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Latest American and European Updates on Infantile Spasms

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Abstract Infantile spasms remain a challenging condition to study and treat, and although they form the commonest epilepsy syndrome with onset in infancy, the challenge is broadened by the wide range of potential underlying causes. The field of study remains dynamic, with debates relating to case definitions and organising structures for classification of seizures and epilepsies in general, and a newly proposed genetic and biologic classification specifically for infantile spasms. There have been recent consensus statements, a Delphi process eliciting prioritised quality-of-care indicators, systematic reviews of treatment, and a survey of clinical practice in the USA. There is increasing evidence that longer duration of spasms is associated with poorer neurodevelopmental outcomes. It has taken many years to develop an animal model that reasonably represents infantile spasms, but there are now several animal models, and they are leading to innovative and valuable studies that suggest novel treatments.

Keywords Infantile spasms · West syndrome · Infantile seizures · Consensus statement · Guidelines · Epilepsy syndrome · ACTH · Vigabatrin · Visual field loss · Animal model · Classification · Aetiology · Neurodevelopmental outcome

Introduction

Infantile spasms is always a focus for intensive and interesting research. It is the commonest of the epilepsy syndromes in infancy, with an incidence of between 0.25 and 0.4 per 1,000, and there is a plethora of underlying causes, many well known and many, particularly genetic causes, recently discovered. There remains debate and doubt about its classification and relationships with other forms of epilepsy in infancy, and about which interventions might help to control the seizures and improve longer-term neurodevelopmental outcomes. There has also been long-standing controversy about the most effective and established first-line treatments because of their relatively high risks of serious adverse effects. This update on recent developments in America and Europe highlights several of these areas.

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Classification, Definitions, and Underlying Causes

Classification

The International League Against Epilepsy (ILAE) Commission on Classification and Terminology has published a revised terminology and concepts for the organisation of seizures [1••]. In this new organisation, the types of seizure are, as with earlier classifications, broadly categorised as either generalised or focal, but epileptic spasms (infantile spasms) remain in a group classified as unknown since there are no objective criteria, either clinical or electrographic, that allow the seizure type to be classified more confidently. Indeed, epileptic spasms form the only seizure type that is categorised as unknown within the proposed organisation. The ILAE 1981 classification of seizures did not include spasms as a seizure type, although the 2001 glossary did use the term "epileptic spasms", a term that is more generic than "infantile spasms" since it can validly be used for seizures with onset or occurrence after infancy. The new organisation states that the terms "idiopathic", "symptomatic", and "cryptogenic" "have taken on a variety of meanings and connotations laden with presumptions which, at times, conflate multiple concepts into a single word." In particular, it seeks to separate the dimensions of cause and prognosis such that, for example, there should be no implication that an

idiopathic cause would have an implied quality of being benign. It also discourages use of the term "symptomatic" as a term modifying underlying causes.

The term "West syndrome" is generally used to describe the combination of infantile spasms with hypsarrhythmia, but many cases of infantile spasms do not have the hypsarrhythmic EEG pattern at presentation. A recent review of 16 such cases of clustered epileptic spasms without hypsarrhythmia but with onset in infancy gives good descriptions of ictal patterns [2].

Aetiology

Paciorkowski et al. [3••] have suggested a genetic and biologic classification of infantile spasms in which they regard the terms "symptomatic", "cryptogenic", and "idiopathic" as increasingly unsuitable because of growing evidence that infantile spasms often occur in children in whom there has been disturbance in key genetic pathways of brain development. They cite as examples of infantile-spasm-associated genes—in other words, genes in which mutations are likely to manifest themselves as infantile spasms even if not with a wholly consistent phenotype—*ARX*, *CDKL5*, *FOXG1*, *GRIN1*, *GRIN2A*, *MAGI2, MEF2C*, *SLC25A22*, *SPTAN1*, and *STXBP1*. These genes, and other candidate genes that have been identified from abnormal copy-number variants detected on microarray comparative genomic hybridisation, suggest that the pathogenesis of infantile spasms is likely in many cases to relate to abnormalities in ventral forebrain development and in synaptic functional pathways. They suggest analogies between infantile spasms and autism, in both of which there is likely to be a broad range of genetic abnormalities, most of which may contribute no more than 1 % of underlying causes. Their classification is broadly congruent with the most recent ILAE commission report, but they contend that there are problems with classifications based on presumed distinctions between genetic and structural/metabolic categories.

There are many newly identified genetic syndromes that might be underlying causes of infantile spasms. These include Ras/mitogen-activated protein kinase syndrome [4] and *STXBP1*-related encephalopathy, which has been reported to present as infantile spasms and a generalised tremor [5, 6]. There is also a syndrome of microcephaly associated with capillary malformations whose features may include infantile spasms [7]. Deletions in the *FOXG1* gene have been described as part of a duplication syndrome on chromosome 14q12 [8] and with maternal uniparental disomy of chromosome 14 [9]. DEND syndrome (developmental delay, epilepsy, and neonatal diabetes), which is associated with an activating mutation in the potassium ATPase channel Kir6.2, may be associated with features that include infantile spasms [10]. One remarkable observation with genetic causes of infantile spasms is that onset of spasms in some cases seems to have strong temporal programming. Coppola et al. [11], for example, described three sets of monozygotic twins in which onset of spasms was initially recognised in each twin-pair on the same day.

Kamien et al. [12••] suggested a broadly scoped diagnostic approach to infantile epileptic encephalopathies in general and that is highly applicable to infantile spasms. This useful and practical article has tables describing a general diagnostic algorithm, well-recognised clinical syndromes, symptoms and signs that suggest specific aetiologic diagnoses, the range of structural brain abnormalities, and potential metabolic causes, highlighting those that are currently treatable, and distinguishing basic and further investigations. Another recent review has focused exclusively on metabolic causes of epileptic spasms [13].

The United Kingdom Infantile Spasms Study (UKISS) reported causes in 207 enrolled infants using the paediatric adaptation of the tenth revision of the International Statistical Classification of Diseases and Related Health Problems [14•]. There was an identified cause in 127 of cases (61 %), with 68 cases (33 %) having no identified cause and 12 cases (6 %) considered to have been incompletely investigated. The commonest causes were hypoxic–ischaemic encephalopathy (10 %), chromosomal anomalies (8 %), malformations (8 %), perinatal stroke (8 %), tuberous sclerosis complex (7 %), and periventricular leucomalacia or haemorrhage (5 %). The other 32 causes were individually uncommon, and most of the infants were not tested for many of the newer genetic diagnoses that are now known to be associated with infantile spasms.

Possible Neuroimmunological Causes

Voltage-gated potassium channels are well known to be associated with limbic encephalitis in adults and older children, and also in children with unexplained status epilepticus. Suleiman et al. [15] have described a 4-month-old female infant who presented with infantile spasms and developmental delay, and who had elevated CSF neopterin levels with mirrored oligoclonal bands. These findings prompted investigation for autoantibodies, and she was found to have elevated levels of voltage-gated potassium channel complex antibodies. She was said to have a partial response to treatment with steroids.

Pyridoxine, Pyridoxal Phosphate, and Folinic Acid

There is often debate about whether infantile spasms should be treated with pyridoxine, pyridoxal phosphate, and/or folinic acid. Stockler et al. [16] have reviewed new developments relating to pyridoxine-dependent epilepsy and deficiency of antiquitin, also known as α-aminoadipic semialdehyde dehydrogenase. One of the most significant developments is

that seizures responsive to tretament with folinic acid are due to deficiency of the enzyme α-aminoadipic semialdehyde dehydrogenase [17]. This condition is likely to present with neonatal seizures rather than infantile spasms, but measurement of urine antiquitin concentration is recommended if no other cause of infantile spasms has been identified.

Epidemiology

Mortality Risks

Epilepsy is associated with an increased risk of death, and this is particularly so for infantile spasms and Lennox–Gastaut syndrome [18•]. A cohort study in the metropolitan area of Atlanta showed that by the age of 10 years there was a mortality ratio—adjusted for the effects of age, race, and sex—of 3.1 for all-cause epilepsy, 11.9 for infantile spasms, and 13.9 for Lennox–Gastaut syndrome.

Effects of Lead Time to Treatment

Previous retrospective studies have suggested that a longer lead time to treatment intervention with infantile spasms may be associated with poorer neurodevelopmental outcomes [19, 20]. Seventy-seven infants with developmental assessments performed at age 4 years for follow-up after enrolment in the UKISS were studied in four categories of lead time to treatment [21]. A multiple regression analysis that adjusted the results for the effects of age of spasm onset, aetiologic category, treatment intervention, and a possible interaction between aetiologic grouping and treatment showed that there was almost a four-point drop in the score obtained by Vineland Adaptive Behaviour Scales for each successively longer period of lead time.

Auvin et al. [22•] reported a multicentre, retrospective, observational study of 84 children using multivariate analysis, and reported a substantially increased risk of neurodevelopmental delay in association with delayed diagnosis. They found that a high proportion of consulted physicians (301/362; 83 %) did not suggest any specific diagnosis, and that the commonest specific erroneous diagnoses were gastro-oesophageal reflux (7 % of all cases), constipation (7 %), and colitis (3 %). A study in western France showed that the lead time to diagnosis was longer than 2 months in 5 % of cases, and that delay was commoner where presentation was to a general practitioner rather than a paediatrician [23].

A retrospective study of 159 children admitted to hospital in Los Angeles suggested that early response to treatment was associated with better longer-term seizure control and neurodevelopmental outcome, but did not identify any clear independent association between shorter lead time to diagnosis and better neurodevelopmental outcome [24]. A retrospective study of 173 children with infantile spasms reported poorer neurodevelopmental outcome when presentation with spasms was associated with hypotonia and preceding developmental delay [25].

Clinical Practice in North America

Mytinger and Joshi [26•] surveyed members of the Child Neurology Society, with responses from 222 members (18.5 % of those polled). Adrenocorticotropic hormone (ACTH) was reported to be the commonest preferred first-line treatment for infantile spasms associated with no identified underlying cause (67 %) and for cases with an underlying structural or metabolic cause (44 %). The preferred doses of ACTH were variable, with over half of respondents suggesting an initial dose of 150 IU/m^2/day, but 10 % of respondents using a starting dose of less than 40 IU/m^2/day. Eighty-four percent of respondents reported using a concomitant medication to suppress gastric acid, and 11 % reported using antibiotic prophylaxis against pneumocystis infection. The treatment regimens for prednisone or prednisolone also varied substantially, with 29 % of respondents using an initial dose of 2 mg/kg/day, and 29 % using the UKISS regimen, which starts at a minimum dose of 10 mg four times a day irrespective of body weight. A "pyridoxine challenge" was used regularly by 42 % of respondents, occasionally by 41 %, and never by 17 %. In cases where the underlying cause was tuberous sclerosis, almost 90 % of respondents used vigabatrin as first-line treatment.

Guidelines

Motivated by the need for further consensus and in order to optimise outcomes with infantile spasms, the Infantile Spasms Working Group produced a US consensus report [27••]. It quoted evidence supporting the use of high-dose corticosteroid in the treatment of spasms, but ultimately endorsed vigabatrin and ACTH as the first-line treatments with proven efficacy. Its concern about prednisolone and prednisone was that a solid electroclinical outcome—a combination of cessation of spasms and resolution of hypsarrhythmia— has not been reported in studies on their use. It also highlighted the potential efficacy of ketogenic diet and epilepsy surgery, and recommended the establishment of an infantile spasms patient registry. A major advantage of such a registry is that it can gather data about second-line treatments, whose effects have not to date been addressed in randomised controlled trials. In a commentary on this consensus statement, Dulac et al. [28] argued that there is no evidence supporting the ketogenic diet as a better second-line treatment than pyridoxine or antiepileptic drugs such as lamotrigine, sodium valproate, sulthiame, or zonisamide.

There has been a 2012 update of the 2004 practice parameter produced by the American Academy of Neurology and the Child Neurology Society [29, 30••, 31]. This recommends low-dose ACTH, and that ACTH be preferred over vigabatrin, particularly in cases where the underlying cause has not been identified.

Quality-of-Care Indicators

A new development is proposed quality-of-care indicators [32•]. These were developed using a modified Delphi method following a focused review of guidelines and related literature by an expert panel nominated by the American Epilepsy Society, the Child Neurology Society, and the National Institute for Neurologic Disorders. These quality indicators covered the following areas: diagnosis, investigation of cause, treatment, education, and outcomes. Of 21 suggested indicators, eight were regarded as having the potentially largest clinical impact on quality of life outcomes. These are shown in Table 1. Other consensus recommendations were that if no cause is identified, a pyridoxine challenge should be performed within 2 weeks; an MRI head scan should be performed within 4 weeks; ACTH and vigabatrin should be considered as first-line treatments; treatment should be initiated within 1 week of diagnosis, with efficacy assessed within 3 weeks; and developmental assessments should be performed at least every 6 months until the age of 3 years.

Guidelines produced by the UK National Institute for Health and Clinical Excellence are broadly congruent with these quality-of-care indicators [33•]. It recommends discussion with and/or referral to a tertiary-level paediatric epilepsy specialist, and first-line treatment with vigabatrin where the underlying cause is tuberous sclerosis. It provides no specific recommendations on second-line treatments, for which there is generally a paucity of evidence.

Treatment Interventions

Hormonal (ACTH and Steroid) Treatments

Arya et al. [34•] have published a systematic review of corticosteroid and ACTH treatments for infantile spasms, with a specific focus on the relative efficacy of these two forms of treatment. On the basis of evidence that they considered methodologically adequate, they concluded that high-dose corticosteroids had efficacy similar to that of low-dose ACTH but less efficacy than high-dose ACTH, which they consider to be the current standard treatment.

Mytinger et al. [35] performed a small uncontrolled study in six infants with infantile spasms using the treatment intervention of pulse intravenous methylprednisolone therapy (20 mg/kg) on three successive days followed by a 2-month taper of orally administered prednisolone. Five of the six infants had remission of spasms within 6 days, and administration of the medication was regarded as simple. This innovative approach was motivated in part by cost differentials, since the intravenous methylprednisolone regimen had an estimated drug cost of $200 compared with an estimated $70,000 for treatment with ACTH in the USA.

Vigabatrin

Vigabatrin is the first antiepileptic drug to be approved specifically for the treatment of infantile spasms by the US

Table 1 The eight quality-of-care indicators that were regarded as most important in the Delphi process performed by Wang et al. [32•]

Indicator number	Area of management	Indicator
1	Diagnosis	All children with concern for infantile spasms by the primary care physician should be evaluated by a physician with expertise in the care of infants with seizures within 2 weeks
2	Diagnosis	An EEG should be conducted within 2 weeks following the concern for spasms by the primary care physician
4	Diagnosis	Prior to a diagnosis of infantile spasms, all infants should have an EEG demonstrating hypsarrhythmia, modified hypsarrhythmia, or ictal manifestations of infantile spasms
8	Treatment	Following confirmation of the diagnosis of infantile spasms, treatment should be initiated within 1 week
9	Treatment	ACTH should be selected as one of the first-line treatments for infantile spasms
10	Treatment	Following the initiation of any first-line treatment, the efficacy of therapy should be assessed within 2–3 weeks. Short-term outcomes include cessation of spasms and EEG confirmation of treatment response showing resolution of hypsarrhythmia
18	Treatment	If there is not a complete response (no spasms and no hypsarrhythmia) to a first-line treatment after 2–3 weeks, then the treatment (dose or drug) should be changed
19	Treatment	In patients in whom treatment with one first-line drug is unsuccessful, another first-line drug should be considered

ACTH adrenocorticotropic hormone

Food and Drug Administration [36, 37]. It also has a specific licence for this use from the European Medicines Agency. However, since 1997 there have been concerns about risks of visual field losses (also referred to as peripheral visual field defects), and more recently, concerns about MRI signal changes.

Because retinal injury is difficult to detect, the manufacturers and distributors of vigabatrin recommend a risk evaluation and mitigation strategy that requires visual testing at the start of treatment and at least every 3 months during treatment [38]. Electroretinogram (ERG) and visual evoked potential tests are recommended, but they are difficult to perform in infants and toddlers. The features of vigabatrin-related visual field losses include changes in the ERG photopic b-wave amplitude and flicker responses, and there may also be optic atrophy. ERGs can be difficult to interpret, and ERG tests require a general anaesthetic in infants [39].

Sergott et al. [40••] presented an evidence-based consensus review of recommendations for visual function testing in association with vigabatrin exposure. An alternative means of monitoring is ocular coherence tomography, which has many advantages: it is non-invasive, painless, requires no sedation, and is generally performed in less than 2 min. In infants and toddlers, even a 2-minute testing time is usually too long, but newer machines possessing facilities for monitoring eye tracking and for post-test processing may make this a very realistic means of monitoring. Sergott et al. suggest that, in order to minimise the risk of visual field losses, use of vigabatrin should be discontinued within 4 weeks if the epileptic spasms have not resolved.

A Canadian study identified 446 children treated with vigabatrin, of whom 160 had adequate ERG data to assess toxicity. It found that toxicity was more likely when vigabatrin was administered as adjunctive therapy alongside one or more other antiepileptic drugs [41]. In neonatal rats, Jammoul et al. [42•] have shown that the retinal nerve fibre layer damage caused by vigabatrin can be significantly ameliorated by administration of the aminosulfonic acid, taurine. The same group and others have recently reported similar protective effects on retinal ganglion cells in two different in vivo rat models, and with in vitro culture and adult explant models [43, 44•].

Vigabatrin has been reported to be associated with abnormal MRI signal changes and restricted diffusion-weighted images in the thalamus, basal ganglia, dentate nucleus, corpus callosum, and brainstem. These changes appear to be reversible and their clinical impact is unknown [30••, 45]. The risk appears to be higher with younger age on exposure and higher dose.

Despite these problems and uncertainties, vigabatrin remains an important and popular treatment for infantile spasms, and the prudent approach is close surveillance and continual reappraisal of benefits and risks. By February 2011, the US vigabatrin patient registry had enrolled 1,500 patients with spasms and 966 patients receiving treatment for other seizure types [46••].

The effects of hormonal treatments and vigabatrin remain under study in clinical trials. The largest of these, the International Collaborative Infantile Spasms Study is investigating the relative effects of hormonal treatments alone (tetracosactide depot and/or prednisolone) versus the same treatment combined with vigabatrin. So far, the trial has enrolled over 250 infants, and it continues to recruit in Europe and Australasia.

Other Treatments

Ketogenic diet is an established treatment for infantile spasms that are refractory to antiepileptic drugs. A group in Baltimore reported its extensive experience with 104 consecutive infants treated with the diet, with 64 % of infants having greater than 50 % reduction in spasm frequency 6 months after initiation of treatment [47]. One third of infants were reported to have adverse effects, which for the most part were minor. A group in Boston, Massachusetts, found no consistent association between reduction in spasm frequency and blood levels of glucose or β-hydroxybutyrate. There was no apparent deleterious effect on growth parameters [48]. A weakness of these studies is that the main outcome measure was reduction in spasm frequency rather than complete resolution of spasms, which is generally considered to be the more important outcome relating to seizure control [49•].

Another study from Boston retrospectively identified 38 infants who had drug-resistant epileptic spasms and who had been treated with adjunctive rufinamide [50]. Eighteen of these patients had persistence or relapse of spasms, and the minimum age at treatment with rufinamide was 17 months (median age 7 years and range up to 23 years). Half of the patients had a reduction in spasm frequency of 50 % or greater, and the authors of the study suggest that rufinamide should be investigated further as a potential treatment for infantile spasms.

A French group found that levetiracetam was less effective for the treatment of infantile spasms and Lennox–Gastaut syndrome than for the treatment of other epilepsies and seizure types [51].

There has been one case report of an 18-month-old infant developing infantile spasms soon after treatment with oxcarbazepine [52]. She was reported to have previously had dyscognitive seizures, and she developed infantile spasms with hypsarrhythmia within 2 weeks of treatment with oxcarbazepine. The spasms and hypsarrhythmia resolved within a few days of this treatment stopping.

Epilepsy surgery remains an option where spasms or other seizures are refractory, and several larger centres have substantial experience of treating infantile spasms surgically.

Chugani et al. [53] recommend fluorodeoxyglucose PET scans in all infants with infantile spasms without any clearly identified underlying cause. They described an interesting association between bilateral temporal lobe fluorodeoxyglucose PET hypometabolism and subsequent developmental delay, autism, or pervasive developmental disorder.

Novel Approaches to Treatment and Management

Animal Models

The ideal animal model of infantile spasms would have to meet a number of criteria that in practice are unlikely to be achieved entirely, and for decades there were no satisfactory animal models at all [54•]. However, some recently developed models are yielding valuable information. These include the corticotropin-releasing hormone model, the *N*-methyl-D-aspartate model of "cryptogenic" infantile spasms, and the tetradotoxin model [55–57]. A mouse model of Down syndrome, Ts65Dn, has on exposure to the $GABA_B$ agonist baclofen developed clustered extensor spasms with polyspike-wave or electrodecremental ictal EEG patterns [58]. Three other models are the X-linked aristaless-related homeobox knockout and knock-in mouse models, and the multiple-hit rat model of symptomatic infantile spasms [59, 60].

The multiple-hit rat model of ACTH-refractory infantile spasms has been used to explore an interesting and novel approach to treatment [61•]. Since overactivation of the TORC1 complex of the mammalian target of rapamycin pathway is linked to the pathogenesis of conditions such as tuberous sclerosis—a well-known underlying cause of infantile spasms—investigators have used this model to study the effects of high-dose pulse treatment with the mammalian target of rapamycin inhibitor rapamycin. They found that rapamycin had a dose-dependent response on suppressing spasms, and an association with improved visuospatial learning.

Internet Resources

I was initially surprised, several years ago, when parents informed me that I could review their son's most recent seizure type on YouTube. Fat et al. [62] performed a search using the terms "infantile spasm", "spasm", "epileptic spasm", and "West syndrome", and found 5,858 videos (in November 2009). They retained the top 25 hits under each search term, and assessed more than half of the videos to be relevant. Many were of high technical quality, but raters regarded several of them as demonstrating diagnoses other than infantile spasms, including dystonia, gastro-oesophageal reflux, self-gratification disorder, and normal behaviours. The availability of information and misinformation on the Internet invites interesting questions and further study.

Conclusion

In a commentary on a retrospective study of outcomes with infantile spasms, Jobst [63] asks, "Do we see the forest for the trees?" She highlights the fact that over 85 % of cases still progress to abnormal neurodevelopment, and that this proportion does not seem to be any less than decades ago [64]. She contends—I think most of us would say, correctly—that cessation of spasms is important but not the most important outcome in this challenging and complex condition. Rather, the key outcome is neurodevelopment.

Although the proportion of children with neurodevelopmental delay subsequent to infantile spasms remains high, there are now many new avenues of exploration and development that are likely to lead to significant improvements over the next few years and decades. Given the gamut of new genetic, metabolic, and subtler structural aetiologic diagnoses, it is clear that the arboretum of infantile spasms has to be explored and managed with patience, persistence, and subtlety.

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