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Management Guidelines for Infantile Epileptic Spasms Syndrome (IESS) Objectives

1. To improve awareness regarding Infantile Epileptic Spasms syndrome and thereby minimize delay in diagnosis and administration of the most appropriate therapy.
2. To streamline the use of recommended first-line medications.

Introduction

Infantile Epileptic Spasms syndrome (IESS) is characterized by the onset of epileptic spasms, mostly within the first year of life. This was previously known as the West syndrome. Unlike in the earlier description for West syndrome, in which hypsarrhythmia was a requirement, in IESS, according to the newer recommendations from ILAE, it is diagnosed with or without hypsarrhythmia on the EEG. In those without hypsarrhythmia, evaluation by a paediatric neurologist with video monitoring to confirm the presence of epileptic spasms is preferred. Developmental regression or stagnation is not a requirement for its diagnosis, though it is often an associated finding. It may be subtle in the initial course of the illness. The parents may report of reduced social responsiveness, reduced frequency of social smile, eye contact or regression of visual attention. However, this may also occur days or weeks preceding the onset of spasms.

Clinical onset

The onset of epileptic spasms is between 1-24 months and peaks between 3 and 12 months of age; although later or rarely neonatal onset may also occur. Those with spasms before one month of age are more likely to suffer from a different epileptic syndrome. Majority have an identifiable aetiology though some infants may have had no history suggestive of an underlying aetiology and have no risk factors. There is a higher incidence in males.

Seizure type

The prototype seizures are epileptic spasms. These epileptic spasms are an essential criterion for a diagnosis of IESS. They consist of brief tonic contractions of any muscle group, particularly axial muscles, each typically lasting less than three seconds. These spasms may be flexor, extensor or mixed. These usually occur in series or clusters, with increasing prominence of the motor features through the cluster, often over a period of minutes (although some clusters may last up to 30 minutes or longer) and are often seen on awakening from sleep. These may be symmetric or asymmetric and may be subtle, with minor head nods, or eye or chin movements. Focal seizures may also be seen and may occur together with epileptic spasms.

Early diagnosis

While the presenting features of many non-epileptic conditions may mimic spasms i.e. Sandifer syndrome and benign myoclonus of infancy. Epileptic spasms are also sometimes misdiagnosed as physiological conditions such as infantile colic. The delay in diagnosis occurs both by parents as well as by healthcare providers. Appropriate diagnosis, particularly in those at increased risk, is very important.

It is important to warn parents of at-risk babies i.e., those with a history of hypoxic ischaemic encephalopathy, extreme prematurity, neonatal seizures, neonatal hypoglycaemia, or meningitis., of the possibility for occurrence of spasms during mid infancy. All paediatricians should be vigilant of this possibility in such an at-risk baby. Healthcare providers such as Public Health Midwives, who are the first contact person to parents should also be equally knowledgeable of this condition so that they can direct the babies for early assessment. If in doubt of the diagnosis, contact with or consultation with a paediatric neurologist is recommended.

Investigations:

EEG

Interictally, hypsarrhythmia (background appearing to be chaotic and dominated by high amplitude, excessively slow activity with multifocal epileptiform discharges) is often seen and the yield of detection is greatest in a recording from non-rapid eye movement (non-REM) sleep. This is seen less frequently in wakefulness but not seen in REM sleep. Hypsarrhythmia may not be evident very early in the illness. Therefore, if an initial EEG is normal, repeating the EEG is recommended if there is a high degree of clinical suspicion.

The ictal EEG recording of an epileptic spasm is characterized by high amplitude, generalized, sharp or slow waves followed by low amplitude, fast activity, which may appear as a brief electro decrement pattern. Hypsarrhythmia typically attenuates or stops during a series of epileptic spasms.

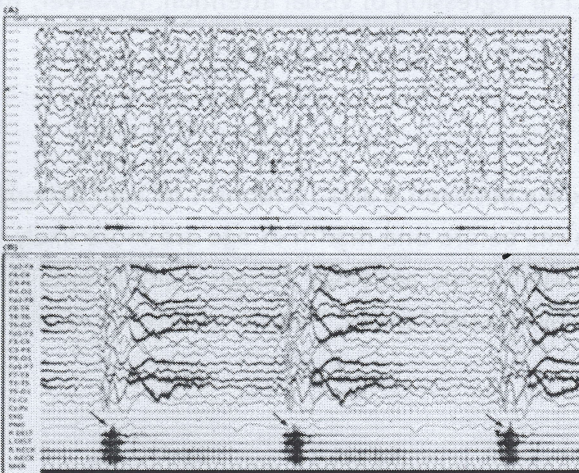


Figure 1: A and B are EEG tracings of a 7-month-old boy with Infantile Epileptic Spasm Syndrome. The interictal EEG (A) shows a hypsarrhythmia pattern. The ictal recording (B) shows a high-amplitude sharp waves followed by a relative decrement with a muscle contraction on EMG.

Imaging

Imaging is strongly recommended as the possibility of a positive yield of underlying structural abnormality is seen in about half of IESS patients. MRI is the recommended imaging modality in this condition. However, in the case of limited resources, a CT scan of brain may be performed.

Abnormalities detected in the MRI scan include focal atrophy (35%), congenital structural anomalies (19%), and generalized and multifocal atrophy (15%).

Performing neuroimaging prior to steroid therapy may be useful as treatment with steroids may result in transient cerebral atrophy. However, unavailability of imaging should not be a reason for delaying treatment.

Genetic, metabolic, infective, and immunological studies may follow the EEG and MRI brain, if deemed necessary.

Aetiology

Following a detailed evaluation including a comprehensive history and basic imaging studies, an underlying aetiology is possible to be identified in about 65% in cohorts from high income settings. However, this percentage is likely to be higher in cohorts from low resource settings.

- Structural brain lesions include both acquired and congenital structural abnormalities, i.e. focal cortical dysplasia, periventricular leukomalacia, absence of corpus callosum, porencephaly, lissencephaly etc. (24%)
- Genetic aetiologies (STXBP1, SLC25A22, CDKL5, ARX, SPTAN1, PCDH19, KCNQ2, SCN2A etc.)
- Metabolic aetiologies (mitochondrial disorders, non-ketotic hyperglycaemia, pyridoxine/pyridoxal-5-phosphate disorders, carnitine palmitoyl transferase deficiency etc.)
- Infective aetiologies
- Immunological aetiology (rarely)

By using a detailed history and basic imaging investigations only, the underlying cause can be identified in close to about 50% of children. Even after extensive investigations, this increases by only another 15%. At this point, those without an identifiable aetiology, are classified as 'aetiology unknown'.

Treatment:

Recommendations

Commencing therapy, always with the recommended first-line options, is strongly encouraged. The recommended options are corticosteroids (ACTH or prednisolone) or vigabatrin for those with underlying Tuberous Sclerosis complex. Use of these first-line medications have shown a better response, when compared to other anti-seizure medications.

Commencing treatment as early as possible from onset has been shown to be associated with better developmental outcome in several studies, if the treatment used is a first line medication. The time from onset of spasms to commencement of therapy is known as the "lead time to treatment" (LTTT). A shorter LTTT results in better developmental outcome later in life. However, the LTTT is related to the use of first line medications only. If any other therapy is used, this time duration also is added to the LTTT. Therefore, early commencement of therapy with first line medications is strongly recommended.

Recommended treatment schedule for first line medications

There are many schedules used in different countries. Using high doses for a short duration is used in most schedules. From available literature, the most frequently quoted doses are those used in the United Kingdom Infantile Spasm Study (UKISS) clinical trial.

Therefore, in this clinical guide, the doses used in the UKISS trial are recommended.

1. Prednisolone

The recommended dosing schedule is Prednisolone 10mg 6 hourly (40mg/day) for 2 weeks (The dose is increased to 20mg 8 hourly (60mg/day) if spasms do not resolve by the 7th day).

2. ACTH – Synthetic or Natural

In Sri Lanka, ACTH is available only as a synthetic preparation. The depot preparation should be used. The recommended dose is intramuscular depot ACTH 40IU every other day (EOD) for 2 weeks. (The dose should be increased to 60IU EOD if spasms do not resolve by the 7th day.)

The duration of therapy with either prednisolone or ACTH is 2 weeks. This is followed by a gradual tailing off which is done over 2-3 weeks using oral prednisolone. Longer course of tailing off is not required.

3. Vigabatrin

This is the 1st line anti-spasm therapy in patients with IESS due to underlying Tuberous sclerosis. To avoid the encephalopathic side effects of Vigabatrin, it is commenced at a dose of 50mg/kg/day for first two days followed by increasing the dose to 100mg/kg/day. If the spasms do not resolve by day 7, and if this high dose is tolerable, the VGB may be increased to a maximum of 150mg/kg/day. Duration of therapy is not clearly defined in many trials. In the UKISS trial a minimum of 3 months is considered to be the standard. In others even 6 months is recommended.

Main concerns of long term VGB therapy include the loss of peripheral vision (tunnel vision) which is irreversible in up to 30%. Other side effect of concern is the movement disorder.

4. Combined therapy

Combined therapy with prednisolone with vigabatrin has shown promising results for quicker control of spasms and a higher proportion achieving spasm cessation by 28 days. However, in view of the cost of therapy as well as absence of a significant advantage over development at 18 months post therapy, combined therapy is not recommended in our setting.

5. Non-standard therapies as first line

Sodium valproate/topiramate/clonazepam have been used but there is no evidence to support a definite therapeutic role with any of these options. Therefore, using them is not recommended, unless there is a contraindication for using the first line medications.

Treatment failures

In the event of a treatment failure, with one standard first line therapy at end of 14 days, a cross over to a second first line medication is recommended. i.e., oral prednisolone to vigabatrin or vigabatrin to ACTH/prednisolone.

Partial responders and relapses

Ketogenic diet: This is recommended as a useful second line treatment strategy in those with treatment failure or a relapse. The response rates include up to 35% achieving spasm control and spasm reduction in up to 65%. Ketogenic diet is available in all tertiary care settings with paediatric neurology services in the country. Though specific ketogenic formulae is unavailable, modified ketogenic diet can be offered to infants commenced on complementary feeds.

There is no clear recommendation on other potential second line medications. The clinician may choose from antiseizure medications such as sodium valproate, topiramate, clonazepam, as add on therapy. Zonisamide and nitrazepam have been found to be useful in some clinical trials.

Carbamazepine, phenytoin and ethosuximide should be avoided as they may aggravate infantile spasms. However, they could be helpful rarely in certain aetiologies such as sodium channel mutations with gain of function or some structural pathologies.

Cautions while on high dose steroids:

- Monitor blood pressure every 2-3 days initially. If normal after a couple of readings, then one could evaluate after one week. The aim is to maintain systolic blood pressure at an upper level of 90mmHg.
- Warn about the risk of infections.
- Early treatment is needed if the child gets chicken pox or comes into close contact with chicken pox or check on varicella immune status in a bigger child.
- Live viral vaccinations (oral polio/MMR and JE) and inactive vaccines should be deferred for at least 1 month after discontinuation of high dose steroids (equal to or more than 2mg/kg/day of prednisolone).
- If a child has been vaccinated with a live or inactive vaccine, it is better if high dose steroid therapy could be deferred up to one month.
- If the child is diagnosed to have IESS, DPT vaccine can be continued according to schedule after clinical and initial radiological evaluation to confirm an underlying static injury. It should be deferred only if the underlying neurological status is unclear and needs time for better clarification and stabilisation.
- Japanese encephalitis vaccine should be avoided if the infant continues to experience seizures. It can be given following seizure freedom for 12 months.

Prognosis

Depends on the aetiology of IESS. The aetiology unknown group have a better prognosis (28%- 50%). Cognitive impairment is severe in 70% of patients, often with neurodevelopmental problems such as autism spectrum disorder or ADHD. Mortality ranges in different series, ranging from 5-31% by 3 years of life in children with global developmental delay.

Response to therapy is poor. Response to steroid therapy records spasm cessation in between 50-75%. However, only about 50% achieve complete spasm control. The relapse rate is high accounting for about one third of cases. About 50-60% of patients develop other types of intractable epilepsy syndromes, such as Lennox-Gastaut syndrome in later life.

Key points

- Infantile epileptic spasms syndrome is a devastating epileptic encephalopathy.
- The only modifiable factor that improves the overall developmental outcome is early reversal of the epileptic encephalopathy.

- This can be achieved by early commencement of treatment by avoiding a long lead time to treatment.
- Clinical suspicion, early diagnosis and treatment will help towards achieving a better developmental outcome.
- Initiation of therapy using only first line therapies (Prednisolone/ ACTH/ Vigabatrin) in high doses is very strongly recommended.



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