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Neuropsychological and behavioural aspects in children and adolescents with idiopathic epilepsy at diagnosis and after 12 months of treatment

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ABSTRACT

Purpose: To study neuropsychological functions in children with idiopathic epilepsy at onset of treatment and after 1 year of therapy and to identify factors associated with cognitive impairment.
Methods: 43 Subjects aged 5.2–16.9 years with newly diagnosed idiopathic epilepsy were enrolled and started treatment with valproate or carbamazepine. At admission and after 12 months, all patients underwent clinical examinations, the Child Behavioural Checklist, EEG and a neuropsychological test battery. The results of each test were correlated to demographic, clinical, electrophysiological and therapeutic variables.
Results: Except for attention, all neuropsychological functions were normal at admission and after 12 months. An improvement with time was noted for memory ($p < 0.05$) and logical-executive functions ($p < 0.01$). Attentive deficit was worse at 12 months (53.5% vs. 32.6%). Low socio-economic level and emotional and behavioural disturbances were the only factors negatively correlated to intelligence, memory and attention. Compared to valproate, carbamazepine was most commonly implicated.
Discussion: Idiopathic epilepsy can affect attention, even before starting treatment. Emotional and behavioural difficulties and a low socio-economical status are associated with cognitive impairment.

1. Introduction

Epilepsy has been found to affect the development of cognitive and learning functions through a number of factors: etiology,[1] age of onset,[2–4] seizure type, duration and severity, interictal epileptiform discharges,[5–9] drug treatment,[2,10] hereditary and psychosocial factors.[1,11,12] Epilepsy may also induce psychopathological disorders or changes in emotional and/or behavioural responses which affect learning functions.[13–16]

For these reasons, newly diagnosed idiopathic epilepsies are the best conditions to investigate the neuropsychological correlates with the disease as there is no underlying brain lesion nor mental retardation.[17] To date, a small number of reports have studied neuropsychological functions in children with new-onset epilepsy.[5,18–21] Based on the results of these studies, the degree to which cognitive impairment is present at seizure onset and the factors that may worsen intellectual abilities over time, remain to be determined. Dissimilar findings across studies tend to reflect, at least in part, a number of methodological problems such as the inclusion of non-consecutive patients with prevalent epilepsy seen in secondary and tertiary centers, the variable age ranges, the assorted epilepsy characteristics, the differing latencies between diagnosis and neuropsychological testing, and the use of different and sometimes non-comprehensive or non-specific neuropsychological instruments.[22] Therefore, when studying cognitive function, it is important to minimize these confounding factors and use a uniform, validated and specific battery of neuropsychological tests, including only previously untreated patients receiving monotherapy.[23]

With these considerations in mind, we carried out a prospective multicenter non-randomized study in a pediatric population affected by generalized or partial idiopathic epilepsy, aiming to describe the neuropsychological profile at diagnosis and after 12 months of treatment.

A second specific issue of interest was to identify prognostic factors (clinical, electrophysiological, therapeutic, social and educational) for neuropsychological outcome.

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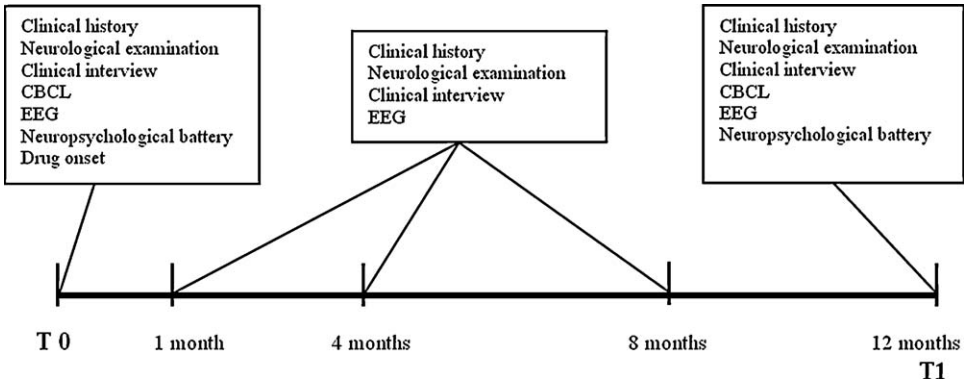

Fig. 1. Study flow-chart. CBCL, Child Behavioural Checklist.

2. Methods

Over a 2-year period, we recruited 43 children and adolescents (mean age 10.4 years; range 5.2–16.9; standard deviation, SD 3.1) with idiopathic generalized or partial epilepsy. The study population included 21 boys (48.8%; mean age 10.5 years; range 6.2–16.1; SD 2.8) and 22 girls (51.2%; mean age 10.2 years; range: 5.2–16.9; SD 3.4) consecutively referred for a first consultation to the Child Neuropsychiatry Units of the University of Insubria, Macchi Foundation Hospital, Varese, to the "Eugenio Medea" Scientific Institute, Bosisio Parini and to the Fatebenefratelli and Ophthalmic Hospital, Milano. According to the Italian Health Service organization, these institutes are tertiary referral centers receiving patients with epilepsy and offering clinical, instrumental and genetic services. In Italy, tertiary centers are health care facilities where a comprehensive diagnostic and therapeutic approach is offered to patients with epilepsy who may have access through the emergency room, from territorial pediatric facilities, or after voluntary request.

Inclusion criteria were: (a) age between 5 and 17 years, (b) normal pre-perinatal history, (c) normal psychomotor and linguistic development before the onset of epilepsy, (d) normal neurological examination, (e) seizure onset after 3 years of age. *Exclusion criteria* were: (a) severe behavioural or psychiatric disorders, (b) intelligence quotient < 70, and (c) abnormal magnetic resonance imaging (MRI) or computerized tomography (CT) findings (where available).

The diagnosis of epilepsy was made according to the 2001 proposed criteria of the International League Against Epilepsy.[24] A detailed clinical history was collected regarding pregnancy, birth, psychomotor and linguistic development, clinical characteristics of epilepsy (age at onset, type, frequency and duration), a family history of seizures, and the parents' social and educational level.

Data about the parents' educational background and occupation were collected for an analysis of the socio-economic status. Educational level was classified as: low (<8 school years), medium (8–13 school years) and high (>13 school years). The socio-economic level was calculated based on the cultural level and the current occupation of both parents. The Hollingshead Index of social position was calculated.[25] Accordingly, the socio-economic level was classified as low (Hollingshead lower-middle or lower), medium or high (Hollingshead upper-middle or upper). Data on school difficulties of the children were obtained by clinical interviews with the parents and in selected cases by telephone interviews with the teachers.

All the children included in the study underwent a neurological examination, clinical interviews and EEG recordings at study entry (T0) and then at 1, 4, and 8 months. EEG during sleep, MRI or CT was performed where clinically indicated. The neuropsychological functions were evaluated as soon as possible after diagnosis (within 1–4 weeks) and before the antiepileptic treatment was started (T0) using a standardized battery of cognitive tests. The choice of drug was decided by the caring physician according to individual clinical and electroencephalographic features. The titration was gradually performed adding a quarter of dose every five days until the maximum dosage of 25 mg/kg/die (valproate) and 20 mg/kg/die (carbamazepine) was reached. The same standardized battery of neuropsychological tests was repeated in all patients after 12 months of therapy (T1). All patients were still on monoteraphy at T1. The design of the study is summarized in Fig. 1.

The following demographic, clinical and therapeutic data were collected: epilepsy syndrome (idiopathic partial or generalized), age at seizure onset (before or after age ten), seizure type (partial, generalized or secondarily generalized), seizure frequency (daily, weekly, monthly or yearly); duration of active epilepsy ($\leq$6 months or >6 months), interictal EEG abnormalities (yes/no), type of drug (valproate or carbamazepine), behavioural–emotional aspects and family socio-cultural level.

The study was approved by the hospitals' Ethics Committees and the parents of the enrolled children gave their informed consent.

2.1. Neuropsychological assessment

The neuropsychological battery included clinical and computerized tests standardized for children and adolescents aged 5 through 17 years, to assess the following functions:

2.1.1. Intelligence

The Wechsler Intelligence Scales were used to measure the children's general intellectual level (full IQ). These scales are universally used for the evaluation of verbal IQ (5 sub-scales) and non-verbal or performance IQ (5 sub-scales).[26] We used the WPPSI scale for children aged 5–6 years and the WISC-R scale for children older than 6 years.

2.1.2. Attention skills

Evaluated by the Conners' Continuous Performance Test, CPT, which is a computerized test requiring the patient to press the space bar of the computer keyboard every time a letter (target) appears on the screen, except when the letter X (non-target) appears. Alertness/arousal, selective attention, reaction time and sustained attention are evaluated.[27] According to the manual,[28] abnormal scores (*T*-scores) are required on at least 2 sub-items in order to reveal attention difficulties. In the present study we considered nine main sub-scales (Hits, Commission, Hit Reaction Time, Hit Reaction Time ST E, Variability SEs, Attentiveness, Risk Taking, Reaction Time block change, Reaction Time ISI change) and

used more restrictive criteria, i.e. at least abnormal scores on at least 4 sub-items[27] to identify children with attention difficulties. *T*-scores are abnormal if >90, except for sub-scales Hit RT% and Risk Taking% in which *T*-scores are abnormal if <10 or >90. To minimize the number of evaluable variables, we collapsed the nine continuous variables into two dichotomic classes: normal (3 or less abnormal *T*-scores) and abnormal (4 or more abnormal *T*-scores).

2.1.3. Verbal and non-verbal memory abilities

Evaluated by the TEMA test that is composed of standardised sub-scales, enabling an assessment of verbal (5 sub-tests) and non-verbal (5 sub-tests) memory, an index of full memory and a delayed memory measure.[29] The TEMA test explores several memory functions of clinical and theoretical interest in children and adolescents. The delayed memory index is a measure of the ability to retrieve acquired information and is a sensitive indicator of combined frontal and temporal dysfunction.

2.1.4. Associative-logical functions and problem solving

Assessed by the Wisconsin Card Sorting Test, WCST, which consists of four stimulus cards and 128 response cards that depict figures of varying forms, colors and numbers of figures.[30] The patient is instructed to match each consecutive response card with one of the four stimulus cards, whichever card he or she thinks it matches. The patient is told only whether each response is right or wrong and is never told the correct sorting principle (or category). Once the patient has made a specified number of consecutive "correct" matches to the initial sorting principle, the sorting principle is changed, without warning, requiring the patient to use the examiner's feedback to develop a new sorting strategy.

The WCST was originally developed to assess abstract reasoning ability and the ability to shift cognitive strategies in response to changing environmental contingencies.[31] As such, the WCST can be considered a measure of "executive function" and requires strategic planning, organized searching, utilizing environmental feedback to shift cognitive sets, directing behaviour toward achieving a goal and modulating impulsive responding.[32] Interest in the cognitive and developmental effects of early frontal lobe injury among children has also sparked considerable interest in the use of WCST as a potential measure of executive function among school-age children.[33] Percentage values of errors, perseveration and conceptual level were used.

As indicated in the manual, these standardized tests can be repeated after 12 months without being affected by practice or retention.

2.2. Behavioural and emotional assessment

The behavioural and emotional aspects were assessed by the Italian version of the Child Behaviour Checklist (CBCL) for ages 4–18 years.[34] Achenbach's CBCL is widely employed for the assessment of adaptive behaviour and emotional problems in the developmental age. Its reliability and validity are corroborated by several studies carried out in both Western and Eastern countries,[35,36] and the psychometric properties of the Italian version have been found to be comparable to Achenbach's findings in U.S. samples.[34,37] The CBCL is a checklist to be completed by parents and includes 118 items that are scored on a 3-point Likert scale (0 = "not true; 1 = "somewhat or sometimes true"; 2 = "very true or often true") and referred to the preceding 6 months of life of their child. These items cover eight syndrome scales that, although not directly equivalent to any clinical diagnosis, have proven to be useful for screening children with behavioural and emotional problems across multiple cultures.[35,36] In our study, the Total Problems score, which was obtained by the sum of the responses to all items, has been used to identify children with behavioural and emotional disorders. Normal vs. borderline/abnormal cutoff values were used.

2.3. EEG recordings

The EEG electrodes were positioned according to the international 10–20 system. Every wake EEG recording lasted 30 min and was performed according to a standard protocol.[38] Sleep EEG recordings were started after lunch and partial sleep deprivation. The recording was continued to reach phase III and IV slow sleep. Then, the child was awakened for a 20-min baseline recording followed by hyperventilation (HP) and intermittent light stimulation (ILS). Background activity, electroclinical events and interictal discharges were evaluated.

The level of agreement regarding the interpretation of the EEG recordings by three different experienced readers working in the participating centers has been found to be satisfactory: Kappa values for presence of interictal or ictal discharges and for all the relevant features of the sleep EEG were 0.74-1.[38]

2.4. Statistical analyses

Statistical analysis was performed using the statistical package SAS/PC version 6.12 (SAS Institute Inc, Cary, NC). The Student's *t*-test for paired samples and the chi-square test were used to compare the changes in the test scores at T0 and T1. Multiple and logistic regression models were also used to assess the influence of the demographic, clinical and therapeutic variables (epilepsy syndrome, age at seizure onset, duration of active epilepsy, ictal and interictal EEG abnormalities, type of drug, behavioural–emotional aspects and family socio-cultural level) on the changes of each test score.

The study was a self-supported independent investigation.

3. Results

3.1. Clinical, behavioural and socio-economic data

The main clinical features in patients with partial and generalized epilepsy are depicted in Table 1. At diagnosis, seizures were generalized in 23 patients (53.5%): non-convulsive in 19 patients (44.2%) and convulsive in four (9.3%). Seizures were partial in eight cases (18.6%) and partial with secondary generalization in 12 (27.9%).

Before starting antiepileptic therapy, seizures occurred on a daily basis in 19 cases (44.2%), weekly in one child, and monthly or less frequently in 23 patients (53.5%). Seizures appeared while awake in 30 cases (69.7%), during sleep in seven (16.3%), and on awakening in six (14%).

After 12 months of therapy (T1), seizures were present in 10 patients (23.3%); 6 with partial epilepsy (3 on carbamazepine and 3 on valproate) and 4 with generalized epilepsy (all on valproate). None of the patients was withdrawn from medication before the neuropsychological retest at 12 months. No significant side effects were reported by patients or parents after 12 months of therapy. During EEG recording at diagnosis (T0), 22 patients (51.2%) had electroclinical paroxysms, which were generalized in 19 (44.2%), partial in two (4.6%) and secondarily generalized in one (2.3%). We recorded interictal EEG abnormalities in 35 patients (81.4%). After 12 months (T1), interictal EEG abnormalities were documented in 11 cases (25.6%). A family history of epilepsy was present in five cases (11.6%) and a family history of febrile convulsions in three (7%). The socio-economic and cultural level was high in five children (11.6%), medium in 30 (69.8%) and low in eight (18.6%).

At T0, behavioural and emotional problems were present in 14 cases (32.6%), as stated by parents through the CBCL. Behavioural

Table 1
General characteristics of the sample by epilepsy syndrome.

	Generalized epilepsy	Partial epilepsy	Total
N (%)	23 (53.5)	20 (46.5)	43 (100)
N (%) absence epilepsy	19 (44.2)	–	19 (44.2)
N (%) frontal epilepsy	–	5 (11.6)	5 (11.6)
N (%) rolandic epilepsy	–	10 (23.3)	10 (23.3)
N (%) occipital epilepsy	–	5 (11.6)	5 (11.6)
N (%) T–C, myoclonic epilepsy	4 (9.3)	–	4 (9.3)
Mean age at onset of seizures (SD)	9.9 years (3.4)	9.5 years (3.2)	9.7 years (3.3)
N (%) with onset before age 10	13 (30.2)	12 (27.9)	25 (58.1)
N (%) with onset after age 10	10 (23.3)	8 (18.6)	18 (41.9)
Mean age at treatment start (SD)	10.7 years (3.0)	10 years (3.2)	10.4 (3.1)
N (%) with AE within 6 months[a]	17[b] (39.5)	14 (32.6)	31 (72.1)
N (%) with AE after 6 months[a]	6 (13.95)	6 (13.95)	12 (27.9)
N (%) with valproate	23 (53.5)	12 (27.9)	35 (81.4)
N (%) with carbamazepine	–	8 (18.6)	8 (18.6)
N (%) with seizure remissions at T1	19 (44.2)	14 (32.5)	33 (76.7)

AE, antiepileptic drugs; SD, standard deviation; T–C, tonic–clonic seizures.
[a] From onset of seizures.
[b] Within 2 months in 14 cases, all with absence epilepsy.

and emotional problems at T1 were present in 15 patients (34.9%). Overall, no significant changes were detected in 36 patients during follow-up, although there was an improvement in three patients and worsening in four.

3.2. Neuropsychological profile

The neuropsychological profile of the study population at T0 and T1 is summarized in Table 2. The results were compared to the normative values at T0 and T1 and the scores were considered abnormal when they were 2 standard deviation (SD) below normative media values.

One child showed clinically relevant difficulties (scores < 2 SD) in verbal memory and 11 (25.6%) had borderline results (i.e. between 1 and 2 SD) in executive functions. At the same time, 14 patients (32.6%) showed a specific attention disorder at CPT (at least 4 abnormal scores), with long reaction times and a cautious procedural style. School difficulties were reported by the parents and teachers in five patients (11.6%) at the onset of epilepsy. One child required special educational assistance.

After 12 months (T1) all the memory and executive function parameters showed a marked improvement. The patient with memory difficulties at T0 performed within the normal range at T1 and only four of the 11 patients with mild difficulties in the executive functions at T0 were unchanged at T1. In contrast, 23 patients (53.5%) at T1 (compared to 14 at T0) had clinically specific attention deficits on CPT (at least 4 abnormal scores). Nevertheless the increase of patients with specific attention deficits from T0 to T1 was not statistical significant ($p = 0.66$). Most children (85.7%) presented long reaction times and a cautious procedural style.

Table 2
Neuropsychological profile at T0 and T1.

Test	Mean ± SD at T0	Mean ± SD at T1	*p*
WISC-R full IQ	104.37 ± 15.1	103.39 ± 15.6	ns
WISC-R verbal IQ	105.09 ± 14.6	103.37 ± 16.1	ns
WISC-R performance IQ	102.86 ± 17.3	103.06 ± 15.1	ns
TEMA full IQ	98.58 ± 19.8	105.39 ± 12.2	0.015
TEMA verbal IQ	99.95 ± 15.0	103.46 ± 11.3	0.053
TEMA non-verbal IQ	101.65 ± 15.2	106.69 ± 15.0	0.011
TEMA differed IQ	99.12 ± 8.6	103.67 ± 9.3	0.013
WCST % errors	96.10 ± 16.2	108.65 ± 17.2	0.000
WCST % perseverations	100.78 ± 15.3	110.89 ± 16.1	0.001
WCST % conceptual level	96.55 ± 16.8	107.81 ± 15.9	0.000
Test	*N* (%) at T0	*N* (%) at T1	
CPT abnormal	14 (36.2)	23 (53.5)	ns

For a description of the tests, see text; SD, standard deviation.

3.3. Relationship between the neuropsychological profile and epilepsy behavioural, socio-cultural and economic features

Multiple and logistic regression analysis failed to document significant correlations between neuropsychological profile (IQ, attention, memory and executive functions) and most of demographic, clinical, electrophysiological and therapeutic variables. Only behavioural–emotional features and socio-cultural level were strongly correlated to the neuropsychological data ($p < 0.05$). Their correlation with the neuropsychological scores was assessed separately at T0 (Table 3) and T1 (Table 4). In contrast, treatment was associated with significant changes in some intellectual scores during the follow-up (Table 5). As shown in Table 3, the presence of behavioural and emotional difficulties at the onset of epilepsy was associated with intellectual and memory problems; although still within the limits of normality, these patients had a lower full and performance IQ, and lower non-verbal and differed memory abilities. Moreover, patients with an abnormal CBCL profile most

Table 3
Neuropsychological profile by socio-economic status and behavioural problems at T0. Multiple regression and *logistic regression analysis.

	Low social level	Medium social level	High social level	TOT
No. of patients	8	30	5	43
Test	Mean ± SD	Mean ± SD	Mean ± SD	*p*
WISC-R (coding)	7 ± 4.2	10.8 ± 3.6	11.6 ± 1.7	0.007
	Abnormal CBCL	Normal CBCL		TOT
No. of patients	14	29		43
Test	Mean ± SD	Mean ± SD		*p*
WISC-R full IQ	98.8 ± 11.1	108 ± 15.5		0.021
WISC-R Performance IQ	94.6 ± 9.3	106.8 ± 19.0		0.029
WISC-R (comprehension)	8.38 ± 1.8	10.6 ± 2.3		0.033
WISC-R (images completion)	8.5 ± 1.5	10.6 ± 3.4		0.018
TEMA non-verbal IQ	95 ± 13.6	104.9 ± 15.1		0.044
TEMA differed IQ	94.9 ± 9.6	101.2 ± 7.4		0.042
Test	*N* (%)	*N* (%)		*p*
Abnormal CPT	8/14 (57.1)	6/29 (20.7)		0.021*

For a description of the tests, see text; only tests with significant results are reported ($p < 0.05$); SD = standard deviation; variables included in the model: epilepsy syndrome, age at seizure onset, disease duration, ictal EEG abnormalities, CBCL score at T0 and family socio-cultural level.

Table 4
Neuropsychological profile by socio-economic status and behavioural problems at T1. Multiple regression and *logistic regression analysis.

	Low social level	Medium social level	High social level	*p*
No. of patients	8	30	5	43
Test	Mean ± SD	Mean ± SD	Mean ± SD	*p*
WISC-R full IQ	97.0 ± 17.5	103.7 ± 14.6	114.8 ± 9.4	0.013
WISC-R performance IQ	96.1 ± 12.6	103.6 ± 15.6	113.4 ± 10.3	0.007
WISC-R (history sequences)	10.2 ± 2.9	10.8 ± 3.2	11.6 ± 2.2	0.026
WISC-R (coding)	8.1 ± 3.7	9.5 ± 3.0	11.6 ± 2.2	0.026
TEMA full IQ	99.3 ± 13.4	105.5 ± 10.7	113.6 ± 17.5	0.011
	Abnormal CBCL	Normal CBCL		TOT
No of patients	15	28		43
Test	Mean ± SD	Mean ± SD		*p*
WISC-R full IQ	95.1 ± 15.2	107.8 ± 14.1		0.003
WISC-R performance IQ	92.9 ± 13.0	108.5 ± 13.4		0.000
WISC –R (images completion)	9.5 ± 2.5	11.3 ± 2.6		0.034
WISC-R (histories sequences)	9.7 ± 3.7	11.8 ± 2.4		0.017
WISC-R (geometric figures)	9.5 ± 2.8	12.3 ± 2.8		0.003
WISC-R (puzzles)	8.3 ± 2.6	10.5 ± 2.4		0.092
TEMA full IQ	97.7 ± 11.3	109.5 ± 10.7		0.000
TEMA non-verbal IQ	98.5 ± 12.6	111.1 ± 14.5		0.007
TEMA verbal IQ	96.5 ± 12.7	107.2 ± 8.7		0.002
Test	*N* (%)	*N* (%)		*p*
Abnormal CPT	14/15 (93.3)	9/28 (32.1)		0.011*

For a description of the tests, see text; only tests with significant results are reported ($p < 0.05$); SD = standard deviation; variables included in the model: epilepsy syndrome, age at seizure onset, disease duration, interictal EEG abnormalities, drug type, CBCL score at T0 and T1 and family socio-cultural level.

commonly had an associated specific attention deficit disorder documented by the CPT test.

The influence of these two variables became more relevant after 12 months (T1) (Table 4). The existence of behavioural and emotional difficulties and the presence of a low socio-cultural and economic level were strongly associated with impairment of the IQ and memory functions. In addition, 93.3% of patients with emotional and behavioural impairment on CBCL presented an attention disorder on CPT.

Drug treatment with carbamazepine, but not with valproate, was found to mildly affect the IQ (Table 5).

4. Discussion

The principal aim of this work was to study intellectual level, memory, attention and executive functions in children and adolescents with newly diagnosed epilepsy (before starting antiepileptic drugs) and after 1 year of therapy. A second aim was to identify which among neurological, behavioural, electrophysiological, therapeutic, social and educational variables were relevant for neuropsychological outcome. As our intent was to assess any possible changes of the neuropsychological profile in a cohort of patients with epilepsy, we decided not to investigate healthy individuals or other control populations. To deal with a homogeneous inception cohort, we enrolled only patients who were consecutively referred to our clinics with newly diagnosed idiopathic generalized and partial epilepsies. To better evaluate the correlation of the patients' neuropsychological profile with the disease itself, we excluded symptomatic epilepsies, prevalent cases and those requiring polytherapy, all factors associated with cognitive impairment.[8,39,40]

We found normal intellectual abilities in our patients. However, at diagnosis, 11% of them had mild educational problems and 25% had borderline logical and executive abilities. In addition, about one-third of them presented with specific attention disorders and psychological disturbances.

Our data are in line with other reports, which showed cognitive and behavioural difficulties and academic underachievement at the onset of idiopathic epilepsy.[41–43] The nature and timing of cognitive and behavioural impairment are probably a consequence of multiple factors, such as the age of epilepsy onset and the persistence of interictal cortical paroxysms during sleep.[9] Some studies documented cognitive impairment in children and adolescents with early epilepsy,[18,20,41] suggesting the influence of an early adverse impact of the disease on cognition. In addition, in keeping with us other authors[14,41,44] reported that (early) neuropsychological and behavioural deficits were correlated to the psychosocial and familial context.

Almost one-third of our patients had attention deficits on CPT and behavioural and emotional problems on CBCL at diagnosis. Behavioural difficulties have been described in about one-fourth of patients with epilepsy.[45–47] Most of our patients with attention deficit presented behavioural and emotional problems, long reaction times and a cautious procedural style. Pre-existing

Table 5
Drug therapy and change of intellectual level from T0 to T1.

	T0		T1		T0–T1		*p*
	VPA	CBZ	VPA	CBZ	VPA	CBZ	
WISC-R full IQ	103.2 ± 15.1	109.2 ± 14.9	104.2 ± 14.1	100.0 ± 21.6	+0.91	−9.25	0.002
WISC-R performance IQ	100.4 ± 16.5	113.7 ± 17.6	102.6 ± 13.8	105.1 ± 21.1	+2.2	−8.63	0.012
WISC-R (images completion)	9.6 ± 3.0	11.7 ± 3.1	10.8 ± 2.7	10.0 ± 2.9	+1.14	−1.7	0.009

For a description of the tests, see text; only tests with significant results are reported ($p < 0.05$); VPA = valproate; CBZ = carbamazepine; variables included in the model: epilepsy syndrome, age at seizure onset, disease duration, ictal EEG abnormalities, drug type, CBCL score at T0 and family socio-cultural level.

behavioural difficulties can be also considered, as evidenced by Oostrom et al.[41] Conversely, attention difficulties could be explained by marked ictal cortical activity during sleep, as shown by Sanchez-Carpintero and Neville.[48] This hypothesis could not be verified in our sample because not all our patients underwent EEG recording during sleep.

After 12 months of treatment, the intellectual level in our sample was as expected virtually unchanged, but specific neuropsychological functions, including memory and logical and executive abilities, showed a significant improvement.

Verbal, non-verbal and also deferred memory abilities appeared to be improved after 12 months of treatment, to the same extent in patients treated with valproic acid and carbamazepine. Bittencourt et al.[49] showed a similar improvement, especially in patients treated with carbamazepine, while Schouten et al.[50] considered the impact of treatment on memory functions in a pediatric population to be non-influential. In our cases, a marked favorable impact of treatment was also registered on executive functions. There are no studies on the effects of treatment on executive functions in children with epilepsy.

At the end of follow-up, a non-significant increase was observed in the number of cases with specific attention disorders and the proportion of children with behavioural disturbances was moderately increased. At T1 attention deficits and behavioural disturbances were more pronounced than at T0.

Chevalier et al.[51] suggested that children with epilepsy may be more impulsive because of a less efficient control of inhibition due to frontal lobe dysfunction. In our subjects we can reasonably exclude this factor as all children improved on WCST and performed quite well on the WISC-R "Similarities" sub-test which taps the logical and inferential processes of the frontal lobes. Moreover, unlike Holtmann et al.,[52] we did not find hyperactive-impulsive (ADHD-like) conduct but merely slowness and easy fatigue, which are more easily correlated with the typical anxiety-depression profile of these children, as reported in a previous work.[47]

Remarkably, at T0 and even at the end of follow-up, the only variables that could explain the evolution of the neuropsychological profile were the behavioural and emotional assets on CBCL, the socio-cultural level and, to a lesser extent, the type of antiepileptic drug.

The impact of behavioural difficulties was extended to the IQ, with special reference to performance abilities, all memory components and attention.

Sturniolo and Galletti[53] correlated the emotional difficulties in pediatric epilepsy to low school achievements, confirming the hypothesis of a direct influence of the emotional asset on neuropsychological outcome. The socio-cultural grading level could also partially explain the gradient seen for the intellectual abilities and global memory functions of our sample. This finding could be correlated to a differing environmental motivation and encouragement toward school and learning. This element could be considered a protective factor toward neuropsychological development in a particularly stressful condition like epilepsy. Our findings agree with recent studies, which documented a strong correlation between psychosocial variables, maladaptive parenting in the earliest months after diagnosis, and behavioural-cognitive difficulties in epileptic children.[14,16,19,41,54]

Unexpectedly, the patients in our sample who were taking carbamazepine had a mild deterioration of the intelligence quotient. Although this finding can be questioned in light of the small sample size (8 patients), a possible explanation could be the preferential use of this drug in partial epilepsy, which may be associated per se to cognitive impairment. This finding is still controversial. Gillham et al.[55] and Dodrill and Wilensky[56] confirmed the negative impact of carbamazepine on cognitive functions.

The study has four major limitations. First, we did not include normal controls for comparison. The lack of a healthy control group would have been valuable not only in identifying subtle cognitive problems at onset but also in controlling for test–retest practice effects on the cognitive measures. However, as well as our main research focus was to outline the cognitive profile of patients with newly diagnosed epilepsy and detect any possible changes after the start of drug treatment. Second, the study population is represented by patients seen in tertiary referral centers. This is a rather skewed sample, which is unlikely to represent the general population of children and adolescents with epilepsy. However, selection bias is perhaps minimized here because included were only patients with previously untreated epilepsy who, at least in Italy have the same opportunity to be seen in primary, secondary, or tertiary institutions. Third, the small sample size prevents us from drawing firm conclusions, as many differences perhaps failed to attain statistical significance. This may be even more important when collapsing continuous variables (e.g. CPT-scores) into dichotomous variables (normal vs. abnormal), which further reduces the sensitivity, and consequently the power, of the measure. However, often the clinical significance of a score is better predicted by a categorical than continuous variable. Fourth, the use of a high number of tests increases the likelihood of interpreting chance findings. However, a large test battery was required here in order to provide a fairly complete assessment of the neuropsychological profile of our study population. In this context, the study of a larger population would have been very expensive and time-consuming.

In conclusion, behavioural disturbance and psychosocial context, rather than epilepsy, were correlated to cognitive difficulties in our population. The pre-existing psychological features, behavioural history and learning abilities of children, together with the parents' adaptation to epilepsy and their ability to continue habitual parenting without excessive anxiety, are probably relevant risk factors for the onset of behavioural and cognitive disturbances at baseline and during the course of the disease. It is crucial to consider these aspects as early as possible in taking a integrated therapeutic approach.

Conflict of interest

None of the authors has any conflict of interest.

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All the authors confirm that they have read the Journal's position on the issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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