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Review article

Infantile spasms syndrome, West syndrome and related phenotypes: What we know in 2013

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Abstract

The current spectrum of disorders associated to *clinical spasms* with onset in infancy is wider than previously thought; accordingly, its terminology has changed. Nowadays, the term *Infantile spasms syndrome* (**ISs**) defines an epileptic syndrome occurring in children younger than 1 year (rarely older than 2 years), with clinical (epileptic: i.e., associated to an epileptiform EEG) spasms usually occurring in clusters whose most characteristic EEG finding is hypsarrhythmia [the spasms are often associated with developmental arrest or regression]. The term *West syndrome* (**WS**) refers to a form (a subset) of ISs, characterised by the combination of clustered spasms and hypsarrhythmia on an EEG and delayed brain development or regression [currently, it is no longer required that delayed development occur before the onset of spasms]. Less usually, spasms may occur singly rather than in clusters [*infantile spasms single-spasm variant* (**ISSV**)], hypsarrhythmia can be (incidentally) recorded without any evidence of clinical spasms [*hypsarrhythmia without infantile spasms* (**HWIS**)] or typical clinical spasms may manifest in absence of hypsarrhythmia [*infantile spasms without hypsarrhythmia* (**ISW**)]. There is a growing evidence that ISs and related phenotypes may result, besides from acquired events, from disturbances in key genetic pathways of brain development: specifically, in the gene regulatory network of GABAergic forebrain dorsal–ventral development, and abnormalities in molecules expressed at the synapse. Children with these genetic associations also have phenotypes beyond epilepsy, including dysmorphic features, autism, movement disorders and systemic malformations. The prognosis depends on: (a) the cause, which gives origin to the attacks (the complex malformation forms being more severe); (b) the EEG pattern(s); (c) the appearance of seizures prior to the spasms; and (d) the rapid response to treatment. Currently, the first-line treatment includes the adrenocorticotropic hormone ACTH and vigabatrin. In the near future the gold standard could be the development of new therapies that target specific pathways of pathogenesis. In this article we review the past and growing number of clinical, genetic, molecular and therapeutic discoveries on this expanding topic.

Keywords: Infantile spasms; West syndrome; Hypsarrhythmia; Genetics; Treatment

1. Historical background

The history of infantile spasms and *West syndrome* (**WS**) develops through three important steps: (1) the publication by the English physician, William James West (1793–1848), in 1841 in the scientific journal "*The Lancet*" [1], of his clinical experience with the condition on his own son – James Edwin West (1840–1860), aged 4 months at the time of onset of his first seizures. West originally named the seizures "*Salaam tics*" and, along with his colleague Langdon-Down, who cared for West's son in later life [2,3], reported that James had at older ages "...lack of language and meaningless

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laughter...and rolling of the head ..... delighted by music and gay colors" and "...a great tendency to automatism and rhythmical actions...", features compatible with those encountered in autism spectrum disorders [3,4]; (2) the description of a typical electroencephalographic (**EEG**) pattern associated to infantile spasms by Gibbs and Gibbs [5], who called these abnormalities "*hypsarrhythmia*"; and (3) the observation of Sorel and Dusaucy-Bauloye [6] who showed that treatment with the adrenocorticotropic hormone (**ACTH**) resulted in amelioration of either clinical and EEG anomalies. Since these first clinical [1] and neurophysiologic [5] descriptions the clinicians involved with the care of neurological and psychiatric children progressively noted that infantile spasms were often accompanied by psychomotor delay and/or developmental regression.

As infantile spasms were the most representative signs of WS, many physicians did no longer distinguish between this seizure type and WS considering the two terms synonymous and used these names interchangeably [7].

Despite many progresses, in many cases the etiology of infantile spasms remained (and still remains) hidden [8–13]. According to the ILAE classification [14,15], infantile spasms and WS were grouped within the epileptic encephalopathies in which the epileptic abnormalities may contribute to progressive cerebral dysfunction. However, over the years, there have been a growing number of studies reporting that the occurrence of infantile spasms was not always associated to hypsarrhythmia and/or mental delay, the age range of onset of seizures of the spasms type was not confined to the first year of life, and that the clinical spectrum of spasms and associated EEG were wider than previously thought. Specific consensus statements took into consideration all these new aspects and controversies aiming to reach broader agreement and newer terminologies [16].

2. Terminology

Nowadays, the inclusive term infantile spasms defines an epileptic syndrome [*infantile spasms syndrome* – **ISs**] occurring in children younger than 1 year and rarely older than 2 years, with clinical spasms usually occurring in clusters and with EEG anomalies whose most characteristic pattern is hypsarrhythmia. The spasms are often associated with developmental arrest or regression. The term WS refers to a form (currently regarded as a *subset* of ISs) characterised by the combination of spasms in clusters and an EEG pattern of hypsarrhythmia and delayed brain development or regression, which must not necessarily occur before the onset of spasms, as it was in some previous definition of the syndrome itself. Additional forms and/or variants of ISs include [16,17]: (a) *infantile spasms single-spasm variant* (**ISSV**), a less common subgroup of ISs in which spasms may occur singly rather than in clusters (a spasm should be regarded as a single spasm if no other spasms occur for 1 min before and for 1 min afterward); (b) *hypsarrhythmia without infantile spasms* (**HWIS**) when hypsarrhythmia is (incidentally) recorded without any evidence of clinical spasms; and (c) *infantile spasms without hypsarrhythmia* (**ISW**) when typical clinical spasms may manifest in absence of hypsarrhythmia.

The recent ILAE classification [18] placed the "epileptic spasms" into a separate ("*unknown*") group of seizures, as it felt that there was "inadequate knowledge to understand whether these are focal, generalized or both".

3. Main clinical features

3.1. Epidemiological aspects

The ISs and related phenotypes is an age-related spectrum of disorders, representing the most frequent type of epilepsy in the first year of life [19]. The incidence is estimated at 2-5/10.000 newborns; the prevalence is around 1-2/10.000 children at the age of 10 years with onset within 1 year of life in 90% of cases [16–21]. The peak is between 4 and 7 months, with a male to female ratio of 6:4. The duration of spasms ranges from 25 to 32 months with 85% ceasing their spasms under the age of 5 years [9,10,20–23].

Late onset occurrence of epileptic spasms, up to 14 years of age, has been reported in rare cases [24] and in the 1991 workshop of the ILAE commission on Pediatric Epilepsy it was suggested that epileptic spasms might occur not only in infancy but also in childhood [15].

3.2. Features of spasms

Clinical spasms. A clinical spasm consists of an abrupt, brief contraction followed by less intense but sustained tonic contraction lasting approximately from a fraction of a second to 1–2 s. [7,9,10,16,18,21,24–26], which involves the muscles of neck, trunk and upper and lower legs [12–14]. The spasms may be flexor, extensor or mixed, the most common being flexor involving head and arms [27,28], with a wide individual variability as regards type and intensity. The jerks occur mostly in clusters, typically just before or on awaking or just before sleep [12,26–28]. They may be present on night. During the attack, arrest, deviation of the eyes and/or changes in respiratory pattern may be seen. Cry or a scream may precede or follow the ictal phase. After the crisis, children may show irritability or transient hyporeactivity [29]. In addition to spasms other type of seizures may be present.