

Epileptic spasms in clusters without hypsarrhythmia in infancy

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ABSTRACT – Spasms are defined as epileptic seizures characterized by brief axial contraction, in flexion, extension or mixed, symmetric or asymmetric, lasting from a fraction of a second to 1-2s, and are associated with a slow-wave transient or sharp and slow-wave complex, followed or not by voltage attenuation. Epileptic spasms usually appear in clusters and are age-dependent. This type of epileptic spasms associated with the particular EEG pattern, hypsarrhythmia, constitutes the basis for the diagnosis of West syndrome.

The question is, how to nosologically define those patients who clearly present epileptic spasms in clusters without modified or typical hypsarrhythmia and with or without focal paroxysmal discharges on the interictal EEG. In the present series, the four patients show that epileptic spasms in clusters may occur in infancy, without hypsarrhythmia. They all presented the following features: normal neuropsychological development before onset of epileptic spasms, clusters of epileptic spasms, focal clinical and/or EEG abnormalities, normal neuroradiological imaging, neurometabolic investigations and karyotypes. In three of the patients, seizures were refractory to AEDs. Epileptic spasms in clusters without hypsarrhythmia that start in the first year of life represent a subtype of infantile spasms that generally are refractory to AEDs. It is not yet clear whether it should be considered as a variant of West syndrome or not [Published with Video sequence].

KEY WORDS: epileptic spasms, infantile spasms, West syndrome, hypsarrhythmia



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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; ES occur almost exclusively during the first year of life, mostly between four and seven months of age. ES in clusters do not appear generally after one to two years of age [1, 2], although late onset up to seven to eight years of age has been reported in rare cases [3]. ES associated with the particular EEG pattern, hypsarrhythmia, constitute the basis for the diagnosis of West syn-

drome (WS) [1]. In all series of WS cases, some patients with typical ES but without either typical or modified hypsarrhythmia have been found [1]. Quite exceptionally, an infant may present hypsarrhythmia without ES [1].

The question is, how to nosologically define those patients who clearly present ES in clusters without modified or typical hypsarrhythmia, and with or without focal paroxysmal discharges on the interictal EEG. The following four patients represent examples of the latter possibility.

Case reports

Case 1

This patient is a 12-year-old girl, whose parents were in good health and nonconsanguineous. Personal and family history were unremarkable. At five months of age, she presented symmetric spasms, predominantly in the proximal and truncal muscles. The episodes occurred in clusters, several times a day while awake and asleep. The clusters of spasms were witnessed by us during the physical examination. Interictal EEG was normal, while no ictal EEG was recorded.

Physical and fundus examinations, as well as neuropsychological development, were normal. Routine laboratory and neurometabolic investigations, karyotype, CT scans and MRI were also normal. Valproic acid was prescribed, at a dose of 50 mg/kg/day and ACTH 10 IU/kg/day.

One month later, the patient continued with spasms and the interictal EEG showed right anterolateral spikes during sleep (*figure 1*). ACTH was discontinued and clobazam was added, with no improvement. She did not respond to pyridoxine either. At the age of 8 months, antiepileptic drugs were discontinued and oral steroid were added (prednisolone 1 mg/kg/day), associated with nitrazepam, but spasm control was incomplete over the next ten months. Some delay in psychomotor development became evident by the age of 12 months. The EEG kept showing unilateral spikes with no resemblance to typical or modified hypsarrhythmia.

At 18 months of age, she started with tonic generalized seizures while awake and during sleep, and continued with sporadic spasms.

The interictal EEG showed frequent right frontotemporal spikes and sporadic, independent, left frontal spikes.

At two and a half years of age, the spasms disappeared and the child continued with tonic generalized seizures that were refractory to treatment with different antiepileptic drugs despite blood levels within the so-called therapeutic range. The neuropsychological profile at the age of 12 years showed moderate mental retardation while the type of seizure and EEG findings remained unchanged.

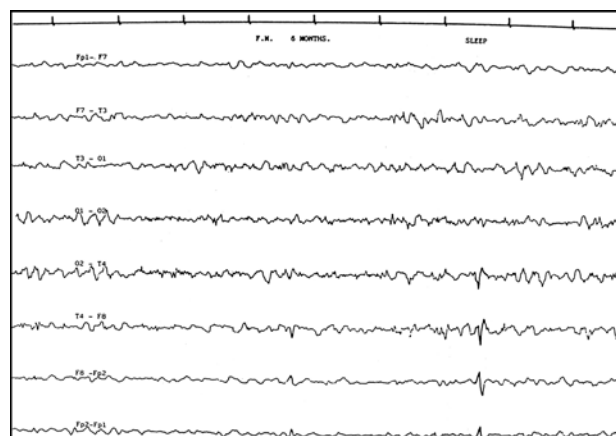


Figure 1. Case 1: Interictal EEG showing right anterior spikes during sleep.

Case 2

This five-year-old girl was born after a 39-week gestation by normal, uneventful vaginal delivery, weighing 3 kg. Personal and family history were unremarkable.

At the age of 6 months, she presented a brief episode of eye deviation to the left followed by secondarily generalized tonic-clonic seizure during nocturnal sleep. She also had seizures with similar ictal symptomatology on awakening. The interictal EEG was normal during sleep.

Physical and neurological examination, routine laboratory investigations as well as brain CT were normal. Phenobarbital was prescribed, at a dose of 5 mg/kg/day, and 40 mg/kg/day of valproic acid was added later.

At age seven and a half months, she started with spasms in clusters, and she continued with sporadic, brief, secondarily generalized tonic-clonic seizures. Neurometabolic investigations and brain MRI were normal. The video-EEG recording showed the spasms, one of them followed by generalized tonic-clonic seizures (See video-EEG).

Phenobarbital was discontinued and vigabatrin was added to the valproic acid, but the spasms were refractory to treatment. The child received different associations of antiepileptic drugs with blood levels within the therapeutic range. Epileptic spasms persisted, while repeated interictal EEGs were normal.

At two years of age, she began to have frequent tonic generalized seizures only during sleep that were refractory to antiepileptic drugs.

At three years of age, cognitive regression and behavioral disturbances became evident. Repeated interictal EEGs while awake and during sleep were normal. The brain MRI did not show abnormalities.

At five years, the girl presented moderate mental retardation and dysphasia. Generalized tonic seizures during sleep every one or two weeks were the only epileptic manifestation. Upon failure of AEDs, a ketogenic diet was tried without results.

Case 3

This girl had no significant perinatal history and demonstrated normal psychomotor development.

At six months of age, she started with mixed spasms in clusters, several times a day. Physical and neurological examination were normal. The interictal EEG was normal. The 24-hour video-EEG showed interictal right frontal spikes and periodic ictal activities characterized by asymmetric, diffuse slow waves. Routine laboratory and neurometabolic investigations, karyotype as well as CT scans and MRI were normal. Clobazam was prescribed at a dose of 0.5 mg/kg/day without good response.

Pyridoxine was added one month later. The patient continued with spasms in clusters every 10 seconds, lasting several minutes, especially upon awakening.

At the age of 11 months, valproic acid 50 mg/kg/day was added to the clobazam. The parents did not visit for a year.

At 23 months of age, spasms in clusters were persisting each day. Interictal EEG showed frequent right frontal spikes. During spasms in clusters, the video-EEG shows single spikes and waves in the right hemisphere and asymmetrical delta activity over the same areas (See video-EEG). The interictal EEG does not reveal any pattern of hypsarrhythmia.

On her last visit at three years of age, neurological examination and neuropsychological development were normal. Although receiving valproic acid 50 mg/kg/day and vigabatrin 100 mg/kg/day, she continued with spasms in clusters, the EEG showing the same focal abnormalities.

Case 4

This 12 year-old boy was born by normal, uneventful vaginal delivery and weighed 3.3 kg. He presented neonatal jaundice due to group O/A incompatibility. At age six months thalassaemia minor was detected. His family history was unremarkable.

Since seven months of age, daily epileptic spasms in clusters had occurred. The spasms were preceded by behavioral arrest and associated with left ocular deviation. Ictal EEG showed mixed clusters of spasms characterized by periodic, diffuse slow wave discharges (figure 2 A,B,C). Clonazepam and pyridoxine were prescribed, at 0.1 mg/kg/day and 300 mg/day respectively. Neurological examination showed mild axial hypotonia. Fundus examination was normal. Routine laboratory and neurometabolic investigations were normal. Brain CT scans and MRI as well as karyotype were normal.

At age nine months he continued with spasms in clusters, clonazepam was discontinued and vigabatrin 50 mg/kg/day was added to the pyridoxine.

At age 16 months, the spasms disappeared. Repeated EEGs while awake and during sleep were normal. At age seven years, vigabatrin was discontinued.

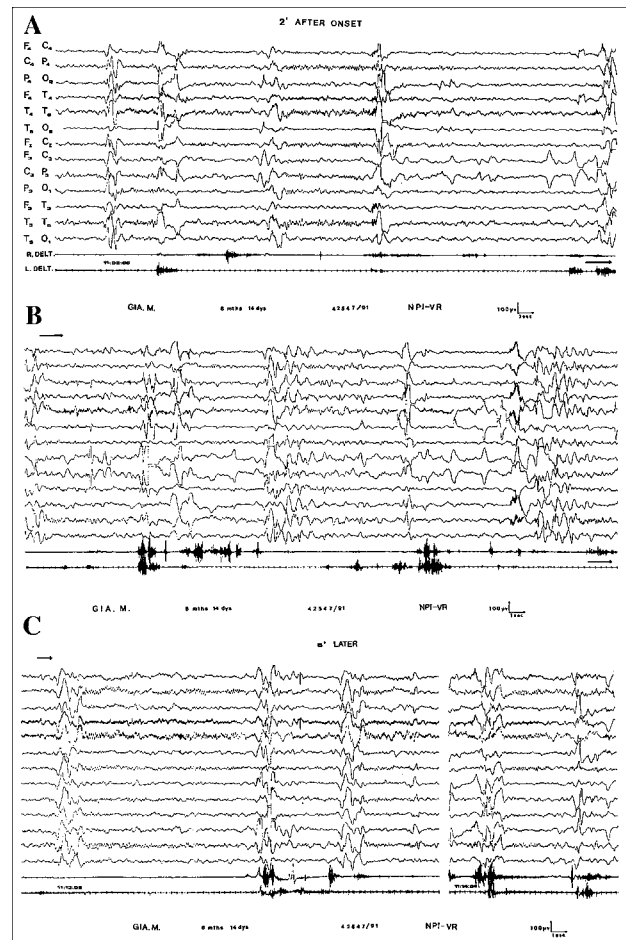


Figure 2. (A): Two minutes after onset of a cluster of epileptic spasms, the ictal EEG shows diffuse paroxysms of slow waves. (B): The infant continues with epileptic spasms with the same EEG features. (C): Six minutes later, the ictal EEG shows diffuse slow paroxysms during a cluster of epileptic spasms.

He is now 12 years old and he is attending normal school. Since the age of 16 months he has been seizure-free. The last EEG was normal.

Discussion

In the present series, four patients showed ES in clusters occurring in infancy without hypsarrhythmia. All four patients presented the following features: normal neuropsychological development before starting with ES, clusters of ES, focal clinical and/or EEG abnormalities, normal neuroradiological imaging, neurometabolic investigations and karyotypes. Seizures were refractory to AEDs in three of them. The fourth patient, instead, showed a good evolution.

These features suggest that our patients presented a variant of infantile spasms, probably symptomatic.

Table 1. Differential diagnosis of IS: Non-epileptic paroxysmal disorders or episodic symptoms with onset during the first year of life (modified Fejerman N. 1994).

1. Abdominal pain (colic)
2. Benign neonatal sleep myoclonus
3. Hyperekplexia
4. Sandifer syndrome
5. Early breath-holding spells and syncopal attacks
6. Adverse reactions or intolerance to exogenous agents
7. Paroxysmal dystonia and choreoathetosis (paroxysmal torticollis, benign infantile dystonia)
8. Increased Moro reflex and attacks of opisthotonos
9. Self-gratification or masturbation-like episodes
10. Benign paroxysmal tonic upward gaze
11. Shuddering attacks
12. Fejerman syndrome (benign myoclonus of early infancy or benign non-epileptic infantile spasms)
13. Tonic reflex seizure of early infancy

Table 1 shows the differential diagnosis of ES and other non-epileptic paroxysmal disorders or episodic symptoms with onset in the first year of life [4, 5].

ES must be differentiated from myoclonic and tonic seizures because of their differential response to antiepileptic drugs (AEDs). Spasms can be differentiated from myoclonic and tonic seizures using clinical, EEG and EMG features [6]. The velocity of the muscle contraction in spasms is faster than that in tonic seizures, but slower than in myoclonic seizures [2]. In two patients of our series, the spasms evolved into tonic seizures. We concur with the opinion that in many patients, ES will evolve into tonic seizures as the brain matures.

The hypothesis of a focal onset of seizures is supported by the presence of spasms in patients with a focal lesion, the asymmetry and focal features of the spasms, the asymmetry in ictal EEG paroxysms, the fact that the spasms are triggered by a focal seizure and the resolution of spasms after surgical removal of focal lesions in refractory patients [7].

Gobbi *et al.* [3] described a series of patients with spasms in clusters that seems to belong to localization-related epilepsy. Seizures were characterized by series of periodic, bilateral spasms in patients with focal or multifocal partial epilepsy. Periodic spasms are often seen in patients with cortical malformations [3]. Ictal EEGs show a pattern of periodic complexes, characterized by slow waves with superimposed fast activity. Diffuse but asymmetric high-voltage slow wave 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 so periodic spasms can be considered as focal seizures with secondary generalization.

The spasms in our cases have many electroclinical features in common with periodic spasms including lack of

Table 2. Epileptic syndromes presenting ES in clusters.

Spasms in clusters

Early myoclonic encephalopathy
Early-infantile epileptic encephalopathy
Typical West syndrome
WS with abnormal non-hypsarrhythmia interictal EEG
Late-onset WS
Lennox-Gastaut syndrome
Periodic spasms in focal epilepsies
Infantile spasms in clusters without
Hypsarrhythmia (our cases)

hypsarrhythmia on EEG, lack of evolution to Lennox-Gastaut syndrome, and association with focal seizures. In our series of patients, the spasms were not associated with cortical malformation. Onset took place in the first year of life, which is not typical for periodic spasms. All the babies had normal neuropsychological development before starting with ES. The ictal EEG patterns did not show a clear superposition of fast activity on slow waves. The occurrence of older patients with ES in clusters may indicate that not only the developing process, but also some selective dysfunction of the brain plays an important role in this type of seizure. Epileptic syndromes with ES in clusters are listed in table 2 [8, 9].

In summary: epileptic spasms in clusters, without hypsarrhythmia, that start in the first year of life represent a subtype of infantile spasms that are usually refractory to AEDs. It is not yet clear whether it should be considered as a variant of West syndrome or not. □



Video-EEG caption

Case 2

1. At the beginning of the recording, the patient is sleeping and the fit awakens him. He presents epileptic spasms characterized by extension and then abduction of the arms and flexion of the hips with extension of the leg. The interictal EEG do not reveal any hypsarrhythmic pattern. During the seizure, the EEG only shows lentification over the posterior region.

2. The second episode is a cluster of three epileptic spasms, the last one followed by a generalized tonic-clonic seizure. This particular event seems to begin with a brief behavioral arrest, with delta activity in the posterior areas on the EEG preceding the spasms. During the tonic-clonic seizure, the EEG first shows bilateral spikes in the anterior regions followed by spike and wave activity over the same areas, which progresses to generalized fast recruiting rhythms in the tonic phase and finally to spike and wave activity in the clonic

phase. As soon as the tonic-clonic seizure finishes, a cluster of epileptic spasms follows. The EEG recording shows diffuse high voltage slow wave paroxysms during the epileptic spasms.

3. A new cluster of epileptic spasms shows essentially the same characteristics and EEG recording. Persistent posterior lentification is evident again.

Case 3

1. The patient presents a large cluster of epileptic spasms characterized by flexion of both the head and trunk, subtle bilateral flexion of the arms and probably legs too. The ictal EEG shows diffuse single spikes and waves that are synchronous with the clinical spasms, predominantly in the right hemisphere, and asymmetrical delta activity lasting one to three seconds over the right hemisphere following some spasms. The interictal EEG does not reveal hypsarrhythmic pattern.

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