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West Syndrome: A Literature Review

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Abstract

The first clinical description was introduced by William James West (1793–1848) in 1841. Definitions of the classic triad are (1) infantile spasms; (2) hypsarrhythmia and (3) developmental delay or regression in the form of "West's syndrome" have been reported in this uncommon disorder. New approaches include the terminology of clinical spasms (eg, infantile (IS) vs. epileptic spasms (ES)), variety of clinical and electroencephalographic (EEG) features (eg, typical ictal appearance without EEG abnormalities), developmental delay, spectrum of associated genetic abnormalities, pathogenesis, treatment options, outcome and prognosis. In addition to the classic presentation, IS or ES may present as atypical electroclinic phenotypes (eg, modified hypsarrhythmia) and may begin outside of infancy. And an increasing number of genes, proteins and signaling pathways play a decisive role in pathogenesis. This condition is currently seen as a spectrum of disorders: the so-called Infantile Spasm Syndrome (IS) in combination with other causal factors including structural, infectious, metabolic, syndromic and immunological events, all act on the genetic background.

Keywords: Epileptic spasms, West syndrome, Infantile spasms, Infantile spasms syndrome, Genetics, Etiology.

Introduction

IS belong to the group of "early epileptic encephalopathies" (EEEs) characterized by severe, drug-resistant epileptic disorders with onset at an early age associated with persistent EEG disturbances and cognitive defects.

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A growing and changing body of terms about this disorder, first described by William James West (1793–1848) and his son James Edwin (1840–1860) in 1841 [1] and subsequently called "West Syndrom", first adopted the term "infantile spasms". IS according to the most significant clinical event, and later named under the term epileptic spasms (ES), since the disorder may have an onset outside of infancy [2, 3]. The classical terms SW and IS are still the most cited terms in the literature and, accordingly, the term ES has been included in the general definition of "infantile spasms". By definition, in this group of disorders, seizures can contribute, in addition to causative effects, to the progression of cerebral dysfunction [5–8]. The ictal phenotype is the result of a cellular-molecular cascade of events, which, in turn, is responsible for anomalies in the development of the nervous system. Ictal phenomenon without accompanying EEG abnormality has been reported [9]. In several reports, West syndrome, infantile spasms, epileptic spasms, and infantile spasms syndrome are still used interchangeably. In this report, we prefer to use the term "IS" to refer to the ictal phenomenon and the term "IS" to describe the (range of) IS-related disorder(s).

In recent years, new relevant and less common aspects of this disorder have been achieved, including its nomenclature, etiology, association with genetic factors, diversity of clinical features and complex phenotypes, as well as treatment methods and prognosis [7, 8]. It is estimated that IS occurs in approximately 0.249 cases per 1000 live births [10] with an overall prevalence of 1/10,000 children under 8 years of age [11, 12]. The number of affected children with this condition is constant over time, which have been reported in the most recent population-based and clinical studies [10, 11]. Both sexes are affected by a relatively small male predominance.

In this review article, we have sought to highlight past knowledge and more recent achievements, literature review according to the search strategy and methodology indicated below.

Search methodology

In this descriptive overview, six online bibliographic databases searched from inception to July 27, 2022: Web of Sciences (2017), PubMed (since 2020), MEDLINE (since 1976), Embase (since 1966), Cochrane CENTRAL (since 1996), and Scopus (since 2004). We used an empirical and topical approach to obtain an objective primary strategic search to identify clinical, laboratory, and therapeutic studies of digital interventions that include West syndrome, infantile spasms, and infantile convulsions.

At the first stage, we defined a test set of critical articles. meeting our broad inclusion criteria by introducing into search string the main term "West syndrome" (7,246 results) or "infantile spasms" (2,458 results); The search strategy was developed at MEDLIFE using article IDs, and the search strategy has been improved many times over to maximize sensitivity and specificity for identifying relevant articles. Then the key search terms obtained from the terms of the medical subject headings used in the tests were established, which included 9 primary sets of terms

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related to studies on "West syndrome" or "infantile spasm syndrome" and digital intervention: these relevant terms included (AND) "clinical seizures" (856; 1061 results), "epileptic convulsions" (1234; 572 results). "electroencephalography" (1007; 534 results), "Video-EEG" (34; 25 results), "mental retardation" (579; 323 results), "developmental delay" (285; 134 results), "developmental regression" (101; 44 results), "intellectual disability" (541; 124 results), "cognitive" (344; 103 results), and "disability" (431; 216 results).

Results

Different terms associated with each of these terms have been entered into each database. References to relevant sources, which were manually reviewed to identify any additional relevant studies, were included in the bibliography. We independently checked the titles and abstracts for relevance, and then extracted and selected the relevant full-text records and main documents known to any reviewer.

Notably, when we combined the terms "West Syndrome" and "Infantile Spasm Syndrome" in our search, the results were more significant across all searches conducted, meaning that the classic term West syndrome is even more embodied and most widely used in the literature.

Etiological factors

The overall spectrum of IS, including epileptic seizures and disorders of cognitive and behavioral development, is caused by various pathogenic causes, some of which are still unknown while others are well-known structural, infectious, metabolic and immunological defects and genetic abnormalities [6]. All these factors can act mainly as single causal events or in combination. In about 35% of cases, the etiological event is (yet) unknown: the outcome in such cases is usually more favorable compared with a group with a recognizable etiology. Yuskaitis et al. [13] reported 133 newborns with IS. of unknown origin, normal development in 15% compared to clinically.

The role of genetics as an etiological factor

According to Schaeffer et al. [6], most of the genes involved in IS [see tab. 1], exhibit phenotypic heterogeneity, as occurs in other neurological disorders. A genetic predisposition to IS has been put forward by Dulac et al. [18] and Hemminki et al. [19], based on the observation that the likelihood of having IS was increased in families in which other members had epilepsy. A genetic predisposition to IS has also been identified. confirmed by reports of IS in twins.

Additional causative factors

Structural brain anomalies IS: lissencephaly, focal cortical dysplasia, polymicrogyria, 3550 Neurol Sci (2020) 41: 3547–3562 hydranencephaly [46] and hemimegalencephaly are some examples of IS underlying brain developmental abnormalities. Walker-Warburg syndrome, IS and sensorineural hearing loss. Down Syndromes. The study involved 83 patients with Down syndrome admitted to the

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hospital. In our institution in 2018, 20 people complained of epileptic seizures, of which 9 suffered from IS [50]. The prevalence of epileptic seizures in patients with Down syndrome ranges from 1 to 13%: among these 6-32% have IS

Table 1 list of the most frequent genes associated to ISS

Gene	Cytogenetic location
ARX	Xp21.3
CDKL5	Xp22.13
PAFAH1B1/LIS1	17p13.3
DCX	Xq23
TUBA1A	12q13.12
STXBP1	9q34.11
KCNQ2	20q13.33
SPTAN	9q34.11
MAGI2	7q21.11
GRIN2A	16p13.2
FOXG1	14q12
NSD1	5q35.3
NEDD4	15q21.3
CALN1	7q11.22
WDR45	Xp11.23
SLC1A4	2p14
RARS2	6q15
UBA5	3q22.1
IARS2	1q41
PHACTR1	6p24.1
ATP2A2	12q24.11
CD99L2	Xq28
CLCN6	1p36.22
CYFIP1	15q11.2
CYFIP2	5q33.3
GNB1	1p36.33
GPT2	16q11.2
HUWE1	Xp11.22
KMT2D	12q13.12
MYO18A	17q11.2
NOS3	7q36.1
RYR1	19q13.2
RYR2	1q43
RYR3	15q13.3-q14
TAF1	Xq13.1
TECTA	11q23.3
PURA	5q31.3

ARX, aristaless related homeobox; *ATP2A2*, ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 2; *CALN1*, calneuron 1; *CD99L2*, CD99molecule like 2; *CDKL5*, cyclin dependent kinase like 5; *CLCN6*, chloride voltage-gated channel 6; *CYFIP1*, cytoplasmic FMR1 interacting protein 1; *CYFIP2*, cytoplasmic FMR1 interacting protein; *DCX*, doublecortin; *FOXG1*: forkhead box G1; *GNB1*, G protein subunit beta 1; *GPT2*, glutamic–pyruvic transaminase 2; *GRIN2A*, glutamate ionotropic receptor NMDA type subunit 2; *HUWE1*, HECT,UBA,WWE domain containing 1; *IARS2*, isoleucyl-tRNAsynthetase 2, mitochondrial; *KCNQ2*, potassium voltage-gated channel subfamily Q member 2; *KMT2D*, lysine methyltransferase 2D; *MAGI2*, membrane associated guanylatekynase; *MYO18A*, myosin XVIIIA; *NEDD4*, neural precursor cell espressed, developmentally down regulated 4-2, E3 ubiquitin protein ligase; *NOS3*, nitric oxide synthase 3; *NSD1*, nuclear receptor binding SET domain; *PAFAH1B1*, platelet activating factor acetylhydrolase; *PHACTR1*, phosphatase and actin regulator 1; *PURA*, purine rich element binding protein A; *RARS2*, arginyl-tRNAsynthetase 2, mitochondrial; *RYR1*, ryanodine receptor 1; *RYR2*, ryanodine receptor 2; *RYR3*, ryanodine receptor 3; *SLC1A4*, solute carrier family 1 member 4; *SPTAN*: spectrin alpha, non-erythrocytic

Congenital pathologies of metabolism

Phenylketonuria (PKU) is a congenital metabolic disorder caused by a mutation in the gene encoding the enzyme phenylalanine hydroxylase (PAH), which converts the amino acid phenylalanine to tyrosine and other components, before screening, the incidence of phenylketonuria reached 1 in 5000 newborns and was characterized by hypopigmentation of the skin, severe developmental delay and seizures including IS.

Neurocutaneous disorders (phakomatoses)

IS may be one of the (earliest) manifestations in some neurocutaneous disorders or phakomatoses. In this context, affected children usually exhibit non-random associations. Congenital anomalies of the skin (and eyes) and structural anomalies of the central (and peripheral) nervous system (and/or

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tumors), as well as neurological manifestations, often associated with systemic damage (for example, heart and blood vessels, lungs, kidneys and bones) [66-68].

Neurofibromatosis type 1 (NF1)

Patients with NF1 have a genetic predisposition to develop benign (less often malignant) central and/or peripheral nervous system and systemic tumors, which are associated with the effect of loss of neurofibromin, the NF1 gene protein product [66, 68, 79, 80].

Sturge-Weber Syndrome

Capillary vascular malformations of the embryonic facial vasculature, leptomeninges (including underlying neuronal disorder), and the choroidal layer of the eye are the main features of MVS [66, 68, 83]. This is complex vascular development GNAQ gene, a nuclear structural gene responsible for vascular and neuronal development [84]. Epileptic seizures (as well as cognitive and behavioral abnormalities) are the most common clinical manifestations of the disease are reported to occur in 77% of patients with unilateral and 92% with bilateral brain involvement [68, 85, 86]. Epileptic seizures are mostly partial, but also generalized tonic-clonic types [86]: ISs have been reported sporadically [86, 87].

The role of immunity

Recent studies have put forward a hypothesis about the possible role of immunological events as trigger factors for IS. Several genes involved in the pathogenesis of IS also play a critical role in various inflammatory cascades and signaling pathways [91]. Lemke et al. [31] reported mutations in the GRIN2B gene (which encodes the NR2B subunit of the N-methylaspartate (NMDA) receptor), in two children with IS: NMDA receptors are involved in a number of neurological disorders [31]. It is noteworthy that elevated titers of antibodies against the complex of voltage-gated potassium channels proteins (VGKC) (i.e. 201 pmol/L; normal values = <100) have been reported in a 4-month-old child with IS [92].

Pathogenesis

The general pathogenesis of IS can manifest itself in many ways: as mentioned earlier, a number of factors can cause IS, and thus it may be difficult to explain each individual event that causes IS [15, 16, 93]. There are well-documented examples of the emergence of IP. from involvement of the entire cortex, as occurs in lissencephaly or focal cortical disorders, as documented in children with polymicrogyria or in individuals with cortical tubers and white matter disorder secondary to TSC or due to subcortical disorders, in children with hydranencephaly. Most plausible would be a disruption of the normal brain neural/interneuronal network(s) (either at the molecular, receptor or cellular level) [15, 16], which in turn leads to abnormal interactions between cortical and subcortical structures [93]. Another problem that requires clarification is the (apparent) inconsistency, the

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general diffuse (EEG) pattern of hypsarrhythmia (combined with a generalized clinical picture of spasms) and focal cortical lesions recorded in many cases of IS. The hypothesis is that a focal cortical lesion may extend down to the basal ganglia, thus providing a basis for it to exhibit both a clinical (generalized) onset of spasms and a hypsarrhythmia pattern [93–95]. Another issue requiring clarification is cognitive/intellectual disability and autism. Autism Spectrum Disorder (ASD), often associated with IS.

Conclusions: All of the above factors certainly could contribute to a worse outcome, however, according to our personal experience and opinion, as well as a review of the literature, the main negative effects in the prognosis of IS are associated with the main (molecular / cellular) etiological event causing the syndrome [148]. According to GulMert et al. [149], the most important prognostic factors are etiology, age at onset, and late and inadequate treatment.

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