

**Management of Infantile Spasms**

**in Infants Under One Year of Age**

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* **This guideline is for the purpose of general paediatricians, trainees, and paediatric neurologists. Any specific cases in which there is diagnostic uncertainty should be discussed with the tertiary paediatric neurology team.**

**Background**

Infantile spasms is a developmental and epileptic encephalopathy with heterogeneous aetiologies including many genetic causes.

Infantile spasms (ISs) vs. West syndrome (WS)

WS is regarded as a subtype of ISs and is the most frequently reported subtype presenting in about 90% of cases of ISs, while ISs are regarded as a component of WS. WS encompasses the triad of infantile spasms, hypsarrhythmia, and developmental arrest or regression.

 The classical presentation of WS consists in short episodes of abrupt flexion of the trunk and neck and adduction of the arms, with onset in infancy or early childhood. The tonic spasms are bilaterally symmetric, each lasting few seconds and occurring at wakening and in clusters. During these episodes, eyes may be fixed or deviated and there can be cardiac and respiratory involvement. Also, there may be associated facial grimacing, eye blinking, or transient focal movements. After the episode, the infant may be irritable or drowsy. Mean age of onset is between 4 and 9 months with a peak around the 6th month of life in about 80–90% of cases.

EEG recording typically shows a chaotic mixture of very high amplitude slow waves with discharges of waves and spikes varying in amplitude, morphology, duration, and site.Most frequently happening during non-rapid eye movement (REM) sleep, and greatly reduced during REM sleep. It may the reach the criteria of hypsarrhythmia.

Atypical presentations of ISs/association of ISs with other seizure types, and atypical EEG patterns

Atypical patterns of clinical (and EEG) manifestations of ISs are well known. This could be related to the age of the child at onset of spasms and to the etiologic factors underlying the disorder.

Subtle Spasms ; is a form of ISs that may present with hypsarrhythmia, but without clearly definable clinical signs, e.g. facial grimacing, isolated fixed eyes, head nodding. Those may be the only clinical expressions of ISs and can be associated to other seizure types, mainly happen in older ages of presentation.

Co-existence with other seizures pattern: in symptomatic rather than cryptogenic cases, focal seizures may precede or co-exist with IS ( e.g. Tuberous sclerosis ).

For EEG , besides the classical hypsarrhythmia pattern, other EEG patterns could be observed during the course of ISs, defined as “ atypical” or“ modified hypsarrhythmia”, and consist of asymmetric features, focal discharges, fragmentation, and semi-periodic burst-suppression

**Aetiology**

Every effort should be made to determine the aetiology of the IS as this can help determine the likelihood of response to treatment, guide therapeutic decisions and help provide a more definitive prognosis for the child. However, this should not delay the start of treatment once the diagnosis is confirmed.

Infantile spasms classified into two, well-known groups of symptomatic and presumed genetic.

**Symptomatic ISs** results from a known or suspected central nervous system (CNS) disorder, which could be either:

* ***Prenatal:*** *e.g****.*** CNS malformations, congenital infections***,*** orgenetic mutations: which could be either:
	+ Syndromes of genomic imbalance: e.g. Down Syndrome, William Syndrome, Miller-Dicker Syndrome ***or***
	+ Single gene disorders: e.g. Lissencephaly syndromes (DCX, LISI, TUBA1A), TSC1/TSC2, FOXG1, ARX, KCNQ2 etc. …
* ***Perinatal:*** *e.g.*HIE***,*** Stroke,Neonatal hypoglycaemia***,*** Low birth weight
* ***Postnatal*** *e.g.*Metabolic (PKU-pyridoxine deficiency)***,*** Traumatic injury***,*** Tumours***,*** CNS infections.

**Presumed genetic (Idiopathic) ISs**  has no identifiable cause. This category includes patients with normal development at onset, normal examination, and neuroimaging, and hypsarrhythmic EEG pattern without focal epileptiform abnormalities. These are associated with a better prognosis as compared to symptomatic IS.

**Establishing the Diagnosis**

1. **Obtain a thorough history:**
* History consistent with Infantile spasms (symmetric or asymmetric)
* Directly witnessed event /video of seizures seen by a senior clinician
* Antenatal and neonatal history, including history of assisted conception and country of birth ( due to variations in newborn screening programs and infectious diseases ).
* A thorough family tree should be constructed, with special attention to consanguinity, ethnicity, and family history of neurological disorder and/or genetic disorder.
* Careful attention should be given to the child’s past and present developmental status (onset of spasms is often associated with plateauing or regression of development)
1. **Clinical assessment** :
* Look for dysmorphic features, growth parameters, head circumference should be plotted, and evidence of IU infections (microcephaly, hydrocephalus, retinitis, petechiae and hepatosplenomegaly/jaundice)
* Complete neurological examination and CVS examination for comorbidities like (Down syndrome, or TS)
* Look for neurocutaneous stigmata and actively look for tuberous sclerosis / NF1 (including wood’s lamp examination)
* Assess development – document pre-morbid developmental delay
* Refer for ophthalmology for fundus examination
* Abnormal clinical signs should initiate specific referrals such as:
	+ Cutaneous stigmata or dysmorphism - referral to a geneticist.
	+ Spleno/hepatomegaly - referral to a metabolic specialist
* Referral to clinical genetics is recommended in all cases where an acquired cause is unlikely.
1. **Video EEG ( Ictal and sleep EEG)**
* Classical/modified hypsarrhythmia or compatible EEG findings (No consensus exists on the exact EEG abnormality required to establish the diagnosis)
* In case of normal EEG and diagnostic uncertainty – obtain sleep EEG
* If clinical or EEG findings are uncertain – discuss with Paediatric neurologist, Addenbrookes Hospital

**Further investigations**

* **Table 1: 1st and 2nd line investigations**

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| **First Line** | **Second line** |
| **Genetic*** Array CGH
* Urgent trio WGS
* Clinical genetics opinion
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| **Biochemical** * Full blood count
* U+E, LFT, blood gas/bicarbonate, glucose, calcium, magnesium, ammonia, plasma lactate
* Plasma amino acids, biotinidase
* Acylcarnitines
* Urine organic acids
* Urine and plasma creatine and guanidinoacetate
* CSF: glucose, lactate, amino acids (with paired plasma samples),
 | **Biochemical*** Serum TFT, uric acid
* Plasma transferrin glycoforms, very long chain fatty acids
* Urine sulfocysteine
 |
| **Electrophysiology*** Sleep / Ictal EEG

( if not achieved already)  | **Electrophysiology*** Review/Repeat Sleep / Ictal EEG
* For prolonged EEG if still diagnostic uncertainty
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| **Imaging*** MRI brain 1.5T

 NB: recommended in all children, even where the aetiology is clear on clinical grounds | **Imaging*** Repeat 1.5T if original poor quality or child < 3 years
* MRI brain 3T
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* For further information , please refer to Appendix 3

**Before Treatment**

1. **Provide information about infantile spasms**

(ICISS trial/Epilepsy action, UK infantile spasms trust) to the parents. (See appendix 1, 2 and 3)

1. **Discuss treatment options** **including side-effects with parents** (Prednisolone, ACTH, Vigabatrin alone or in combination). Discussion should be carried out with parents about all pros and cons of combination therapy, including lack of evidence for improved developmental outcome or relapse rate with its use .
2. **For steroid treatment**

-Document baseline blood pressure

-Are there any contraindications for steroid?

-Rule out active bacterial infection (clinical +/-investigations)

**Aim of successful treatment** Early diagnosis and shorter lead time to treatment is the gold standard to get an effective response which is measured by : freedom from IS , usually after a treatment interval of not more than 2 weeks, and without relapse of seizures over a prespecified interval such as 1–3 months .

**Infantile Spasms <1yr**

* Tuberous sclerosis
* C/I for steroids
* Cardiomyopathy

Symptomatic (Other than TS)

Likely Genetic

Vigabatrin – 1st choice

Other AED on relapse

Steroids+ Vigabatrin (Recommended) or

Steroids/VGB alone on parents’ choice

Steroids + Vigabatrin

(Recommended)

or Steroids alone

on parents’ choice

 If no response, repeat EEG after 2 weeks of treatment and discuss further plan with Addenbrooke’s neurology team

Please contact Paediatric Neurology Registrar at Addenbrookes on 01223 245151 pager 157488 or CDC on 01223 216662.

**STEROIDS TREATMENT (**Excluding children < 5kg or younger than 2 months)

**Treatment from Day 1 to Day 14 (Prednisolone or ACTH – not both)**

* **Oral Prednisolone**: **10mg** per dose, **four times a day** for **14 days**.

If spasms continue on Day 7 or reappear between Day 8 and Day 14 inclusive, increase the dose to **20mg** per dose **three times a day** for the remaining doses.

**or**

* **Tetracosactide (ACTH):** Intramuscular injection using depot injection, **500 micrograms once daily on alternate days** for **3 days in a week** (Mon, wed, Fri).

If spasms continue on Day 7 **or** reappear between Day 8 and Day 14 inclusive, increase the dose to 750 micrograms once daily **on alternate days** for the remaining doses.

ACTH injection should be given by health care professional who can deal with allergic reactions and in a hospital setting. Keep necessary equipment and drugs to deal with anaphylaxis. Watch for reactions such as marked redness, pain at reaction site, urticaria, pruritus, flushing and dyspnoea. Switch to prednisolone, if reactions are noted.

**Weaning Steroid Treatment after Day 14 in those with no spasms**

If receiving Prednisolone 10mg four times a day/ACTH 0.5mg on Day 14, the dose of prednisolone will be;

30 mg daily for 5 days

20mg daily for 5 days

10mg daily for 5 days

then stop

If receiving Prednisolone 20mg three times a day/ACTH 0.75mg on Day 14, the dose of prednisolone will be

40 mg daily for 5 days then

20mg daily for 5 days and finally

10mg daily for 5 days

then stop

Alternatively if on ACTH at Day 14, it can be weaned as below

 If receiving 500 micrograms during first 2 weeks

 250 micrograms IM on alternate days (Mon, Wed, Fri) week 3

 250 micrograms IM twice in week (Mon, Thu) week 4

 250 micrograms IM once in a week week 5

 then stop

If receiving 750 micrograms during first 2 weeks

 500 micrograms IM on alternate days (Mon, Wed, Fri) week 3

 250 micrograms IM on alternate days (Mon, Wed, Fri) week 4

 250 micrograms IM twice in week (Mon, Thu) week 5

 250 micrograms IM once in a week week 6

 then stop

**Monitoring steroid treatment**

* Please add omeprazole/lansoprazole until end of treatment (To avoid gastric irritation).
* Monitor blood pressure every 3 days (At least twice in a week) for 14 days. Monitoring can be discontinued during weaning unless elevated at the end of 14 days (If elevated on day 14 monitoring should be continued until stopping treatment and blood pressure returns to normal range after stopping treatment.
* Treat genuine elevation in blood pressure above the 95th centile for age (usually above 120/90) with thiazide diuretic or nifedipine as per BNFC and monitor 48 hourly thereafter until acceptable, being prepared to increase antihypertensive dose as necessary.
* Provide urine dipsticks and ask to check urine sugar at 48 hours and then weekly till end of treatment.
* After 3 days treatment with prednisolone or 2 doses of ACTH, consider child to be immunosuppressed and treat fevers as per local febrile neutropenia protocol.
* Counsel regarding chicken pox exposure - consider zoster immune globulin if exposed, and treat with IV Aciclovir if vesicles appear whilst on treatment. The preventive effect of VZIG lasts for about three weeks. Antibodies degrade after that time. If there is a new contact (after three weeks) or continued contact from the same index patient (household?), VZIG will be needed again after three weeks. The dose for oral Aciclovir prophylaxis is 40mg/ kg/ day in four divided doses for one week starting from day seven of contact (contact only once) If there is continued contact start Aciclovir from day 7 till the end of contact + 7 more days.
* Arrange open access to paediatric ward for acute febrile illnesses during first 6 weeks.
* Consider the child to have adrenal suppression for 6 weeks after the

end of treatment and consider need for hydrocortisone replacement if the child develops an acute illness during this period.

**VIGABATRIN TREATMENT**

* **Route**: Oral
* **Dose**: Day 1 25mg/kg/dose, twice a day

 Day 2 50mg/kg/dose, twice a day

* + If no spasms: continue the same dose until weaned.
	+ If spasms continued until day 4 or reappeared between Day 5 and 14

increase the dose to 75mg/kg/dose twice a day before day 14. (Max daily dose of 3 g/day to avoid visual field defects)

* **Practical information**: Each sachet of 500 mg of Vigabatrin is made up in 10 ml of water making a mixture containing 50 mg per ml water. The dosage will be given to the nearest 25 mg dose (0**.**5 ml), i.e. round up or down to the nearest 0.5 ml.

NG administration: Sachet contents dissolve completely in 10 mL of water and flush down an 8Fr NG tube without blockage.

* **Duration of treatment**: 3 months, withdraw at 3 months (Dose adjusted as per weight gain, increasing as the body weight increases, in increments of 25 mg per dose (50 mg per day) as required until 3 calendar months from Day 0). Duration may be less than 3 months on clinician’s discretion when early remission is observed.
* **Monitoring**: Watch for drowsiness and confusion, excitation and agitation can also happen. Feeding failure may occur as well, and may require NG tube feeds. Visual field defects are not possible to monitor. Renal failure: dose should be reduce if creatinine clearance is less than 60 ml/minute/1.73 m2.
* **Weaning**: Gradual reduction in 4 weeks and then stop.

**Combination treatment:**

Doses, escalation and weaning with both agents would be same as for individual agents, which, means 2 weeks of steroids and 3 months of Vigabatrin followed by weaning as advised for each agent.

* **Table 2: Side Effects**

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| Steroids | Vigabatrin |
| IrritabilityHypotonia/HypertoniaIncreased appetiteWeight gain Gastro- intestinal upset.Fluid and electrolyte disturbance, including systemic hypertension HyperglycaemiaNeuropsychiatric disturbance including sleep disturbanceImmunosuppression with infection susceptibilityAllergic rash (Tetracosactide depot only) or anaphylaxis | DrowsinessHypotoniaIncreased appetiteWeight gainVisual field constrictionSusceptibility to infectionGastro-intestinal upsetNeuropsychiatric disturbance including sleep disorderBasal ganglia calcification can occurMRI toxicity ( especially with combination therapy) |

**Further considerations:**

* ACTH is not recommended as first choice, because of difficulties with Injections
* Usually the first step following relapse after steroid course alone will be combination treatment.
* Consider other agent if used steroids/Vigabatrin vice versa.
* Pyridoxine treatment is not normally considered if IS present > 3 months, unless there are other considerations e.g. consanguinity , FHx
* Alternative treatments to be considered are Sodium Valproate ( extreme caution is required in probable genetic cases due to possible mitochondrial disease), Benzodiazepines, Topiramate, Levetiracetam and Ketogenic diet.
* Epilepsy surgery should be considered in those with atypical, asymmetrical spasms, or other suggestion of focality in seizure semiology, supported by lesional identification on neuroimaging and localization on EEG.
* Repeat EEGs are not recommended unless relapse or unclear as to clinical remission.

**Prognosis:**

* Several factors can influence the outcome of children with ISs , as underlying aetiology, developmental delay at presentation, poor response to treatment/recurrence of seizures and evolution to other types of seizures.
* For seizure outcome at 18 month of age , according to ICCIS study, epileptic seizures of any type were seen in 17% in whom have achieved early primary clinical response versus 52% in children who haven’t responded. While seizures were found in 36.9% in children who had high risk of developmental impairment at randomization versus 20.9% in low risk group. Similarly seizures were seen in 35% in patients with a proven cause , and in 22.4% when no cause was identified
* Children with ISs could have a variable degrees of learning and intellectual disability in their adult life, also autism spectrum disorders have been frequently reported with ISs.
* According to ICCIS study, continuing epilepsy at 18 month of age and longer lead time to treatment particularly >2 month, were identified as a strong negative predictor factors for developmental outcome.
* Until now, the efficacy of available treatments for ISs are limited, when the underlying etiology is severe. Targeted genetic treatments represent the future hope for these conditions.

**Appendix**

1. Information leaflet on West Syndrome (infantile spasms) from Epilepsy Action website; <https://www.epilepsy.org.uk/info/syndromes/west-syndrome-infantile-spasms>
2. For Parent’s support; UK infantile spasms trust website :

<https://ukinfantilespasmstrust.org/>

1. <https://discovery.ucl.ac.uk/id/eprint/10118916/22/Perry_The_Efficient_Investigation_of_Infantile_and_Childhood_Epileptic_Encephalopathies_in_the_Era_of_Modern_Genomics%20-%20accepted%20ADC.pdf>

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