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Infantile spams without hypsarrhythmia: A study of 16 cases

Roberto Horacio Caraballo [a,*], Victor Ruggieri [a], Gabriel Gonzalez [b], Ricardo Cersósimo [a], Beatriz Gamboni [c], Andrea Rey [b], Juan Carlos Perez Poveda [d], Bernardo Dalla Bernardina [e]

[a] Hospital Nacional de Pediatría "Prof. Dr. Juan P Garrahan", Buenos Aires, Argentina
[b] Centro Hospitalario Pereira Rossell, Cátedra de Neuropediatría, Facultad de Medicina, Montevideo, Uruguay
[c] Hospital de Pediatría, Humberto Notti, Mendoza, Argentina
[d] Pontificia Universidad Javeriana, Bogotá, Colombia
[e] Neuropsichiatria Infantile, Ospedale Gianbattista Rossi, Università di Verona, Italy

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ABSTRACT

In this study, we present the electroclinical features and evolution of patients with epileptic spasms (ES) in clusters without hypsarrhythmia and with or without focal or generalized paroxysmal discharges on the interictal EEG. We also discuss how to nosologically define these cases.

Methods: Between February 1, 1990, and December, 2009, sixteen patients met the electroclinical diagnostic criteria of ES in clusters without hypsarrhythmia.

Results: ES were cryptogenic in thirteen patients and symptomatic in three. Age at onset of ES was between 4 months and 30 months, with a mean age of 9 months and a median age of 7 months. Seven patients had seizures before the onset of ES. Focal spikes were observed in seven patients, bilateral spikes and spikes and waves in five, multifocal spikes in two, and two patients had a normal EEG. The ictal EEG recording showed diffuse high-amplitude slow waves in ten patients, diffuse slow waves followed by voltage attenuation in four patients, and diffuse fast rhythms in two. ES were cured in five patients. Mean follow-up was 6 years. Neuropsychological development has been normal in the five latter patients. Eleven patients continue with seizures refractory to antiepileptic drugs after a mean follow-up of 10 years. Of these eleven patients, five have severe mental retardation, three have moderate mental retardation, and two have mild mental retardation. All of them show behavioral disturbances.

Conclusion: The patients in this series may be considered to have a variant of West syndrome rather than an electroclinically distinct epileptic syndrome.

1. Introduction

Epileptic spasms (ES) are defined as seizures characterized by brief axial contraction, in flexion, extension, or mixed, symmetric or asymmetric, lasting from a fraction of a second to 1–2 s, and are associated with a slow-wave transient or sharp and slow-wave complex, followed or not by voltage attenuation.[1,2] ES usually appear in clusters and are age dependent, occurring almost exclusively during the first year of life, mostly between 4 and 7 months of age.[1,2] Nevertheless, late onset up to 14 years of age has been reported in rare cases[3–9] and in the 1991 workshop of the ILAE Commission on Pediatric Epilepsy it was suggested that epileptic spasms may occur in infancy or childhood.[10]

Infantile spasms (ISs) are considered an epileptic syndrome that rarely has onset in children older than 2 years, but usually begins in children younger than 1 year characterized by epileptic spasms—either in clusters or single—with or without hypsarrhythmia (ESwoH).[11] The main clinical manifestation is clinical spasms that usually occur in clusters and the most characteristic EEG finding is hypsarryhthmia. However, hypsarrhythmia is not found in all cases, nor is it found throughout the clinical course of the condition.[3–14] A series of infants with ES in clusters without hypsarrhythmia was published by Caraballo et al.[12] Other infants with similar electroclinical features have also been reported.[13,14] Hypsarrhythmia usually disappears during a clinical attack of epileptic spasms. ISs may have various potential etiologies and may be associated with different conditions. The spasms are often associated with developmental arrest or regression.[11] West syndrome (WS) is a form of ISs characterized by the combination of spasms in clusters and an EEG pattern of hypsarrhythmia. It does not require, as some previous definitions of WS did, that evidence of delayed development occurs before the onset of spasms.[5] In all series of WS cases, some patients with typical ES but without either

* Corresponding author at: Neurology Department, Hospital de Pediatría "Prof Dr Juan P Garrahan", Combate de los Pozos 1881. CP 1245, Buenos Aires, Argentina. Tel.: +54 11 49436116; fax: +54 11 49436116.
E-mail address: rhcaraballo@arnet.com.ar (R.H. Caraballo).

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typical or modified hypsarrhythmia have been found.[1–14] Less usually, single epileptic spasms with or without hypsarrhythmia may also occur[11] and exceptionally, children may present with hypsarrhythmia without epileptic spasms.[1,11]

In this study, we present the electroclinical features and evolution of patients with ES in clusters without modified or typical hypsarrhythmia and with or without focal or generalized paroxysmal discharges on the interictal EEG. We also discuss how to nosologically define these cases.

2. Methods

Between February 1, 1990, and December, 2009, sixteen patients met the electroclinical diagnostic criteria of epileptic spasms in clusters without hypsarrhythmia. They had been referred to the Juan Gaharran Hospital (Buenos Aires, Argentina), the Centro Hospitalario Pereira Rossell, (Montevideo, Uruguay), the Gianbattista Rossi Hospital (Verona, Italy), and the Humberto Notti Hospital (Mendoza, Argentina). Four of the patients have been published previously.[12] ES were identified as brief axial contractions occurring in clusters, observed by a trained pediatric neurologist, and registered on EEG recordings, polygraphic-EEG recordings, or video-EEG recordings. The ictal EEG recordings were considered to be evidence of ES when they consisted of a diffuse, high-amplitude slow wave followed or not by voltage attenuation, and fast rhythms accompanying each contraction of the cluster. Gender, age at onset, personal antecedents, and family history of epilepsy and febrile seizures, duration, manifestations, circadian distribution, frequency of previous seizures and ES, response to therapy, and final outcome were analyzed. Repetitive ictal and interictal EEG recordings were performed in all patients and polygraphic and video-EEG recordings were performed in four and ten patients, respectively. A mean of 18 ± 6 EEGs was obtained and a mean of 10 ± 3 seizures was analyzed for each patient. All seizures were registered with EEGs recordings and the majority of the seizures were also documented with 12–24-h video-EEG recordings. As this is a retrospective study, the EEG methodology may have differed among the centers.

Clinical and neurological examinations and etiologies were analyzed. All patients underwent brain computed tomography (CT) scan and magnetic resonance imaging (MRI) (four with spectroscopy). Additional studies performed were neurometabolic investigations and karyotyping. Neurometabolic analysis included serum ammonia, serum pyruvate and lactate, acylcarnitine profile, serum amino acids, biotinidase, serum copper and urine organic acids. Cerebrospinal fluid (CSF) lactate/piruvate (four patients) and CSF amino acids (four patients) were also studied.

Etiology was defined according to the ILAE classification.[15] All patients were classified as either symptomatic or cryptogenic. Symptomatic cases were considered those with abnormal neurological findings, delayed psychomotor development prior to ES, and/or recognizable etiology. The cryptogenic group included patients without any identifiable etiology and normal psychomotor development prior to the onset of ES. All patients were psychometrically evaluated with the Wechsler Intelligence or Terman Merrill Scales.

3. Results

3.1. General characteristics

A total of sixteen patients (nine boys and seven girls) were identified between March 1990 and April 2009 at the Garrahan Hospital of Buenos Aires (eleven patients), the Gianbattista Rossi Hospital of Verona (one patient), the Centro Hospitalario Pereira Rossell of Montevideo (three patients), and the Humberto Notti Hospital of Mendoza (one patient). All children were born after normal gestation, but two were premature. Three patients had a first-degree relative with a history of febrile seizures and one had a first-degree relative with a history of epilepsy. Physical examination was unremarkable in all patients and none of them was dysmorphic. In three patients, the neurological examination showed hypotonia and two patients had moderate spastic quadriplegia. In all cryptogenic cases, neuropsychological evaluation was normal before the onset of ES.

At onset, brain CT scans and MRIs were normal in thirteen patients. MRIs showed bilateral polymicrogyria in one, brain atrophy in one, and complex cortical dysplasia in one. Electroretinogram and visual, somatosensory, and auditory evoked potentials were normal in all cases. Neurometabolic investigations and kariotyping were also normal in all patients. In Table 1 the electroclinical features and evolution of this series of patients with ES in clusters without hypsarrhythmia are listed.

3.2. Characteristics of the seizures

All patients had ES in clusters. In ten patients the ES were in flexion and in the other six they were mixed. ES were asymmetric in nine patients. They occurred mainly on awakening in all patients. ISs were cryptogenic in thirteen patients and symptomatic in three. Age of onset of ES was between 4 months and 30 months, with a mean age of 9 months and a median age of 7 months. Seven patients had seizures before the onset of ES. Four patients had focal seizures, two had focal and generalized seizures, and one had focal seizures with secondary generalization. In seven patients who had seizures before the ES, onset was between 2 months and 7 months, with a mean age of 4 months and median age of 3.5 months.

3.3. EEG findings

The interictal EEG recordings did not show hypsarrhythmia in any of the patients. Focal spikes were observed in seven patients, bilateral spikes and spikes and waves in five, multifocal spikes in two. Two patients had a normal interictal EEG. Background EEG activity was normal in six patients and abnormal in ten. Ictal EEG recordings were obtained in all patients. Diffuse high-amplitude slow waves were found in ten patients (Figs. 1 and 2), diffuse slow waves followed by voltage attenuation in four patients, and diffuse fast rhythms ($<$13 Hz) in two (Fig. 3).

3.4. Treatment

Five patients became seizure free within 11 months after treatment initiation. Pyridoxine was the first antiepileptic drug administrated in six patients, vigabatrin in four patients, valproic acid in three, and ACTH in two. Vigabatrin alone was effective in one patient, vigabatrin associated with pyridoxine was effective in one, vigabatrin associated with valproic acid was effective in two, and topiramate alone was effective in one. All these five patients belonging to cryptogenic group are seizure free. The two patients who received ACTH, were refractory to the treatment. Other antiepileptic drugs to treat refractory ES, such as clobazam, hydrocortisone, clonazepam, pyridoxine, lamotrigine, alone or in combination, were also used and proved to be ineffective. Three patients were put on the ketogenic diet; seizure-reduction was between 50% and 75% in one, 25% and 50% in one, and without good response in the remaining one.

3.5. Follow-up

Five patients with ES became seizure free and were followed-up for a mean period of 6 years (range 1–18 years). Neuropsychological development has been normal in all five patients.