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Short communication

Idiopathic West Syndrome followed by childhood absence epilepsy

Nicola Specchio [a,*], Marina Trivisano [b], Federico Vigevano [a], Lucia Fusco [a]

[a] Division of Neurology, Bambino Gesù Children's Hospital IRCCS, P.za S. Onofrio, 4 00165 Rome, Italy
[b] Clinic for Nervous System Diseases, University of Foggia, Foggia, Italy

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ABSTRACT

West Syndrome (WS) is a severe epileptic encephalopathy occurring in the first year of life. According the ILAE classification of epileptic seizures and epilepsy the etiology could be symptomatic or cryptogenic. Some authors identified a small group of patients (5%) with a particular good outcome, a complete recovery from seizures and a normal cognitive development within the cryptogenic group that they suggested to be idiopathic. Between 1996 and 2007, at the Neurology Division of the Bambino Gesù Children's Hospital in Rome, we collected 241 patients with WS. Sixteen (6.6%) were considered with idiopathic aetiology. All clinical notes of these patients were reviewed in order to evaluate the prevalence of other epileptic syndrome after WS. Two of them had at the age of 8 and 3 months idiopathic WS, and at the age of 6 and 4 years respectively, they presented with childhood absence epilepsy (CAE) successfully treated with valproate.

The favorable evolution of the WS and the later occurrence of an idiopathic form of epilepsy, such as CAE, confirm the possibility of an idiopathic aetiology for WS that, although rare, can represent one of the etiologies of otherwise severe syndrome. Even if a common physiophatogenetic role, probably related to a genetic predisposition, could be hypothesized and appears to be intriguing, no data are available and more studies are needed to confirm this hypothesis.

1. Introduction

West Syndrome (WS) is an age-dependent epileptic syndrome of the first year of life, characterized by the occurrence of clusters of epileptic spasms, arrest or regression of psychomotor development, and a specific EEG pattern called hypsarrhythmia. WS is considered a severe type of epileptic syndrome on account of frequent drug resistance and serious repercussions on cognitive and psychomotor development.[1]

This syndrome is symptomatic of known and unknown etiologic factors in 80% of cases. All cerebral congenital and acquired pathologies can be associated with WS and the group of unknown etiologies is constantly shrinking. The long-term prognosis of symptomatic forms is generally severe, and depends on cerebral lesions and dysfunctions underlying the syndrome rather than the WS itself. The remaining 20% are cryptogenic and among them have been identified some patients who have a good outcome with a complete recovery from seizures and a normal motor and cognitive development (5% of WS).[2–4] As no etiologic factors were identified, except for a general family predisposition to epilepsy, an idiopathic etiology was considered. However, the definition of an idiopathic WS is based on the later outcome and cannot be confirmed at the time of presenting symptoms or at the time of diagnosis.

Recently, several cases of idiopathic WS due to cytogenetic abnormalities have been reported.[5–7] In these cases, a slight cognitive delay is reported during development.

We wish to contribute to the reports of idiopathic form of WS describing two children who presented with WS in the first year of life and with typical absence seizures during childhood.

2. Methods

We reviewed all patients with WS referred, between January 1996 and December 2007, to the Neurology Division of the Bambino Gesù Children's Hospital in Rome. This is a private non-profit research organization, providing health care and research on behalf of the Italian National Health System. It receives directly first care patients, secondary patients regarding general paediatrics and tertiary patients for specialist consultations. We classified WS into three groups following the etiologies: (1) symptomatic, if there is a history of pre-, peri-, or postnatal damage or disease and the predisposing etiology can be identified. (2) Cryptogenic if there is not known cause or the underlying cause remains hidden. (3) Idiopathic if there are no focal signs during the cluster of spasms,, hypsarrhythmia does not show focal prevalence, MR is normal,

* Corresponding author. Tel.: +39 06 68592645; fax: +39 06 69592463.
E-mail address: nicola.specchio@opbg.net (N. Specchio).

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cognitive development before and after the disease is normal. Epileptic spasms as hypsarrhythmia quickly disappear with ACTH and no other antiepileptic drugs are necessary. Long-term prognosis is excellent.

All clinical notes were reviewed in order to evaluate the prevalence of other epileptic syndrome after WS. We focused on idiopathic cases and we considered the follow-up duration, the cognitive and motor skills before and after WS, the remission of WS, and the appearance during the follow-up of other epileptic syndromes or EEG abnormalities.

3. Results

Two hundred forty-one children affected by WS were collected. One hundred eighty-seven cases have been diagnosed with symptomatic WS (77.6%), and 54 with cryptogenic WS (22.4%). Within cases with cryptogenic WS we identified 16 cases (29.6%) which fulfilled the criteria for idiopathic WS.[2,3,8]

3.1. Patients' population in idiopathic WS

Sixteen cases had idiopathic WS, 6.6% of the total population considered (Table 1). The mean follow-up duration is 7.1 years (SD 4.2, median 7.3). During the follow-up 11 patients did not experienced other seizures nor EEG abnormalities; 2 patients had CAE, 3 had photoparoxysmal epileptiform response (PPR), and 1 of them had an occasional generalized-tonic–clonic seizure at the age of 10 years. All patients had a normal cognitive development.

We describe the detailed history of 2 patients in which idiopathic WS was followed by CAE.

3.2. Case report #1

This 10-year-old boy was born at term after an uneventful pregnancy and delivery. Motor and cognitive development was normal. His father had experienced an isolated, generalized-tonic–clonic seizure in adulthood. No family history of febrile seizures was reported. At the age of 8 months, he presented with clusters of epileptic spasms, and was referred to our Division 2 days after the onset. Neurological examination, laboratory and metabolic tests were normal. EEG showed hypsarrhythmia. Brain MR was normal. He was successfully treated with synthetic ACTH 0.1 ml per day, administered i.m., with a scalar dose protocol for 1 month with complete remission of spasms after the second administration and disappearance of hypsarrythmia. During follow-up his cognitive development remained normal. At the age of 2 years and at 4 years, he experienced simple febrile seizures. At the age of 4 years and 6 months, paroxysmal, diffuse, 3 Hz spikes and spike and wave discharges not related to any clinical manifestations appeared on routine EEG. At the age of 6 years, he began to have clinical absence seizures, several times per day. Episodes were recorded during a video-EEG monitoring. Valproate was added at a dose of 20 mg/kg/day, and definitive and complete remission of seizures was reached within 3 months. All EEGs since then were normal. Valproate was gradually stopped after 2 years and actually valproate was withdrawn without relapse. Array-CGH analysis failed to identify deletions. He attends primary school with good results and cognitive development is normal.

Table 1
Demographic and clinical characteristics in Idiopathic WS patients.

Sex	Patients ($n = 16$) (%)
Female	5 (31.2)
Male	11 (68.7)
Age at onset	Months
Mean (±SD)	6.8 (±1.7)
Median	6.5
Range	3.2–10.1
Follow-up	Years
Mean (±SD)	7.1 (±4.2)
Median	7.3
Range	1.8–4.1
Treatment	Patients (%)
ACTH	15 (93.7)
Vigabatrin	1 (6.3)

3.3. Case report # 2

This 5-year-old boy was born at term after an uneventful pregnancy. No delivery problems were reported. At the age of 3 months, until which time psychomotor development had been normal, he began to present clusters of epileptic spasms. The neurological examination was normal apart a reduction in participation. EEG showed diffuse hypsarrhythmia (Fig. 1A). A cluster of epileptic spasms was recorded on EEG (Fig. 1B). Cerebral MR was normal. All laboratory and metabolic tests were normal (organic amino acid both in plasma and urine, acetylcarnitine, acylcarnitine). He was treated with synthetic ACTH 0.1 ml per day, administered i.m., with a scalar dose protocol for 1 month was started, with complete remission of spasms after 1 week of treatment and disappearance of EEG abnormalities.

During follow-up, neurological examination and EEGs were normal. At 4 years of age, he experienced typical absence seizures while awake correlated to generalized 3 Hz high voltage spikes and spikes and waves lasting 5–9 s (Fig. 2). He was given valproate at a dose of 25 mg/kg/day which led to a significant reduction in the frequency of absences. During 1 year of follow-up the EEGs continued to show generalized paroxysmal spikes and wave discharges of short duration without clinical correlate.

Neuropsychological evaluation was performed at the age of 4.5 years using Wechsler Preschool and Primary Scale of Intelligence (WPPSI, III edition) and revealed a FIQ of 119 (PIQ 111 and VIQ 122) indicating normal intelligence. The Processing Speed Quotient (PSQ), which measures short-term visual memory, attention and visual motor coordination, revealed a score of 115.

4. Discussion

WS is an epileptic syndrome considered to have a poor prognosis, being associated to cognitive deterioration and drug resistance. WS could have different etiology: symptomatic (80%), cryptogenic (15%), and idiopathic (5%) as proposed also recently by Riikonen.[8] This etiological differentiation is not yet formally considered in the present ILAE epilepsy classification and an idiopathic form of WS is still not recognized.[1] The overall prevalence of an idiopathic aetiology in our population of WS patients was 6.6%, this is in accordance with previously described cases.[2,3,9,8]

During the follow-up 2 patients presented with CAE and 3 patients with PPR (one of them experienced also a GTC seizure). All other patients did not experienced successive seizures or EEG abnormalities. However, as the mean follow-up duration was 7.1 years (range 1.8–14.1 years), we might have lost the occurrence of other types of seizures or epileptic syndromes typical of older ages.

The described cases were referred to us at the onset of WS. Interictal and ictal EEGs were typical, and a slight cognitive regression was noted only in one case. The lack of a cognitive regression in case #1 was probably due to the short period between the onset of spasms and the neurological assessment.[10] The idiopathic etiology in our patients fulfilled the criteria previously described. The later occurrence of CAE, belonging to IGE, suggests an association between two idiopathic epileptic syndromes. A link or an overlapping was also described for other

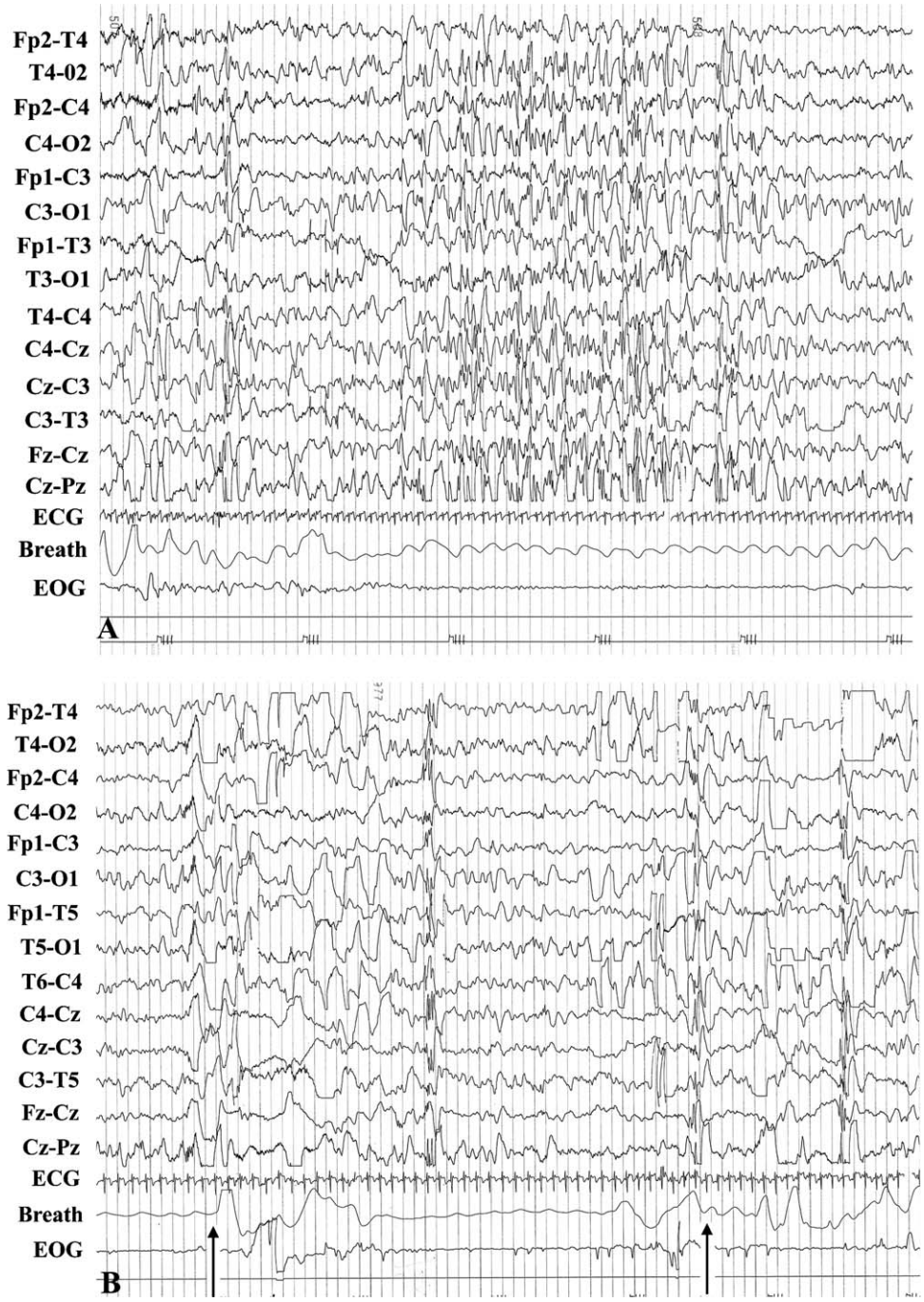

Fig. 1. (A) Interictal sleep EEG of Case #2 at the onset (age 3 months) EEG recorded after few days from the onset of spasms showed a pathological brain electrical activity. The EEG shows a posterior activity characterized by the recurrence of delta waves, which can be also found in the anterior regions with a certain asynchrony. Spikes and spikes waves complexes are recorded all over the scalp: a maximum peak is evident over the centro-temporal areas of both hemispheres. Gain: 100 μV/mm, speed 15 mm/1 s. (B) Ictal EEG of Case #2. Flexor epileptic spasms with a diffuse EEG counterpart characterised by low voltage fast activity followed by a diffuse slow waves. Gain: 100 μV/mm, speed 15 mm/1 s.

idiopathic epilepsies, focal and generalized.[11] This link may be suggested by the occurrence of EEG generalized discharges and generalized convulsive or absence seizures either during the active phase or more often at a later stage of benign childhood seizure susceptibility syndrome (BCSSS)[11] and by the occurrence of EEG focal spikes with any type of seizures of BCSSS in a small proportion of patients with syndromes of IGE, including childhood absence epilepsy.[12,13]

In our patients the two epileptic syndromes were both age-dependent. This condition could be due to a common, mild and reversible functional derangement of the brain maturational process, which is probably genetically determined. A possible common physiopathogenetic role related to cortical and sub-cortical structures interaction could be hypothesized.[14–16] Even if this peculiar common physiophatogenetic role appears to be intriguing no data are available to support this hypothesis and a chance association could not be ruled out. We looked at incidence of CAE and WS between 0 and 15 years. It has been evaluated to be between 6.3/100,000[17] and 8/100,000[18] in CAE, and between 2.9/100,000[19] and 4.5/100,000[20] in WS. The comparison between incidence of CAE and WS reveal a double ratio in favor of CAE. These epidemiological data could explain the possible chance association of both syndromes in the same patient.

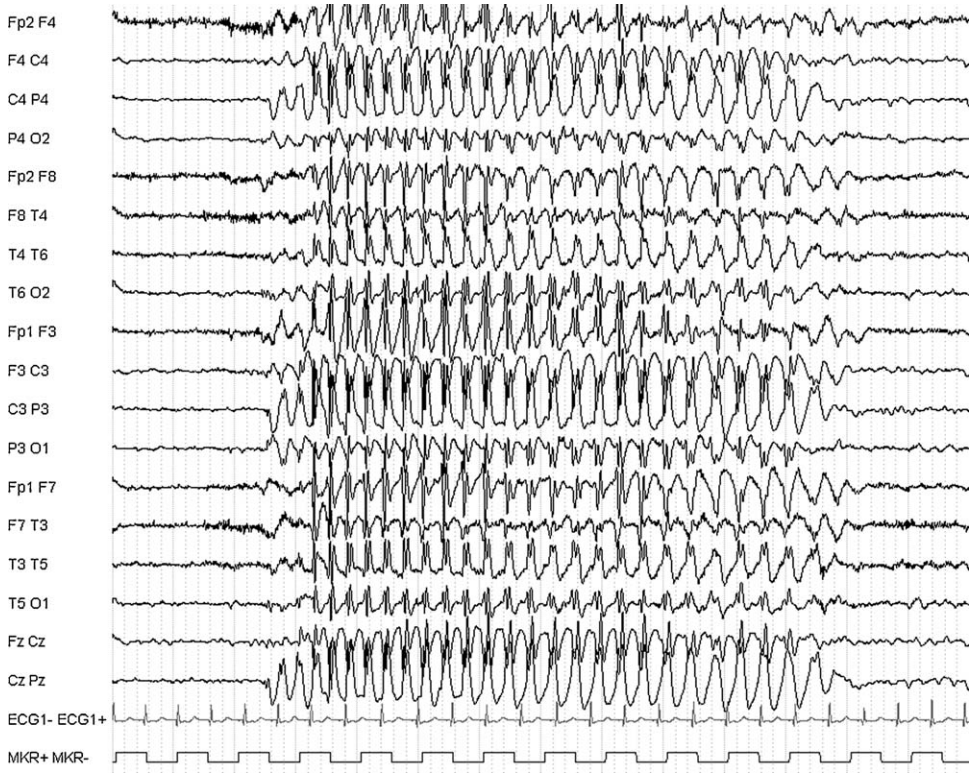

Fig. 2. Case #2, at the age of 4 years, generalized 3 Hz high voltage spikes and spikes and waves lasting 9 s are evident, associated with loss of contact. Gain: 100 μV/mm, speed 15 mm/1 s.

Moreover to support that a genetically determined derangement of the brain maturational process could be responsible, in our cases, of both WS and CAE, in the last report of the ILAE Commission on Classification and Terminology has been proposed to replace the term *idiopathic* with the term *genetic*. According to this proposal, the genetic epilepsies are the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder.[21] It was also described the simultaneous occurrence of West Syndrome in both siblings of two families, with variable clinical expression suggesting the existence of a genetic susceptibility for WS not related to a single gene but a polygenic because the variable phenotypic expression.[22]

The transition between syndromes suggests an overlapping pathophysiology and confirms, in our cases, the idiopathic aetiology of both WS and absence epilepsy based on a genetic predisposition, although the possibility that environmental factors (outside the individual) may contribute to the expression of disease, and more studies are needed to confirm our hypothesis.

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