Neurobehavioral consequences of continuous spike and waves during slow sleep (CSWS) in a pediatric population: A pattern of developmental hindrance

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ABSTRACT

Introduction: Continuous spike and waves during slow sleep (CSWS) is a typical EEG pattern defined as diffuse, bilateral and recently also unilateral or focal localization spike–wave occurring in slow sleep or non-rapid eye movement sleep. Literature results so far point out a progressive deterioration and decline of intellectual functioning in CSWS patients, i.e. a loss of previously normally acquired skills, as well as persistent neurobehavioral disorders, beyond seizure and EEG control. The objective of this study was to shed light on the neurobehavioral impact of CSWS and to identify the potential clinical risk factors for development.
Methods: We conducted a retrospective study involving a series of 16 CSWS idiopathic patients age 3–16 years, considering the entire duration of epilepsy from the onset to the outcome, i.e. remission of CSWS pattern. All patients were longitudinally assessed taking into account clinical (sex, age at onset, lateralization and localization of epileptiform abnormalities, spike wave index, number of antiepileptic drugs) and behavioral features. Intelligent Quotient (IQ) was measured in the whole sample, whereas visuo-spatial attention, visuo-motor skills, short term memory and academic abilities (reading and writing) were tested in 6 out of 16 patients.
Results: Our results showed that the most vulnerable from an intellectual point of view were those children who had an early-onset of CSWS whereas those with later onset resulted less affected (p = 0.004). Neuropsychological outcome was better than the behavioral one and the lexical-semantic route in reading and writing resulted more severely affected compared to the phonological route.
Conclusions: Cognitive deterioration is one but not the only consequence of CSWS. Especially with respect to verbal skills, CSWS is responsible of a pattern of consequences in terms of developmental hindrance, including slowing of development and stagnation, whereas deterioration is rare. Behavioral and academic problems tend to persist beyond epilepsy resolution.

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1. Introduction

Epilepsy is a symptom of brain dysfunction with ictal and interictal phenomenon that can be demonstrated on electroencephalographic (EEG) recordings. Higher order brain functions such as intelligence, memory, and behavior are also involved and often affected [1,2]. Thus, neurobehavioral assessment plays a fundamental role in the diagnosis, treatment and prognosis of epilepsy. The nature, timing, and course of neurobehavioral impairment in epilepsy are of substantial concern in developmental age and may be more devastating in pediatric population rather than in adults [3].

Continuous spike and waves during slow sleep (CSWS) is a typical EEG pattern recognized as diffuse, bilateral and recently also unilateral or focal localization spike–wave occurring in slow sleep or non-rapid eye movement (NREM) sleep and persisting on three or more recordings over a period of at least 1 month [4–7]. It can be recorded in childhood epileptic encephalopathies such as Atypical Benign Epilepsy with Centro-temporal Spikes (BECTS), acquired opercular syndrome, Landau–Kleffner Syndrome (LKS) [8], and Encephalopathy with Electrical Status Epilepticus during Sleep (ESES) [9].

Patients with CSWS have been reported to have normal neuropsychological and behavioral development before its onset in 67% to 74% of cases [5,10]. Sometimes behavioral problems are the first to appear preceding the onset of the epilepsy [11]. Later, most of the literature shows that children can present a variable deterioration in cognitive, language, behavioral, and/or motor aspects [12,13]. In the study of Caraballo et al. [14], intellectual deterioration was recognized in 76

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out of 117 patients (64.1%) with both symptomatic and idiopathic causes. A similar result was revealed in the study of Pera et al. [15], where cognitive performance and especially verbal scores worsened during CSWS in virtually all lesional and non-lesional patients. 44% of children demonstrated permanent cognitive impairment, even if the cognitive outcome seemed variable. Besides cognitive disorders like language deterioration, nonverbal agnosia, memory deficit, impaired temporo-spatial orientation, and nonverbal communication deficit, behavioral disturbances have been observed, such as aggressive or compulsive behavior, poor interpersonal contact, emotional liability, disinhibition, and even a psychotic-like condition, attention deficit hyperactivity disorder [16–18].

Taken together, literature pointed out a progressive deterioration and decline of cognitive functioning in CSWS patients, i.e. a loss of previously normally acquired skills, as well as persistent neurobehavioral disorders, beyond seizure and EEG control [19]. The heterogeneous results also seem to depend on the etiology [20]. This study aimed to evaluate the impact of CSWS on behavior and neuropsychological functioning in a population of only idiopathic cases (without structural etiology) and considering the entire duration of epilepsy, from the onset to the outcome.

Were did not include patients with CNS structural lesion in order to obtain neuropsychological data free from bias related to a pre-existing cognitive disability.

The authors focused on the results to shed light on the neurobehavioural impact of CSWS and tried to identify the potential clinical risk factors for cognitive evolution considering clinical variables associated with CSWS.

2. Methods

2.1. Patient selection

This is a retrospective study involving 16 children aged between 2.4 and 9 years (mean 6.25), 8 males and 8 females, with established diagnosis of CSWS in accordance with Commission on Classification and Terminology of the ILAE (1989) [21]. All patients were regularly followed-up at Fondazione Istituto Neurologico Nazionale C. Mondino (Pavia, Italy) between years 2007 and 2014. Informed consent was obtained from the children's parents. The ethics board of the said institution approved the study protocol.

Patients with Atypical BECTS, ESES and LKS who met the inclusion criteria were included in the study.

Inclusion criteria were as follows: (1) seizures with focal or apparently generalized onset (atypical absences, myoclonic, atonic or generalized seizures, focal motor, complex-partial); (2) reported global or selective cognitive or language and/or behavioral disturbances connected to the CSWS period; (3) motor impairments (such as ataxia, dyspraxia, dystonia or unilateral motor deficits) related to the CSWS period; (4) typical EEG findings characterized by an activation of spike wave discharges during the non-REM sleep; (5) overnight EEGs, clinical and neuropsychological evaluations available at least at CSWS onset and at the end of the follow-up and 6) absence of structural lesions on brain imaging.

According to the International League Against Epilepsy (ILAE) criteria that do not specify a minimum percentage value for diagnosing ESES [21] a cut-off spike wave index (SWI) was not considered, even if our sample is represented by patients with >50 SWI.

2.2. Follow-up evaluations

Baseline (T0) and last follow-up (remission of CSWS pattern, T1) data on clinical variables and behavioral comorbidities along with neuropsychological examination were collected.

At T0, for each patient included in the study information such as sex, seizure age at onset, seizures semiology, prenatal/birth/postnatal history, lateralization and localization of EEG discharges, SWI, comorbidities, and number of antiepileptic drugs (AEDs) were collected. At T1, clinical variables analyzed in relation to neurobehavioral evolution were sex, age at onset and duration of CSWS, localization and laterality of electrographic discharge (interictal and ictal focus), SWI, type and number of AEDs. All patients underwent awake and prolonged sleep EEG recording applying the 10–20 international system and each recording session lasted for a minimum of 8 h, with or without hyperventilation, and intermittent photic stimulation.

2.3. Behavioral assessment

Behavioral problems as comorbidities were evaluated both through anamnestic investigations, parents' interview and psychological evaluations through standardized tests (Youth Self-Report and/or Child Behavior Check List [22] to identify the presence of internalizing problems (anxiety, depression, withdrawn-depression and somatic complaints) and externalizing problems (rule-breaking and aggressive behavior).

2.4. Neuropsychological assessment

All children were assessed through neuropsychological standardized tests chosen depending on the age of the patient, which were administered at T0 and T1. The cognitive functioning was expressed as Total Intelligence Quotient (TIQ), Verbal Intelligence Quotient (VIQ) and Performance Intelligence Quotient (PIQ) and measured with WIPPSI III [23] or WISC-III scale [24].

The population was divided into 3 groups on the basis of the age of onset: 1) early onset: before the age of 6 years (6 patients), 2) mild-onset: at the age of 6–7 years (5 patients), and 3) late onset: after the age of 8 years (5 patients).

In case of IQ score decrease at T1, raw score (rs) and corresponding standard score (ss) for each subtest were considered. The rs corresponds to the total number of correct responses, whereas ss is the signed number of standard deviations by which an observation or data is above the average. 5 possible combinations were considered: an increase of rs corresponding to stable ss, or a decreased ss, or an increased ss; moreover, decrease of rs corresponding either to decreased ss or to stable ss. Thus, the decrease of IQ could have been determined either by a stagnation or by a decrease of ss, to a stagnation of rs, to a decrease of rs.

Moreover, the assessment included neuropsychological domain-specific tests: visuo-spatial attention, visuomotor skills, short-term memory and academic skills. For a clearer representation of the data, we assigned each set of functions to a domain: visuo-spatial attention (domain 1), visuomotor skills (domain 2), short-term memory (domain 3), and academic skills (domain 4).

2.4.1. Domain 1: visuo-spatial attention

The visuo-spatial test [25] consists in searching visual symbols (bells) as fast as possible. Children were given four sheets and the time limit was two minutes for each sheet. Rapidity score resulted from the number of items identified within 30 s while accuracy score was based on the total number of visual symbols identified within 8 min. Both scores were expressed in terms of percentile as normal if superior to 25° percentile, borderline if between 10 and 25°, and pathological if inferior to 10° percentile.

2.4.2. Domain 2: visuomotor skills

The visuomotor integration (VMI) developmental test [26] consisted in drawings of geometric forms arranged in order of increasing difficulty that the child was asked to copy. The final score was the sum of the number of correct reproductions. Performance was considered normal if superior to 25° percentile, borderline if fell between 10 and 25°, and pathological when inferior to 10° percentile.

2.4.3. Domain 3: short-term memory

Short-term memory was tested through the forward word span, digit span and visual span tasks [27]. A series of words, digits and geometric figures were read or presented to the participant, who was required to repeat them in the precise order. The score was the number of the exact responses. The final score was transformed to a z-score (x-Mean/Standard Deviation) as compared to Italian norms. Scores with z-scores > -0.99 were considered typical, those with scores ranging between -2 and -1 as mildly impaired and those with scores < -2 as severely impaired.

2.4.4. Domain 4: academic skills

Academic skills, i.e. reading and writing, were assessed through lists of words and non-words [28]. The subject was asked to read aloud and four lists of words and three lists of non-words as fast as possible. Performance was evaluated in terms of both accuracy (number of errors) and speed (number of syllables per second).

In the writing test [28], one list of words and one list of non-words were dictated. Accuracy (number of errors) was considered and the examiner qualitatively evaluated the graphomotor skills in executing the graphemes.

The final score was transformed in a z-score (x-Mean/Standard Deviation) as compared to Italian norms. Scores with z-scores > -0.99 were considered typical, those with scores ranging between -2 and -1 as mildly impaired and those with scores < -2 as severely impaired.

2.5. Statistical analyses

Statistical analysis was performed using SPSS statistical software version 19.0 for Windows (SPSS Inc., Chicago, IL, USA) [29]. Nonparametric data were assessed using the Mann–Whitney U-test and expressed as medians and ranges. Categorical variables were described as absolute numbers and percentage.

Linear regression was then used to identify potential risk factors for cognitive deterioration in the whole sample. For all regression analyses, the cognitive domain served as the dependent variable and the predictors (i.e. sex, seizure semiology at T0, lateralization and localization of EEG discharges, SWI, total AEDs, comorbilities) were entered into the model simultaneously.

The chi-square or Fisher exact test was used to compare T0 and T1 total IQ, verbal IQ and performance IQ. Secondary analyses were conducted to determine if CSWS age of onset could explain cognitive impairments. Cognitive performance across domains was compared between 3 subgroup divided into early onset, mild onset, late onset using ANCOVA. A p-value of <0.05 was considered statistically significant.

3. Results

The series comprised of 16 patients (8 males and 8 females) with newly diagnosed idiopathic/non-lesional CSWS and had regular follow-up since the diagnosis (mean follow-up 7.6 years, range 3–16 years). All patients had normal MRI, negative family history of epilepsy and unremarkable pre-/peri-/postnatal insult or infection. Sample characteristics are reported in Table 1.

The mean age at epilepsy onset was 4.6 years (range 0.4 to 7.6 years) and the initial diagnosis was BECTS for all the patients. Later on, based on ILAE syndromic classification, 6 patients (37.5%) were classified as atypical BECTS, 2 (12.5%) were LKS and 8 patients (50%) were classified as ESES syndrome. The disease duration before the diagnosis of CSWS based on nocturnal EEG registration was 6.25 years (range 2.4–8.4 years) and the average duration of CSWS were 47 months (range 20–87 months).

3.1. Clinical data

Applying the linear regression, there was no correlation between T1 IQ or behavioral evolution, and T0 clinical variable such as sex, seizure semiology, lateralization and localization of EEG discharges, SWI, comorbidities and the AEDs.

3.1.1. Seizure and EEG

At T0, all patients except one had clinical seizures (94%). The most common seizure types were focal motor seizures in 10 patients (62.5%) followed by generalized tonic–clonic in 2 (12.5%). The last seizure types were atonic (1 patient), tonic (1 patient) and myoclonic (1 patient) epilepsy.

The background EEG activity during the awake state was normal in 37% (6/16 patients), and moderately abnormal in 56.2% (9/16). Interictal EEG during awake state showed presence of epileptiform discharges in all patients with unifocal discharges in 37.5% (6 patients) and multifocal discharges in 62.5% (10/16 patients). Epileptiform activities were seen over temporal, vertex and frontal regions in descending order of frequency. The majority of patients had epileptiform activities in one hemisphere, which was the same for both the right (6 patients) and left (6 patients) side, then bilateral abnormalities (4 patients). At T0 nocturnal sleep EEGs showed 50% SWI during non-REM sleep in 2 patients (12.5%), 50–80% SWI in 5 patients (31%) and 80–100% SWI in 9 patients (56.5%), in all patients T1 EEG was normal.

3.1.2. Treatment

The majority of the patients were on polytherapy (10 patients) at T0. Combinations were Valproic Acid (VPA) + Ethusuximide (ESM) in 4 patients; VPA + ESM + Clobazam (CLB) in 3 patients; VPA + Levetiracetam (LEV) in 2 patients; and VPA + Acetazolamide (ACZ) in 1 patient. The remaining 6 patients were on monotherapy with VPA (4 patients), ESM (1 patient), Carbamazepine (CBZ, 1 patient). Second line treatment [30] was mainly the discontinuation of CBZ and then addition of CLB in 5 patients. Sulthiamine was attempted in 3 patients during the follow-up and the other 8 patients were treated with corticosteroids [31].

The introduction of CLB permitted the disappearance CSWS in a mean of 7 months (5–9) in 4 patients and it failed in 1 patient; add-on therapy with Sulthiamine permitted the disappearance of ESES in 2 patients after 13 and 17 months and it failed in 1 patient. Corticosteroids permitted the resolution of CSWS in all patients treated after a mean of 12 months (6–19), 1 patient showed the reappearance of CSWS EEG pattern after the discontinuation of steroids. The other AEDs alone or in polytherapies did not permit the resolution of CSWS pattern.

3.1.3. Behavioral assessment

On initial evaluation, comorbidities present were speech delay in 7 (44%), externalizing/behavioral problems in 3 (25%), emotional and social problems in 3 (19%), hyperactivity in 4 (25%) and anxiety in 1 (6.25%).

At the end of the follow-up with the remission of ESES pattern on EEG, speech delay was resolved, but the externalizing problems worsened from 25% to 33% of the patients, while emotional and social problems, hyperactivity and anxiety remained unchanged. The behavioral worsening was highlighted in particular in 3 patients (pts1, 9 and 16), whose neuropsychological profile improved in 2 patients whereas only 1 patient presented an important drop in VIQ (PTS 16: from 72 to 47 points).

3.1.4. Neuropsychological data

IQ measured by Wechsler Intelligence Scales was available in all patients at T0 and T1. At T0, mean full scale IQ (TIQ) was 71.76 (34 to 106) that indicate a borderline intelligence level. There was no statistically significant reduction of TIQ values at T1 with mean IQ score of 76.25 (32 to 106) (Fig. 1). Verbal IQ (VIQ) decreased from CSWS onset to follow-up with mean value of respectively 71.84 (40 to 104) and

Table 1

Clinical characteristics of the CSWS patients at baseline (T0) and at the CSWS remission (T1). CSWS Continuous Spike and Wave discharges during Sleep; emot social probl, emotional social problems; SWI, spike and wave index; ESES, Electrical Status Epilepticus during Sleep; BECTS, Benign Epilepsy with Centro-Temporal Spikes; LKS, Landau–Kleffner Syndrome. CSWS therapy refers to AEDSs treatments received by the patients during the period of CSWS. ESM ethusuximide; CLB, clobazam; VPA, valproic acid, STH, sulthiame; HC hydrocortisone; LEV, levetiracetam. TIQ, total Intelligence Quotient; VIQ, verbal Intelligence Quotient; PIQ, performance Intelligence Quotient.

| Patient	CSWS onset (year)	Duration of Follow-up (year)	Sex	T0 Comorbilities	T1 Comorbilities	T0 Seizures	T0 EEG discharge	T0 SWI	Diagnosis	CSWS Therapy	T0 Intelligence quotient	T1 Intelligence quotient
#1	5	6	M	Delayed speech	Behavioral problems	Motor focal	Temporal left	80	Atypical BECTS	HC + VPA + ETS	TIQ 76 VIQ 78 PIQ 79	TIQ 101 VIQ 112 PIQ 113
#2	6,6	3	M	Delayed speech Emot social probl	Emotional social problems	Atonic	Temporal right	50	LKS	HC + CLB + VPA	TIQ84 VIQ75 PIQ96	TIQ82 VIQ72 PIQ93
#3	5,5	6	M	Delayed speech Hyperactivity	Hyperactivity	Tonic	Temporal left	80	LKS	HC + LEV + ETS	TIQ 79 VIQ 74 PIQ 90	TIQ 94 VIQ 85 PIQ 104
#4	8	10	F	Delayed speech Behavioral problems	Behavioral problems	Myoclonic	Frontal bilateral	70	ESES	STH + VPA + CLB	TIQ74 VIQ77 PIQ77	TIQ64 VIQ65 PIQ72
#5	8,08	4	F	Anxiety	Anxiety	Motor focal	Frontal bilateral	75	Atypical BECTS	HC + VPA	TIQ68 VIQ59 PIQ85	TIQ81 VIQ67 PIQ100
#6	6,3	5	M	Emotional–social problems	Emotional–social problems	Motor focal	Temporal right	80	Atypical BECTS	HC + VPA	TIQ 75 VIQ 71 PIQ 84	TIQ70 VIQ63 PIQ85
#7	2,4	6	F	No	No	Tonic–clonic	Central bilateral	50	ESES	ETS + CLB	TIQ 88 VIQ 86 PIQ 92	TIQ 67 VIQ 80 PIQ 62
#8	4,11	8	M	Delayed speech Hyperactivity	Hyperactivity	Motor focal	Central left	90	ESES	VPA + CLB	TIQ 87 VIQ 74 PIQ 103	TIQ 91 VIQ 79 PIQ 103
#9	4,5	9	F	No	Behavioral problems	Motor focal	Temporal left	80	ESES	STH + ETS	TIQ 99 VIQ 84 PIQ 116	TIQI106 VIQ 90 PIQ 120
#10	4,5	12	F	Delayed speech	No	Tonic–clonic	Temporal left	80	ESES	ETS + CLB	TIQ 59 VIQ 56 PIQ 72	TIQ 80 VIQ 65 PIQ 100
#11	6,25	16	F	Delayed speech Behavioral problems	Behavioral problems	Motor focal	Frontal right	80	ESES	VPA + CLB	TIQ 101 VIQ93 PIQ 103	TIQ 94 VIQ 82 PIQ 107
#12	6,4	9	F	No	No	No	Central right	70	ESES	HC + VPA + ETS	TIQ 63 VIQ 52 PIQ 52	TIQ 53 VIQ62 PIQ61
#13	6,5	12	F	Behavioral problems Hyperactivity	Behavioral problems Hyperactivity	Motor focal	Central bilateral	75	ESES	STH + CLB	TIQ93 VIQ81 PIQ107	TIQ 91 VIQ80 PIQ102
#14	8,4	8	M	Hyperactivity	Hyperactivity	Motor focal	Temporal left	80	Atypical BECTS	VPA + HC	TIQ34 VIQ40 PIQ42	TIQ64 VIQ54 PIQ56
#15	11	5	M	Emotional–social problems	Emotional–social problems	Motor focal	Temporal right	70	Atypical BECTS	STH + VPA + LEV	TIQ35 VIQ43 PIQ42	TIQ32 VIQ43 PIQ36
#16	6,25	5	M	No	Behavioral problems	Motor focal	Central right	80	Atypical BECTS	HC + ETS + VPA	TIQ69 VIQ72 PIQ72	TIQ60 VIQ47 PIQ83
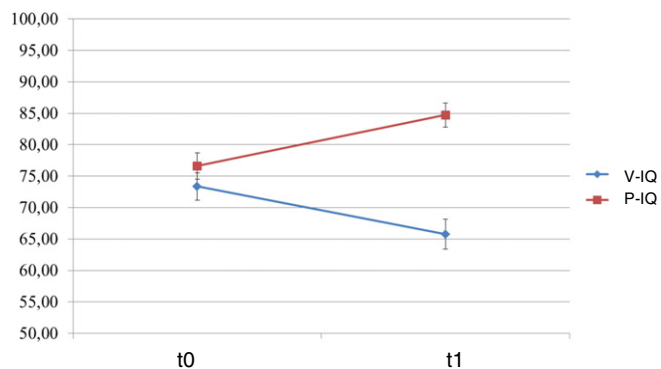
Fig. 1. Evolution of the Verbal and Performance Intelligence Quotient (IQ) at ESES onset (time 0, t0) and at the end of the follow-up (time 1, t1). Verbal score (VIQ) was affected with a significant decline from ESES onset to follow-up with mean value of 71.84 and 68.55 respectively. On the contrary performance score (PIQ) showed a significant improvement from a mean value of 77 at t0 to 85 at t1 (p-value 0.004).

Table 2
Verbal IQ subtests profile in patient who had a verbal IQ reduction during follow-up. This demonstrate 5 classifications according to the raw scores (rs) in accordance to the standard scores (ss) for age: Increase:↑rs ↑ss, Slow increase: ↑rs = ss, Stagnation: ↑rs ↓ss or =rs ↓ss and Decline: ↓rs ↓ss. Majority of patients presented stagnation of the Verbal IQ subtests or slow increase, only 2 patients presented in 3 subtests a real decline. + = 1 verbal IQ subtest.

Patient	Increase (↑rs ↑ss)	Slow increase (↑rs = ss)	Stagnation (↑rs ↓ss)	Stagnation (=rs ↓ss)	Decline (↓rs ↓ss)
#2	+++		++		
#4		+	+++		+
#6	+	++	++		
#7		+	++		++
#11	+++		+	+	
#16			+++++		

68.55 (43 to 90). On the contrary, performance score (PIQ) showed a significant improvement from 77.29 (42–107) at T0 to 85.05 (36–129) at T1 with a p-value of 0.004 (Fig. 1).

Considering the subdivision depending on the age at onset, TIQ scores changed respectively from 61 to 62 in group 1, from 72 to 75 in group 2, and from 85 to 95 in group 3; meanwhile, VIQ decreased from 63 to 59 in group 1, from 75 to 73 in group 2, and from 82 to 75in group 3; lastly, PIQ increased from 66 to 69 in group 1, from 73 to 83in group 2, and from 92 to 106 in group 3 (Fig. 2). At T1, the early onset group remained with the lowest IQ (mean T1 IQ = 62) compared to the late onset group (mean IQ = 95) (p-value 0.02), with worse results in verbal scores as mentioned above (Fig. 2).

In details, 7 patients showed VIQ decrease but complete data were available for 6 patients (Table 2). Considering the results, in most of the verbal subtests with decreased ss, there was an increase of rs (15 out of 19), whereas in 1 out of 19, there was a stable rs and in 3 out of

19 there was a decrease of rs. In 4 subtests, stable ss corresponded to an increase of rs. Consequently, most of the verbal subtests (19 out of 30) reflected an increase of the number of correct responses, whereas only in a minority (3 out of 30) the number of good responses declined from T0 to T1.

6 patients were assessed including neuropsychological domain-specific tests: domain 1 (visuo-spatial attention), domain 2 (visuomotor skills), domain 3 (short term memory), and domain 4 (academic skills) (Table 3).

3.1.4.1. Domain 1: visuo-spatial attention. As shown in Fig. 3, attention skills resulted normal in 5 out of 6 patients at T0 with respect to both rapidity and accuracy; only 1 out of 6 patients showed a deficit in visuo-spatial skills at T0, whereas all children reached a normal performance at T1. From T0 to T1, mean rapidity increased from 50° to 65° percentile, whereas mean accuracy from 51° to 75° percentile.

3.1.4.2. Domain 2: visuomotor skills. As shown in Fig. 3, at T0 only 1 patient showed a deficit, whereas at T1 all of them had a normal performance. The mean VMI performance increased from 45° to 64° percentile.
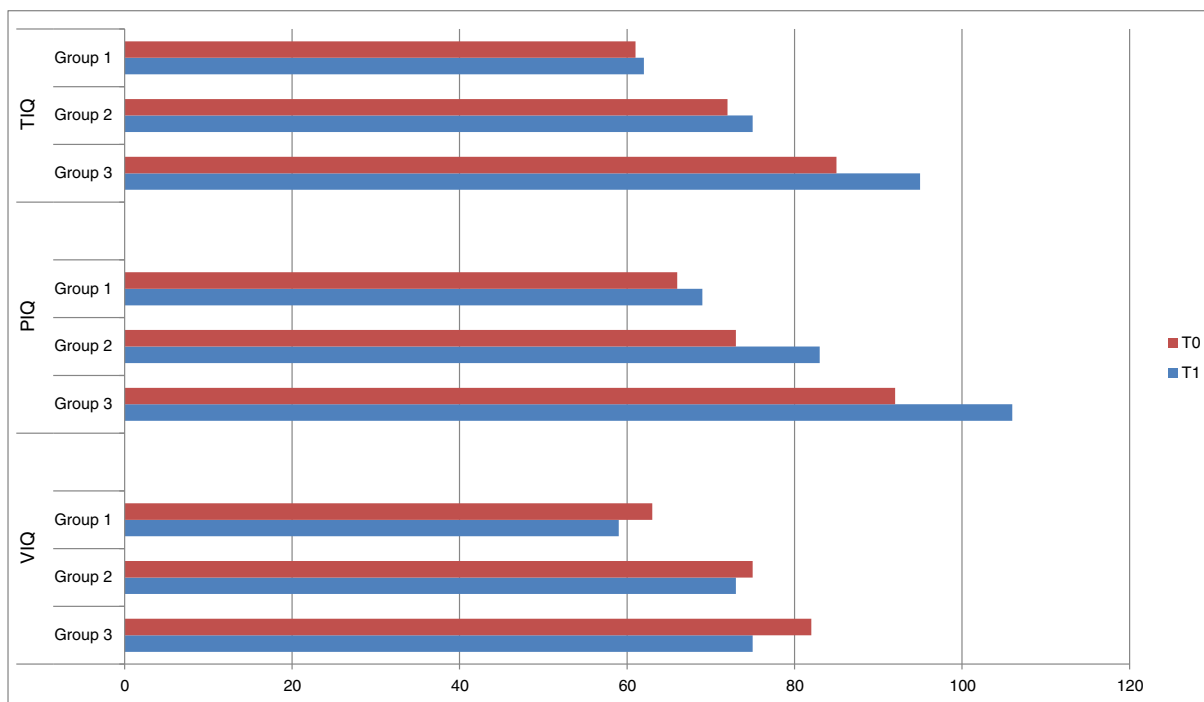

Fig. 2. Cognitive evolution of the 3 ESES groups of patients. Group 1: early onset (before the age of 6 years); Group 2: mid-onset (age of 6–7 years); Group 3: late onset (over age of 8 years). The early-onset group remained to have the lowest IQ over time, from T0 to T1 with group 1 having the most significant lower TIQ compared to group 3 (p-value 0.02). Furthermore, verbal IQ (VIQ) was affected worse than the performance IQ (PIQ) over a period of time. Scores: TIQ: Group 1: 61 to 62; Group 2: 72 to 75; Group 3: 85 to 95; VIQ: Group 1 63 to 59; Group 2: 75 to 73; Group 3 82 to 75; PIQ: Group 1 66 to 69; Group 2 73 to 83; Group 3 92 to 106.

Table 3
List of all of the neuropsychological test results of the 6 patients.
Domain 1: Visuo-spatial attention; Domain 2: visuo-motor skills; Domain 3: short-term memory; Domain 4: academic skills. % = percentile for age; SD: standard deviation for age.

| Patient | Follow-up | Age | Domain 1 | | Domain 2 | Domain 3 | | | Domain 4 | | | | | |
| | | | | | | | | | Reading (SD) | | | | Writing (SD) | |
			Rapidity (%)	Accuracy (%)	VMI (%)	Verbal span (SD)	Digit span (SD)	Visual span (SD)	Non-word speed	Non-word accuracy	Word speed	Word accuracy	Non-word accuracy	Word accuracy
#1	t0	5	75	75	39	−0,31	0,81	1,04	−3,5	−3,4	−2,1	−3	−2,6	−4,25
	t1	11	90	90	99	0,36	−2	−0,52	−2,1	−2,75	−2,7	−4,6	−1	−9
#2	t0	6,6	50	25	87	−0,33	−0,88	2,1	−2	−2,8	−2	−4,5	−1	−5,75
	t1	9,6	75	50	50	−0,83	−0,64	−0,52	−0,85	−1,2	−1,5	−1	−1,66	−6
#3	t0	5.5	50	75	21	0,23	−1	−0,83	−1	−2	−1,68	−2	−4,5	−12
	t1	11.5	50	90	65	−1,21	−1,71	−1	−0,6	1,3	−0,8	−2	−3	−5
#4	t0	8	90	75	3	−0,86	0,07	0,5	−0,21	−0,6	−1,7	1	1,5	1
	t1	18	90	90	34	0,3	0,25	0,16	−0,9	−0,6	−0,5	0,3	0,2	0,3
#5	t0	8	10	10	45	−0,83	−0,64	−0,52	−2,72	−3	−3,4	−2	−6	−15
	t1	12	10	25	45	−1,21	−0,82	−0,1	−2,52	−1,3	−3,4	−0,3	−1,6	−2,3
#6	t0	6,3	25	50	79	−1,2	−0,8	−0,65	−1,4	−1,2	−0,5	−0,8	−2,2	−3
	t1	11.3	75	75	91	−0,02	−0,08	−0,1	−0,74	0	3,56	0	−2	−2

3.1.4.3. Domain 3: short-term memory. At T0 and at T1, most of the subjects obtained normal scores considering all three memory subtests (Fig. 3). As a matter of fact only 1 patient showed a borderline performance at the digit span (z-score corresponding to −1.71 ds).

3.1.4.4. Domain 4: academic skills. With regards to reading speed, non-word reading performance remained in borderline during the follow-up (standard deviation mean values: T0 = −1.8 and T1 = −1.3) whereas word performance passed from borderline to normal scores (standard deviation mean values: T0 = −1.9 and T1 = −0.9).

On reading accuracy, non-word reading improved from pathological to normal (standard deviation mean values: T0 = −2 and T1 = −0.6) while word reading accuracy improved from pathological to borderline (standard deviation mean values: T0 = −1.9 and T1 = −1.3).

Writing accuracy improved from pathological to borderline in non-word (standard deviation mean values: T0 = −2.5 and T1 = −1.5) while remained significantly pathological with respect to words (standard deviation mean values: T0 = −6.5 and T1 = −4). (Fig. 4)

Thus, while phonological route evaluated through non-word writing and reading accuracy and reading speed improved during the follow-up, lexical route evaluated through word writing and reading accuracy and reading speed resulted as mainly affected since T0 and still at T1.

4. Discussion

4.1. The neurobehavioural profile emerging at the end of the follow-up: beyond the concept of deterioration

The first remarkable result of our study is that cognitive impairment is one but not the only consequence of CSWS. TIQ was borderline at CSWS onset and slightly improved at the end of follow-up. Considering both PIQ and VIQ, whereas the first showed a median increase, the second decreased in almost half of the sample. Going deeper into the nature of this decrease using both the raw and the standard score, it results that in most of the patients the decrease of verbal IQ corresponded to an increase of raw scores, i.e. an improvement of the measured ability. Instead, a few children worsened and lost competencies showing a real decline of raw scores. Thus, from a cognitive point of view, and especially with respect to verbal skills, CSWS may cause a pattern of consequences in terms of developmental hindrance, not only deterioration.
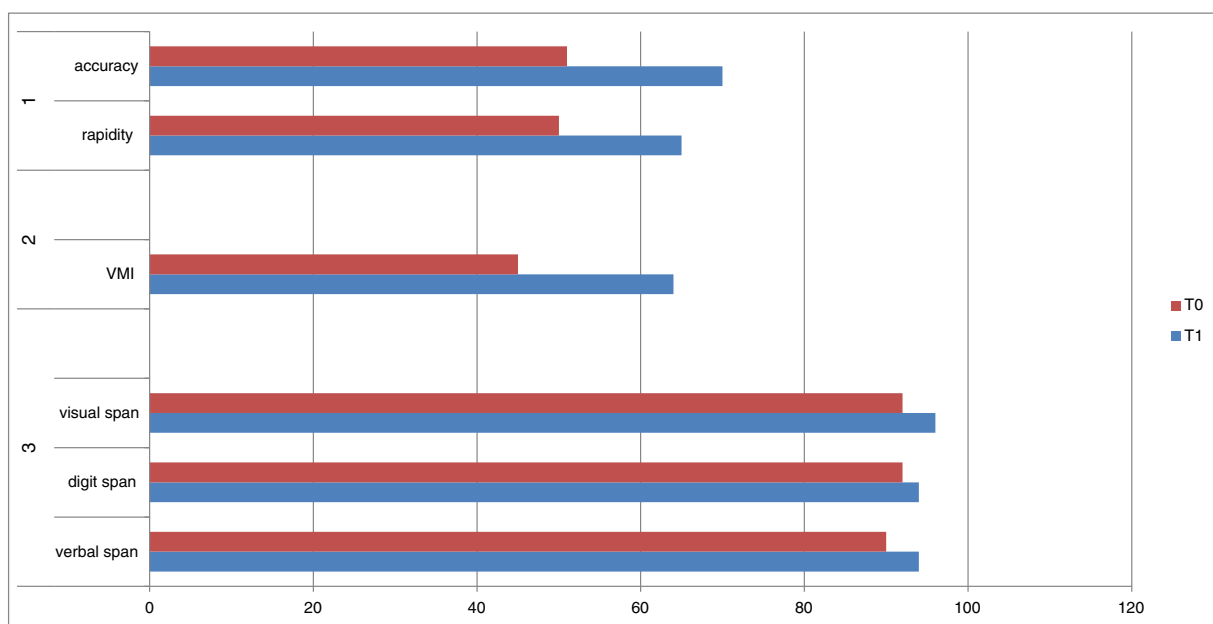

Fig. 3. A model of the follow-up evolution (T0 and T1) of the 3 domains (mean of percentiles of the 6 patients). 1 = Visuo-spatial attention; 2 = visuo-motor skills; 3 = short-term memory.
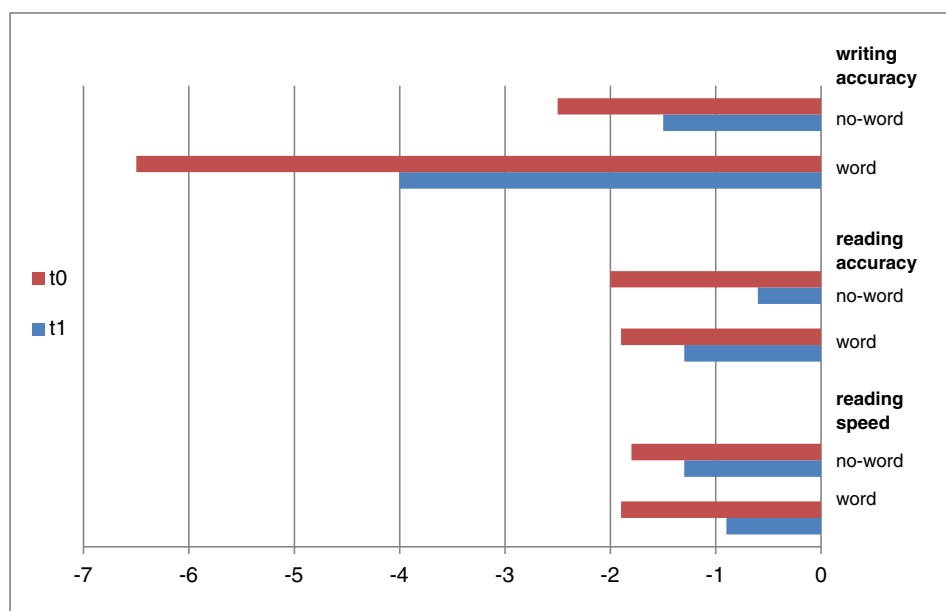
Fig. 4. A model of the follow-up evolution (T0 and T1) of the domain 4: academic skills (mean of standard deviations of the 6 patients). Normal values = 0 SD to −1 SD; Borderline values −1 SD to −2 SD; Pathological values >−2 SD.

Slowing of development may refer to the increase of raw scores, i.e. of competencies, albeit not sufficient to reach the median range expected according to chronological age, thus determining a decrease of normative scores. *Stagnation* occurs when skills stop progressing, sometimes determining a worsening of performance with respect to chronological age. *Cognitive decline/regression/deterioration* is properly used only when referring to the decrease of raw scores, i.e. loss of previously acquired competencies. As our results point out, deterioration may be very rare. Moreover, considering the neuropsychological profile, visuo-spatial attention and visuo-motor skills improved and normalized over time. Short-term memory remained in the normal range. Thus, at CSWS resolution basic cognitive processes such as attention, visuo-motor organization and memory result as released from the negative impact of encephalopathy, without enduring deficits.

Reading and writing fluency is defined as the ability to read with speed, accuracy and expression/prosody. Two routes have been described in reading and writing: the phonological and the lexical-semantic route [32,33]. The first is involved in non-word decoding and utilizes the grapheme to phoneme conversion. The second involves the visual lexicon through semantic route attaching meaning to words and facilitating comprehension. On the one hand, the improvement in our patients' scores in non-word reading speed and accuracy and non-word writing accuracy may imply that phonological route improved over time. On the other hand, word reading and writing accuracy and word reading speed remained significantly deficient at T1. Such disorder could be a consequence of a slow and inefficient lexical-semantic route that remains more severely affected compared to the phonological route. With these results, referring to the dual route model of reading, a single component developmental dyslexia may be associated with CSWS patients, i.e. affecting the progressive automatization of the lexical-semantic pathway.

Literature data pointed out a progressive deterioration and decline of cognitive functioning in CSWS patients [12–14,19] especially on the verbal aspects [15]; however, a correlation with our data is not simple both because literature patients have and heterogeneous etiology and because a deepen study of academic skills and raw scores was not applied so far.

From the behavioral point of view, our population demonstrated hyperactivity, anxiety and social/emotional problems that persisted unchanged during the course of the disease; in addition, externalizing problems worsened. Interestingly, in most of the patients this type of worsening was associated with an improvement of the neuropsychological functioning. These results agree with some literature showing that in children with CSWS behavioral difficulties may be present at the onset and persist [10–34] In addition, our patients" evolution seems to point out a dissociation between behavioral and neuropsychological functioning at the follow up: indeed, whereas the first remains abnormal, the second restores to normal range. Literature has also reported behavioral disorders and academic underachievement [35,36] as comorbidities leading to the hypothesis that the learning disorder of our patients" is strictly linked to the behavioral difficulties, and vice versa. In our sample the neuropsychological outcome was better than the behavioral one but a limitation of our study is the small sample and the retrospective collection of data, sometimes through caregivers" reports as for behavioral assessment.

Further prospective studies with larger samples are needed to confirm these developmental differentiated trajectories.

4.2. The impact of clinical variables on development in children with CSWS

Among the clinical variables, only age at onset was predictive for cognitive evolution. Indeed, our results show that the most vulnerable from an intellectual point of view were those who had an early-onset of CSWS, i.e. before the age of 6, whereas those with later onset resulted less affected. Since CSWS occurs to a specific age group of children, the harm is even greater if the epileptogenic process occurs when cognitive functions undergo critical maturational changes [37]. Indeed, epileptogenesis has been described as a form of excessive uncontrolled plasticity, since it refers to the cascade of molecular and cellular signaling, synaptic transmission and network rewiring leading to the formation of aberrant networks, possibly contributing to seizure progression, refractoriness and neurodevelopmental disorders [38,39]

The impact of CSWS on neurodevelopment has been highly debated and a causal relationship between the occurrence of CSWS and the appearance of neurobehavioral impairments has been favored [40,41]. The variability of neuropsychological impairments has been associated with the epileptogenic focus localization and the age at onset [42,43].

Neurocognitive function may be disrupted by localized subclinical epileptiform discharges. CSWS in the perisylvian areas may result in language deficits whereas dysexecutive patterns may be linked with

spikes in frontal regions [44]. Our patients' discrepancy between PIQ and VIQ may reflect the involvement of different anatomic regions of the brain. Considering the absence of a clear structural pathology, a relationship between the IQ result and the topographic representation of EEG discharges, i.e. the common location over the temporal regions during slow-wave sleep may be hypothesized. Seemingly, in the study of Chase et al. [45] using PET fluorodeoxyglucose F-18 technique, VIQ was associated with metabolism in the left temporoparietal region, whereas PIQ in the right posteroparietal region. However, the effect of lateralization was not established in this study because of equal population having subclinical seizure over both hemispheres.

The grapheme-to-phoneme route involves left temporo-parietal junction (including the posterior superior temporal gyrus, the angular gyrus and the supramarginal gyrus) and the opercular part of Broca's area [46,47] via arcuate fasciculus. The lexical-semantic route involves the left occipito-temporal region near the fusiform gyrus [32] the posterior portion of the middle and inferior temporal gyrus and the triangular part of the inferior frontal gyrus [48], connected by the inferior fronto-occipital fasciculus (IFOF) and the inferior longitudinal fasciculus (ILF) [41,49,50]. Considering the prevalent temporal and parietal localization of EEG discharges in our patients, these crucial regions may be altered especially for lexical semantic route. This result exemplifies how a prolonged focal epileptic activity during sleep – as occurring in CSWS – interferes with local slow wave activity at the site of the epileptic focus, impairing the local plastic changes during maturation of developing networks subserving learning [11]. Nevertheless, prospective studies through the use of anatomical and functional neuroimaging techniques are warranted to identify brain activation patterns during learning tasks and pinpoint the brain region that shows specific dysfunctional pattern activity related to focal epileptogenic process and subserve dysfunctional networks.

Taken together, our results point out a complex pattern of neurodevelopmental evolution of CSWS children. Even if an earlier age at onset correlates with a lower intellectual functioning, considering the entire duration of CSWS a global improvement of intellectual and neuropsychological functioning emerges, besides enduring academic deficits and persisting behavioral difficulties. Thus, differently from the pervasive deficits reported in literature, these data attest that the pattern of developmental hindrance is multifaceted, and deterioration is fortunately rare. Finally, the neuropsychological improvement may be accounted not only for the "idiopathic" etiology and for the normalization of CSWS EEG pattern, but also for the right choice of AEDs [30]. Prospective studies through the use of functional neuroimaging techniques are needed to better identify the abnormal developmental trajectories of network organization in CSWS patients.

5. Conclusion

We presented clinical features in a series of 16 CSWS idiopathic patients followed in a long term follow-up focusing on the neurobehavioral impact of CSWS.

Our results showed that the most vulnerable from an intellectual point of view were those children who had an early-onset of CSWS whereas those with later onset resulted less affected.

A complex pattern of neurodevelopmental evolution was illustrated pointing out that cognitive impairment is one but not the only consequence of CSWS and in our sample neuropsychological outcome was better than the behavioral one.

Moreover with respect to verbal skills, CSWS is responsible of a pattern of consequences in terms of developmental hindrance, rather than deterioration; and a slow and inefficient lexical-semantic route in our sample was more severely affected compared to the phonological route.

These data exemplify how a prolonged focal epileptic activity during sleep in CSWS patients interferes with local slow wave activity at the site of the epileptic focus but larger case series prospective studies through the use of functional neuroimaging techniques are needed in order to better and precisely identify brain activation patterns in CSWS patients.

Disclosure of conflicts of interest

Prof. Veggiotti Pierangelo has received speaker's fee from Eisai and Nutricia. The remaining authors have no conflicts of interest.

Ethical publication statement

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

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References

[1] Nolan MA, Redoblado MA, Lah S, Sabaz M, Lawson JA, Cunningham AM, et al. Intelligence in childhood epilepsy syn- dromes. Epilepsy Res 2003;53:139–50.

[2] van Rijckevorsel K. Cognitive problems related to epilepsy syndromes, especially malignant epilepsies. Seizure 2006;15:227–34.

[3] Bjornaes H, Stabell K, Henriksen O, Loyning Y. The effects of refractory epilepsy on intellectual functioning in children and adults: a longitudinal study. Seizure 2001; 10:250–9.

[4] Tassinari CA, Rubboli G, Volpi L, Meletti S, d'Orsi G, Franca M, et al. Encephalopathy with electrical status epilepticus during slow wave sleep or ESES syndrome including the acquired aphasia. Clin Neurophysiol 2000;111(Suppl. 2):94–102.

[5] Tassinari CA, Michelucci R, Forti A, Salvi F, Plasmati R, Rubboli G, et al, Bureau M, Dalla Bernardina B, Roger J. The electrical status epilepticus syndrome. Epilepsy Res Suppl 1992;6:111–5 [Review].

[6] Liukkonen E, Kantola-Sorsa E, Paetau R, Gaily E, Peltola M, Granstrom ML. Long-term outcome of 32 children with encephalopathy with status epilepticus during sleep, or ESES syndrome. Epilepsia 2010;51:2023–32.

[7] Veggiotti P, Beccaria F, Guerrini R, Capovilla G, Lanzi G. Continuous spike-and-wave activity during slow-wave sleep: syndrome or EEG pattern? Epilepsia 1999;40: 1593–601.

[8] Smith MC, Hoeppner TJ. Epileptic encephalopathy of late childhood: Landau–Kleffner syndrome and the syndrome of continuous spikes and waves during slow-wave sleep. J Clin Neurophysiol 2003;20:462–72.

[9] Brazzo D, Pera MC, Fasce M, Papalia G, Balottin U, Veggiotti P. Epileptic encephalopathies with status epilepticus during sleep: new techniques for understanding pathophysiology and therapeutic options. Epilepsy Res Treat 2012;2012:642725.

[10] Tassinari CA, Cantalupo G, Rios-Pohl L, Giustina ED, Rubboli G. Encephalopathy with status epilepticus during slow sleep: "the Penelope syndrome". Epilepsia Aug 2009; 50(Suppl. 7):4–8.

[11] Tassinari CA, Rubboli G. Cognition and paroxysmal EEG activities: from a single spike to electrical status epilepticus during sleep. Epilepsia 2006;47(Suppl. 2):40–3.

[12] Loddenkemper T, Sánchez Fernández I, Peters JM. Continuous spike and waves during sleep and electrical status epilepticus in sleep. J Clin Neurophysiol 2011;28: 154–64.

[13] Scholtes FB, Hendricks MP, Renier WO. Cognitive deterioration and electrical status epilepticus during slow sleep. Epilepsy Behav 2005;6:167–73.

[14] Caraballo RH, Veggiotti P, Kaltenmeier MC, Piazza E, Gamboni B, Avaria MFL, et al. Encephalopathy with status epilepticus during sleep or continuous spikes and waves during slow sleep syndrome: a multicenter, long-term follow-up study of 117 patients. Epilepsy Res 2013;105:164–73.

[15] Pera MC, Brazzo D, Altieri N, Balottin U, Veggiotti P. Long term evolution of neuropsychological competences in encephalopathy with status epilepticus during sleep: a variable prognosis. Epilepsia 2013;54(7):77–85.

[16] Singhal NS, Sullivan JE. Continuous spike–wave during slow wave sleep and related conditions. ISRN Neurol 2014;2014:619079 [6 pages].

[17] Giovanardi Rossi P, Parmeggiani A, Posar A, Scaduto MC, Chiodo A, Vatti G. Landau–Kleffner syndrome (LKS): long-term follow-up and links with electrical status epilepticus during sleep (ESES). Brain Dev 1999;21:90–8.

[18] Kramer U, Sagi L, Goldberg-Stern H, Zelnik N, Nissenkorn A, Ben-Zeev B. Clinical spectrum and medical treatment with electrical status epilepticus in sleep (ESES). Epilepsia 2009;50 [1617–1524].

[19] Robinson RO, Baird G, Robinson G, Simonoff E. Landau–Kleffner syndrome; corse and correlates with outcome. Dev Med Child Neurol 2001;43:243–7.

[20] Filippini M, Arzimanoglou A, Gobbi G. Neuropsychological approaches to epileptic encephalopathies. Epilepsia 2013;8:38–44.

[21] Engel Jr J. International league against epilepsy (ILAE) a proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. Epilepsia 2001;42:796–803.

[22] Achenbach TM. Manual for the child behavior checklist/4–18 and 1991 profile. Burlington: Department of Psychiatry, University of Vermont; 1991.

[23] Wechscler D. Wechsler preschool and primary scale of intelligence. 3rd ed. USA: Pearson Education, Inc.; 2008.

[24] Weschler D. Scala d'intelligenza Wechsler per bambini. Firenze: Organizzazioni Speciali; 2012.

[25] Biancardi A, Stoppa E. Il test delle campanelle modificato (TCM) una proposta per lo studio dell'attenzione in età evolutiva. Psichiatria dell' Infanzia e dell'Adolescenza 1997;64:73–84.

[26] Beery KE, Buktenica NA, Beery NA, Keith E. Developmental test of visual-motor integration 6th edition. Minneapolis, MN: NSC Pearson; 2010.

[27] Reynolds C, Voress JK. Test of memory and learning. 2nd ed. Austin, TX: PRO-ED; 2007.

[28] Sartori G, Job R, e Tressoldi PE. Batteria per la valutazione della dislessia e della disortografia evolutiva. Firenze: Organizzazioni Speciali; 1995.

[29] IBM Corp. Released. IBM SPSS statistics for windows, version 19.0. Armonk, NY: IBM Corp.; 2010.

[30] Veggiotti P, Pera MC, Olivotto S, De Giorgis V. How to manage electrical status epilepticus in sleep. J Clin Neurophysiol Feb 2016;33(1):3–9.

[31] Pera MC, Randazzo G, Masnada S, Dontin SD, De Giorgis V, Balottin U, et al. Intravenous methylprednisolone pulse therapy for children with epileptic encephalopathy. Funct Neurol Jul-Sep 2015;30(3):173–9.

[32] Cohen L, Dehaene S, Naccache L, Lehericy S, Haene-Lambertz G, Henaff MA, et al. The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients. Brain 2000;123:291e307.

[33] Tree JJ, Kay K. Phonological dyslexia and phonological impairment: an exception to the rule? Neuropsychologia 2006;44:2861–73.

[34] Roulet Perez E, Davidoff C, Despland PA, Deonna T. Mental and behavioral deterioration of children with epilepsy and CSWS: acquired epileptic frontal syndrome. Dev Med Child Neurol 1993;35:661–74.

[35] Wu SY, Gau SS. Correlates for academic performance and school functioning among youths with and without persistent attention-deficit/hyperactivity disorder. Res Dev Disabil Jan 2013;34(1):505–15.

[36] Ismail FY, Fatemi A, Johnston MV. Cerebral plasticity: windows of opportunity in the developing brain. Eur J Paediatr Neurol 2016;30:1–26.

[37] Seri S, Thai JN, Brazzo D, Pisani F, Cerquiglini A. Neurophysiology of CSWS-associated cognitive dysfunction. Epilepsia 2009;50(Suppl. 7):33–6.

[38] De Tiege X, Ligot N, Goldman S, Poznanski N, de Saint Martin A, Van Bogaert P. Metabolic evidence for remote inhibition in epilepsies with continuous spike-waves during sleep. Neuroimage 2008;40:802–10.

[39] De Tiege X, Goldman S, Van Bogaert P. Insights into the pathophysiology of psychomotor regression in CSWS syndromes from FDG-PET and EEG-fMRI. Epilepsia 2009;50(Suppl. 7):47–50.

[40] Vingerhoets G. Cognitive effects of seizures. Seizure 2006;15:221–6.

[41] Martino J, Brogna C, Robles SG, Vergani F, Duffau H. Anatomic dissection of the inferior fronto-occipital fasciculus revisited in the lights of brain stimulation data. Cortex 2010;46(5):691e699.

[42] Gonzalez LM, Upeka Embuldeniya A, Harvey S, Wrennall JA, Renee Testa R, Anderson VA, et al. Developmental stage affects cognition in children with recently-diagnosed symptomatic focal epilepsy. Epilepsy Behav 2014;39:97–104.

[43] Tomasino B, Marin D, Maieron M, D'Agostini S, Fabbro F, Skrap M, et al. Double-letter processing in surface dyslexia and dysgraphia following a left temporal lesion: a multimodal neuroimaging study. Cortex 2015;73:112e130.

[44] Siniatchkin M, Groening K, Moehring J. Neuronal networks in children with continuous spikes and waves during slow sleep. Brain 2010;133(9):2798–813.

[45] Chase TN, Fedio P, Foster NL, Brooks R, Di Chiro G, Mansi L. Wechsler adult intelligence scale performance cortical localization by fluorodeoxyglucose F18-Positro n emission tomography. Arch Neurol 1984;41(12):1244–7.

[46] Burton MW, Small SL, Blumstein SE. The role of segmentation in phonological processing: an fMRI investigation. J Cogn Neurosci 2000;12:679e690.

[47] Pugh KR, Mencl WE, Shaywitz BA, Shaywitz SE, Fulbright RK, Constable RT, et al. The angular gyrus in developmental dyslexia: task-specific differences in functional connectivity within posterior cortex. Psychol Sci 2000;11:51–6.

[48] Jobard G, Crivello F, Tzourio-Mazoyer N. Evaluation of the dual route theory of reading: a metanalysis of 35 neuroimaging studies. Neuroimage 2003;20:693e712.

[49] Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex 2008;44:1105e1132.

[50] Fernandez-Miranda JC, Rhoton AL, Alvarez-Linera J, Kakizawa Y, Choi C, de Oliveira EP. Three- dimensional microsurgical and tractographic anatomy of the white matter of the human brain. Neurosurgery 2008;62(6 Suppl 3):989e1026.