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Original article

Neurodevelopmental evolution of West syndrome: A 2-year prospective study

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ABSTRACT

Objective: The aim of this study was to evaluate the epileptic and developmental evolution in infants with West syndrome.
Methods: A prospective study of 21 infants was performed, with a follow-up at 2 years. Serial assessment included long-term EEG monitoring, visual and auditory evaluation and assessment of neurodevelopment.
Results: Neurosensory and developmental impairments at the spasm onset were transitory in seven cases, including four cryptogenic forms. In all other cases, there was a progressive worsening in neurosensory and developmental impairments. The epileptic evolution was generally better: in 11 of the 16 infants without seizures at outcome, spasms had already disappeared by 2 months after disease onset. Statistic analysis of results showed a correlation between neurosensory impairment and development throughout the whole follow-up. In addition, visual function at T1 resulted significant predictor of developmental outcome. Among the epileptic features, disorganization of slow sleep was an unfavorable prognostic factor.
Conclusion: Some forms of West syndrome are confirmed to have a benign evolution: among them there are not only cryptogenic cases but also symptomatic ones without significant neurodevelopmental impairment. Abnormalities of sleep organization, expression of the pervasive epileptic disorder, seem to play a role in determining a developmental deterioration. Neurosensory impairment since the onset of the disease could be a relevant cause of the developmental disorder.

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1. Introduction

Neurosensory impairment at the onset of disease is a typical feature of West syndrome. Visual impairment, reported in clinical studies several decades ago,[1,2] has recently been confirmed by behavioral and electrophysiological studies.[3–8] Similarly, impaired auditory and somatosensory functions have been observed in auditory brain response (ABR), auditory orienting response,[9,10] and sensory evoked potential.[11]

Brain injuries are known to cause epileptic and developmental impairments in symptomatic West syndrome. Antiepileptic drugs (AED) are suspected to play a role in developmental dysfunctions.[12,13] On the other hand, epileptic disorder (seizures and electrographic abnormalities) has been widely shown to cause developmental deterioration, particularly in early ages.[14,15]

We have recently reported that at the onset of spasms visual and auditory functions are significantly related to cognitive development, suggesting a possible mechanism underlying mental deterioration. We have also suggested that the epileptic disorder *per se* may play a causal role in sensory-cognitive regression.[16–18] In the present paper, we report epileptic and neurodevelopmental data from a 2-year prospective study.

The aim of the present study is

(a) to establish the clinical evolution of the patient cohort,
(b) to determine whether there is a significant relationship between neurosensory function and development during the 2-year follow-up,
(c) to identify predictors of neurodevelopmental outcome present in the acute phase of the disease, specifically examining brain injury, seizure type and frequency, EEG patterns, and neurosensory and developmental data, and
(d) to evaluate the negative side-effects of AEDs on neurosensory functions.

2. Methods

2.1. Participants

The participants included in this study are a cohort of 25 infants with West syndrome in whom spasm onset first occurred between 2 and 13 months. The infants were previously examined at the onset of spasms (T0) and after 2 months (T1)[16–18] as part of a multicentric study involving three Child Neurology Divisions (Universities of Pavia, Pisa and Rome). Twelve infants were identified in Rome, eight in Pisa, and five in Pavia. As part of the present study, the infants were systematically reassessed at T2, T3, and T4 (6, 12, and 24 months after spasm onset, respectively).

Of the 25 children in the original cohort four were lost at follow-up. Of the remaining 21 infants described in this study, four were classified as having cryptogenic West syndrome. Cryptogenic cases were defined as being without structural brain changes or signs of neurological disorder or history with neuropathological risk. Of the remaining seventeen infants, four had West syndrome associated with tuberous sclerosis complex (TSC), and 13 cases had symptomatic West syndrome due to early (prenatal or perinatal) vascular brain injury (EVBI).

The follow-up assessments included serial clinical behavioral and electrophysiological assessments. At each center, the same person always performed the developmental assessments. Interviewers were unaware of the patients' epileptic (clinical and electrographic) features. All patients also underwent detailed monitoring of both seizure semiology and video-EEG registration.

All patients underwent a brain MRI at spasm onset using a 1.5T apparatus. In order to exclude subtle cortical and subcortical changes that may not always be appreciated in young patients because of immature myelination, all infants had a second MRI new scan after 14 months of age.

Besides neurological clinical examination, *neurological function* was assessed and scored using the Hammersmith Infant Neurological Examination (HINE).[19,20] The examination consists of 26 items including cranial nerve function, posture, movements, tone, and reflexes/saving reactions. One of the advantages of using this examination is that it provides normative data and an optimality score for both individual items and overall function.[19] An optimality subscore can be given for each section and the overall global optimality score can be calculated by summing up the scores for all the 26 items, with a maximum overall score of 78. We considered an optimal score to be between 70 and 78.

All infants underwent a battery of age-specific tests assessing *visual function*, including acuity, fixation and tracking, visual field, ocular motility, and visual attention. Visual function was scored from 0 to 24 (0 being the best) according to criteria previously reported.[16] We considered scores 0–1 to be normal, scores of 2–6 to indicate mild impairment, and scores over 6 to indicate definite impairment.

Hearing ability was assessed through behavioral tests and auditory brainstem responses (ABR). In addition, auditory orienting responses were scored from best to worst score (0–3), as already reported.[17] We consider a score of 0 to be normal, a score of 0.25–1 to indicate mild impairment, and a score of over 1 to indicate definite impairment.

All infants underwent a *developmental assessment*, using the Griffiths' Mental Scales.[21] Most of the items of the test include a cognitive component. The test consists of five subscales: motor, personal-social, hearing and speech, eye-hand coordination, and performance.

Developmental outcome at the 2-year follow-up assessment, was classified according to a method proposed by Ivens and Martin.[22] This method considers the 2–8 years Griffiths' scales and corrects the raw scores of each scale and the general quotient (GQ) into score equivalents for ICD10 ranges of mental retardation: profound, severe, moderate, and mild retardation.

Behavioral disorders were reported on the basis of clinical observation and family reports and scored according to their severity from 1 to 3+.

2.2. *Video-EEG*

Video-polygraphies were recorded using 21 EEG electrodes according to the 10/20 International System (nine electrodes for the youngest infants) and deltoid surface EMG. Recordings lasted at least 1 h and always included at least 30 min of sleep.

The EEG was analyzed in two ways:

(a) *Organization of sleep states*: The organization of sleep states was based on the identification of EEG stages and the presence of physiological features, namely sleep spindles. Tracings were classified as normal (0) or abnormal (1).
(b) *Interictal EEG*: EEG abnormalities typical of hypsarrhythmia were assessed on a representative segment of the EEG trace taken while the infant was awake and free of seizures.

Hypsarrhythmia, when present, was classified as either typical or atypical. A scoring system based on three slightly modified features from Kramer et al.[23] was used.[16] Each feature was scored on a scale of increasing severity, from 0 to 3. The features scored included the percentage of delta activity, delta maximum voltage, and the frequency of spikes and sharp waves. The final score ranged from 0 (lowest degree of abnormalities) to 9 (highest degree of abnormalities). For statistical purposes, we coded the hypsarrhythmic scores into four groups: 0 (no abnormalities), 1 (scores between 1 and 3, generally not representative of a real hypsarrhythmia), 2 (scores between 4 and 6); and finally 3 (scores between 7 and 9).

During the follow-up assessment, when hypsarrhythmic chaos was no longer recognizable, we continued to code any other EEG awake-state abnormalities according to the same criteria (percentage of delta activity, delta maximum voltage, and frequency of spikes and sharp waves).

2.2.1. *Statistical analysis*

Since the sample size was small and variable scores were not normally distributed (Kolmogrov–Smirnov test), non-parametric tests were used.

Spearman correlation coefficient analysis was used to establish the possible correlations between visual/auditory function and neurological examination/neurodevelopmental scales.

The non-parametric Mann–Whitney test for independent samples was used to test the correlation between epileptic disorder and neurosensory/developmental impairment. The same test was used to identify the correlation between individual drugs and visual function or auditory attention; in particular, the relationship between visual field and Vigabatrin (VGB) administration.

Univariate and multivariate linear regression models were used to look for predictive factors of developmental outcome (Griffiths' GQ and individual scales). In the univariate models, we looked at age of onset of West syndrome, EEG sleep patterns (T0–T3), hypsarrhythmia (T0–T3), seizures (T0–T3), visual and auditory scores (T0–T3), cerebral lesions (T0–T3), and number of administered drugs (T0–T3) as possible predictive factors. In the multivariate models we included the variables whose univariate test p-value was lower than 0.20. We considered the variables at T1, the time corresponding to the end of the acute stage of the disease, because it was the first time at which the covariates were consistently significant in the univariate analysis. For multivariate regression models, we applied the stepwise method with backward elimination.

To test if potential factors such as epilepsy, drugs or brain lesions could have an influence on the evolution of developmental and neurosensory function, we used the repeated measures MANOVA (Pillai's test). In order to focus on the aspects of development that are most related to cognitive function, we used a modified global score from the Griffiths' scales, excluding subscale A, that is most related to gross motor function.

A p-value $\leqslant 0.05$ was considered significant. The data were analyzed using the SPSS 12.0 software for Windows.

3. Results

All 21 infants completed all the assessments. The control MRI, performed after 14 months of age, confirmed previous findings in all cases.

As shown in Table 1, 2 years after the onset of seizures, 16 of the 21 infants were seizure free. Eleven had been seizure free since T1. The remaining five infants all had partial seizures; two had seizures associated with spasms (patients 5 and 12).

Typical or modified hypsarrhythmia disappeared at T1 in 13 cases (four cryptogenic, two TSC, and seven EVBI). Five patients still presented with atypical hypsarrhythmic pattern at T4 (one was associated with TSC and the remaining with EVBI cases).

The most frequently used AED were VGB and ACTH. VGB was the antiepileptic drug initially administered in 13 patients and was successively added to the drug regimen of three others. ACTH was initially administered to three patients, and added to the regimen of 13 other patients. **Only in one infant (patient 21) there was a spasm relapse, but he did not receive a second treatment with ACTH**. Drugs had been thoroughly weaned by the 2-year outcome in three patients (patients 1, 3, and 20).

As shown in Table 2, *neurological examination* was normal or mildly abnormal in nine cases, including all the cryptogenic cases, those associated with TSC, as well as one EVBI patient (patient 16). As to HINE scoring, among these nine cases all but one presented with an optimal value at outcome, whereas four were suboptimal at onset. In terms of visual function, four were normal at onset (one cryptogenic case, two with TSC and one EVBI case), and nine patients were normal at outcome (all the cryptogenic patients, all but one of the patients with TSC, and 2 EVBI infants).

In all cases but one (patient 11), ABR was normal at T1. AORs were normal at onset in four cases (one cryptogenic, two with TSC, and one EVBI case) and became normal by outcome in 11 (all the cryptogenic and TSC cases, and three EVBI patients).

Table 1 – General clinical and epileptic data

Cases #	Etiology	Neuroroimaging	Spasm at onset (months)	PS at onset (months)	EEG patterns Sleep/hypsshar or abnormal		Antiepileptic drugs	Epilepsy evolution	
					Onset	Outcome		Spasms	PS
1	Cryptogenic	Normal	8	–	1/2	0/0	VGB, ACTH (weaned at 2 years)	Seizure-free since T1	
2	Cryptogenic	Normal	4	8	0/3	1/0	VGB, ACTH	Disappear at T1	Disappear at T2
3	Cryptogenic	Normal	7	–	0/3	0/1	VGB, ACTH (weaned at 2 years)	Seizure-free since T1	
4	Cryptogenic	Normal	5	–	1/2	0/0	VGB, ACTH	Seizure-free since T1	
5	TSC	Cortical and subcortical tubers with ependimal nodules	4	4	0/1	0/1	VGB, ACTH, PB	Sill present at T4	Still present at T4
6	TSC	Cortical and subcortical tubers with ependimal nodules	7	–	1/3	0/2	VGB, VPA	Seizure-free since T1	
7	TSC	Cortical and subcortical tubers with ependimal nodules	8	14.5	1/3	0/1	VGB, CBZ, TPM, VPA, BDZ	Disappear at T1	Still present at T4
8	TSC	Cortical fronto-parietal and subcortical tubers	7	5.5	1/3	0/1	ACTH, BDZ, CBZ, PB, VGB	Seizure-free since T3	
9	Perinatal injury	Multicystic encephalomalacia	13	–	1/3	1/2	VGB, BDZ, PB, TPM	Seizure-free since T3	
10	Perinatal injury	Cortical occipital and WM injuries including OR and BG	4	–	1/1	1/1	BDZ, PB, ACTH	Seizure-free since T3	
11	Perinatal injury	Bilateral cortical and periventricular WM injuries	3	2.5	1/2	1/2	VPA, PB, ACTH	Seizure-free since T3	
12	Perinatal injury	Bilateral cortical and WM injuries	7	31	1/3	1/1	VGB, ACTH, PB	Still present at T4	Onset at T4
13	Perinatal injury	Cortical (PO) and WM changes	5	–	1/3	1/3	VGB, VPA, BDZ	Seizure-free since T3	
14	Perinatal injury	PVL	4	20	0/3	0/2	ACTH, PB	Disappear at T1	Still present at T4
15	Perinatal injury	Paratrigonal PVL	4	6.5	1/3	1/1	BDZ, PB, VGB, VPA	Disappear at T1	Disappear at T4
16	Perinatal injury	Left ventricular dilatation	4	–	1/3	0/1	PB, ACTH	Seizure-free since T1	
17	Perinatal injury	PVL	10	7.5	1/2	1/1	VGB, ACTH, BDZ, VPA	Seizure-free since T2	
18	Perinatal injury	PVL and BG injuries	3	–	1/3	0/0	VGB, ACTH, PB	Seizure-free since T1	
19	Perinatal injury	Left cortical (P) and subcortical injuries	6	6	1/3	1/1	VGB, ACTH, VPA	Seizure-free since T2	
20	Perinatal injury	Left MCA stroke	6	–	0/3	nv/0	ACTH, PB (weaned at 2 years)	Seizure-free since T1	
21	Perinatal injury	Right cortical (PT) and periventricular WM injuries	2	2	1/2	1/1	VPA, ACTH, PB, VGB, B6, TPM	Disappear at T1, relapse still present at T4	At T3 and disappear at T4

TSC: tuberous sclerosis complex; WM: white matter; OR: occipital radiation; BG: basal ganglia; PO: parieto-occipital; PVL: periventricular leucomalacia; P: parietal; MCA: medium cerebral artery; PT: parieto-temporal; PS: partial seizures; VGB: vigabatrin; ACTH: adrenocorticotropichormone; P: Phenobarbital; VPA: valproate; CBZ: carbamazepine; TPM: topiramate; BDZ: benzodiazepine.

Table 2 – Neurological, neurosensory and behavioral data

Case #	Neurological exam at outcome	Neuromotor assessment		Visual function		Auditory attention		Behavioral disorders
		Onset	Outcome	Onset	Outcome	Onset	Outcome	
1	Clumsy	78	78	9	1	1	0	No
2	Normal	72	78	1	0	0	0	No
3	Normal	72	78	3	0	0.5	0	No
4	Normal	68	75	4	0	0.66	0	No
5	Clumsy	61	54	3	8	2.25	0	+++
6	Normal	77	78	0	0	0	0	No
7	Hypotonic	58	71	4	1	0	0	++
8	Normal	77	78	0	1	0.75	0	No
9	Tetraparesis	3	3	15	16	2.75	1	No
10	Tetraparesis	18	9	16.5	17	3	3	No
11	Tetraparesis	28.5	32.5	14	13	Np	Np	No
12	Tetraparesis	5	7	15	15	3	0	No
13	Tetraparesis	42	40	7.5	10	3	3	No
14	Tetraparesis	10	22	13	5	2.25	1	No
15	Tetraparesis	27	33	15	14	2.5	3 (T2)	No
16	Normal	69	72	5	1	0	0	No
17	Tetraparesis	23	26.5	9	9	3	0.25	No
18	Tetraparesis	34.5	22	14	8	Np	1	No
19	Tetraparesis	33	34	15	10	1	0.25	No
20	Hemiparesis	54	54	0	1	2.5	0	No
21	Tetraparesis	20	58	15	9	2.75	1 (T3)	No

Times at outcome are indicated in brackets when they were not T4.
Np: not performed.

The results of Griffiths' Mental Scales are shown in Table 3. The patients can be classified into two groups, according to their developmental evolution during the 2-year follow-up.

The *first group* includes seven children with normal developmental outcome; four were cryptogenic, two had associated TSC (patients 6 and 8), and one had associated EVBI (patient 20) with unilateral lesion and mild neurological impairment. As previously described,[16–18] six of the seven cases presented at onset with a GQ of above 80, with sporadic specific falls in some subscales (language, eye and hand, and performance), and with frequent, although mild, sensory impairment in both visual and auditory functions. The remaining case (patient 8) had associated TSC and showed a relatively low GQ (62) at spasm onset, together with more marked neurosensory impairment. Neurosensory and neurodevelopmental features were fully recovered by the 6th month of life in all these cases.

The *second group* includes all the other 14 cases, all of which showed an abnormal developmental outcome, two had associated TSC and 12 had associated EVBI. Among these 14 cases, the two infants with TSC presented with GQ value above 80 (patients 5 and 7) at spasm onset; their evolution showed a progressive worsening until outcome, when their GQ values corresponded to the ICD10 score equivalents for mild and moderate retardation.[22]

Of the 12 EVBI cases with abnormal development, four presented at onset with GQ values around 50–60, whereas the other eight showed a severe developmental impairment. The latter cases were persistently severe throughout the 2-year follow-up, while the former group showed a progressive worsening; two of these infants (patients 16 and 18) had outcome scores corresponding to only mild retardation.[22]

Behavioral disorders, consisting of a spectrum of autistic abnormalities, were found in two patients, both with tuberous sclerosis (patients 5 and 7). **Although they were also mentally retarded, some behavioral features showed an evident autistic character (autistic withdrawal, perseverance, stereotypies, specific communication and language disorders)**.

3.1. *Neurosensory function vs. developmental/ neurological examination*

The Spearman correlations were statistically significant in every instance (T2–T4) between auditory attention/visual function and GQ/neurological examination, both for global and subscale values. The correlation between visual function and both Griffiths' GQ/neurological examination and individual scales were high at all time points ($p<0.01$), whereas the comparison of auditory attention at T3 and T4 with the single neurological features (cranial nerves, tone, and reflexes at T3 and all neurological features at T4) were less significant ($p = 0.05$).

3.2. *Epileptic disorder vs. neurosensory and developmental functions*

Among the studied parameters of the epileptic disorder (seizures, hypsarrhythmia, and sleep EEG patterns), the Mann–Whitney test showed that EEG sleep abnormalities

Table 3 – Griffiths' mental scales

Case #	General quotient		Locomotor		Personal/social		Language		Eye and hand		Performance	
	Onset	Outcome	Onset	Outcome	Onset	Outcome	Onset	Outcome	Onset	Outcome	Onset	outcome
1	80 (T1)	114	83 (T1)	111	83 (T1)	123	79 (T1)	135	83 (T1)	88	71 (T1)	112
2	117	94	108	94	133	97	117	105	108	88	110	82
3	94	101	104	81	104	138	81	116	75	125	96	113
4	100	116	83	112	108	131	108	106	89	112	117	106
5	90	49 (MoR)	90	52 (MoR)	105-	48 (MiR)	114	61 (MiR)	64	43 (MiR)	86	43 (MiR)
6	103	87	114	84	86	97	100	84	107	76	107	94
7	82 (T1)	67 (MiR)	114(T1)	72	95(T1)	68 (MiR)	57(T1)	70	71(T1)	59 (MiR)	71(T1)	64 (MiR)
8	62	110	57	104	48	110	54	110	64	116	54	112
9	Severe	Severe (PR)	Severe	Severe (PR)	Severe	Severe (PR)	Severe	Severe (PR)	Severe	Severe (PR)	Severe	Severe (PR)
10	32	5 (PR)	20	5 (PR)	40	7 (PR)	40	7 (SR)	0	0 (PR)	60	5 (PR)
11	50	21 (PR)	67	19 (SR)	33	26 (SR)	67	26 (MoR)	17	14 (PR)	50	18 (SR)
12	16 (T2)	11 (PR)	8(T2)	10 (PR)	22(T2)	10 (PR)	8(T2)	10 (SR)	33(T2)	17 (SR)	8(T2)	5 (PR)
13	48 (T1)	8,9 (PR)	43(T1)	7 (PR)	64(T1)	12 (PR)	71(T1)	10 (SR)	50(T1)	7 (PR)	14(T1)	8,6 (SR)
14	42	25 (PR)	15	17 (SR)	46	29 (SR)	60	24 (MoR)	40	29 (SR)	30	24 (SR)
15	12	15 (PR)	8	8 (PR)	12	21 (SR)	12	23(MoR)	8	8 ((PR)	12	11 (SR)
16	62	49 (MoR)	60	52 (MiR)	46	47 (MiR)	60	49 (MiR)	55	47 (MoR)	60	49 (MiR)
17	32	26 (PR)	26	24 (SR)	41	35 (MoR)	41	34 (MoR)	21	15 (PR)	29	14 (SR)
18	50	50 (MoR)	58	58 (MiR)	58	58 (MiR)	58	58 (MIR)	38	38 (MoR)	50	50 (MiR)
19	33	33 (SR)	28	33 (MoR)	25	37 (MoR)	56	43 (MoR)	6	23 (SR)	50	27 (MoR)
20	94	103	75	100	97	110	81	95	97	110	88	102
21	58	38 (SR)	89	34 (MoR)	35	45 (MoR)	35	38 (MoR)	89	35 (MoR)	58	31 (MoR)

Time at onset is indicated in brackets when it was not at T0.
Outcome score equivalents for ICD10 ranges of mental retardation according to Ivens and Martin[22] are indicated in brackets: PR = profound retardation; SR = severe retardation; MoR = moderate retardation; MiR = mild retardation.
Times at onset or outcome are indicated in brackets when they were not T0.

are significantly correlated with poor performance in visual and auditory functions, as well as to lower scores in GQ and neurological examination. This was true at any given time but T0, when only visual function defects were significantly related to EEG sleep abnormalities (Table 4). Hypsarrhythmia had a significant effect at T1 ($p = 0.014$).

3.3. *Predictive factors of development at outcome*

Univariate analysis was used to test whether neurosensory dysfunction, or other early findings, such as hypsarrhythmia, abnormalities in EEG sleep patterns, seizures (both spasms and partial seizures), brain lesions or drugs, can predict developmental outcome. Visual and auditory function was already significantly predictive at T0, while the other factors, with the exception of seizures and drugs, achieved significant predictive value at T1 (Table 5). Sleep EEG abnormalities, in particular, were good predictors of neurosensory and developmental outcome, with a sensitivity of 100% and good specificity (72%).

In the multivariate analysis (referred to T1 values), brain lesions were associated with all neurodevelopmental outcomes, while visual function was significantly associated with Griffiths' scales A, B, D, and E. Auditory attention was significantly correlated with Griffiths' GQ and scale C (Table 6).

3.4. *Neurosensory and developmental variability during the follow-up (MANOVA) vs. epileptic features (seizures and EEG patterns), drugs and brain injury*

Variability of neurodevelopment (Griffiths' developmental quotients excluding motor scale) seems significantly associated with brain lesions ($p = 0.008$), abnormal sleep EEG pattern ($p = 0.034$) and hypsarrhythmia ($p = 0.045$), while visual variability seems to depend on hypsarrhythmia ($p = 0.049$).

3.5. *Relationship between AED and neurosensory functions*

The Mann–Whitney test was used to examine the relationship between AED and changes in neurosensory (visual and auditory) and development. A significant relationship was shown only for phenobarbital (associated with worse visual scores, $p = 0.041$), VGB (associated with better visual scores at T0 and T2, $p = 0.022$ and 0.031, respectively), benzodiazepins (associated with worse visual scores at T1, $p = 0.048$), and ACTH (associated with worse visual scores, $p = 0.045$). Visual field, specifically studied in cases of VGB administration, did not show any significant deterioration.

4. Discussion

Our study is the first 2-year prospective study exploring epileptic, neurosensory and developmental evolution in infants with West syndrome. The evolution of epilepsy in our cohort varied according to etiology. It was very favorable in cryptogenic cases, generally poor in EVBI-associated cases, and more variable in TSC-associated cases. After the 2-year follow-up, only five infants were still presenting with seizures, partial seizures in three, and partial seizures with associated spasms in the other two. In 11 of the 16 infants without seizures at T4, spasms had already disappeared at T1. Compared to the literature, these are relatively good epileptic outcome.[24] This difference could be explained by the different etiologies in our cohort, which included less severe cases.

It is interesting to note, however, that the neurodevelopmental outcome was less favorable. Only seven cases, including the four cryptogenic patients, had a normal GQ at outcome. These seven patients all had normal neurological and neurosensory (visual and auditory) functions, although one infant presented with hemiparesis due to an EVBI. This is consistent with other reports in the literature concerning some cryptogenic cases considered as idiopathic forms.[25,26] But it should be stressed that in our series, one EVBI case and two of the four TSC patients showed the same evolution. The variable developmental outcome in TSC-associated cases that we observed has been previously described.[27] It should also be emphasized that in the acute period of the disease, these seven children generally presented with a slight neurosensory impairment. Some of them had sporadically poor results on some subscale of the Griffiths' test, and one infant had a low GQ. This shows that even in cases with good outcome, there are initially neurodevelopmental impairments,[16–18], with favorable neurosensory and developmental functions

Table 4 – EEG sleep patterns vs. visual/auditory function and neurodevelopment

Sleep EEG	Visual function		Auditory attention		Development		Neurological features	
	Mann–Whitney *U*	*p*	Mann–Whitney *U*	*p*	Mann–Whitney *U*	*p*	Mann–Whitney *U*	*p*
At T0	16.00	0.020	34.50	n.s.	13.00	n.s.	33.00	n.s.
At T1	21.00	0.002	18.00	0.005	8.00	0.001	22.00	0.002
At T2	7.00	0.009	3.50	0.005	5.00	0.010	5.50	0.006
At T3	1.00	0.004	2.50	0.007	2.00	0.006	3.00	0.008
At T4	6.50	0.003	12.00	0.020	7.00	0.018	1.00	0.018

n.s.: not significant.

Table 5 – Univariates analysis for Griffiths' GQ and quotients of individual scales at T4

Covariates	GQ		Scale A		Scale B		Scale C		Scale D		Scale E	
	β coefficient	p	β coefficient	p	β coefficient	p	β coefficient	p	β coefficient	p	β coefficient	p
Onset age	0.562	**0.019***	0.554	**0.021***	−0.536	**0.027***	0.560	**0.019***	0.565	**0.018***	0.591	**0.012***
Visual score at T0	−0.716	0.001*	−0.713	0.001*	−0.693	0.002*	−0.687	0.002*	−0.729	0.001*	−0.714	0.001*
AOR at T0	−0.831	<0.001*	−0.841	<0.001*	−0.801	<0.001*	−0.811	<0.001*	−0.804	<0.001*	−0.837	<0.001*
Sleep pattern at T1	−0.740	**0.001***	−0.742	**0.001***	−0.694	**0.002***	−0.718	**0.001***	−0.758	**<0.001***	−0.731	**0.001***
Hypsarrhithmia at T1	−0.346	**0.174^**	−0.380	**0.132^**	−0.320	**0.210^**	−0.348	**0.171^**	−0.346	**0.174^**	−0.307	^
Visual score at T1	−0.699	**0.002***	−0.715	**0.001***	−0.674	**0.003***	−0.659	**0.004***	−0.701	**0.002***	−0.705	**0.002***
AOR at T1	−0.527	**0.044***	−0.566	**0.028***	−0.467	**0.079**	−0.567	**0.027***	−0.425	**0.115**	−0.512	**0.051**
Brain lesions at T1	−0.828	**<0.001***	−0.779	**<0.001***	−0.843	**<0.001***	−0.840	**<0.001***	−0.848	**<0.001***	−0.803	**<0.001***
Sleep pattern at T2	−0.791	0.001*	−0.761	0.003*	0.801	0.001*	−0.749	0.003*	−0.791	0.001*	−0.834	<0.001*
Hypsarrhithmia at T2	−0.577	0.031*	−0.572	0.033*	0.584	0.028*	−0.612	0.020*	−0.483	0.080	−0.593	0.025*
Visual score at T2	−0.736	0.001*	−0.719	0.002*	−0.740	0.001*	−0.707	0.002*	−0.753	0.001*	−0.742	0.001*
AOR at T2	−0.737	0.004*	−0.737	0.004*	0.711	0.006*	−0.685	0.010*	−0.795	0.001*	−0.742	0.004*
Sleep pattern at T3	−0.763	0.002*	−0.730	0.005*	−0.773	0.002*	−0.729	0.005*	−0.753	0.003*	−0.816	0.001*
Hypsarrhithmia at T3	−0.589	0.021*	−0.608	0.016*	0.565	0.028*	−0.614	0.015*	−0.527	0.044*	−0.555	0.032*
Visual score at T3	−0.853	<0.001*	−0.846	<0.001*	−0.837	<0.001*	−0.815	<0.001*	−0.837	<0.001*	−0.858	<0.001*
AOR at T3	−0.646	0.009*	−0.624	0.013*	−0.627	0.012*	−0.612	0.015*	−0.674	0.006*	−0.622	0.013*

Variables reported in the table are only those significantly associated to at least one outcome.
In bold the covariates with p-value<0.20 and selected for multivariate regression models.
* p-Value <0.05.
^p-Value <0.20.

Table 6 – Multivariate analysis of covariates at T1 for developmental outcome

Covarites	GQ		Scale A		Scale B		Scale C		Scale D		Scale E	
	β coefficient	p	β coefficient	p	β coefficient	p	β coefficient	p	β coefficient	p	β coefficient	p
Onset age	0.091	0.592	0.071	0.693	0.114	0.463	0.055	0.692	0.151	0.281	0.123	0.479
Sex	−0.137	0.322	−0.317	0.062	−0.153	0.338	−0.221	0.057	−0.011	0.951	−0.171	0.269
Sleep pattern	−0.006	0.981	−0.039	0.890	0.075	0.777	0.088	0.683	−0.080	0.735	−0.042	0.875
Hypsarrhythmia	−0.117	0.462	−0.272	0.072	−0.112	0.403	−0.117	0.371	−0.121	0.328	–	–
Visual score	−0.250	0.126	−0.399	**0.017**	−0.373	**0.017**	−0.099	0.451	−0.385	**0.010**	−0.426	**0..013**
AOR	−0.384	**0.010**	−0.187	0.326	−0.077	0.760	−0.388	**0.002**	0.073	0.735	−0.220	0.191
Brain lesions	−0.750	**<0.001**	−0.705	**0.001**	−0.688	**<0.001**	−0.855	**<0.001**	−0.691	**<0.001**	−0.624	**0.001**
R^2	0.820		0.820		0.818		0.906		0.839		0.875	

In bold p-value <0.05.

attained within 6th months after the onset of spasms. These cases could be classified as benign forms of West syndrome. The other 14 cases showed more marked abnormal development since spasm onset, and most had GQ outcomes corresponding to severe retardation.

The dual neurosensory impairment in our patients, i.e. auditory and visual, was present at the onset of the disease[16,17] and persisted throughout the whole follow-up, possibly suggesting an underlying common mechanism. Both visual and auditory functions were significantly related to neurological and developmental competency throughout the study, with the exception of the AOR, which was not strongly associated with development at T0 and T1.

That the neurosensory impairment is consistent with the neurological examination is not surprising, since both could simply be considered as effects of brain injury from the associated epileptic disorder. More intriguing is the relationship between neurosensory impairment and cognitive development. Indeed, the relationship between the functionality of vision or hearing and cognitive organization in early development is a primary topic of research in human cognitive neuroscience.[28] Many studies stress that visual impairment is associated with cognitive disorders in infants with early brain injury.[29–31] As a result, visual function in the first months is considered a strong predictive factor for cognitive evolution. This hypothesis is confirmed by our present study. Our multivariate analysis testing the predictive value of neurosensory functions at the acute stage of the disease (corresponding to the T1 control), showed that visual function was significantly associated with development in all of the Griffiths' scales except subscale C. As expected, AORs were significantly associated with the hearing and speech subscale, which has the highest auditory content and is the most linked to language development.

Interestingly, a disorder of sleep organization, related to defective neurosensory and neurodevelopmental functions, is already present at T1 (even at T0 for visual function) and is persistently present throughout all time points. The EEG sleep abnormalities seen in infancy, in particular the lack of maturation of features of slow sleep, such as spindles, may be a stronger marker of abnormal basal electrographic activity than hypsarrhythmia itself, which was critical discriminant only at T1. Indeed, there is evidence that sleep state organization in infancy is associated with neurosensory and neurodevelopmental functions.[32] The function of slow sleep in consolidating learning in children is well known.[33,34]

The role of persistent disorganization of slow sleep, as well as brain injury, in sensory and developmental function is confirmed by the repeated measures MANOVA. The presence of hypsarrhythmia also affects developmental and visual functioning, and could explain some of the variability seen over time. No role is apparently played by seizures, either spasms or partial fits.

In terms of the effects of AED on neurodevelopment, the present study suggests that ACTH is associated with poor visual function. This impairment, however, disappeared after weaning from the drug. Visual function also appears impaired in patients treated for partial seizures with phenobarbital, consistent with previous reports.[35] The most significant side effect of VGB, concentric visual field defect, has previously

been described in children,[36,37] although the occurrence in infants under 1 year of age is still unknown.[38] Our data, obtained with a standardized technique,[39] are the first reported in infants, and require further confirmation. In this study, none of the infants treated with VGB experienced visual field deterioration. Rather, six cases showed an improvement in visual field. In addition, the global visual function assessment was improved in infants treated with VGB.

Our study is limited by the small sample size, which is barely adequate for multiple statistical analyses, and by the lack of comparative epidemiological data. Furthermore, the time span of the follow-up is too short to assess the later cognitive deficits reported in the literature.[40] Suggestions arising from this study deserves thus further confirmations. An analysis of the role played by specific etiologies could clarify the expected evolution in each individual case and perhaps give some further insight into the possible pathogenic mechanism.

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