Visual Function in Infants with West Syndrome: Correlation with EEG Patterns

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Summary: *Purpose:* Several studies have reported behavioral and electrophysiological evidence of visual impairment during the active stage of West syndrome. The underlying mechanisms are, however, poorly understood, and little has been reported about the correlation between visual impairment, EEG patterns, and brain lesions. The aim of the study was to assess visual function at the onset of spasm and 2 months thereafter and relate visual findings to brain lesions and EEG features.

Methods: Twenty-five infants with West syndrome were enrolled and studied with (a) a full clinical assessment including a battery of tests specifically designed to assess visual function, (b) a video-polygraphic study, and (c) brain magnetic resonance imaging (MRI). Besides brain neuroimaging and EEG comparison with visual function, an intra-EEG analysis was performed to investigate the possible relation of EEG patterns to fluctuating visual behavior (fixation and following).

Results: Twenty-two children had at least one abnormal result on one or more of the tests assessing visual function at T_0. Visual impairment at the spasm onset was related to the sleep disorganization rather than to the hypsarrhythmic pattern in awake EEG. After 2 months, both EEG features become significantly linked to visual function. Visual function improved in several cases after 2 months, in parallel with the seizure regression. No relation was found between EEG patterns and fluctuating visual behavior.

Conclusions: The study supplies new evidence of the involvement of visual function in West syndrome. The presence of abnormal visual findings in infants without lesions on brain MRI suggests that visual abnormalities are due not only to brain injury but also to epileptic disorder per se. New insight is also provided into the possible mechanisms underlying clinical and EEG abnormalities. **Key Words:** West syndrome—Visual function—Brain lesions.

It has been previously reported that various aspects of visual function are impaired during the active stage of West syndrome. Visual abnormalities that can already be detected by using behavioral and electrophysiological tests during the first weeks of the disease and even before (1–4) include poor visual responsiveness (5–8), abnormal visual evoked potentials (9,10), and deficits in other aspects of visual function such as fixation shift (4).

The mechanisms underlying visual abnormalities, however, are not fully understood, and little has been reported regarding the possible role played by epilepsy or brain lesions, which are frequently seen in infants with West syndrome.

The aim of this study was twofold: first, to assess visual function both at the onset of West syndrome and 2 months thereafter, and second, to correlate these findings with EEG and magnetic resonance imaging (MRI) patterns. More specifically we wished to establish (a) the range and severity of visual abnormalities in West syndrome; (b) the possible relation between visual abilities, EEG patterns, and brain lesions; and (c) the role played by the epileptic disorder in modulating the fluctuation of visual skills.

PATIENTS AND METHODS

Twenty-five successive patients with West syndrome, admitted in three Child Neurology Divisions (Universities of Pavia, Pisa, and Catholic of Rome) since 2001, were prospectively enrolled in the study. All patients showing an onset of visible spasms more than 1 week

TABLE 1. *Clinical data*

Case	Etiology	Spasm onset	Antiepileptic drugs	MRI	Epilepsy evolution after two months
1	Cryptogenic	8m, 2w	ACTH	Normal	No more spasms
2	"	4m	VGB	Normal	No more spasms, partial seizures
3	"	7m	VGB, ACTH	Normal	No more spasms
4	"	5m, 2w	VGB, ACTH	Normal	No more spasms
5	Tuberous sclerosis	4m, 2w	VGB, ACTH, PB	Cortical and subcortical tubers with ependimal nodules	Spasm and partial seizure worsening
6	"	7m	VPA, VGB	Cortical and subcortical tubers with ependimal nodules	No more spasms
7	"	8m	VGB, CBZ, TPM	Cortical and subcortical tubers with ependimal nodules	No more spasms
8	"	7m	ACTH, CBZ, BDZ, PB	Cortical (F.P.) and subcortical tubers	Spasms
9	Other symptomatic	13m	VGB, BDZ, PB	Multicystic encephalomalacia	Spasms
10	"	8m	BDZ, PB, ACTH	Cortical (all regions) and white matter injuries	Spasms
11	"	4m	BDZ, PB	Cortical (O.) and white matter injury including optic radiation and basal ganglia	Spasms
12	"	3m	VPA, PB	Cortical (all regions) and periventricular white matter injuries	No more spasms, partial seizures (poor frequency)
13	"	7m	ACTH, PB	Cortical (all regions) and white matter injuries	Partially controlled
14	"	5m	VGB	Cortical (P.O.) and white matter injury (dysplasia)	Partially controlled
15	"	7m	VPA	Cortical (P.O.) and white matter injury	No more spasms, partial seizures (poor frequency)
16	"	4m	ACTH, PB	Periventricular white matter injury	Partially controlled
17	"	4m	BDZ, PB	Paratrigonal periventricular leucomalacia	No more spasms, partial seizures
18	"	4m	ACTH, PB	Left ventricular dilatation	No more spasms
19	"	10m	VGB, ACTH, VPA, BDZ	Periventricular white matter injury	Spasm worsening
20	"	2m, 2w	ACTH, PB	Periventricular white matter injury	No more spasms
21	"	3m, 2w	VGB, ACTH, PB	Periventricular white matter and basal ganglia injuries	No more spasms
22	"	7m	VPA, VGB, PB, TGB, TPM	Cortical (F.T.) injury	Spasm worsening
23	"	6m	VGB, ACTH, VPA	Unilateral cortical (P.) and subcortical malacia	Spasm and partial seizure worsening
24	"	6m	ACTH, PB	Cortical (F.P.) and sub-cortical unilateral malacia (MCA stroke)	No more spasms
25	"	2m	ACTH, VPA, PB	Cortical (P.T.) and periventricular white matter injuries	No more spasms, partial seizures

F: frontal, T: temporal, P: parietal, O: occipital, regions.
ACTH: adrenocorticotropine hormone, VGB: vigabatrin, PB: phenobarbital, VPA: valproic acid, CBZ: carbamazepine, TPM: topiramate, BDZ: benzodiazepine, LTG: lamotrigine, TGB: tiagabine.

before Hospital admission were excluded. The main clinical data are reported in Table 1. As to the etiology of cases, four were cryptogenic, four were associated with tuberous sclerosis, and the remaining symptomatic patients had different causes: most of them (13 patients) were due to perinatal causes, whereas cerebral malformations accounted for two patients, infectious disease for one, and a suspected metabolic disease for the last one.

All patients underwent a full clinical, MRI, and EEG assessment at the spasm onset (T_0) and again, with the exception of brain MRI, after 2 months (T_1).

Clinical assessment

Clinical assessment included an ophthalmic examination and a battery of tests specifically designed to assess visual function (11) in the first years of life. Grating acuity was assessed binocularly by means of the Keeler or Teller acuity card procedure (ACP) (12). This method is based

on an inborn preference for a pattern (black and white gratings of different stripe widths) over a uniform field, depicted on cards with decreasing stripe widths. Acuity values were expressed in minutes of arc (or cycles per degree) and were compared with normative data reported in the literature (13). Visual fields were assessed by using kinetic perimetry, according to the technique described in detail elsewhere (14). Normative data for term and preterm infants are available (14). Oculomotor behavior was assessed by testing fixation, pursuit, and visual attention. This assessment was scored according to the criteria reported in Table 2. The global score, from 0 to 24, was the result of the sum of the scores for each item.

Video-EEG

Video-polygraphic study using 21 EEG electrodes according to the 10/20 International System or nine electrodes for the youngest infant, and deltoid surface

TABLE 2. *Scoring of visual function*

Score	Acuity (cy/degree)	Visual field	Fixation	Pursuit	Eye movement	Visual attention
0	Normal (more than −1 SD)	Normal (more than −2 SD)	Present and constant	Smooth, with wide arch	Emmetric saccades	Constant
1	Borderline (between −1 SD and −2 SD)	Mild bilateral reduction (between −2 SD and −3 SD) or severe monocular (more than −3 SD)	Sporadic and brief	Poor smoothness, with incomplete arch	Dismetric saccades and/or with increased latency	Fluctuating
2	Low acuity (less than −2 SD)	Severe bilateral reduction (more than −3 SD)	Possible only with favorable environmental conditions or after stimulation	Possible only with favorable environmental conditions or after stimulation	No saccades (severe hyper-fixation and/or compensatory movements)	Poor
3	Very poor: evaluation is not possible	Very poor	Absent	Very poor	Chaotic and erratic movements	Absent
4	Not testable due to poor collaboration	Not testable due to poor collaboration	Not testable due to poor collaboration	Not testable due to poor collaboration	Not testable due to poor collaboration	Not testable due to poor collaboration

electromyogram (EMG) was performed. Recordings lasted ≥1 h and always included ≥30 min of sleep EEG.

The EEG was analyzed in two ways.

1. Intra-EEG analysis of visual behavior (fixation and pursuit). During a part of the video-EEG in the awake state, free of seizures, a block of nine 10-s visual tests was administered, consisting of the fixation and pursuit of a standardized luminous toy. The visual performance was scored from 0 to 3 according to the performance level: full (0) or partial (1) pursuit, fixation without pursuit (2), or no fixation (3). In case of fluctuating visual performances, each score was considered in relation to the EEG features during the period concurrent to the visual test. A hypsarrhythmia scoring system based on three features slightly modified from Kramer et al. (15) was used. Each feature was scored on a scale from 0 to 3 according to growing severity: the percentage of delta activity (<50%, between 50 and 75%, >75%, and 100%), delta maximum voltage (<120 μV, between 120 and 200 μV, between 200 and 300 μV, and >300 μV), and the frequency of spikes and sharp waves (no spikes or sharp waves, spikes at a frequency of ≤1/5 s; spikes at a frequency of 1/5 s to 1/s; or spikes at a frequency of ≥1/s). Hypsarrhythmia was considered "severe" when the global score was between 7 and 9, "moderate" when it was between 4 and 6, and "mild" between 1 and 3.

2. Analysis of EEG in awake and sleep states. To investigate the correlation between the organization of sleep and awake EEG and the results of the tests of visual function, we also analyzed sleep patterns (organization, sequence of stages, presence of sleep spindles), classifying them as either normal or abnormal, and hypsarrhythmic features in a 10-s segment of the most representative part EEG recording in the awake state. Hypsarrhythmic features were scored according to criteria previously described.

MRI

MRI was performed by using an MR 1.5-Tesla apparatus available in the different neuropediatric centers.

Statistical analysis

The Spearman *r* coefficient was used to compare awake-state hypsarrhythmia (severe, moderate, mild, and absent) and sleep organization (normal and abnormal) versus global neurovisual scores. Moreover, a multivariate analysis was conducted by using the generalized linear model technique to compare the scores of fixation and following performed during the EEG versus the three different EEG parameters.

The statistical significance of p < 0.05 was set. Data were analyzed by using SPSS for Windows.

RESULTS

Patients were classified according to the category of brain features shown on MRI: (a) normal MRI (cryptogenic West) (n = 4) (cases 1–4); (b) symptomatic patients due to tuberous sclerosis (n = 4) (cases 5–8), with several tubers spread cortically and subcortically plus, in three patients, subependymal nodules; (c) symptomatic patients with cortical injuries including occipital cortex and/or optic radiation (n = 7) (cases 9–15); (d) symptomatic patients with white matter lesions (periventricular leukomalacia) not involving optic radiation (n = 6) (cases 16–21; and

TABLE 3. *Visual function*

		Normal MRI		Tuberous Sclerosis		Cortical lesion involving visual structures		Periventricular lesion not involving optic radiation		Cortical lesion not involving occipital structures	
Acuity	T_0	X○◑◑		○○	○◔	●●X	●●◔●	◑	◑●○●●	○◔	○●
	T_1	X◑◑○		◑○	○○	●●X	●●◑◔	◑	◑X○◑◑	◔●	○●
Visual field	T_0	X○○○		◔○	○○	●●X	●●X●	◑	●●○●●	●●	○●
	T_1	X○○◔		◔○	○○	●●X	●●◑●	◔	●X○●◔	●◑	○●
Fixation	T_0	◔○○○		○○	○○	◑●●	◔○◑○	○	◑◔○◑◔	◑◑	○◑
	T_1	◔○○○		○○	○○	◑●●	◔○◑◔	◑	◑○◑○◔	◔◑	○◔
Pursuit	T_0	◔○○○		○○	○◔	◑●●	●○◔●	◑	◑●◑○○	◑◑	○●
	T_1	◔○○○		○○	○◔	◑●●	●○◔○	◑	◑X○◑○	◑◔	○○
Eye movement	T_0	◔○◔◔		◔○	○◔	●●◑	◑●X◑	◑	◑◑◑●◑	X◑	○◑
	T_1	◔○◔◔		◔○	○○	●●◑	◑●◔○	◑	◑●◔●◑	◑◑	○◔
Visual attention	T_0	●○○○		◔○	○◔	◑●●	◑◑◑●	◔	◑●◔◑●	◑●	○◑
	T_1	◑○○◔		○○	○◔	●●●	◑◑◑◔	◔	◑●◔○◑	◔◑	○◔

In each row, concerning the six items of visual function, circles indicate the twenty-five cases, examined first in T_0 (upper line), then in T_1 (lower line); the symbol of T_1 row directly below that of T_0 row corresponds to the same case.

Visual impairment score ○=0; ◔=1; ◑=2; ●=3; X=not testable due to poor cooperation. According to our scoring system, 0 is normal and 3 is the worst functional score (see Table 2 for explanation).

The shadowed areas identify infants who showed an improvement or control of seizures.

(e) symptomatic patients with cortical injury not involving occipital areas (n = 4) (cases 22–25).

Visual function (at T_0)

All patients had a normal ophthalmologic examination. Three (two with tuberous sclerosis and one otherwise symptomatic: cases 6, 8, and 24) had normal results on all tests assessing various aspects of visual function, and 22 had at least one abnormal result. Only one symptomatic case (10) among these had severe abnormalities on all tests (Table 3). Besides fixation and pursuit, the most discriminating parameters in our series seemed to be ocular motility and visual field: whereas cryptogenic and tuberous sclerosis were normal or almost normal (level 0 or 1), all but three of the other symptomatic cases had a level of performance equal to or higher than level 2.

Visual function and brain MRI findings

Both cryptogenic and tuberous sclerosis patients had generally good visual abilities, whereas the other symptomatic patients were more often associated with abnormal visual findings. Only three (14, 18, and 24) of the 17 cases in the latter group had normal results on visual tests,

and they were randomly spread in different groups (c, d, and e) of MRI changes.

Relation of hypsarrhythmic awake EEG and sleep patterns with visual function (at T_0)

EEG findings (hypsarrhythmic awake EEG and sleep patterns), in relation to neurovisual global scores, are reported in Table 4. Statistical analysis showed no significant correlation between awake hypsarrhythmic features and global neurovisual scores ($r = 0.049$; $p = 0.817$). In contrast, sleep patterns, in particular, spindle organization adequate for age, were related to visual performances ($r = -0.475$; $p = 0.016$).

Intra-EEG analysis of visual behavior (fixation and pursuit)

Seventeen patients at onset of the syndrome and 14 after 2 months had a fluctuation in the visual performances of fixation and pursuit concurrent with EEG monitoring. Comparing the results of the visual test with three different EEG parameters (delta maximum voltage, delta frequency, and spike or sharp-wave frequency), multivariate analysis (generalized linear model analysis) did not find any statistical significance.

TABLE 4. *EEG patterns and visual function*

| | Neurovisual global score | | | |
| | T_0 | | T_1 | |
	0–5	>5	0–5	>5
Disorganized or absent sleep pattern	●●●●◐	●●●●●	◐	●●●◐◐
		●●●●◐		◐◐◐◐◐
		◐◐◐◐○		◐○
Organized sleep pattern	●●●◐	●	◐◐◐◐◐	◐◐
			◐◐○○○	

●=severe, ◐=moderate, ◐=mild or ○=absent awake hypsarrhythmia.

Visual function after 2 months (T_1): correlation with EEG and epileptic disorder

A general waning of hypsarrhythmic features was noted; the residual hypsarrhythmic cases were related to neurovisual performance ($r = 0.518$; $p = 0.008$) like EEG sleep organization ($r = -0.635$; $p = 0.001$). Some improvement of visual function was observed (Table 3). This improvement more frequently concerned those patients with a good, or at least partial, control of seizures and in whom the risk of overmedication was, conversely, generally low (nine cases vs. only four without seizure control showing a visual improvement).

DISCUSSION

This study confirms previous observations that visual function is impaired when spasms due to West syndrome first appear (5,6,16,17). Whereas previous studies reported mainly abnormalities in ocular motility and fixation/pursuit, we were able to show that impairment also concerns more cortically mediated aspects of visual function like acuity, visual field, and visual attention.

Drawing general conclusions about the profile of the single groups of our series is not possible, because of the poor number of cases and the lack of an epidemiologic value of our sample. However, the most severe and persistent abnormalities of visual function were found in infants with lesions involving the basal ganglia, central and posterior cortical areas, as well as in those with optic radiation, but the presence and the severity of visual abnormalities was not always related to the presence of brain lesions, given that abnormal visual findings also were common in infants with normal MRIs or with lesions not primarily concerning the basal ganglia, optic radiation, and/or primary visual cortex. In such infants, the presence of abnormal visual function suggests the possible effect of the epileptic disorder per se, as previous studies have reported that infants with similar MRI findings but without epilepsy always have normal visual function (11,18). The possible effect of epilepsy on visual function is further suggested by the recovery of visual function when seizures improved.

We also found that the presence and the severity of visual abnormalities was not always related to the severity of hypsarrhythmia at T_0. The organization of the sleep pattern, in contrast, had a better association with visual findings, as infants with a recognizable sleep organization more often had good visual function. Kramer et al. (15) did not find any relation between the presence of sleep spindles and outcome. Kramer's results, however, are a mixture of epileptic and developmental outcomes, and our results do not concern outcome but only the possible relation between EEG patterns and visual functions at the onset of West syndrome. It is therefore difficult to make a fair comparison. Results showing that a disorder of sleep EEG organization, rather than hypsarrhythmia during awake EEG, is associated at the onset of West syndrome with poor visual performance are not surprising, as it has already been reported that hypsarrhythmia per se is not always linked to visual impairment, whose absence was considered among the distinct features of an idiopathic form of West syndrome (19,20). Conversely, evidence indicates that state organization in infancy is associated with neurobehavioral functions including visual and cognitive abilities (21–23).

It is of interest that hypsarrhythmia becomes significantly related to low scores in visual function only after the first 2 months. This could be because transitory hypsarrhythmia observed at T_0 in less severe or more drug-responsive infants with epilepsy is not generally associated with poor visual function. This can weaken the statistical correlation between EEG pattern and visual function at T_0. Thus if confirmed by the follow-up, good visual function at T_0 could be considered another aspect of the definition of the benign (idiopathic?) form of the West syndrome. In contrast, a persistent hypsarrhythmia at T_1, like sleep disorganization, becomes another index of the severity of West syndrome.

In this study we also wished to establish whether fluctuations of visual attention were related to EEG changes.

Previous studies reported that visual impairment at the onset of West syndrome is often fluctuating, but although this variability was initially considered an effect of ictal activity (24), more recent studies reported that it can also be observed independently (4,19).

We did not find any significant correlation between interictal EEG features and performances of fixation and pursuit in our cases. The poor association might reflect the choice of fixation and pursuit as the test assessing visual attention. Even though one cannot exclude some cortical endogenous control of low-order attentional functions such as alertness, fixation and pursuit have previously been found to be normal even in infants with severe holoprosencephaly (25) and are the result of a prevalently subcortical function, depending on the integrity of ascending brainstem pathways and oculomotor nerves. It is not surprising that fixation and pursuit are abnormal in infants with West syndrome, as the disruption of sleep organization and the dysfunction of ascending pathways with imbalance of sensitive inputs probably due to a brainstem disorder have been reported in this syndrome (24,26). The poor correlation of fixation/pursuit with EEG changes might reflect the fact that these functions are subcortically mediated and that the expression of their impairment at cortical level, as shown by EEG, may be looser.

In summary, our results provide further evidence of the presence and severity of visual abnormalities in infants with West syndrome and provide further insight into their association with EEG findings and the possible mechanisms underlying clinical and EEG abnormalities.

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