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Infantile spams without hypsarrhythmia: A study of 16 cases

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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

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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.

Table 1
Electroclinical features and evolution of 16 patients with ES in clusters without hypsarrhythmia.

Patient number (gender)	Etiology	Age at onset ES (months)	Epileptic seizures before onset ES	Interictal EEG	Ictal EEG	Subsequent epilepsy	Age at last control (years)	Mental retardation
1 F	Unknown	5	No	Right anterolateral spikes	Diffuse slow waves	Yes	19	Yes
2 F	Unknown	6	Focal seizures with secondary generalization	Normal	Diffuse slow waves and voltage attenuation	Yes	12	Yes
3 F	Unknown	6	No	Right frontal spikes	Diffuse slow waves	Yes	8	Yes
4 M	Unknown	7	Focal seizures	Bilateral spikes and waves	Diffuse slow waves	No	19	No
5 M	Unknown	6	No	Normal	Diffuse fast rhythms	Yes	20	Yes
6 M	Unknown	8	No	Bilateral spikes	Diffuse slow waves and voltage attenuation	Yes	9	Yes
7 M	Bilateral PMG	9	Focal seizures	Multifocal spikes	Diffuse slow waves	Yes	6	Yes
8 F	Unknown	8		Left temporal spikes	Diffuse slow waves	No	5	No
9 M	Complex cortical dysplasias	4	Focal and generalized seizures	Left parieto-occipital spikes	Diffuse fast rhythms	Yes	11	Yes
10 M	Brain atrophy (perinatal hypoxia)	5	Focal and generalized seizures	Bilateral spikes	Diffuse slow waves and voltage attenuation	Yes	10	Yes
11 F	Unknown	6	Focal seizures	Normal	Diffuse slow waves	No	2	No
12 F	Unknown	23	No	Bilateral spikes and spike-waves	Diffuse slow waves	No	4	No
13 F	Unknown	30	No	Bilateral and asymmetric spikes and spike-waves	Diffuse slow-waves	Yes	4	No
14 M	Unknown	7	No	Frontal spikes	Diffuse slow waves and voltage attenuation	Yes	17	Yes
15 M	Unknown	6	Focal seizures	Bilateral anterior spikes and waves	Diffuse slow waves and voltage attenuation	Yes	4	Yes
16 M	Unknown	8	No		Diffuse slow waves	No	5	No

Eleven patients continue with seizures refractory to classic and new antiepileptic drugs after a mean period of follow-up of 10 years (range 1–19 years). In these eleven patients ES disappeared between 2 and 10 years of age. Two of them evolved into Lennox-Gastaut syndrome, three patients currently have generalized tonic seizures, three patients have focal seizures with or without secondary generalization, and three have focal and generalized seizures. One patient with generalized tonic seizures refractory to antiepileptic drugs and the ketogenic diet was recently implanted with vagus nerve stimulation. Four refractory cryptogenic patients

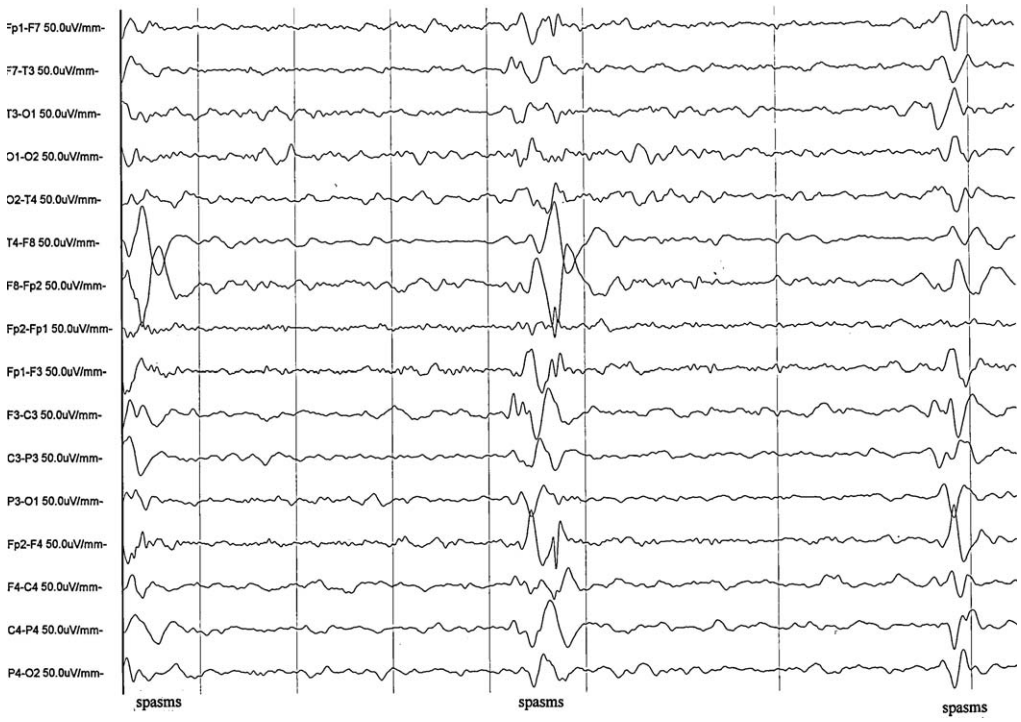

Fig. 1. An 8-month-old infant with epileptic spasms in clusters. The ictal EEG recording shows diffuse paroxysms of slow waves.

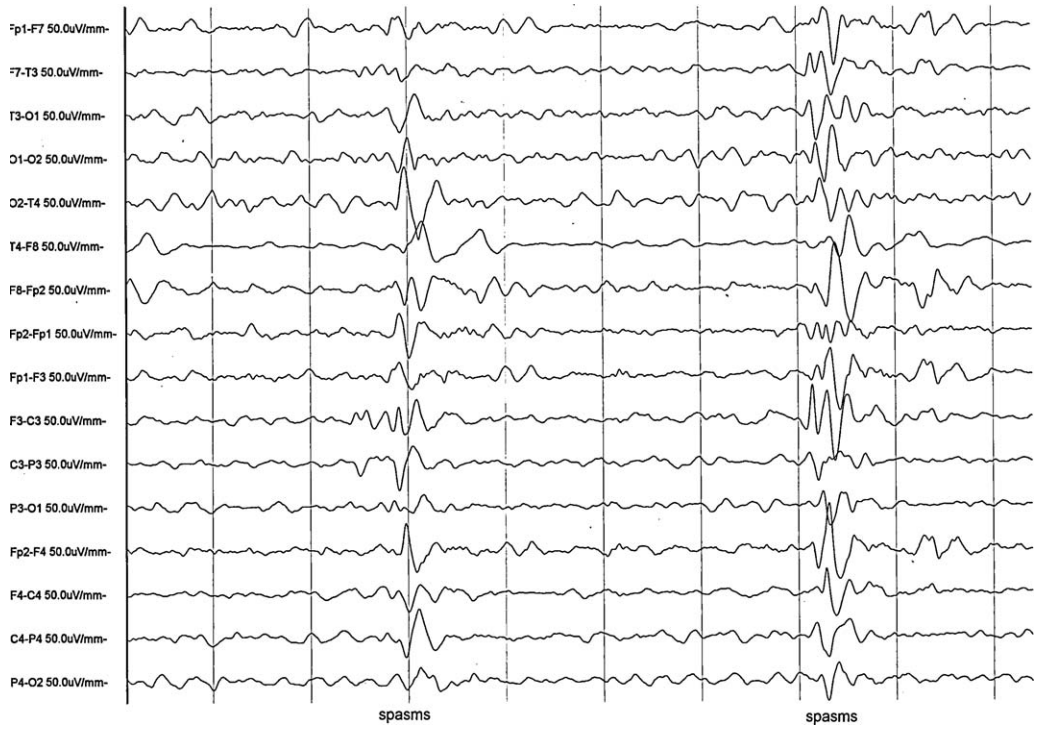

Fig. 2. A 10-month-old normal infant with epileptic spasms. 2 min after onset of a cluster of epileptic spasms, the ictal EEG recording shows diffuse paroxysms of slow waves.

and three refractory symptomatic patients developed cognitive deterioration during the time they had ES.

On the last examination, six patients had a normal IQ, five patients had severe mental retardation, three patients had moderate mental retardation, and two had mild mental retardation. Four patients showed autistic behavior, four patients hyperkinesia, and three aggressive behavior.

4. Discussion

In the present series, fifteen patients show that ES in clusters may occur in infancy without hypsarrhythmia. Only one patient of our series started with ES in the third year of life. All sixteen patients also presented the following features: clusters of ES and focal and generalized clinical and/or EEG abnormalities. Seven patients had focal seizures before the onset of ES; four of them were cryptogenic and three were symptomatic. All these seven patients developed refractory epilepsy. The patients with ES that were not preceded by focal seizures had a better outcome.

Thirteen patients had cryptogenic and three had symptomatic ES. The electroclinical features of the present series of patients were similar to those of patients with WS. Moreover, we have studied patients with electroclinical features of WS who presented with ES without hypsarrhythmia during their evolution. This finding supports the relationship between ES with hypsarrhythmia and ES without hypsarrhythmia. Seizures were refractory to antiepileptic drugs in 11 children. All five patients that became seizure free had cryptogenic ES. Patients with a good prognosis have previously been published.[9] The features of our patients suggest that they presented with epileptic spasms in clusters without hypsarrhythmia as a variant of infantile spasms. Similar cases have been reported by Oguni et al. and Goldstein and Slomski[13,14]. Series of patients with late-onset infantile spasms in clusters without hypsarrhythmia have also been published.[4–9] In these series of patients with late-onset ES, the authors included patients with spasms that started in infancy.[4,9]

All these patients with ES in clusters without hypsarrhythmia of early and late onset present with similar electroclinical features and evolution. In the two patients of our series with late-onset ES, the ES were not preceded by focal seizures and the EEG showed bilateral, interictal EEG abnormalities.

We believe that this group of patients, regardless of the age at onset, represent a variant of WS rather than well-defined epileptic syndrome. Since most of these patients develop cognitive deterioration, they may also be included in the category of epileptic encephalopathy. Results published in the literature as well as our results confirm that ES without hypsarrhythmia may occur not only in infancy but also in childhood.[4–9,12–14] Hypsarrhythmia is age dependent, but ES on the other hand, may occur in different age periods. To consider both groups of early- and late-onset ES without hypsarrhytmia in the same epileptic syndrome, this syndrome may be named "epileptic spasms without hypsarrhythmia in infancy and childhood".[15]

It is important take into account that ES may occur in patients without hypsarrhythmia. Moreover, in some patients ES may be associated with normal interictal EEG recordings. ES in clusters should be identified early for proper and rigorous management in order to avoid cognitive deterioration. ES should also be differentiated from other types of seizure, such as myoclonic and tonic seizures, because of their differential response to antiepileptic drugs. Spasms can be differentiated from myoclonic and tonic seizures based on clinical, EEG, and EMG features.[16] The velocity of the muscle contraction in spasms is faster than that in tonic seizures, but slower than that in myoclonic seizures.[2] In two patients of our series, the spasms evolved into tonic seizures.

The hypothesis of a focal onset of the seizures is supported by the presence of spasms in patients with a focal lesion, the asymmetry and focal signs in the spasms, the asymmetry in the ictal paroxysms, the fact that the spasms are triggered by a focal seizure, and the disappearance of spasms after surgical removal of focal lesions in refractory patients.[6,7,17] However, as yet not enough knowledge is available to determine whether spasms

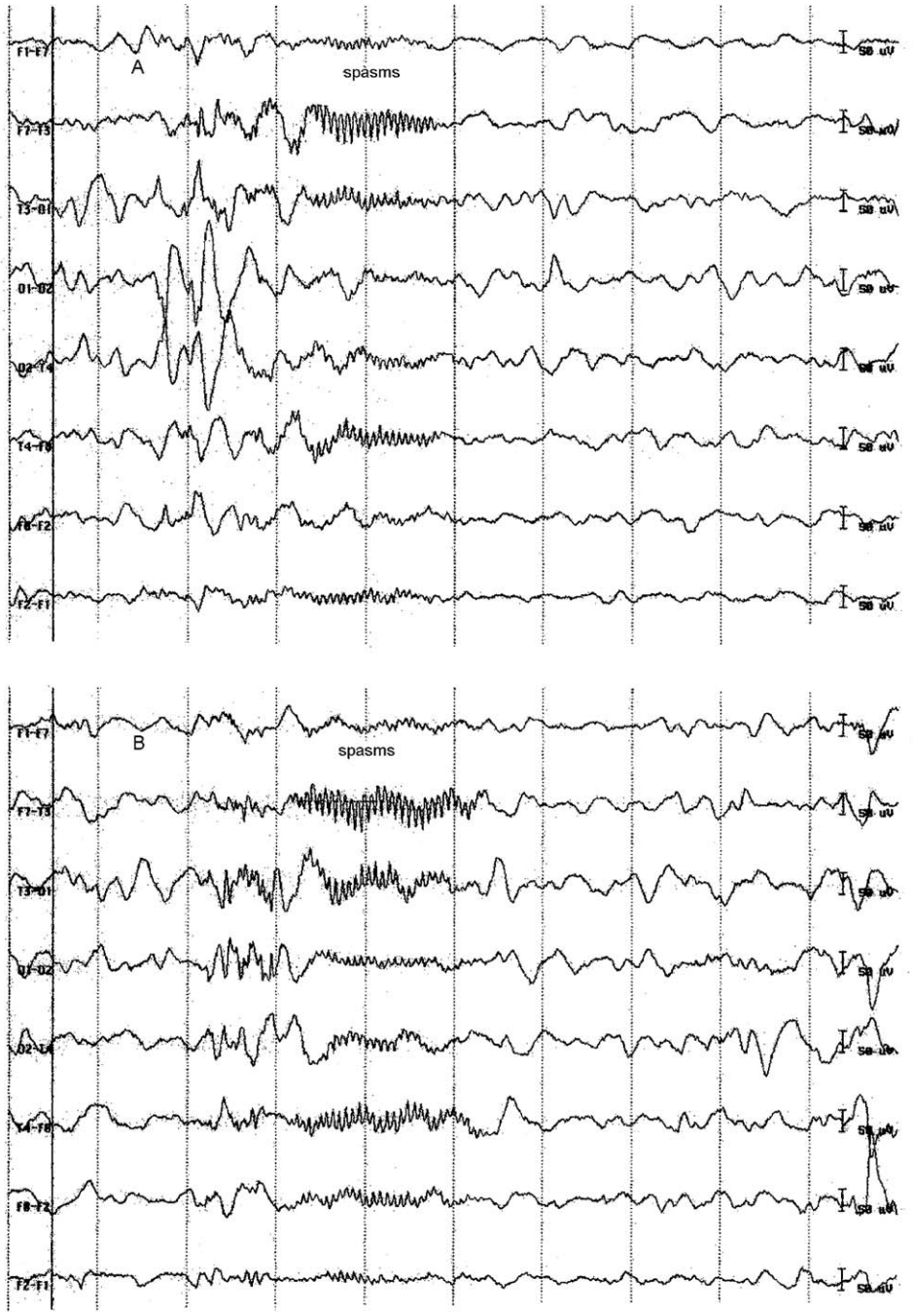

Fig. 3. A 7-month-old infant. (A) The ictal EEG recording shows diffuse fast rhythms. (B) 3 min after onset, the patient continues with epileptic spasms with the same EEG pattern.

should be classified as focal, generalized, or both. They have been placed in the group of ''unknown''.[15]

Gobbi et al.[3] described a series of patients with spasms in clusters that seem to belong to localization-related epilepsy. Seizures are characterized by series of periodic bilateral spasms in patients with focal or multifocal partial epilepsy. These seizures can be categorized as periodic spasms. Periodic spasms are often seen in patients with cortical malformations.[3] Ictal EEGs show a pattern of periodic complexes, characterized by a slow waves with superimposed fast activity. Diffuse but asymmetric high-voltage slow waves associated with a sharp wave and a diffuse slow wave alone are also observed on ictal EEGs. A cluster of periodic spasms is a single complex ictal event and periodic spasms are focal seizures with secondary generalization. The spasms in our cases have many electroclinical features in common with periodic spasms including lack of hypsarrhythmia on EEG and association with focal seizures. In our series of patients, the spasms were associated with a cortical malformation in two. In these two patients, onset was in the first year of life, which is not typical for periodic spasms, and the ictal EEG patterns did not show a clear superposition of fast activity on slow waves. The existence of older patients with ES in clusters may indicate that not only the process of development, but also some selective dysfunction of the brain plays an important role in the occurrence of this type of seizure.

Nordli et al.[18] published ten patients with electroclinical features characterized by myoclonias, a shrug, or brief tonic posture, but they did not have epileptic spasms in clusters and the ictal EEG recording did not show characteristics of ES. This

particular electroclinical epileptic syndrome should be considered as another differential diagnosis.

5. Conclusion

Our series of patients may be considered a variant of infantile spasms characterized by epileptic spasms in clusters associated with focal and/or generalized seizures without hypsarrhythmia and focal and/or generalized EEG paroxysms, similar to those of late-onset ES without hypsarrhythmia.

The syndrome may also be considered an epileptic encephalopathy. The cognitive deterioration is due to the frequent and repetitive ES in clusters rather than to electrical abnormalities.

The patients in this series may represent a variant of WS rather than a well-defined electroclinical epileptic syndrome.[4–9]

This particular electroclinical picture may be named ''epileptic spasms without hypsarrhythmia in infancy and childhood'' as a variant of WS.

Regardless of its nosological place, it is crucial to early identify ES for adequate management to avoid cognitive deterioration.

Conflict of interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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