Epileptic spasms without hypsarrhythmia in infancy and childhood: tonic spasms as a seizure type

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ABSTRACT – Epileptic spasms were defined by the International League Against Epilepsy Task Force on Classification and Terminology in 2001 as a specific seizure type. Epileptic spasms without hypsarrhythmia have been described in some series of patients, occurring either in infancy or childhood. More prolonged epileptic spasms without hypsarrhythmia were previously defined as a different seizure type, and referred to as “tonic spasm seizures”. Here, we present a 5-year-old boy who started having epileptic spasms without hypsarrhythmia at 8 months of age, effectively treated with oxcarbazepine. With the withdrawal of medication, epileptic spasms returned. Video-EEG monitoring revealed high-voltage slow waves superimposed by low-voltage fast activity, followed by an electrodecremental phase and a burst of asymmetric fast activity, time-locked to clinical tonic spasm seizures. Brain MRI showed left temporal atrophy with temporal pole grey/white matter junction blurring and ictal PET-CT showed left basal frontal hypermetabolism. Seizures were refractory to several AEDs and vigabatrin was introduced with seizure cessation. Despite efforts to classify epileptic spasms, these are still considered as part of the group of unknown seizure types. In some cases, a focal origin has been suggested, leading to the term “periodic spasms” and “focal spasms”. In this case, epileptic spasms without hypsarrhythmia, associated with tonic spasms, may be a variant of focal spasms and might be considered as an epileptic syndrome. [Published with video sequence]

Key words: epileptic spasm, tonic spasm, spasm, hypsarrhythmia, oxcarbazepine, EEG
Epileptic spasms (ES) are defined as a sudden flexion, extension, or mixed extension-flexion of predominantly proximal and truncal muscles, usually more sustained than a myoclonic movement, but not as sustained as a tonic seizure (i.e. lasting for about one second) (Blume et al., 2001).

Based on the Commission on Classification and Terminology of the International League Against Epilepsy (1989), ES were considered as infantile spasms under West Syndrome, defined as generalized cryptogenic or symptomatic epilepsy, characterized by infantile spasms, arrest of psychomotor development, and hypsarrhythmia. According to the ILAE Task Force on Classification and Terminology (2001), epileptic spasms (ES) were considered a specific seizure type. As well as West syndrome, ES may occur in other conditions, such as Ohtahara syndrome and focal epilepsies, in which they are described using the specific terms “periodic spasms” (Gobbi et al., 1987) and “focal spasms” (Caraballo et al., 2003).

Hypsarrhythmia is not found in all cases and ES without hypsarrhythmia (ESWH) have been described in some series of patients, occurring either in infancy or childhood, and are associated with different conditions (Goldstein and Slomski, 2008; Caraballo et al., 1994). Hypsarrhythmia is not found in all cases and ES without hypsarrhythmia (ESWH) have been described in some series of patients, occurring either in infancy or childhood, and are associated with different conditions (Goldstein and Slomski, 2008; Caraballo et al., 1994).

Rather than the ictal EEG findings, which can assume various different patterns, the hallmark of ES is a phasic muscle contraction lasting for one to two seconds, producing a rhombic or diamond shape on deltoid EMG (Fusco and Vigevano, 1993). As initially mentioned by Kellaway et al. (1979), more prolonged ES were later defined as a different seizure type by Fusco and Vigevano (1994), who proposed to separate them from true ES, and suggested the term “tonic spasm (TS) seizures”. These are characterized on EEG by diffuse complexes of high-voltage slow waves, superimposed with low-voltage fast activity during spasms, followed by fast activity during the tonic phase.

We discuss the presence of ESWH associated with TS in a clinical commentary.

Case study

A 5-year-old boy started presenting apparent symmetric clusters of ES at 8 months of age, while awake. The interictal EEG showed slow background activity without hypsarrhythmia. He had a history of foetal distress during vaginal delivery, but had normal psychomotor development. Soon after onset, the seizures were effectively treated with oxcarbazepine (OXC) for three years. With the withdrawal of this medication, ES returned. An interictal EEG at this time showed asymmetric background activity with slow waves on the left hemisphere and frequent focal epileptiform discharges (200-400 μV lasting for about 100 ms) at left temporal leads. Seizures were refractory to OXC, carbamazepine (CBZ), phenobarbital, valproate and lamotrigine. At 4 years and 7 months of age, neurological examination was unremarkable and Denver Developmental Screening Test II disclosed only mild language impairment, compatible with that of a 3-year-old child. Video-EEG monitoring revealed asymmetric background activity with slow waves on the left hemisphere and frequent left focal frontotemporal discharges (200-400 μV lasting for about 100 ms). A total of five clusters of stereotyped, flexor ES were recorded. Ictal EEG showed diffuse periodic complexes of high-voltage (70-260 μV) slow waves lasting for approximately 200 ms, superimposed with low-voltage fast activity (16-23 Hz), followed by an electrodecremental phase and a burst of fast activity (16-29 Hz), and time-locked to the clinical TS (see video sequence). Deltoid EMG during TS revealed muscle contraction lasting for 0.2 to 5.3 seconds with a typical diamond-shape aspect (lasting for 0.3 seconds), followed by an asymmetric tonic phase, predominant in the right deltoid (lasting for 2.6 seconds) (figure 1A and B).

Brain MRI revealed left temporal atrophy with temporal pole grey/white matter junction blurring and ictal PET-CT showed left basal frontal hypermetabolism (figure 2A and B).

Vigabatrin (VGB) was introduced (at 50 mg/kg/day and increased to 100 mg/kg/day after one week), in association with taurine (250 mg, twice daily), with remission of seizures within 14 days and cognitive gains. Video-EEG monitoring one month after VGB therapy showed left focal frontotemporal discharges and no evidence of TS. A re-evaluation three months later revealed normal background activity. At the age of 5, the Columbia Mental Maturity Scale showed mild delay in mental maturity level (range: 4 years and 6-11 months) and Raven’s Matrices tests showed lower-middle-range general intelligence (percentile 10).

Discussion

There is a need to describe case studies of ES, detailing modalities of interventions and outcomes and their measures, since despite significant efforts to classify these seizures (Lux and Osborne, 2004), they are still considered as part of the group of unknown seizure types (Berg et al., 2010). Fusco and Vigevano (1994) described ESWH associated with TS in seven patients aged 2 to 14 years; all of whom had had WS in the first year, and six had no known aetiology. All patients also had typical ES, manifesting mainly in clusters on awakening.

The present case exhibited ES in clusters at 8 months of age, as is typical in WS, but in the absence of hypsarrhythmia and with response to OXC, which led to
complete seizure control for more than three years. These atypical characteristics challenge the concepts of ES and WS. Is this description suggestive of a focal symptomatic seizure? Was this an intermediate phase of ES in the evolution to Lennox-Gastaut syndrome? In 2011, Caraballo et al. described 16 patients with clusters of ESWH (Caraballo et al., 2011). The authors considered that early and late-onset ESWH might be included under the same epileptic syndrome and suggested the term “ESWH in infancy and childhood”. In this series, spasms evolved into tonic seizures in only two cases.

Table 1 summarizes the literature on TS. In most of the reports, ES were considered in general, including TS

Figure 1. (A) Ictal EEG: diffuse periodic complexes of high-voltage slow waves superimposed with low-voltage fast activity, followed by an electrodecremental phase with fast activity associated with tonic spasms. (B) Details of complexes: a brief low-voltage fast activity burst, superimposed onto a slow wave, with the characteristic diamond shape (*) on deltoid EMG. This was followed by an asymmetric contraction of deltoids, more prolonged on the right.

Figure 2. (A) MRI performed at 4 years and 8 months showed left temporal lobe atrophy, grey/white matter blurring, and increased T2/FLAIR signal in the left temporal pole (arrows). (B) Ictal PET-CT performed at 4 years and 9 months showed left frontal hypermetabolism (dots).
as one of the seizure types, making data extraction difficult. In six articles, 37 TS cases were analysed and the nosology of each discussed. Regarding seizure onset, 19 had spasms beginning after 12 months, defined as late-onset ES (Bednarek et al., 1998). With regards to aetiology, 18 were cryptogenic. None had interictal hypsarrhythmia, and ictal EEG was characterized by high-voltage slow waves, followed by an electrodecremental phase and fast activity.

In our case, a focal seizure was suggested by: left frontotemporal discharges; asymmetry of muscle contraction during TS, greater on the right deltoid; left temporal pole blurring on MRI, possibly representing a type 1 focal cortical dysplasia or decreased myelinated axon fibres (Najm et al., 2014); ictal PET showing left basal frontal hypermetabolism; as well as initial seizure freedom with OXC. The focal origin of ESWH was also previously described by Caraballo et al. (2013) in two patients who were responsive to surgical treatment.

A cortical trigger driving subcortical structures might be necessary for ES expression (Caraballo et al., 2003). However, Lee and Yeh (2015) described a case of continuous myoclonus and TS related to enterovirus 71 brain stem encephalitis without EEG correlates.

A focal origin of ES was also suggested by Gobbi et al. (1987) in their description of late-onset periodic spasms (at 14 months to 13 years). In this study, seizures were characterized by a series of periodic, bilateral spasms in patients with focal or multifocal partial epilepsies, related to cortical malformations. Ferrari et al. (2011) reported an anecdotal case of Rasmussen’s encephalitis with periodic spasms. By reasoning whether periodic spasms should be considered a variant of ES and WS, Caraballo et al. (2003) discussed four normal children with cryptogenic ES, focal seizures and neither hypsarrhythmia nor evolution to Lennox-Gastaut syndrome. As in the case reported here, onset occurred in the first year, which is not typical for periodic spasms.

Regarding Lennox-Gastaut syndrome, some authors reported ESWH/TS evolving into typical tonic seizures (de Menezes and Rho, 2002; Ishikawa et al., 2014). In our case, this evolution was not observed during the four-year follow-up.

Epileptic Spasms Without Hypsarrhythmia (ESWH), as for ES in general, are commonly treated with hormonal therapy (Eisermann et al., 2006; Ishikawa et al., 2014). OXC and CBZ may induce ES (Mutoh et al., 1993; Veerapandiyan et al., 2012). After failure.

### Table 1. Tonic spasms: literature data review

<table>
<thead>
<tr>
<th>Patients with TS/Total</th>
<th>Age (months)</th>
<th>Seizure onset</th>
<th>Aetiology</th>
<th>HPA Ictal spasms</th>
<th>Ictal tonic component</th>
<th>Seizure control/ Patients with TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusco and Vigevano, 1994</td>
<td>7/7</td>
<td>24 to 168</td>
<td>&lt;12 mo</td>
<td>6 cryptogenic, 1 symptomatic</td>
<td>No HVSW</td>
<td>Rhythmical spikes</td>
</tr>
<tr>
<td>Talwar et al., 1995 -ES beyond infancy</td>
<td>3/5</td>
<td>54 to 170</td>
<td>3 days to 1.75 yr</td>
<td>-</td>
<td>No Electrodecrement</td>
<td>Rhythmical FA</td>
</tr>
<tr>
<td>de Menezes and Rho, 2002 -ES beyond the second year of life</td>
<td>8/26</td>
<td>48 to 204</td>
<td>4 to 15 mo</td>
<td>-</td>
<td>2/8 HVSW with some sharp component</td>
<td>Electrodecrement with FA</td>
</tr>
<tr>
<td>Eisermann et al., 2006 -Late-onset ES</td>
<td>12/22</td>
<td>-</td>
<td>&gt;12 mo</td>
<td>cryptogenic</td>
<td>No HVSW</td>
<td>Electrodecrement with FA</td>
</tr>
<tr>
<td>Auvin et al., 2010 -Late-onset ES</td>
<td>3/19</td>
<td>-</td>
<td>&gt;12 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ishikawa et al., 2014 -Late-onset ES</td>
<td>4/8</td>
<td>13 to 17</td>
<td>&gt;12 mo</td>
<td>symptomatic</td>
<td>No HVSW with FA or electrodecrement</td>
<td>Electrodecrement with FA or theta activity</td>
</tr>
</tbody>
</table>

ES: epileptic spasms; FA: fast activity; HPA: hypsarrhythmia; HVSW: high-voltage slow wave; mo: months; TS: tonic spasms; yr: year.
with several AEDs, we administered VGB, also previously reported as a treatment for ESWH, and seizure freedom and cognitive gains were observed. Taurine was prescribed in order to prevent VGB-induced retinal phototoxicity (Jammoul et al., 2009).

ESWH associated with TS may be a variant of focal spasms (Caraballo et al., 2003) and, as suggested by Caraballo et al. (2011), might be considered an epileptic syndrome referred to as “ESWH in infancy and childhood.”

Supplementary Data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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References


Legend for video sequence

A cluster of three tonic spasms, characterized by sudden flexion of the head and proximal muscles, lasting 5, 4.3 and 1 second, respectively. The spasms were accompanied simultaneously by upward deviation of the eyes and oral automatisms at the end.

Key words for the video research on www.epilepticdisorders.com

Syndrome: epileptic spasms without hypsarrhythmia
Etiology: symptomatic
Phenomenology: tonic spasms
Localization: left frontotemporal region

TEST YOURSELF

1. What are tonic spasms?
2. What are the other terms that have been used to describe variants of epileptic spasms?
3. Are tonic spasms suggestive of focal seizures or do they represent an intermediate phase of epileptic spasms in the evolution to Lennox-Gastaut syndrome?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section “The EpiCentre”.