Epileptic Spasms & West Syndrome Guideline

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Contributors: M Ong; WP Whitehouse, CEWT Steering Group

1. Definitions

Epileptic spasms (previously referred to as Infantile Spasms) are the characteristic seizures that form part of West Syndrome (WS). This is a severe infantile epilepsy syndrome with a characteristic age of onset (2-14 months), pattern of seizures and electroencephalogram (EEG). There is high morbidity (intellectual impairment) associated with the resulting epileptic encephalopathy. Patients without developmental delay at diagnosis and without a known aetiology, if treated appropriately, have the highest probability of a good outcome.

The epileptic spasms are movements of longer duration than myoclonus and shorter than tonic seizures. They typically consist of a sudden truncal flexion with stiffening of arms and legs (flexor spasms) but can also be extension of the back, arms and legs (extensor spasms). They may also be subtle, such as a head nod. The spasms often occur in clusters and multiple times each day, often on waking. The child may have regressed or plateaued in their development.

Confirmation of the diagnosis of WS requires an urgent EEG. Hypsarrhythmia, disorganized activity with high voltages, is the characteristic EEG finding in WS. If an EEG shows supportive features of WS without showing the full features of hypsarrhythmia this is termed 'modified' (if periodic) or 'atypical' (if otherwise atypical) hypsarrhythmia. EEG changes are identified more sensitively in sleep.

2. Scope

This guideline is for paediatric health professionals in a secondary and tertiary care setting in the East Midlands / Trent region.

3. Diagnosis

If a child is suspected to have WS, a thorough history and physical examination and EEG, is necessary. They should be referred urgently (same day) for this assessment. Many other conditions can mimic ES (benign sleep myoclonus, Moro reflex, etc) in this age group.

Once the diagnosis is confirmed, efforts should be made to establish the underlying aetiology, as this significantly affects treatment decisions and prognosis. The differential diagnosis in ES and WS is broad. Evaluation

should be urgent and follow a step-wise process to limit the number of low-yield or unnecessary tests being performed.

3.1 HISTORY & EXAMINATION

3.1.1 History should focus on:

- Semiology of the events (video recording from family often invaluable)
- Frequency & clusters (versus single spasms)
- Development prior to, and changes associated with, onset of spasms
- Family history of similar events in infants
- Thorough birth and pregnancy history

3.1.2 Examination should include:

- Full systemic and neurological examination
- Head circumference
- Neurocutaneous stigmata (using Wood's / UV lamp)
- Blood pressure
- Identifying possible syndromes (e.g. Trisomy 21)

3.2 EEG

- EEG should be performed urgently if WS is suspected. Ask for video-EEG with surface EMG over neck and deltoids to pick up spasms. It should be done within 3 days. Acute admission is usually required to achieve EEG and other investigations in a timely fashion. \
- A standard EEG, ideally capturing sleep, should be performed in the first instance. Sleep is an important part of the EEG evaluation for WS. Hypsarrhythmia may be present in non-REM sleep even if absent while awake.
- If initial EEG does not reveal hypsarrhythmia (or a variant of hypsarrhythmia) but did not capture sleep, a sleep EEG should be performed (e.g. at usual nap time or after feed).
- If the EEG has captured sleep and awake periods without revealing hypsarrhythmia and WS is still suspected, a repeat sleep EEG should be performed in 7-10 days as epileptic spasms may sometimes precede electrographic changes. If in doubt contact the paediatric neurology team.

3.2 REFERRAL TO PAEDIATRIC NEUROLOGY

All children with probable and confirmed WS should be discussed with the paediatric neurology team.

4. Treatment and Investigations

Treatment should be initiated as soon as possible once the diagnosis of WS is confirmed on EEG. The goals of therapy are a complete cessation of the clinical events and resolution of hypsarrhythmia or modified hypsarrhythmia on video EEG.

Treatment is also directed by the aetiology of the spasms. Patients with tuberous sclerosis complex (TSC) are more likely to respond to treatment with vigabatrin compared to steroids. In patients without TSC, combined steroid treatment with vigabatrin is significantly more effective at stopping epileptic spasms than hormonal therapy alone.

4.1 FIRST LINE TREATMENT

- Treatment should be commenced as soon as possible, ideally on the same day as diagnosis confirmed on EEG.
- All patients *without* known TSC should be offered combination therapy of vigabatrin and steroids. Patients *with* known TSC should be offered vigabatrin monotherapy as first line. Discussion with the family about both treatment options whether monotherapy with vigabatrin or combined therapy should be made as there is currently no evidence for combined therapy in patients with TSC (see flow chart in appendix).
- Potential adverse reactions to medication should be discussed with the family.

CORTICOSTEROIDS for WS is given in the form of prednisolone or tetracosactide. Oral prednisolone is the preferred form in the East Midlands.

Prednisolone dose is 10 mg four times a day for 14 days.

If spasms continue on Day 7, or reappear between Day 7 and Day 14, the dose is to be increased to 20 mg three times a day for the remaining doses.

Adverse reactions to steroid therapy (prednisolone) include

- Irritability
- Increased appetite and weight gain
- Gastro-intestinal upset
- Fluid and electrolyte disturbance (hyponatraemia)
- Hyperglycaemia, glycosuria

- Systemic hypertension
- Immunosuppression lasting up to 3 months after stopping steroids: risk of severe chicken pox, and measles infections (potentially life threatening) and infection from live vaccines (which should be avoided), oral and perianal candida

- Increase in cardiac rhabdomyoma (in TSC patients)

VIGABATRIN is given orally, twice a day. One 500mg sachet of vigabatrin is dissolved in 10 ml of water to produce a mixture containing 50 mg/ml water. Child's weight at diagnosis is used for dosages in the first 14 days. Round up the dosage to the nearest 50 mg dose (1ml).

Day 1	50mg/kg/day in 1-2 divided doses
Day 2	100mg/kg/day in 2 divided doses
If spasms occurred in the last 24 hours:	
Day 5 or after	150mg/kg/day in 2 divided doses
If spasms occurred in the last 24 hours:	
Day 7 or after	200mg/kg/day in 2 divided doses

If spasms occur after day 14, discuss with the paediatric neurology team.

Adverse reaction to vigabatrin include

- Irritability
- Drowsiness / lethargy
- Visual field constriction (in 1/3 patients receiving it for 6 months or more)
- Movement disorder

MONITORING AND PROPHYLAXIS WHILST ON TREATMENT

Steroids:

- Concomitant gastric protection (H2-receptor antagonist or proton pump inhibitor) for the duration the child is on steroids
- Blood pressure before treatment and on days 2 and 7 of treatment
- Urine for glycosuria daily if in-patient, and days 2 and 7 if outpatient
- Urea and electrolytes pre-treatment and on day 7 (+/-2 days)
- Varicella serology status pre-treatment
- Echocardiogram for patients suspected/confirmed with TSC prior, at weekly intervals until cessation of steroid treatment.

Vigabatrin: No specific monitoring is required so long as duration of treatment is shorter than 6 months, after which visual fields should be assessed once old enough (generally aged 6-10 years).

WEANING TREATMENT

Steroid weaning should start on day 15, regardless of whether spasms continue or abnormal EEG persists.

If receiving prednisolone at 10 mg four times a day wean as follows:
10 mg three times a day for 7 days
10 mg two times a day for 7 days
10 mg once daily for 7 days
5mg once daily for 7 days then stop.

If receiving prednisolone at 20 mg three times a day wean as follows:
10 mg four times a day for 7 days
10 mg twice a day for 7 days
10 mg once daily for 7 days
5mg once daily for 7 days then stop.

Vigabatrin weaning should occur after 3 months from initiation of treatment (day 0) if the child has responded to the initial treatment by day 14. The vigabatrin dose will continue at the same dose if effective for 3 months.

At 3 months wean vigabatrin over 4-6 weeks with weaning doses rounded up to nearest 50mg or 1ml

If child has not responded by day 14 please discuss with the paediatric neurology team regarding weaning vigabatrin.

4.2 SECOND LINE TREATMENT

- If first line treatment has not stopped spasms on or after day 14 second line treatment should be discussed with the paediatric neurology team.
- If relapse of spasms occur after 3 months from initial treatment of spasms clinicians are recommended to discuss this with the paediatric neurology team.
- Potential second line treatment are:

- **pyridoxal phosphate -** Give two doses of oral pyridoxal phosphate (10 mg/kg/dose) 2 hours apart. (if the epilepsy persists try two doses of **folinic acid** 5 mg, 6 hours apart). If remission achieved continue maintenance pyridoxal phosphate at 30–50 mg/kg/day.[7.5]
- **pyridoxine** is an alternative to pyridoxal phosphate: 30 mg/kg/day oral/NG for 7 days then stop if no remission. If remission continue maintenance at 15 mg/kg/day.[7.6]
- **sodium valproate**
- **nitrazepam**
- **topiramate**
- **zonisamide**
- **ketogenic diet**
- **epilepsy surgery**

4.3 MONITORING ELECTROGRAPHICALLY

- All patients should have an EEG at 2 weeks (day 12-16) after commencing treatment regardless of whether the spasms have stopped.
- Steroids should start to be weaned at day 14 regardless of EEG results.
- Those with persistent EEG abnormalities supporting ES should be discussed with the paediatric neurology team for consideration of second line treatment.

4.4 OTHER INVESTIGATIONS (DIAGNOSTIC) *(APPENDIX 1)*

- Effort should be made to determine the aetiology of the WS as this can help determine the likelihood of response to treatment, guide therapeutic decisions and help provide a more definitive prognosis for the child.
- The most common aetiologies were: hypoxic-ischemic encephalopathy (10%), chromosomal (8%), malformations (8%), stroke (8%), TSC (7%), and periventricular leukomalacia or haemorrhage (5%).
- An **MRI brain scan is the first diagnostic investigation recommended** even if an aetiology is already obvious from clinical evaluation. Clinical evaluation and MRI provided a specific diagnosis in 55% of children presenting with WS.
- Most children will require **CGH array testing** unless a specific genetic disease is suspected, e.g. TSC, which would require specific gene testing.
- If the CGH array has not provided definitive aetiology, **discuss performing an epilepsy gene panel** with the paediatric neurology team.
- Perform **plasma lactate, plasma amino acids and urine organic acids** as well.

- **Ophthalmology assessment** may be helpful in identifying a diagnosis.
- Other investigations may be required once a cause has been found (e.g. echocardiogram and renal ultrasound scan for TSC).

5 Information for families

Ensure verbal and written information is provided for families.

- Infantile Spasms & West Syndrome. An Explanatory Booklet for Parents & for Professionals (2007)[7.7] (www.iciss.org.uk)
- AED drug information leaflets (www.cewt.org.uk)

6 Additional Investigations that may be required in a small subset of patients

- Those under 3 months should have a
  - Cardiac ECHO for TSC (and possibly a renal USS for TSC)
  - Tests for congenital infection "TORCH screen": urine for CMV, throat swab for viral culture, blood for: toxoplasma, rubella, CMV, and possibly hepatitis, herpes, syphilis, HIV

- Metabolic and genetic diseases should be considered, if clinical signs/symptoms suggests them, although rarely identified:
  - Blood: chromosomes; lactate, glucose, U&E, LFT, Ca, Mg, urate, blood gas, ammonia, biotinidase, plasma amino acids; possibly VLCFA, transferrin electrophoresis for Congenital Disorders of Glycosylation (CDGs); copper & caeruloplasmin; pipecolic acid
  - Urine: amino acids, organic acids, GAGs, oligosaccharides, pipecolic acid, thiosulphate
  - Fasting CSF and paired blood: lactate, glucose, protein, glycine and serine, microscopy and culture

- Other tests:
  - May be considered in some cases in discussion with the paediatric neurology team.

7 References & Resources

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8 Disclaimer

Clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. Caution is advised when using guidelines after a review date.

Appendix 1
West Syndrome (Epileptic Spasms) management algorithm (refer to guideline for specific detail)

Initial assessment & diagnosis

- History & examination (including OFC, Wood's (UV) light, BP, developmental status)
- Urgent EEG (within 3 days) capturing sleep and awake periods confirming 'hysparrhythmia' or 'modified hysparrhythmia'
- Discuss with paediatric neurology

First line treatment

- Treatment to be commenced as soon as possible after confirmatory EEG
- Discuss potential adverse reactions of treatment with family
- Take varicella serology pre-treatment
- Start combined treatment, if no known evidence of TSC, of:
  - Prednisolone 10 mg four times daily plus gastric protection
  - Vigabatrin 25 mg/kg twice daily and increasing to 50mg/kg twice daily on day 2

  (Refer to guideline for further information)

  *if at any point a diagnosis of TSC is made it is recommended that discussions with the family about potentially using monotherapy treatment with vigabatrin should be made
- Start monotherapy, if known to have TSC, of:
  - Vigabatrin 25 mg/kg/twice daily and increasing to 50mg/kg twice daily on day 2
- Monitor BP, urine for glycosuria, U&E

Further investigations

- Repeat EEG at 2 weeks
- Diagnostic investigations if cause of ES unknown performed in the following order until cause identified:
  - MRI brain
  - CGH array, plasma lactate, plasma amino acids and urine organic acids
  - Consider testing for epilepsy gene panel in discussion with paediatric neurology
  - Ophthalmology assessment (may be helpful in identifying a diagnosis)
  - Discuss further investigations with paediatric neurology team