



Review Article

Infantile spasm: A review on the severity of epileptic encephalopathy

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ARTICLE INFO

Article history:

Received 30-12-2021

Accepted 20-01-2022

Available online 05-03-2022

Keywords:

Infantile spasm (IS)

Neurobiology

Hypsarrhythmia

Pathophysiology

Electro Encephalo graph (EEG)

ABSTRACT

Infantile spasm (IS) comprises of both an age dependent epileptic seizure and distinctive seizure Onset in infants. In the recent past the key observation in classification and standardization of infantile spasm has culminated many recommendations in distinguishing and recognizing the seizure type and the epileptic syndrome or the West syndrome. The Infantile spasm is an early onset epileptic encephalopathy which presents unique electrographic and clinical features, these features are found in children in the middle of the first year of their birth. However the pathophysiology and the heterogeneity of the infantile spasm remains partially or incompletely understood. In the neurobiological basis there are multiple aetiologies converge to form similar clinical interpretations. The description of the electroencephalographic features of the spasm and its hypsarrhythmia plays a pivot role in early diagnosis. The treatment options for infantile spasm are very limited and it is also called a “catastrophic” due to the poor developmental, cognitive and epileptic progress. In the recent past more detailed information about the electrographic and clinical features of the spasms and hypsarrhythmia in EEG has emerged. The advances in the neuro imaging techniques have revealed about the aetiology and the pathophysiology of infantile spasm to yield a prognosis in patients with infantile spasms. The pathophysiology of infantile spasm needs to be better clarified for any kind of novel treatments and a wide range of preclinical animal studies are essential for advancing the knowledge. Here, in this review paper we focus on the preclinical models of Infantile spasm, with information’s regarding the existing models and research findings, elaborate on some novel models and discuss on new data that can help in advancing the understanding of the cellular mechanisms underlying the specific EEG changes such as ictal electrodecrement and interictal hypsarrhythmia presented in Infantile spasm IS.

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1. Introduction

Infantile spasm can be defined as epileptic encephalopathy (EE) are a spectrum of disorders that mostly onsets during infancy and have poor behavioural and neurological outcomes.¹ Infantile spasm IS presents a seizure disorder with unique electroencephalographic and clinical features, these features included visible hypsarrhythmia and poor clinical prognosis that included psychomotor retardation and intractable epilepsy that can be with or without mental retardation. This association of spasms and hypsarrhythmia

is defined as west syndrome. There are increasing high incidence of new cases of west syndrome each year in many countries around the globe. Over the last 150 years since the first description, there has been a steady progress in the understanding of the pathophysiology of the infantile spasm.² Although some advance has been made over the years in classification of the disease the treatment has remained very empirical.

In accordance to the international league against epilepsy defined the syndrome in which inter-ictal epileptiform or the seizure leads to brain dysfunction which is key underlying pathology of infantile spasm.¹ The infantile spasm exerts an

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high toll on the families, society, health care systems and the patients. In many cases the affected population greatly suffers with the seizure and cognitive dysfunction and the condition is highly resistive to pharmacological treatments. These key points emphasize the need for development of more novel treatments and also a preclinical evaluation to clarify the pathophysiology of the disease.²

Infantile spasm or West syndrome is a severe epilepsy encephalopathy that has a number of features unique from other epilepsy. Keeping in mind with the recent literature work, we will refer to West syndrome as infantile spasm IS, in relationship with to a broader spectrum of epileptic spasms. This includes characteristic seizure semiology ie extension spasm, flexion spasm, age-specific seizure onset, ictal and inter-ictal electroencephalogram (EEG) findings and also treatment and therapy responses. In animal models the spasm occur in the equivalent age range as in humans. The inter ictal EEG recordings of infantile spasm is called hypsarrhythmia, it is called so due to its mixed slow wave and sharp spike waves that are chaotic and high amplitude, the ictal EEG amplitude of an actual spasms is electrodecremental which is sometimes mixed with very fast oscillations typically above 70Hz.^{3,4}

The seizure mechanism of infantile spasm is noticed to occur often in clusters during sleep, sleep to awake state transition. The underlying EEG patterns are hypsarrhythmia which is also a responds to the stress hormone such as corticosteroids or adrenocorticotrophic hormone, but are not responsive to most conventional epileptic drugs considering the underscores the pathophysiology of this disorder. The early stage research with adrenocorticotrophic hormone has shown greater responsiveness to infantile spasm, which lead to unveiling mechanism and therapies.⁵

Infantile Spasm in an average affects 3-5 /10000 infants; this makes it the most catastrophic epileptic disorder in the first year of life.⁶⁻⁸ The mechanistic implications of infantile spasm is specific to certain age windows in infancy. Although there is various etiology that contributes to the disease, it can be cryptogenic with no known cause, symptomatic with known causes. though many advances in imaging diagnosis, genetic tools and diagnostic methods the incidences of cryptogenic cases have reduced over time. Infantile spasm can also occur in full term labours and premature labours. In premature labour the most commonly associated causes for infantile spasm is intra ventricular haemorrhage and periventricular leukomalacia.⁹ The causes for Infantile Spasm are heterogeneous aetiologies have been linked to acquired brain injuries like intracranial haemorrhage, perinatal hypoxia and gene mutation in ion channels, neuron migrations, circuit formation and synaptogenesis.¹⁰ Currently the greatest challenge is the poor prognosis of patients with infantile spasm, the inadequacy of current understandings and therapies pose a greater challenges and the pathophysiology remains elusive.

2. Clinical Manifestation

The spasms in infantile spasms may have different bodily responses, they generally consist of rapid muscle twitching and contraction which involves the neck, torso, the upper and lower extremities in a symmetric fashion¹¹ Video EEG analysis of the spasms have been classified into three subtypes (flexion, extension, and mixed flexo-extension) with reference to the basis of posture, the manifestations of the seizure and patterns of the muscle involvement during the episode.^{11,12} The term flexion typically involves the crunching of the neck, torso and the upper and lower extremities and self-crunching motions from adducting the arms, while extension comprises of extensor spasms of the neck, torso and the extremities. There are also some mixed flexion-extension spasms involving combination of neck, torso, arm flexion or leg extension, and leg flexion or arm extension. Asymmetric spasms are almost seen exclusively in patients with symptomatic focal brain lesions. Isolated contraction of neck and/or abdominal muscles may result in slight head nods and trunk movements only.¹¹ The other associated features of spasms includes occasional occurrences of abnormal eye movements, such as nystagmus or eye deviation and autonomic changes, in alterations in heart rate and respiratory lacrimation and diaphoresis. Temporal patterns are found to be common in many patients. More than nearly 60% of epileptic spasms appears in two or more seizures clusters.^{12,13} The patients may experience dozens of seizures and spasms per day. However the spasms tend to occur mostly occur during awakening and seizures are activated during sleep-arousal stages. There are many other plausible triggers such as loud noises, photic stimulation sensitivity etc. There are other reasons for spasm to occur occasionally triggered by loud noises that can cause arousal and photic sensitivity triggered responses. Approximately one half of patients with the epileptic spasms also tend to have other seizure types preceding or along the onset of the spasms.¹⁴⁻¹⁷ The Associated seizure types include tonic, tonic-clonic, partial and myoclonic seizures. The spasms are said to cease by the age of 5 years and are mostly replaced by other seizure types but rarely continue into young adulthood. Cerebral palsy and Mental retardation occur in about 50% to 70%, in children with infantile spasm.^{12,16-19}

3. Etiology and Pathophysiology

The total infantile spasms cases are classified into symptomatic and cryptogenic, recently the reported percentage of symptomatic cases has risen and identified more easily with aetiology. Studies conducted at early 1980s, have estimated that more than 50% of patients have symptomatic origin.¹⁶ Infantile spasm can be attributed mostly to improve sensitivity of diagnostic test on patients, especially neuroimaging studies such as Magnetic

resonance imaging MRI, Computer tomography CT has a higher sensitivity in detecting the focal abnormalities of West syndrome patients.²⁰ The symptomatic group can be further divided into prenatal, perinatal and postnatal based on the causes. Although many studies have identified prenatal aetiologies as the predominant cause for 50% of the cases.^{19,21–28} Generally the prenatal diseases are malformations of cortical development, metabolic disorders intrauterine infection and insults and other chromosomal defects or genetic disorders. Recent advances provides insights on the genetic evidences of idiopathic and cryptogenic infantile spasm. Although cases of infantile spasm are sporadic, evidence for an X-linked infantile spasm in two different families which pertain to the distal part of the X chromosome is found in recent reports.²⁹ Many hypotheses relatively has little established about the pathophysiology of infantile spasms. Considering the diverse aetiologies of this disease, an unproven but a popular idea is that an infantile spasm presents a nonspecific and age-dependent reaction of the improper maturation of acquired brain to injury. Using this hypothesis it is ideal to consider that the insults caused in infantile spasms are focal or unilateral damage or multifocal or diffuse in nature. We can consider the subcortical structures such as brainstem to contribute to the clinical spasms and hypsarrhythmia. Also abnormal brain function can influence the hemispheres through widespread of cortical projections. A substantial amount of research have specified the involvement of brainstem regions in infantile spasm.^{30–34} Other studies have hypothesized the involvement of brain stem nuclei such as noradrenergic, serotonergic and cholinergic neurons have not been substantiated.^{32,33} The roles of other hormones such as glucocorticoids and adrenocorticotrophic hormone are widely considered, the hypothalamus and pituitary –adrenal axis are implicated. Despite considering the abundance of hypotheses, no unifying or comprehensive mechanism for the pathophysiology of infantile spasms has yet been established.

4. EEG Features

The epileptic spasms or interictal EEG patterns of a patient is called hypsarrhythmia.^{12,16,22} It is widely accepted that epileptic spasm are typically associated with hypsarrhythmia. There are very data on the proportion of patients who have clinical spasms that do not have hypsarrhythmia.²⁴ Most of the studies in infantile spasm include EEG features with hypsarrhythmia as a diagnostic criterion. In most cases hypsarrhythmia and epileptic spasm is an essential feature for west syndrome classification.²¹ Conversely, hypsarrhythmia can't be treated as a bio marker for infantile spasms because it may also be seen in other neurological disorders.²² Hypsarrhythmia is generally classified with completely disorganized and chaotic background pattern which comprises of high

amplitude slow wave and spikes that are non-rhythmic, asynchronous and variable in duration. The spikes usually are random between focal, multifocal, and generalized discharges at different time points within the recording. Hypsarrhythmia represents a dynamic high amplitude patterns that may change dramatically. Hypsarrhythmia usually is seen through infancy and gradually reduces in the childhood. Although in Lennox-Gastaut syndrome or ohtahara syndrome the abnormal EEG patterns are a burst –suppression in found mostly in neonatal period of the patient.^{25,26} In the recent studies a number of variations in pattern of hypsarrhythmia have been described, labelled and are called modified hypsarrhythmia.^{20,27,28,35–37} These variations include episodes of attenuation, inter hemispheric synchronization, presences of consistent epileptiform focus, high-voltage slow activity with spike wave discharge and asymmetric hypsarrhythmia. Modified hypsarrhythmia is found common in patients with typical hypsarrhythmia. These variant patterns impairs prognosis of the patients.

5. Prognosis

Many studies over the decade have examined the efficacy of long-term epileptic drugs and prognosis of

patients with infantile spasms. There is substantial variability in specifics that are catalogued from different studies, the majority of patients with infantile spasms tend to suffer a poor outcome with respect to mental retardation, chronic epilepsy, and other neurodevelopmental dysfunction. Epileptic spasms spontaneously resolve without treatment or with treatment using anti-epileptic drugs in the majority of patients.^{15,19} However there are other seizure types that are chronic and intractable in approximately 50% of the patients.^{16,19,38} Many studies have observed close relationship between infantile spasm and lennox-gastaut syndromes as they have similar electrographic and clinical features that relate to intractable seizures, interictal EEG abnormalities and mental retardation.^{21,37} Approximately 30-50% of patients with Lennox-Gastaut syndrome have a history of infantile spasms and patients with infantile spasms tends to change into lennox-gastaut syndrome.^{20,24–28} Mental retardation and developmental delay is observed in nearly in 70-90% of patients with infantile spasms,^{15–17,19,39} and the scale of mental retardation is severe-to profound retardation³⁸. In case of symptomatic infantile spasms they have a poor prognosis, down syndrome and neurofibromatosis notable exceptions, both with a benign course associated with infantile spasms. By far the most important factor in predicting the neurologic prognosis in infantile spasm, includes developmental outcome and long-term epilepsy reductions. In patients with cryptogenic infantile spasm have lesser chances of mental retardation compared to that of patients with symptomatic aetiology.^{17,40} It is reported that ACTH treat is an early effective treatment for infantile

spasm . Although the higher mortality numbers come from studies that followed patients with severe epilepsy. The most common cause of death is infection, followed by reasons related to the underlying disease process in childhood and later preceded to the adulthood.[51]

6. Conclusion

Infantile spasm in children is one of the greatest challenges in the field of paediatric neurology. The Accurate understanding and diagnosis of infantile spasm depends greatly on the clinical and electrographic features of spasms. In diagnostic evaluation of infantile spasms there should be a use of rational approach in identifying the potential aetiologies of the symptomatic infantile spasm cases^{29–31,37,41–44}. Decisions about the treatment plan must be taken in considering the poor prognosis of the spasm reduction, side effects of anti-epileptic drug treatments and data on impacts of treatment outcomes over a long period of time. With more research on the pathophysiology of infantile spasm, in future there will be more effective and safer treatment methods be developed.^{16,17,19–28,34} Considering the severity of the infantile spasm the ultimate objective will be to primary prevention of the disease.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

8. Source of Funding

None.

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Cite this article: Srinivas S. Infantile spasm: A review on the severity of epileptic encephalopathy. *IP Indian J Neurosci* 2022;8(1):16-20.