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Original article

Auditory attention at the onset of West syndrome: Correlation with EEG patterns and visual function

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Abstract

At the onset of West syndrome a specific impairment of visual function has been clearly demonstrated, while other aspects of sensorial development, and in particular of the auditory function, have been less studied. The aim of this study was to evaluate auditory function and orienting responses at the onset of West syndrome, and to relate the results with EEG patterns, visual function and neurodevelopmental competence. A prospective multicentric study was performed on 25 successively enrolled infants with West syndrome; all the patients underwent a full clinical assessment, including MRI and video-EEG, visual function and auditory orienting responses (AORs) as well as Griffiths' developmental scales. The whole assessment performed at the onset of spasms (T_0) was repeated after two months (T_1). AORs resulted significantly impaired both at T_0 and T_1. At the onset of spasms a highly significant relationship of auditory attention with visual function and neurodevelopmental competence was shown in both cryptogenic and symptomatic forms, but it was no longer present after two months. Our results may suggest a possible pervasive effect of the epileptic disorder on sensory processing, associated to a deficit of neurodevelopment. Although we failed to show a significant correlation between auditory orienting responses and EEG patterns, some evidence seems to support at least partially an influence of the epileptic disorder per se on the genesis of the sensorial impairment. A longer follow up and a larger cohort will be useful for a better clarification of these findings.

Keywords: West syndrome; Auditory orienting responses; Auditory attention; Visual function; Cognitive development

1. Introduction

West syndrome is a well-defined epileptic encephalopathy occurring during the first year of life and characterized by a severe EEG derangement associated with spasms and an arrest or deterioration of cognitive development. A main clinical sign at the onset of the syndrome consists of a specific visual impairment confirmed by several behavioural and electrophysiological studies [1–6]. Less attention has been devoted to other aspects of sensorial moldalities such as auditory stimuli processing [7,8], even though a frequently reported clinical sequela of the syndrome concerns language and social acquisitions [3,4].

In a recent longitudinal study, we have confirmed the early impairment of visual function in infants with West syndrome showing some evidence of a direct etiologic role of the epileptic disorder per se on visual impairment [9,10]. As part of the same multicentric study, we report the results of the longitudinal assessment of auditory function in the same cohort. In particular, the aim of this study has been to evaluate auditory function and orienting responses at the onset of West syndrome and to relate the results with EEG patterns, visual function and neurodevelopment.

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2. Patients and methods

Twenty-five patients with West syndrome, successively admitted from January 2001 in three Child Neurology Divisions (Universities of Pavia, Pisa and Catholic of Rome), were enrolled in the study. At the onset of the syndrome, all patients underwent a full clinical assessment including: magnetic resonance imaging (MRI), prolonged video-EEG, assessment of auditory and visual functions, and neurodevelopment. The whole assessment performed at the onset of spasms (T_0) was repeated after two months (T_1), with the exception of brain MRI.

2.1. Neuroimaging

MRI was performed using a 1.5 T apparatus available in the different neuropediatric centers. According to the clinical results and the MRI, patients were classified in three categories: (a) cryptogenic West, (b) symptomatic West with tuberous sclerosis complex (TSC) (cortical and sub-cortical tubers with or without sub-ependymal nodules); (c) symptomatic West with different types of brain injury.

2.2. Assessment of auditory function

All the infants underwent an otorhinolaryngological examination. Hearing ability was assessed by means of electrophysiological measures, the auditory brainstem responses (ABR), and behavioural tests, the auditory orienting responses (AORs).

In order to better correlate the auditory function with the overall brain activity, AORs were tested during EEG monitoring. The infant was supported in a semi-supine position on mother's lap, in a quiet awake state, about one hour after feeding. A standard rattle was used to produce sounds with an intensity of around 80 dB, at a distance of about 30 cm from the infant ears. The sound lasted approximately 2 s and was presented at least twice for each ear alternatively. Responses were graded as follows: (3) quieting, no reactive eyes or general movements; (2) quieting, some reactive general motor responses, either interruption or over-activation of motor responses; (1) incomplete orienting response with eyes turning only or with partial head turning; (0) eyes brightening and searching with complete head turning to the side of sound. The median value for each subject was considered, and possible right–left asymmetries were recorded.

The results in the cohort of infants with West syndrome were compared with those obtained in a group of normal infants matched for age, sex, and gestational age.

2.3. Assessment of visual function and neurodevelopment

A full battery of age specific tests assessing visual function was used, including acuity (Keeler cards), fixation and following, visual field, ocular motility and visual attention. The results were scored according to the criteria previously reported [10]. Neurodevelopmental quotients were obtained by means of the Griffiths' developmental scales.

2.4. Video-EEG

Video-polygraphic study was performed using 21 EEG electrodes according to the 10/20 International System or 9 electrodes for the younger infants, and deltoid surface EMG. Recordings lasted at least 1 h and always included at least 30' of sleep.

The EEG was analyzed in two ways:

(a) Organisation of awake and sleep states. The organization of awake and sleep states was assessed on the basis of the identification of EEG stages and the presence of physiological features, namely sleep spindles. Tracings were accordingly classified as either normal (0) or abnormal (1).

(b) Hypsarrhythmia. The degree of hypsarrhythmia was assessed on a representative segment of the EEG tracing, during the awake state and free of seizures. A scoring system based on three features slightly modified from Kramer et al. [12] was used. Each feature was scored on a scale from 0 to 3 according to increasing severity: the percentage of delta activity (less than 50%, between 50 and 75%, higher than 75, 100%), delta maximum voltage (<120 μV, between 120 and 200 μV, between 200 and 300 μV, >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–1/s, spikes at a frequency of $>/=1$/s). The final score ranged from 0 (lowest degree of hypsarrhythmia) to 9 (highest degree of hypsarrhythmia).

2.5. Statistical analysis

The comparison of AORs between cases and controls, both at T_0 and T_1, was performed by means of the non parametric Mann–Whitney test for independent samples, with a significance level set at $P<0.05$. The inter-group differences were analysed by means of the Kruskall–Wallis test for several independent groups.

The Spearman r coefficient was used to compare the degree of hypsarrhythmia and sleep organization vs. global AOR scores. Moreover, a multivariate analysis was conducted using the generalized linear model technique to compare the AOR scores obtained during the EEG vs. the three different EEG parameters of hypsarrhythmia. The statistical significance was set at $P<0.05$.

All statistical analyses were performed using SPSS for Windows.

3. Results

Twenty five infants were eligible for the study (Table 1), subdivided in 3 groups: (1) cryptogenic West, 4 patients; (2) symptomatic West with tuberous sclerosis complex (TSC), 4 patients; (3) symptomatic West due to a prenatal or perinatal brain lesion, 17 subjects. The onset of spasms occurred between 2 and 13 months (mean age: 5.8 months); in two patients (#6,12) partial seizures preceded the onset of spasms, whereas in other seven cases (#1,5,10,11,13,15,16) partial seizures occurred at about the same time of spasms or clearly after.

Data concerning the assessments at T_0 and T_1 are shown in Table 2.

3.1. Assessment of auditory function at T_0

ABR showed an auditory threshold over 80 dB in four patients, while all the remaining 21 had a normal threshold (<80 db). In two of the 21 patients with normal auditory threshold we were unable to assess the AORs, because of poor compliance. The remaining 19 cases all completed the assessments of AOR.

No significant asymmetries, i.e. a right–left difference higher than 1, were present either in the study group or in the control group. Five of the 19 subjects assessed (26%) had bilateral responses with complete head turning to the side of sound (score 0); in another five infants (26%) the responses were less complete but the overall score was equal or

Table 1
Clinical data

#	Spasm onset	Aetiology	MRI	Partial seizures (age of onset)	Antiepileptic drugs	Epilepsy evolution
1	4 m	Cryptogenic	Normal	No	VGB	No more spasms, partial seizures
2	7 m		Normal	No	VGB, ACTH	No more spasms
3	5 m 2 w		Normal	No	VGB, ACTH	No more spasms
4	8 m 2 w		Normal	No	ACTH	No more spasms
5	4 m 2 w	Sympto:TSC	C and SC tubers with ependimal nodules	Yes (4 m 2 w)	PB, VGB, ACTH	Spasm and partial seizure worsening
6	7 m		C (FP) and SC tubers	Yes (5 m 2 w)	PB, ACTH, CBZ, BDZ	Spasms
7	8 m		C and SC tubers with ependimal nodules	No	VPA, VGB	No more spasms
8	7 m		C and SC tubers with ependimal nodules	No	VGB, CBZ, TPM	No more spasms
9	7 m	Sympto: non-TSC	Left unilateral C (FT) injury	No	VPA, VGB, TGB, TPM	Spasm worsening
10	4 m		Paratrigonal PV leukomalacia	No	PB, BDZ	No more spasms, partial seizures
11	6 m		Left unilateral C (P) and SC malacia	Yes (6 m)	VGB, ACTH, VPA	Spasm and partial seizure worsening
12	10 m		PV WM injury	Yes (7 m 2 w)	VGB, ACTH, VPA, BDZ	Spasm worsening
13	3 m		C (all regions) and PV WM injuries	Yes (3 m)	PB, VPA	No more spasms, partial seizures
14	3 m 2 w		PV WM and BG injuries	No	PB, VGB, ACTH	No more spasms
15	2 m		R unilateral C (PT) and PV WM injuries	Yes (2 m)	PB, ACTH, VPA	No more spasms, partial seizures
16	7 m		C (PO) and WM injury	No	VPA	No more spasms, partial seizures from 7.5 m
17	8 m		C (all regions) and WM injuries	No	BDZ, PB, ACTH	Spasms
18	13 m		Multicystic encephalomalacia	No	PB, VGB, BDZ	Spasm worsening
19	4 m		L ventricular dilatation	No	PB, ACTH	No more spasms
20	6 m		C (FP) and SC L unilateral malacia	No	ACTH, PB	No more spasms
21	4 m		PV WM injury	No	ACTH, PB	Spasms
22	2 m 2 w		PV WM injury	No	PB, ACTH	Spasms
23	7 m		C (all regions) and WM injuries	No	PB, ACTH	Spasms
24	4 m		C (O) and WM injury including OR and BG	No	PB, BDZ	Spasms
25	5 m		C (PO) and WM injury (dysplasia)	No	VGB	Partially controlled spasms

TSC, tuberous sclerosis complex; C, sortical; SC, subcortical; PV, periventricular; WM, white matter; BG, basal ganglia; OR, optica radiatios; L, left; R, right; F, frontal; P, parietal; T, temporal; O, occipital; ACTH, Adrenocorticotropine Hormone; VGB, Vigabatrin; PB, Phenobarbital; VPA, Valproic Acid; CBZ, Carbamazepine; TPM, Topiramate; BDZ, Benzodiazepine; LTG, Lamotrigine; TGB, Tiagabine.

Table 2
Auditory, visual, neurodevelopmental, EEG, and epilepsy data at T_0 and T_1

#	T_0						T_1					
	Hypoacusia (ABR> 80 dB)	AOR (median values)		Visual function	DQ	VideoEEG sleep/hypsar	Hypoacusia (ABR- ≥80 dB)	AOR (median values)		Visual function	DQ	VideoEEG sleep/ hypsar
		Cohort group	Control group					Cohort group	Control group			
1	No	0	0	1	117	0/8	No	1	0	3	nt	0/1
2	No	0.5	0	3	94	0/8	No	1	0	3	106	0/1
3	No	0.5	0	4	100	1/6	No	2	0	3	96	0/1
4	No	1	0	9	Nt	1/6	No	0	0	7.5	80	0/1
5	No	2	0	3	90	0/3	No	1	0	4	83	0/2
6	No	1	0	0	62	1/7	No	1	0	0	62	0/5
7	No	0	0	0	103	1/7	No	0	0	0	103	0/4
8	No	0	0	4	Nt	1/8	No	0	0	2	82	0/0
9	No	2.5	0	10.8	28	1/7	No	na	–	10	28	1/6
10	No	2.5	0	15	12	1/9	No	na	–	20	11	1/7
11	No	1	0	15	33	1/9	No	2	0	12	26	1/5
12	No	3	0	9	32	1/4	No	0.5	0	10	33	1/0
13	No	na	–	14	50	1/5	No	na	–	14	40	1/8
14	No	na	–	14	50	1/7	No	1.5	0	10	45	½
15	No	3	1	15	58	1/5	No	2	0	11	59	1/6
16	No	2.5	0	16	Nt	1/9	No	3	0	13	33	1/7
17	Yes	–	–	18	Nt	1/8	No	0	0	18	nt	1/6
18	Yes	–	–	15	Nt	1/7	No	2	0	16	nt	¼
19	No	0	0	5	62	1/7	No	0	0	1	62	0/0
20	No	2.5	0	0	94	0/7	No	0	0	0	94	0/0
21	No	2.5	0	13	42	0/7	No	2	0	13	42	1/3
22	No	0	1	15	27	1/7	No	0	0	14	27	0/6
23	Yes	–	–	15	nt	1/7	No	1	0	15	nt	0/1
24	Yes	–	–	16.5	32	1/1	Yes	–	–	16.5	20	1/2
25	No	3	0	7.5	nt	1/9	No	2	0	3	48	1/7

below 1. The remaining 9 cases (47%) had incomplete or absence of responses with scores ranging from 2 to 3. In the control group 17 out of 19 (90%) had bilateral complete responses (score 0), and the remaining two had a score of 1 (10%).

The comparison between the study group and the control group showed a significant difference ($P<0.001$) (Fig. 1). When subdividing our cohort in 3 groups, on the basis of the etiology and brain MRI, a significant difference in the median AORs was shown between each of the subgroups and the controls. Moreover, the non-parametric analysis of the 3 independent samples by means of the Krukall–Wallis test showed significant inter-group differences ($P=0.05$).

3.2. Relationship between AORs and EEG patterns at T_0

There was no significant relationship between AORs and either the organization of awake and sleep states, or the degree of hypsarrhythmia.

3.3. Auditory orienting responses vs. visual function and neurodevelopmental competence at T_0

There was a significant correlation between AORs and the scores of visual function ($P<0.001$). There was also a significant correlation between AORs and the results of the neurodevelopmental assessment, both with global developmental quotient ($P=0.025$), and with three individual subscales (language: $P=0.043$; eye-hand co-ordination: $P=0.030$; performance: $P=0.013$).

3.4. Evolution after two months (T_1)

Two of the 19 subjects who performed AORs at T_0 were not tested at T_1. Of the 17 infants with longitudinal data 5 had complete bilateral AORs (score 0) at T_0 and 4 of the 5 still had the same score at T_1, while the remaining one with persisting partial seizures had a score of one. Another 5 had scores equal or below 1 at T_0; only one improved reaching

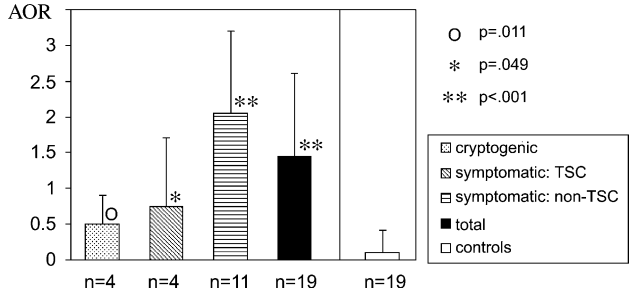

Fig. 1. Mean values and standard deviations of the AORs at T_0 in West syndrome and normal controls. The statistical significance of the correlation between each single group and normal controls is shown.

score 0, another one remained unchanged and three worsened. Among the other 7 with score between 1 and 3 at T_0, 6 improved and the remaining one worsened. No significant right–left asymmetries were present in any of the infants.

As the controls showed only median scores of zero, high significant differences in the AORs were present between each of the subgroups and the controls. However, the non-parametric analysis of the 3 indipendent samples by means of the Krukall–Wallis test failed to show any significant inter-group difference.

No relationship was found between the evolution of AOR and EEG patterns, seizures and antiepileptic drugs. Moreover, AOR were no longer related to both visual function and neurodevelopmental competence.

4. Discussion

At the onset of West syndrome, a deep derangement of brain activity as indicated by hypsarrhythmia and poor sleep organisation on EEG, is associated to a global developmental arrest or regression. A specific involvement of visual function has been clearly demonstrated in these early phases, which is at least partially related to the epileptic disorder per se. Accordingly, it has been assumed that other domains of sensorial function may be similarly affected, and particularly the auditory function, but no prospective studies specifically addressing this hypothesis have been performed so far. In the present study we assessed the auditory function in a cohort of prospectively enrolled infants with West syndrome, by means of both electrophysiological and behavioural tests, and correlated the results with EEG patterns and visual and neurodevelopment competences.

In our patients, similarly to what has been found by other authors [7,8,13], we observed an hypoacusia detected with ABR audiometry (no *V* peak potential up to 80 dB) in a relatively small percentage of cases (16%). In these patients the site of the dysfunction is by definition assumed to be located at the level or beneath the inferior colliculus. As the abnormal ABRs have only been found in infants with symptomatic West, a straight correlation between the hypoacusia and a direct damage of the brainstem may be hypothesised. However, three out of four patients with abnormal ABR in our cohort showed a full recovery of the evoked potentials after two months, rather suggesting, at least in some cases, a transient disorder of brainstem function related to the global derangement of the nervous system occurring during the early phases of the syndrome. In this mechanisms of alertness that allow stimuli to be conveyed to the medial corpus geniculatus up to the primary cortical auditory area. The low-level reticular arousal system might therefore be involved in infants with West syndrome, suggesting a brainstem (reticular formation) impairment as a possible mechanism of the auditory dysfunction [7,13].

In the large majority of our patients, no auditory dysfunctions could be identified by means of the ABR. In these subjects a behavioural assessment was performed at spasm onset, namely the assessment of AOR, showing impaired responses in a significant proportion of patients, compared to normal controls. The incidence of abnormal responses was higher in the group of infants with symptomatic West due to pre-perinatal lesions, while it was relatively lower in those with tuberous sclerosis or cryptogenic syndrome. However, when comparing the control group with each one of the three groups separately, statistically significant differences were found in all cases. These results may be in favour of an influence on the auditory behaviour of the epileptic disorder per se, which is, however, strongly enhanced by the existence of an underlying brain damage. The lack of a significant correlation between orienting responses and EEG findings, on the other hand, emphasizes the pathogenic role of the etiologic factors. This seems to be particularly true for lesions acquired during the prenatal and perinatal period, and less in our cases of tuberous sclerosis, as already reported in relation to visual and neurodevelopment [10,11].

When the response in auditory orienting behaviour is lacking, it is difficult to state where along the information processing stream the failure is located, whether at cochlear or at retro-cochlear level up to the auditory radiations and to the specific cortical areas. The difficulty of interpretation is further increased by the maturational aspects. The mechanism of auditory orientation is an important and complex component of auditory attention. During the first weeks of life it may be considered as a reflex behaviour, a sort of pre-attentive behaviour belonging to the same category of subcortical neonatal reflexes. In the following weeks, between 2 and 4 months of life, auditory orienting responses may be transiently weakened reflecting the cortical maturation and the consequent inhibition and modulation of the subcortical centres [14]. This phase is ultimately followed by a full recovery of the responses, particularly activated by the novelty of the stimulus[15].

This pattern of evolution reflects an involvement of increasingly higher cortical functions. Thus, even though it is not easy to establish at early stages a lack of cortical processing of information related to specific auditory systems (CAPD, central auditory processing disorder), the loss of the AOR may reflect both a low level arousal disorder as well as a high level cortical processing ability, the latter being more likely involved in those infants with normal ABR but abnormal behavioural auditory responses. Similar pathogenic mechanisms have been previously proposed for other aspects of sensorial function and in particular for visual development. In fact, the understanding of visual disorders characteristically found during the acute stage of West syndrome is not univocal. A possible impairment of the arousal system mediated by the reticular

formation may account for the visual behaviour [3] with the typical loss of eye contact, supported by a possible disorder of the brainstem [13,16–18]. Nevertheless, there is also evidence of a cortical involvement, as shown by studies on visual function [9,10].

The hypothesis of a tight relation between different aspects of sensorial development seems to be confirmed by the results of our study, that show in infants with West syndrome a significant correlation between AOR and visual behaviour. This dual (auditory and visual) impairment seems also significantly related to a deficit of the global neurodevelopmental competence. The auditory central impairment in our series is consistent with the specific involvement of the language scale, but the significant relationship also with the eye-hand and performance scales may express a more general effect of the auditory deficit on neural networks as it is shown in follow-up studies of congenital hypo-acousic patients [19], or, particularly, as an effect of the multimodal sensorial impairment in West syndrome.

Two months after the spasm onset, there was no longer a significant correlation between auditory orienting responses and visual function or neurodevelopmental competence. This seems to be in particular due to considerable variations of AORs occurring between T_0 and T_1, basically consisting in a slight worsening of the responses in cryptogenic cases and a mild improvement in symptomatic ones. As these variations are not associated to any of the parameters analysed, such as EEG patterns, seizures, or antiepileptic treatment, we are not able to suggest any possible underlying mechanism. However, as a consequence of this variations, inter-group differences are no longer detectable, suggesting a stronger relation of the auditory function with the epileptic disorder and a relative independence from the presence of an underlying brain damage. This is in contrast with what has been found with visual and neurodevelopmental competences that appeared persistently connected to the etiological group.

A further possible confounding factor may be represented by the interaction between the actual auditory impairment and the maturational trend. In fact, as previously underlined, orienting responses to auditory stimuli may be transiently impaired during the phase of shifting from a mainly subcortical to a higher cortical control, phase which can be possibly delayed in infants with West syndrome. A low global sensitivity of the auditory assessment needs also to be taken into account as possible confounding factor for the interpretation of the longitudinal variations. In all these respects, the looser correlation between AOR and other clinical features may be probably better understood after a longer follow-up.

In our previous studies on visual development in West syndrome a correlation between vision and EEG activity, and in particular with sleep organisation, was demonstrated [10]. In the present study, we have been unable to confirm a similar correlation with the auditory function, possibly due to the poor number of cases of our series or to the lower sensitivity of the auditory assessment, as the instruments for the evaluation of visual function are significantly more detailed and accurate. Alternatively, a greater weight of the role of aetiology rather than epileptic disorder in the mechanism of auditory dysfunction could be considered.

In conclusion, this is the first prospective study assessing auditory function in infants with West syndrome and comparing the results with the characteristics of the EEG and with other aspects of development. In our series auditory function resulted significantly impaired at the early stages of the syndrome, both as a consequence of low level arousal dysfunction as well as high level cortical processing. Although we failed to show a significant correlation between AOR and different aspects of the EEG, some evidence seems to support at least partially an influence of the epileptic disorder per se on the genesis of the sensorial impairment. This is also confirmed by the highly significant relationship of auditory attention with visual function and neurodevelopmental competence at spasm onset, in both cryptogenic and symptomatic forms. A longer follow up and the extension of the cohort, and in particular of cryptogenic cases, will be useful for a better clarification of these findings.

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