Current Practice

Diagnosis and treatment of infantile spasms

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Infantile spasms (IS) is an age related specific epileptic encephalopathy that may cause devastating effects on the developing brain. The onset generally occurs between the ages of 3-10 months, with a peak onset between 4 to 6 months[1]. The true onset is often earlier than reported. A delay in recognition occurs due to the subtle nature of spasms at the beginning. Occurrence beyond 1 year is rare; however cases up to 5 years have been reported. The incidence is estimated at 3 to 5 per 10,000 live births[2,3] with a prevalence rate of 0.2 to 0.5 per 1000 children aged 10 or younger[4]. It contributes to 10% of all mental retardation and more than 50% evolve to different epilepsy syndromes, which are often difficult to control.

Over 160 years ago West described the condition characterized by spasms associated with abnormal EEG pattern known as hypsarrhythmia and developmental regression known to many of us as West syndrome. However one element may be missing from this triad. In the current nomenclature epileptic spasms are the preferred terminology and the terms West syndrome and epileptic spasms are used interchangeably.

Semiology and timing of spasms

Infantile spasms is a brief contraction that may occur in any group/s of muscles such that it may be very subtle as a drop in eyelid, head nod or massive with involvement of different groups of axial and limb muscles as in classical salaam spasms or clasp knife pattern spasms. Majority (42%) involves both flexor and extensor type muscle groups, while others may be flexor (34%) or extensor (22%)[5]. In the spasm there is a tonic phase which follows the spasms during which time the flexed or extended body position is maintained. The spasms should be distinguished from myoclonus which is generally briefer (<0.2s) and occurs without clustering. Spasms occur in a cluster and even more than 100 spasms may be experienced over a short period. Identifying spasms at an early stage when they are subtle may be difficult. These clusters are more likely to occur on arousal and in the alert state, less often in NREM sleep (3%) and exceptionally in REM sleep. The twilight state (just before and after sleep) acts as a precipitating factor. Loud noises, tactile stimulation, light and rarely feeding may provoke clusters[5].

Aetiology

There are 3 varieties of IS, symptomatic, cryptogenic and idiopathic. The symptomatic variety characterized by evidence of previous brain damage, or a known aetiology, accounts for the large majority. Classically, 80% is attributed to this type, although this may vary depending on the investigative capacity and technical advancement of the imaging modalities used. For example, this may increase up to 95% with use of advanced imaging techniques such as MRIs with larger magnets, PET scanning, metabolic testing and advanced genetic testing.

In the cryptogenic variety, there is lack of preceding brain damage or a known aetiology and there are negative investigation findings. The main inclusion criterion in this variety is the presence of psychomotor deficits prior to the development of spasms. This distinction is important since this group does better than those with symptomatic IS when treated with steroids[6,7]. Further, the psychomotor outcome is better in 70% of those with this variety compared to improvement in only 15% in the symptomatic group[8]. The idiopathic group is extremely rare and occurs in those with normal pre-morbid development and possible hereditary genetic predisposition to epilepsy. An X linked inheritance pattern affecting male offspring of asymptomatic mothers has been reported. Mutations in CDLK5, ARX genes amongst several others have been implicated in this variety[9]. The role of immunization, particularly the DPT vaccination, in the causation of IS has been explored. No direct association or

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relationship has been established, making this merely coincidental.

Mechanism

The exact mechanism of generation of this unusual form of seizures that are specific to a certain time phase in life is still being understood. The classical concept of centrencephalic epilepsy considers that IS are caused by subcortical structures i.e. the thalamus, with subsequent ascending activity causing cortical activation and hypsarrhythmia, followed by descending activity producing spasms[10]. The spasm resolution following lesionectomy generated the theory of cortical lesions activating the subcortical structures to generate bilateral cortical activation and spasms. Baram supported a theory of transient developmental peculiarity. The excessive secretion of a highly convulsant peptide, the cortico-releasing factor, as well as proconvulsant vasopressin by the immature hypothalamus are some other postulated theories[11]. In spite of major advances in epileptology, including intracranial electroencephalographic recordings, many questions remain unanswered. These include:

- Why do infantile spasms occur in a particular age group?
- Why do they occur after a short delay from the insulting cause?
- Why is this syndrome associated with cortical dysfunction even after cessation of spasms?
- Why do they regress at a particular age?
- Why do they respond to corticotrophin?

Electroencephalography in infantile spasms

Hypsarrhythmia is the classical phenomenology used in describing the archetypal interictal pattern that occurs in infantile spasms affecting close to two thirds of patients. The high amplitude spike and slow waves of variable amplitudes, in a multifocal distribution, varying with time gives rise to a chaotic mixture of arrhythmic and asynchronous brain activity. The typical EEG pattern is generally noted at the initial stages of the epilepsy. An atypical or modified hypsarrhythmia occurs in the balance one third. These include hemihypsarrhythmia or asymmetric hypsarrhythmia, hypsarrhythmia with constant unifocal epileptic activity, hypsarrhythmia with episodes of attenuation, intermittent hypsarrhythmia, hypsarrhythmia with increased synchronization etc.[12]. However, these patterns are highly dependent on the conscious state of the patient. The classical EEG appearance is seen during the early stages of sleep. It is markedly activated in some stages of sleep though it may be absent in the alert state and disappears during REM sleep. It may show other abnormalities such as focal epileptic activity only instead of hypsarrhythmia. Occurrence of symmetrical hypsarrhythmia is more likely to be associated with cryptogenic or idiopathic varieties. Recently a variation known as epileptic spasms without hypsarrhythmia has been described[13].

Impact on development

The developmental arrest is part of the triad complicating the epileptic spasms and affects approximately 70% of infants with spasms. This occurs with the onset of the spasms. In those who are already delayed in development, it may cause further regression. Main domains of regression include severe loss of gross motor abilities, loss of hand functions, auditory agnosia and loss of cortical vision. This developmental regression and the extreme abnormality on EEG lead to consideration of epileptic spasms as an epileptic encephalopathy. This theory emphasizes the need for early treatment and attempts for normalization of the EEG. This is supported by observational studies showing better developmental outcome with reduced interval between onset and cessation of spasms[14]. The developmental outcome on long term follow up is described minimally in the literature. Some studies indicate a better developmental outcome in cryptogenic IS group if treated with steroids[8].

Outcome

In spite of the devastating nature of the spasms, they progressively resolve with age. A study, which followed up infants who had IS up to adulthood, showed that up to 24% may eventually have normal or slightly impaired intelligence[15]. In many other studies the majority (80-90%) is shown to develop severe psychomotor retardation and many later go on to evolve into different epilepsy syndromes[15]. Factors associated with better prognosis for a good developmental outcome include cryptogenic aetiology, normal development prior to onset of epilepsy, shorter treatment lag, and good response to ACTH therapy[15].

Treatment of infantile spasms

Treating this unique, age specific, virulent form of epilepsy has remained a challenge to date. This is partly due to the poorly understood underlying pathophysiology. On the other hand, evidence based recommendations for its treatment are constrained by lack of prospective studies and lack of well planned

randomised clinical trials (RCTs). As a result, the treatment of this condition over the years has been largely empirical. Some of these treatment forms are not universally licensed for use. Though there have been a few well-designed RCTs on treatment of infantile spasms, the numbers of patients enrolled in most have been small. Overall methodology has been poor in most; use of the drug being investigated is frequently delayed from the true onset of spasms. They are often used in addition to or after use of other anticonvulsants which may also contribute to modifying the spasm control. Further, there is wide variation in the drug doses and the duration for which the drugs are used. Therefore, interpretation of the optimal form of treatment for spasms is often not clear. Different outcome measures have been utilized in these trials making comparison difficult. In the majority spasm control / quantitative reduction of spasms had been used as a primary treatment goal. Resolution of EEG changes, though described as another outcome measure, is difficult to be generalised considering the inter-observer variation, the change in the EEG pattern depending on the state of consciousness and the evolving patterns described with age. Improvement in the development is an essential outcome investigated minimally[16].

The majority of trials on treatment of IS are not RCTs[16]. Of the limited RCTs only a handful are placebo controlled. One such placebo controlled study by Appleton et al looked at the efficacy of vigabatrin at high doses (50-150 mg/kg) over short term duration[17].

Of all the treatment options, corticosteroids and their derivatives have been supported as the dominant option. The strongest evidence also favours their use over other antiepileptics including vigabatrin. However, vigabatrin remains the drug of choice for IS in tuberous sclerosis[18]. Other first line anticonvulsant medications trialed include sodium valproate and benzodiazepines. In RCTs on benzodiazepines, though nitrazepam was effective in controlling spasms over a short term, there was early development of tolerance. Valproic acid has shown 40% efficacy but treatment of IS requires relatively high doses with greater potential for hepatotoxicity particularly when used in infants. More recent studies with mainly class IV evidence describe use of newer antiepileptic such as topiramate, leveteracetam, intravenous immunoglobulin and zonisamide without definite evidence of a proven efficacy.

Use of steroids in IS

Though different in pharmacological properties, corticotrophin (ACTH) and corticosteroids (prednisolone) in literature are considered the steroid preparations used in the treatment of IS. The mechanism of their action is still not clear. The increase of serum levels of cortisol, its direct effect on the brain, suppression of cortical and hypothalamic corticotrophin-releasing hormone levels have been discussed as potential mechanisms, along with reduced cerebral blood circulation, reduction of cerebral oedema, increase of glucose levels, change of protein metabolism, and acceleration of intracerebral enzyme activity. Two different forms of ACTH, natural and synthetic, have been used, doses being highly variable from low doses of 0.2iu/kg to high doses of up to 150iu/m^2 and the durations ranging from 1-6 weeks[19]. One class I study has reported cessation of spasms in 87%[20].

Several clinical trials have been instrumental in proving the efficacy of steroids in treatment of IS[21,22]. The first report of effective treatment of IS using ACTH was in 1958[23]. Since then various studies have favoured one over the other or have shown no significant difference in their efficacy. Earlier studies showed that ACTH was the more effective form of therapy but several studies subsequently have failed to demonstrate its supremacy. The study by Hrachovy et al using comparable dosage forms i.e. 20-30 unit/day of ACTH versus 2mg/kg/day of prednisolone showed no significant difference[22]. Baram's study utilizing high doses of ACTH versus low dose prednisolone showed ACTH to be superior with spasm cessation in 87%[20]. However, there is doubt whether this effect is related to the differences in the doses rather than to the therapeutic agent itself and is supported by findings in the above study by Hrachovy et al. The UKISS study which used comparable doses of recombinant ACTH and oral predinisolone did not have an adequate power to compare the efficacy between the two therapeutic formulations[31].

To date there is no consensus on the dose or duration of therapy. Hrachovy looked at efficacy of high dose and longer duration versus low dose and shorter duration of ACTH therapy[24] and showed no significant difference between the different dosing – duration regimes.

The side effects during hormone therapy include irritability in 37-100%[19], hypertension in 0-37% and infection in 6-14%[19]. Cerebral atrophy was frequently described particularly when high doses were used. Most patients tolerated the therapies with minimal withdrawal[19].

The practice parameter of the American Academy of Neurology and the Child Neurology Society recommended the following in 2004:[19]

a) ACTH is "probably" effective for short-term treatment of epileptic spasms but there is insufficient evidence to recommend optimum dosage or duration.
b) Insufficient evidence to determine whether oral corticosteroids are effective,
c) Vigabatrin is "possibly" effective for short-term treatment of IS and is possibly also effective for the treatment of epileptic spasms of tuberous sclerosis.
d) Insufficient evidence to recommend any other treatment of epileptic spasms.
e) Insufficient evidence to conclude that successful treatment of IS improves long term prognosis,

However, these recommendations have recently been challenged. A prospective RCT performed in the United Kingdom using a large number of children (United Kingdom Infantile Spasms Study- UKISS) clearly showed an advantage of using steroids (73%) over vigabatrin (56%)[21]. They described that steroid therapy (ACTH and oral prednisolone considered together) resulted in better spasm control in the short term than with vigabatrin. The UKISS study further showed that better cognitive outcome (assessed at 18 and 42 months) occurs in those with cryptogenic IS if treated with steroids than with vigabatrin[6,25] .

Oral prednisolone and intramuscular tetracosactide (ACTH) were the two therapeutic agents under the steroid arm used in the UKISS study. Due to inadequate power of the study there was no answer to which of these two formulations (prednisolone or ACTH) had a greater efficacy in control of epileptic spasms. The same group has expanded the study to a multicentre international study known as the International Collaborative Infantile Spasms Study (ICISS), which is still in the recruitment phase. However, possible better outcome both short and long term with combined vigabatrin and hormone therapy versus hormone therapy alone is being investigated.

In those with tuberous sclerosis vigabatrin remains the drug of choice in the treatment of epileptic spasms. However, whether prednisolone is as effective for spasm control in TS has never been considered. This may be worth exploring considering the risk of retinal toxicity sustained with high dose vigabatrin therapy in close to one third of patients.

Lamotrigine, levetiracetam, nitrazepam, pyridoxine, sulthiame, topiramate, valproate and zonisamide are also used in IS as adjunctive medications when steroids and vigabatrin fail. Ketogenic diet, immunoglobulin therapy, thyrotrophin releasing hormone are some of the others that have been trialed. Carbamazepine may even worsen the spasms, particularly in those treated for combination of IS with focal seizures.

The recommendations in the latest Cochrane review[16] on "treatment of infantile spasms" states:

"Hormonal treatment resolves spasms in more infants than vigabatrin but this may or may not translate into a better long-term outcome. If prednisone or vigabatrin are used then high dosage is recommended. Vigabatrin may be the treatment of choice in tuberous sclerosis. Resolution of the EEG features may be important but this has not been proven. Further research using large studies with robust methodology is still required."

Surgical resection has also been implicated as a form of successful therapy in those with clearly defined causative epileptic lesion such as in congenital major vessel infarctions, cortical dysplasias etc. This results in cessation of spasms and improvement in the psychomotor development[26].

Sri Lankan experience

We encounter a large number of patients with epileptic spasms. The greater prevalence of hypoxaemic cerebral damage is possibly contributory. A greater percentage is considered cryptogenic due poor investigative capacity resulting in an over expression of this variety. Idiopathic groups are almost never established.

At the Lady Ridgeway Hospital, since establishment of paediatric neurology services, we have been using the UKISS protocol to treat our patients and the results have been promising. Either oral prednisolone or ACTH (depot preparation) is used interchangeably depending on the clinician's preference. Oral prednisolone in a dose of 10 mg 6 hourly or ACTH 40iu intramuscularly every other day is used for 14 days, increased to prednisolone 15 mg 6 hourly or ACTH 60iu every other day if not responding on day

7. Use of vigabatrin was limited only to those with tuberous sclerosis for a period of 3 months at a dose of 100mg/kg, increased to 150mg/kg if not responding on day 7. In a study of 35 infants, a large proportion (74%) became seizure free at the end of the steroid (n=32) and vigabatrin (n=3) treatment schedule[27]. The necessity to stop treatment due to side effects was experienced very rarely. Ability to use this protocol in overcrowded hospital environments such as ours without an increased rate of infections or mortality is encouraging. Use of vigabatrin was markedly limited due to the high cost. However, using for shorter durations such as 3 months may provide some hope for patients with TS. Presently use of ACTH is mainly limited to the Lady Ridgeway Hospital.

The future

With the recent development of mouse models, it is hoped that the pathophysiology of infantile spasms will be better understood. It is hoped that this new knowledge will help identification of better anti-spasm medications. In spite of the practical difficulties, well planned, large scale double blinded studies are needed to find answers to issues on the ideal drug/drugs of choice, the better form of hormonal therapy, the most appropriate dose and the minimum effective duration of therapy etc. The impact on the long term developmental outcome and subsequent development of epilepsy rather than mere short term spasm control are important areas needing further evaluation.

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