Clinical Guidance

Infantile Epileptic Spasms Syndrome

Summary: This guideline is intended for use for infants presenting with epileptic spasms.

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Change History		
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5 July 2023	Expansion of background to reflect ILAE terminology. Clarification of genetic aetiologies. Expansion of management section to include more information to convey to families, and to provide easier treatment algorithm for clinicians. No changes to the drug recommendations. Updated references.	PCGC

Table of abbreviations used in this document

Abbreviation	Meaning
AASA	Alpha-amino adipic semialdehyde
ACTH	Adrenocortiotropic Hormone
ASMs	Anti-Seizure Medications
ARX gene	Aristaless related homeobox gene
CDKL5 gene	Cyclin dependent kinase like 5 gene
CGH Array	Comparative genomic hybridisation array
CSF	Cerebrospinal Fluid
DEE	Developmental and Epileptic Encephalopathy
EEG	Electroencephalogram
IESS	Infantile Epileptic Spasms Syndrome
TORCH screen	Toxoplasma, Other (Syphilis), Rubella, Cytomegalovirus, Herpes Simplex Virus
TSC	Tuberosclerosis Complex
VLCFA	Very Long Chain Fatty Acid

Infantile Epileptic Spasms Syndrome (IESS) – previously termed West Syndrome

Introduction-Basic concepts [1-3]

Infantile epileptic spasms are part of an age-related epileptic encephalopathy characterised by typical spasms and an abnormal EEG. The triad of epileptic spasms, with concordant EEG abnormality alongside developmental plateauing or regression was previously termed West Syndrome, but this terminology has been modified in the recent ILAE classification.

A spasm is a sudden flexion, extension or mixed flexion-extension (i.e. the commonest) of proximal and truncal muscles, lasting 1-2 seconds. Spasms typically occur in a series (clusters), usually on wakening or during transition between sleep stages or from wakefulness to sleep. Rarely, a patient can have single spasms instead of clusters. Subtle forms may occur with only chin movement, grimacing, or head nodding. Spasms may be bilaterally symmetric, asymmetric, or unilateral, depending on whether they are generalized onset or focal onset.

The EEG is always abnormal. The characteristic EEG pattern is termed hypsarrhythmia or modified hypsarrhythmia. However, this may not always be present throughout the EEG, and particularly in the early stages may only be demonstrated in sleep. In the presence of an abnormal interictal EEG and clinical evidence for spasms, treatment should not be delayed.

Infantile spasms usually begin between 3 and 12 months, with a range of 1–24 months and a peak of 4-9 months. If onset occurs prior to 3 months, other early-onset developmental and epileptic encephalopathies (DEE) should be considered.

The estimated incidence of IESS is around 30/100,000 live-born infants. Both sexes are affected with a higher incidence in males. Aetiology is heterogeneous and may not be apparent, but includes underlying structural, genetic and metabolic disorders. Spasms may emerge on the background of a previously recognised brain abnormality eg following a perinatal hypoxic ischaemic encephalopathy or in context of tuberous sclerosis. Where spasms are asymmetric or have a focal element, a structural aetiology should be strongly considered. Symmetrical spasms do not exclude a structural aetiology.

The ILAE Task Force[1] has also introduced a definition of a ***possible evolving syndrome***: Infants with preceding brain injury, developmental brain malformations, or specific genetic conditions, including early-infantile DEE, who show significant interictal EEG abnormalities (high amplitude, background slowing, and/or multifocal discharges) **should be watched carefully for the development of clinical epileptic spasms.** However, the syndrome of IESS cannot be diagnosed prior to onset of the mandatory seizure type.

Diagnosis and Referral to a Specialist [4-7]

NICE UK Guidelines (2022)[4], now recommends that once a child under 2 years is seen with suspected or confirmed infantile spasms, then the secondary care team should seek guidance within 24 hours from, and refer urgently to, a tertiary paediatric neurologist. Referral initially is likely to mean discussion with a paediatric neurology service to ensure rapid assessment, including a sleep EEG and appropriate treatment to try to stop the spasms.

Assessment to include:

- Detailed description of events including video footage where available
- Developmental history
- Background pregnancy, perinatal history and family history
- Physical examination including careful documentation of head circumference and developmental assessment.
- Wood's lamp examination if possible

Frist line Investigations:

1. **EEG[5]:** Urgent referral for an awake and sleep EEG (within 72hours). Should also obtain home video of the events. If available, the vcreate video sharing system may be used for viewing and storing video clips. In IESS the interictal EEG (awake and sleep) can show hypsarrhythmia or multifocal or focal epileptiform discharges. If the awake and sleep EEG is normal and spasms still suspected, then an ictal recording is required.

   For Evelina EEG dept:
   External referrals email to gst-tr.paediatricneurophysiology@nhs.net
   Internal EEG request referrals should be requested on electronic ordering system

2. **Imaging[6]:** MRI Brain with epilepsy protocol scan (unless previous diagnostic scan available e.g. in a child with pre-existing developmental delay or previous perinatal difficulties)

3. **Genetic tests[6,7]**: CGH array and save blood for DNA analysis – send for WGS with R59 panel (after discussion with tertiary neurology) or rapid whole exome sequencing if appropriate

4. **Biochemical and Metabolic tests[6]**: Blood – FBC, renal profile, liver profile, bone profile, lactate, ammonia, blood gas, glucose, Mg, plasma amino acids, biotinidase, Urine organic acids, Urine AASA (for pyridoxine dependent seizures)

5. **Referral for ophthalmology** review (usually non-urgent)

Second-line investigations: (depending on individual case and following discussion with tertiary neurology)

1. In selected cases to look for congenital infection- urine for CMV, throat swab for viral culture, blood for toxoplasma, rubella and CMV IgG/ IgM.
2. Blood - Copper, caeruloplasmin, acylcarnitine profile, VLCFA, transferrin electrophoresis for Congenital Disorders of Glycosylation (CDGs).
3. Urine - oligosaccharides, sulphocysteine.
4. CSF (ideally after 4 hour fast) - glucose, lactate, protein and cell count (with paired plasma samples, CSF amino acids (with paired serum samples) and CSF neurotransmitters including CSF pyridoxal phosphate.
5. ECG and Echo – if abnormal cardiac examination or suspecting Tuberous Sclerosis Complex (TSC).
6. Renal USS – if TSC suspected.

Differential Diagnosis [1]

Differential diagnosis includes epileptic (i.e. myoclonic epilepsy of infancy, early infantile DEE or Ohtahara syndrome) and non-epileptic events (i.e. benign sleep myoclonus, benign myoclonus of infancy, infantile colic, gastroesophageal reflux or Sandifer syndrome, benign shuddering attacks of infancy, benign infantile head drops, hyperekplexia).

Management [4, 8-15]

Discussion with parents [8,9]

Provide parents/carers with appropriate informative material.

Information for families about infantile spasms:

- Epilepsy Action www.epilepsy.org.uk
- UK Infantile Spasms Trust https://ukinfantilespasmstrust.org

Areas of discussion with parents/carers may include:

1. The need for early initiation of treatment. Historically longer lead-time to treatment was associated with poorer outcomes.
2. ICISS trial outcome suggests combined hormonal therapy with vigabatrin is significantly more effective at stopping infantile spasms than hormonal therapy or vigabatrin alone but only in infants with ‘idiopathic’ spasms
3. Early clinical response to treatment is associated with improved developmental and epilepsy outcomes at 18 months.
4. Potential adverse events from treatment and steps of management
5. Prognosis of IESS, neurodevelopmental outcome and expectations from treatment

Treatment (based on NICE UK 2022 guidelines[4,10-13])

First line treatment [4,10-13]

- Offer combination therapy with high-dose oral prednisolone and vigabatrin as first-line treatment for infantile spasms that are not due to tuberous sclerosis, unless the child is at high risk of steroid-related side effects. ACTH injections are not considered superior to oral prednisolone in treatment of infantile spasms
- Offer vigabatrin alone as first-line treatment for infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective after 1 week, add high-dose oral prednisolone.
- Consider vigabatrin alone as first-line treatment for infantile spasms in children at high risk of steroid-related side effects.

COMBINATION THERAPY WITH PREDNISOLONE AND VIGABATRIN

Please refer to the paediatric formulary' (Clinibee) for drug doses, with escalation and weaning regime.

If monotherapy is chosen, by clinician or parent preference, follow same doses as above for steroid/vigabatrin.

Possible adverse events [10,14,15]

STEROIDS [10,14]

Before starting oral prednisolone for infantile spasms:
1. Discuss the possible side effects of steroid treatment with parents and carers: decreased immunity (particularly risk with chicken pox contact), irritability, increased appetite, weight gain, hypertension, rarely high blood sugars (usually not needing treatment)
2. If not immune to varicella, advice on steps to be taken if comes into contact with chickenpox (valid up to 3 months post steroid treatment; advice to be adapted as per local arrangements)
3. Gastric protection (eg omeprazole/esomeprazole) to be given during the entire steroid course
4. Give the parents and carers information (including a steroid card if available through pharmacy), about when to seek medical help for side effects.
5. Monitoring
    - whilst inpatient, with daily blood pressure and urine sugar.
    - outpatient – alternate daily BP and urine sugar weeks 1 and 2, then twice weekly if stable thereafter. If BP>95th percentile consistently, please discuss with the relevant speciality
    - investigate for infection if becomes unwell/febrile

VIGABATRIN [10,15]

- Counsel regarding drowsiness, irritability and rarely a movement disorder as side effects.
- Discuss regarding the potential side effect of peripheral visual field constriction if used for longer than 6 months.
- MFC leaflet: Vigabatrin for preventing seizures – Medicines For Children

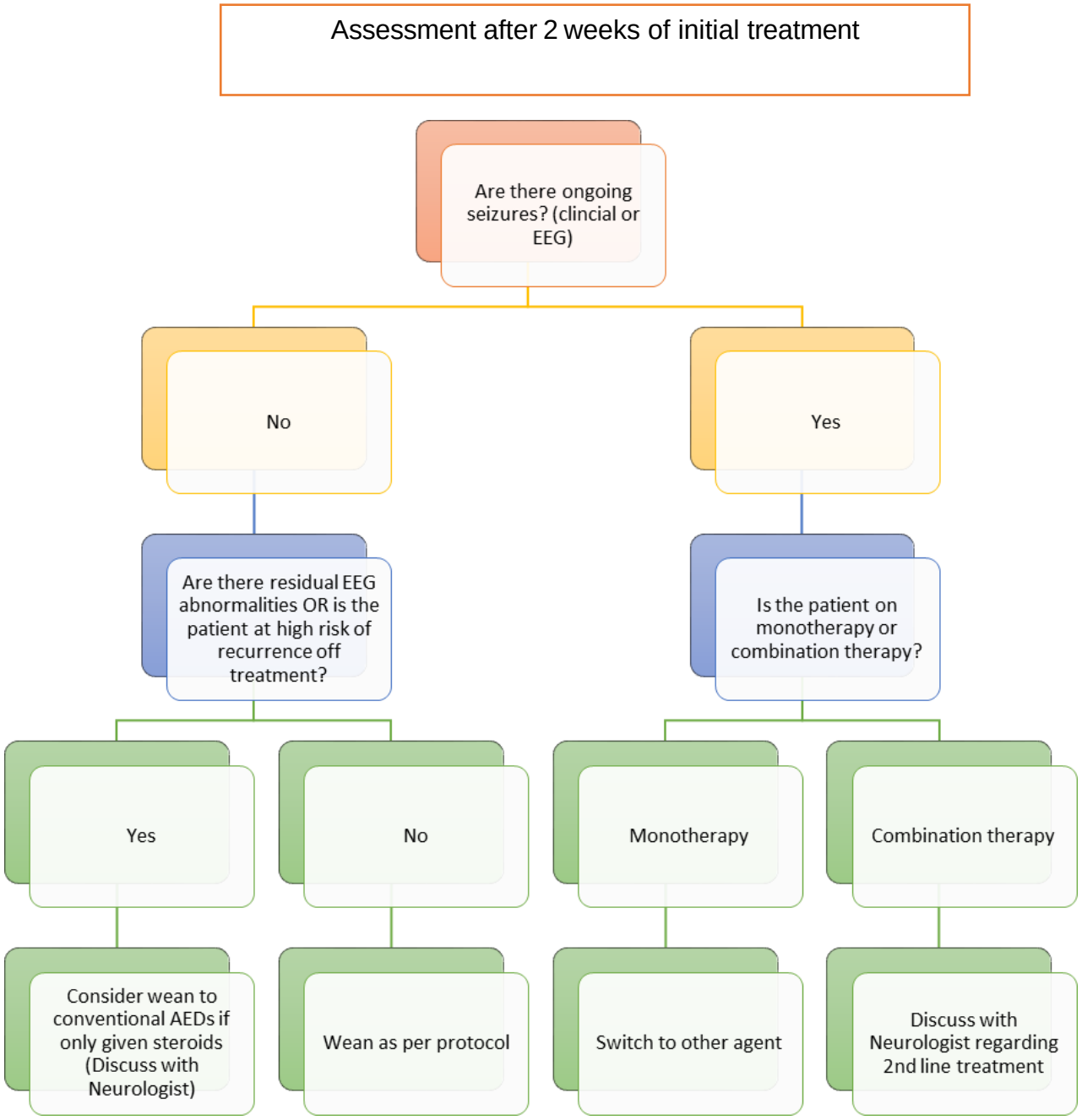
Follow up [1,4]

- Review children under 2 years with infantile spasms at least weekly during initial phase of treatment (this may be a F2F or telephone review) and repeat sleep EEG at 2 weeks after starting treatment.
- When infantile spasms have stopped, review children monthly initially and repeat sleep EEG if spasms recur or there are clinical concerns.

After 2 weeks on high dose steroids and/or vigabatrin, reassess for any clinical spasms or other seizures as well as EEG (between 14-21 days) response.

If seizure free but on-going residual EEG abnormalities or considered high risk for seizure recurrence off treatment – consider weaning to conventional ASMs if only given steroids - discuss with tertiary neurology team. Otherwise wean off treatment as per protocol.

Close follow up required for developmental monitoring by a Community Paediatrician, following referral and ongoing treatment of seizures.



Second-line treatment [10]

If continuing seizures, then switch to other agent if previously had monotherapy with either vigabatrin or steroids. If continuing seizures in spite of trials of vigabatrin and steroids or one of these agents contraindicated for any reason, will need to discuss second line treatment again in consultation with Regional Epilepsy or Neurology service.

Consider the following as a second-line monotherapy or add-on treatment options for infantile spasms:
- ketogenic diet guided by a ketogenic diet team or tertiary paediatric epilepsy specialist, as appropriate:
- levetiracetam
- nitrazepam
- sodium valproate: note that there may be regulatory changes in future that will influence prescribing
- topiramate.

References

1. Zuberi SM, Wirrell E, Yozawitz E, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions. Epilepsia. 2022;63:1349-1397.

2. ILAE classification https //www.ilae.org/guidelines/definition-and-classification

3. Pavone P, Striano P, Falsaperla R, Pavone L, Ruggieri M. Infantile spasms syndrome, West syndrome and related phenotypes: What we know in 2013. Brain Development. 2014;36:739-51.

4. Epilepsies in children, young people and adults: NICE guideline 2022.

5. Infantile Spasms and West Syndrome. In: The role of EEG in the diagnosis and classification of the epilepsies and the epilepsy syndromes. 2021, Ed: M. Koutroumanidis, John Libbey Eurotext, pp. 227-233.

6. Wirrell EC, Shellhaas RA, Joshi C, Keator C, Kumar S, Mitchell WG, et al. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia. 2015;56:617-25.

7. Perry MS. Genetic Testing in Epileptic Encephalopathy: Rosetta Stone or Just an Expensive Rock? Epilepsy Currents. 2016;16:12-3.

8. O'Callaghan FJK, Lux AL, Darke K, Edwards SW, Hancock E, Johnson AL, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: Evidence from the United Kingdom Infantile Spasms Study. Epilepsia. 2011;52:1359-64.

9. O'Callaghan F, Edwards SW, Alber FD, et al. & International Collaborative Infantile Spasms Study (ICISS) investigators. Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial. The Lancet. Child & adolescent health. 2018; 2:715–725.

10. Iyer A, Appleton R. Improving Outcomes in Infantile Spasms: Role of Pharmacotherapy. Paediatr Drugs. 2016 Oct;18(5):357-6.

11. Wanigasinghe J, Arambepola C, Ranganathan SS, Sumanasena S, Attanapola G. Randomized, Single-Blind, Parallel Clinical Trial on Efficacy of Oral Prednisolone Versus Intramuscular Corticotropin on Immediate and Continued Spasm Control in West Syndrome. Pediatric Neurology. 2015;53:193-9.

12. Kossoff EH, Hartman AL, Rubenstein JE, Vining EPG. High-dose oral prednisolone for infantile spasms: An effective and less expensive alternative to ACTH. Epilepsy & Behavior. 2009;14: 674-6.

13. O'Callaghan FK, Edwards SW, Alber FD, Hancock E, Ljohnson A, Kennedy CR, et al. Safety and effectiveness of hormonal treatment versus hormonal treatment with for infantile spasms (ICISS): a randomised, multicentre, open-label trial. Lancet Neurology. 2017;16:33-42.

14. UK Infantile Spasms Trust https://ukinfantilespasmstrust.org/

15. Biswas A, Yossofzai O, Vincent A, Go C, Widjaja E. Vigabatrin-related adverse events for the treatment of epileptic spasms: systematic review and meta-analysis. Expert Rev Neurother. 2020; 20:1315-1324.