and interactive process with each other. Hence, rather than impaired cognitive modules, more indirect, lower-level causes of abnormality are sought, affecting some components of the discrete modules. Modules of executive and visuospatial abilities are thought to emerge from a developmental process of modularization and in accordance with Vygotskian approach (Vygotsky 1988); some form of biologically specified starting points are considered to be initially "domain-relevant", only becoming domain-specific with the process of development and specific social-environmental interactions. In this study, interactions between development and the social-environment need further investigation with the application of longitudinal design.

Our findings support the relationships found between academic ability and epilepsy (Bagley 1970, Seidenberg *et al.* 1986, Aldenkamp 1983, Aldenkamp *et al.* 1990, Shalev and Gross-Tur 2001). The performance of the IPE group was lower than the control group for achievement in mathematics. It may be that IPEs exert a strain on a child's capacity to organize and integrate sensory information, which in turn negatively affects academic outcome in mathematics, which requires the integration of several low and high levels skills. It is likely that mathematics may be the most vulnerable academic ability with respect to its cerebral organization, as well as its neuropsychological complexity. Recently, some aspects of mathematical ability were located bilaterally, in the intraparietal areas (Dehaene *et al.* 1998). It was also shown that more complex calculations necessitate involvement of visuospatial regions while a distinct, parietal-premotor area is activated during finger counting and calculation (Zago *et al.* 2001, Pesenti *et al.* 2000). The variations in neuropsychological functions may depend on several parameters such as the frequency of seizures and spike-wave discharges, or the lateralization of the epileptic focus in relation to the involved domain function (Metz-Lutz *et al.* 1999). The results of longitudinal studies of cognitive functions in benign partial epilepsies show difficulties in language, but no single cognitive profile with language; so lower scores in one isolated domain (*e.g.* isolated spelling deficit that was not accompanied by a reading deficit) are not considered to be a specific learning disability (Deonna *et al.* 2000). Variations in achievement in mathematics may also depend on several parameters. Lower scores in one isolated domain (*e.g.* isolated counting deficit which was not accompanied by a general mathematical deficit) do not necessarily imply a mathematical disability.

One of the flaws in the study of epilepsies could stem from the possible adverse impact of antiepileptic medication on neuropsychological functioning. Even though all children apart from two in the present study, were using a single antiepileptic drug in mild to moderate doses at the time of testing, possible negative effects of medication (Vining 1987, Mitchell *et al.* 1993, Mandelbaum and Burack 1997, Trimble and Cull 1998, Seidel and Mitchell 1999, Riva and Devoti 1999) could not be ruled out as a variable contributing to the deficits observed. Another issue of concern might be the negative effects of subclinical EEG discharges on neuropsychological functioning (Aarts *et al.* 1984). A recent review however, of transient cognitive effects of interictal discharges, showed that such adverse effects were much smaller than previously thought (Aldenkamp and Arends 2004).

In conclusion, the findings of this study suggest the possible long-term adverse effects of idiopathic partial epilepsies on learning abilities such as visuomotor abilities, memory deficits, and problems in intellectual functioning. Many factors could be considered as possible correlates of learning problems, or more specifically learning disabilities, such as seizures, antiepileptic medications, brain abnormalities, and discrete neuropsychological deficits (Bailet and Turk 2000). Neuropsychological assessment is a valuable tool in the diagnosis and the treatment of learning problems in children with IPE and follow-up

testing may be helpful in detecting the long-term course and consequences of epilepsy. □

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