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Review

Epileptic spasms — 175 years on: Trying to teach an old dog new tricks

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ABSTRACT

Purpose: This text provides an overview of how the condition "infantile spasms" has evolved in the last 175 years.
Method: Key references are summarised to assimilate this review. Results: Infantile spasms, first described by Dr West in 1841, has undergone extensive investigation to understand the pathogenesis, aetiologies, optimal intervention and most likely prognosis for the affected child. The terminology has recently evolved such that the preferred term for the condition is now "epileptic spasms" in recognition of the fact that cases can present outside infancy. The aetiologies are diverse and can be structural, genetic, metabolic or acquired. Increasing numbers of presumed causative genetic mutations are now being identified. The condition is an epileptic encephalopathy such that without adequate control of the clinical seizures and correction of the abnormal EEG, ongoing neurological damage occurs. In some cases neuroregression is inevitable despite intervention. First-line treatments are either hormonal therapies, adrenocortcotrophic hormone or prednisolone, or vigabatrin. In the sub-group of patients with tuberous sclerosis complex, vigabatrin is the preferred treatment. High dose prednisolone may be a more viable option in resource limited settings. Recent research has suggested that combining hormonal therapies with vigabatrin will result in more patients achieving spasm cessation.
Conclusions: Despite extensive study, the pathogenic mechanisms remain an area of debate and in need of further exploration. The enigma, however, may be explained as the role of resting state and dysfunctional brain networks are elucidated further.

1. Introduction

Infantile spasms (IS) were first described by Dr West in 1841 when he wrote a letter to the Lancet about his own child's clinical events. His son was healthy until 4 months of age when Dr West noticed that he had "slight bobbings of the head forward" which increased in frequency and intensity with time. He reported that whilst he was a "fine grown child" he lacked "intellectual vivacity" and "power of moving his limbs, of a child of his age" [1]. Over 100 years later, in 1954, Gibbs et al. published their description on hypsarrhythmia in Pediatrics [2]. This electroencephalographic finding in IS was described as chaotic and disorganized background activity with asynchronized large amplitude slow waves mixed with single focal, multifocal spikes and slow wave followed by attenuation. In 1958, Dusaucy-Bauloye reported that adrenocorticotrophic hormone (ACTH) controlled the spasms in a number of cases [3]. Previously there were no known effective treatments for the condition. After this report numerous other studies have confirmed the efficacy of ACTH, corticosteroids and vigabatrin.

Since then the semiology of infantile spasms, both clinically and electrically, has been extensively reviewed and the term West Syndrome established, consisting of the triad of spasms, intellectual disability and hypsarrythmia.

Infancy is the highest risk period for epileptic seizures and epileptic spasms are the most prevalent infantile epilepsy type [4]. The morbidity from this type of epilepsy is often significant.

As the condition was studied more it became evident that cortical malformations and genetic disorders were important causes of IS.

A large single centre study of 150 infants with infantile spasms, assessed their long term outcome [5]. The subsequent prognosis of this group was that 22% died, 16% attended normal school and the remainder required school learning support or day-care, with 34% severely affected. Fifty-five percent went on to develop other seizure types and 47% had abnormal neurological signs. Overall

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they illustrated the legacy of neurodisability associated with the majority of children who had infantile spasms [5]. This was further supported by the findings of Riikonen in the epidemiological study of patients with IS in Finland [6]. Poor prognosis related to early onset, long duration of spasms and presence of developmental delay at onset. But the infants with "cryptogenic aetiology" had a better prognosis [5,6].

2. Definitions

The West Delphi study group, following input from 31 clinicians in 15 countries, devised criteria for diagnosing infantile spasms based on clinical signs [7]. The group concluded that the primary clinical outcome, namely cessation of spasms, should be defined by the absence of witnessed spasms from within 14 days of commencement of treatment, and 28 consecutive days, or more, from the last witnessed spasm. Primary electroclinical outcome was defined by cessation of spasms with resolution of hypsarrhythmia. The group defined West syndrome as a subset of the syndrome of infantile spasms. They supported the idea that an infantile spasms single-spasm variant should be recognized. The report provides a standard for reporting modifying and atypical features of hypsarrhythmia. It also suggests a minimal set of baseline characteristics and outcomes that should be reported in trials of patients with infantile spasms, and suggests a standard definition of relapse. The group were unable to reach consensus on a definition of hypsarrhythmia.

Clearly access to electroencephalography (EEG) is important in the diagnosis and management of infantile spasms. But access to EEG in resource limited settings is a major challenge, as in most settings the tool is not available, or is limited to psychiatric or adult neurology services [8]. Pre-symptomatic monitoring with regular EEGs is recommended in high-risk populations such as infants with TSC [9]. Also for assessment of subtle spasms, prolonged EEG monitoring has been supported with video-EEG studies between 8–24 h in duration [4]. These logical recommendations are also not viable in most resource limited settings.

The condition of late-onset infantile spasms is an accepted entity, to the extent that the preferred term is no longer infantile spasms but now referred to as late-onset epileptic spasms [10,11]. This condition is often associated with focal cortical dysplasia type 1 [12]. Patients may have severe mental impairment but seizures can be remedial to surgical interventions. These late-onset epileptic spasms (ES) are distinct from West syndrome and Lennox–Gastaut syndrome. In a study of 8 symptomatic patients with late-onset ES [11] all patients had neurological deterioration in addition to multiple seizure types, which were intractable in seven. Interictal EEG showed no typical hypsarrhythmia. The predominant tonic seizures were ES, spasms followed by tonic seizures (SFT), and tonic seizures. The clinical characteristics were reported to be consistent with infantile epileptic encephalopathy with late-onset spasms in those infants with core seizure types of ES, SFT, and tonic seizures, ES beyond the age of 1 year, and neurological deterioration.

It is through the recognition that infantile spasms are not restricted to the infantile period that the terminology has moved away from this to re-terming the condition "epileptic spasms" (ES) [13].

3. Epidemiology

Epileptic spasm is an age related disorder. It is the most common epileptic syndrome in infancy. The incidence of IS has been estimated to range 2–5/10,000 newborne. Studies from high income countries showed wide range incidence rate (0.05–0.6/1000 liveborne) higher reported incidence were reported from the higher geographic latitudes; Sweden, Finland and Denmark and lowest incidence in United States of America, Britain and Korea. It is not clear if this difference were due to environmental factors or specific genetic predisposition. The age specific prevalence is around 1–2/10,000 children by age of 10 years. Like incidence the highest prevalence values also corresponds to high geographical latitude [14,15,16]. There are scant report from sub-Saharan Africa on the incidence or prevalence of ES. In the review of the epidemiology of epilepsy in resource limited countries Senanayaka and Roman did not include epileptic spasm among the seizure types reviewed [17], while in a survey of childhood epilepsy in rural Uganda, though none of the 440 children reviewed then had ES, 7 of them had previous history suggestive of ES [18].

The age of onset is reported to vary from the first week of life up to 3 years. The peak is between 4 and 7 months, age of onset is within one year in 94% of cases. Almost all cases occur within 3 years of age. However, rare cases of epileptic spasm with onset at up to 14 years of age are reported, hence the new preferred term of epileptic spasm which was first suggested in the 1991 workshop of the ILAE commission on paediatric epilepsy [19].

Whilst studies suggest a slight male predominance in the prevalence of ES in the average ratio of 6:4, this finding is not consistent. The reason for this differences is not clear, Brna et al. suggested that the observed male predominance in some studies simply reflects the predominance in males in the referring population [20]. An alternate explanation is the increased complication rate in predisposing conditions such as neonatal hypoglycaemia and HIE reported to occur in male infants [21].

4. Aetiologies

A study of 269 infants with ES in a national childhood encephalopathy study, found that 34% had antecedent factors which may have caused the spasms, the commonest of these were perinatal hypoxia in 38 cases and TSC in 16 cases [22]. This case control analysis showed no significant association between ES and pertussis immunisation in the 28 days before onset. There was some clustering of cases immunised with either diphtheria, tetanus and pertussis (DTP) or DT vaccines in the 7 days before onset.This study was important to emphasise and support that vaccinations did not cause ES but could trigger their onset in infants in whom the disorder was predestined to develop.

A further study of 207 infants with epileptic spasms found that, 127 (61%) had a proven aetiology, 68 (33%) had no identified aetiology, and 12 (6%) were not fully investigated [23]. Aetiologies were prenatal in 63, perinatal in 38, postnatal in 8, and 18 had other causes. The most common aetiologies were: hypoxic-ischemic encephalopathy (HIE) n = 21 (10%), chromosomal n = 16 (8%), malformations n = 16 (8%), stroke n = 16 (8%), tuberous sclerosis complex (TSC) n = 15 (7%), and periventricular leukomalacia or haemorrhage n = 11 (5%). The remaining 32 aetiologies were all individually uncommon.

The National Infantile Spasms Consortium in North America prospectively evaluated the aetiology of new-onset epileptic spasms and evaluated the yield of genetic and metabolic investigations in those without obvious cause after initial clinical evaluation and magnetic resonance imaging (MRI) [24]. Twenty-one United States paediatric epilepsy centres prospectively enrolled infants with newly diagnosed West syndrome in a central database. A total of 251 infants were enrolled (53% male). A cause was identified in 161 (64.4%) of 250 cases (genetic, 14.4%; genetic-structural, 10.0%; structural-congenital, 10.8%; structural-acquired, 22.4%; metabolic, 4.8%; and infectious, 2.0%). An obvious cause was found after initial clinical assessment (history and physical examination) and/or MRI in 138 of 161, whereas further genetic