Association of Child Neurology (AOCN) – Indian Epilepsy Society (IES) Consensus Guidelines for the Diagnosis and Management of West Syndrome

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Justification: West syndrome is one of the commonest causes of epilepsy in infants and young children and is a significant contributor to neurodevelopmental morbidity. Multiple regimens for treatment are in use. **Process:** An expert group consisting of pediatric neurologists and epileptologists was constituted. Experts were divided into focus groups and had interacted on telephone and e-mail regarding their group recommendations, and developed a consensus. The evidence was reviewed, and for areas where the evidence was not certain, the Delphi consensus method was adopted. The final guidelines were circulated to all experts for approval. **Recommendations:** Diagnosis should be based on clinical recognition (history/home video recordings) of spasms and presence of hypsarrhythmia or its variants on electroencephalography. A magnetic resonance imaging of the brain is the preferred neuroimaging modality. Other investigations such as genetic and metabolic testing should be planned as per clinico-radiological findings. Hormonal therapy (adrenocorticotropic hormone or oral steroids) should be preferred for cases other than tuberous sclerosis complex and vigabatrin should be the first choice for tuberous sclerosis complex. Both ACTH and high dose prednisolone have reasonably similar efficacy and adverse effect profile for West syndrome. The choice depends on the preference of the treating physician and the family, based on factors of cost, availability of infrastructure and personnel for daily intramuscular injections, and monitoring side effects. Second line treatment options include anti-epileptic drugs (vigabatrin, sodium valproate, topiramate, zonisamide, nitrazepam and clobazam), ketogenic diet and epilepsy surgery.

Keywords: *Epileptic spasms, Hypsarrhythmia, Infantile spasms, Treatment.*

West syndrome (WS) is one of the commonest types of epilepsy in infants and toddlers and is a significant contributor to neurodevelopmental morbidity in children. Common co-morbidities include global developmental delay/intellectual disability, autism spectrum disorder, cerebral palsy, and visual and hearing impairment. The currently preferred term for infantile spasm is epileptic spasm.WS is now understood to be an age-dependent epileptic encephalopathy, an expression of brain injury to any cause; which may be pre-natal, perinatal or postnatal. The pathophysiological mechanisms are not well understood.

In India, the situation is compounded by a huge time lag from onset to diagnosis – reported median lag is almost 6-12 months as compared with a few weeks in the developing countries. There is also a lack precise knowledge on the disease among pediatricians. Other challenges include paucity of trained personnel to report pediatric electroencephalograms (EEG), high cost of investigative work up, and availability issues with first line treatments such as adrenocorticotropic hormone (ACTH) and vigabatrin. The plethora of regimens mentioned in the literature adds to the confusion. A consensus guideline for the diagnostic evaluation and management of children with WS in India has been a long felt need.

PROCESS

The process of preparing a consensus document on the diagnosis and management of WS was initiated by the members of Association of Child Neurology (AOCN). In association with Indian Epilepsy Society (IES), a

consensus document was envisaged on the same. The invited experts included pediatricians, pediatric neurologists, neurologists, and epileptologists (**Annexure 1**), who were categorized into one of five groups: definitions, etiology, early diagnosis and prognosis; diagnostic evaluation; hormonal treatment; vigabatrin and other drugs; and diet, surgery and supportive care. First the evidence was reviewed. For areas where the evidence was not certain, the Delphi consensus method was adopted [6]. The writing group members of each group identified a set of open- ended questions which were discussed in their respective groups. These open-ended questions were administered using Google form to all experts. In this process, the experts gave their opinions to the moderator, who anonymized the responses and sent them back to all experts. A guarantor ensured that responses were blinded and the methodology of Delphi was adopted.

The responses to the open-ended questions obtained were qualitatively analyzed, and similar responses were categorized, clubbed and converted into closed ended responses. Based on these responses, new questions with close-ended responses were framed. These questions were again sent to experts in the second round. Their responses were collated and presented in the meeting of experts. Categorical responses where more than 75% of experts agreed on single response were considered to have reached a consensus. The concerns, discrepancies and responses where consensus was not reached (<75% agreement) were polled again using audience response system. Questions where polling did not reach 75% consensus were re-polled. Any question where second polling also failed to establish a consensus were considered as having failed to reach the same, and the data was presented as a range rather than a definitive response.

A final consensus meeting was held on 1 September, 2019 at Delhi. The coordinator of each group made a presentation of the draft document for consensus. Deliberations were held, and inputs and suggestions by the various participating members were incorporated into the document. The final document was prepared and circulated to all the participating members for inputs and approval.

RECOMMENDATIONS

Definition

As per the 2004 International Delphi consensus statement on WS[1], definitions of clinical spasms, epileptic spasms, and WS were framed (**Box 1**). Spasms may be confused with myoclonic seizures but the longer duration, presence of a tonic phase, occurrence in clusters and the relationship with the sleep wake cycle help to differentiate spasms from myoclonic seizures [1]. Differentiation from paroxysmal non-epileptic phenomena in typically developing children such as benign myoclonus, benign myoclonic epilepsy of infancy, Sandifer syndrome, etc may require video telemetry with concurrent surface electromyography. As per the International League Against Epilepsy (ILAE) 2017 seizure and epilepsy classification, epileptic spasms may be of focal, generalized or unknown onset [2].

1. *Consensus Statement: Definitions*

- WS is defined as the presence of epileptic spasms (usually in clusters) and the presence of hypsarrhythmia or variant hypsarrhythmia on EEG [7].
- Children with clinical spasms but EEG not showing hypsarrhythmia or its variants should have an overnight EEG and be referred for expert evaluation. A repeat EEG may be considered in such patients as an early EEG may miss hypsarrhythmia. Specialist may also consider treating these children similar to West syndrome.

Box I Terms Related to Infantile Spasms and West Syndrome

- *Clinical spasms*: Brief, synchronous movements involving head, trunk, and limbs, or sometimes of the head, trunk, or limbs alone occurring for around 1 second (0.5-2 sec). These may be flexor/extensor/ mixed and may be symmetric/ asymmetric [8]. Spasms typically occur in clusters and are seen before falling asleep or when waking up from sleep [8].
- *Subtle spasms*: Episodes of activities such as head-nod, facial grimacing, eye movements, yawning, gasping associated with hypsarrhythmia.
- *Infantile spasms – single spasm variant (ISSV):* Infantile spasms occurring singly and not in clusters [8].
- *Epileptic spasms*: Clinical spasms associated with an epileptiform electroencephalogram [EEG].
- *Epileptic spasms without hypsarrhythmia*: Presence of clinical spasms and epileptiform abnormalities other than hypsarrhythmia or its variants on EEG [8].
- **West syndrome*: Children with epileptic spasms in clusters with EEG showing hypsarrhythmia or its variants [7].

**Some definitions include the presence of pre-morbid or co-morbid developmental delay or regression, but in the West Delphi 2004 consensus, the development criterion has not been included.*

- Children who have hypsarrhythmia on EEG but no clinical spasms must be referred for expert evaluation. Such children may have subtle spasms, which may be missed by parents and may be picked up on a video EEG recording. Home videos may also assist in picking up subtle spasms.

Etiology

Most recent studies classify spasms into two broad categories- known and unknown etiology. Known causes can further be classified into pre-natal, perinatal and postnatal, depending on the timing of central nervous system insult. Another classification scheme is as per the new ILAE 2017 classification [2], wherein the etiology is classified into structural-metabolic, genetic, infectious, etc. However, this can be a bit confusing as there may be overlaps; e.g. tuberous sclerosis may be classified as both structural and genetic. For practical purposes, the etiology should be classified as known or unknown. If known, the exact etiology should be mentioned.

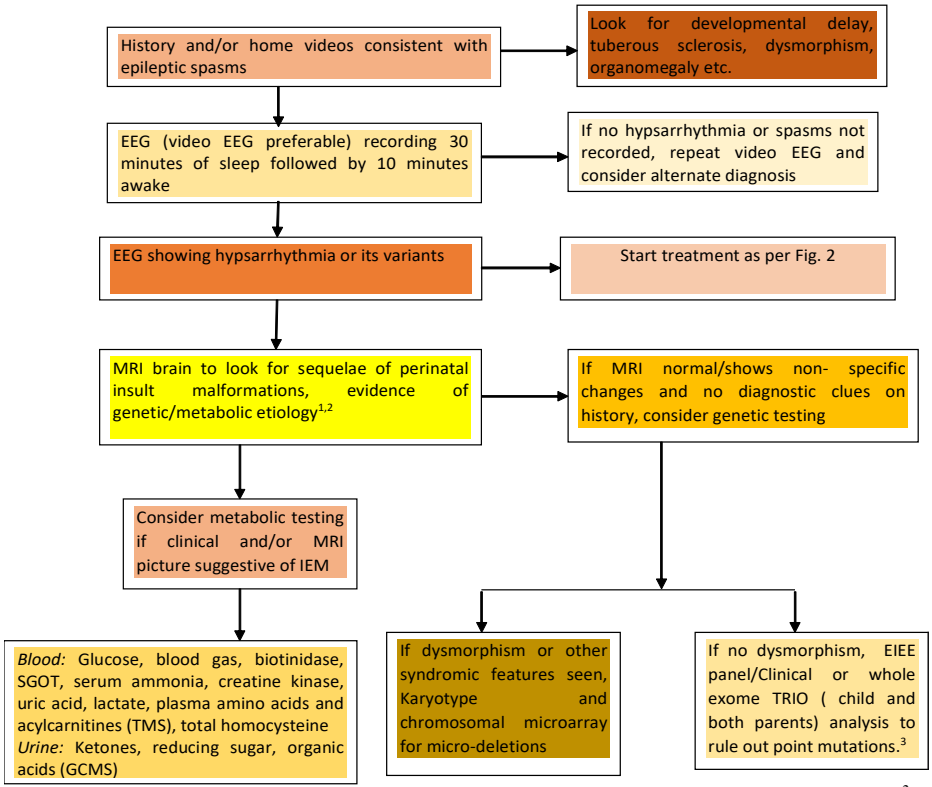
The etiological profile of WS in India is different, as compared with the developed world, where genetic and presumed genetic (unknown etiology) is higher. In India, the etiology is known in 80-85% of affected children [3,4]. Perinatal causes, including perinatal hypoxia and neonatal hypoglycemia are the most predominant [3,4].

Diagnosis of WS

Clinical suspicion remains the cornerstone of diagnosis of epileptic spasms. An evaluation including a thorough history, examination and EEG are important in the diagnosis of infantile spasms. As etiology is the most important predictor of outcome, efforts should be made to establish the underlying etiology, as this may also affect the treatment decisions and prognosis; e.g. children with tuberous sclerosis complex are more likely to respond to VGB, while most with unidentified etiology may respond better to steroids. The evaluation should follow a step wise process to avoid unnecessary tests, due to the costs involved **(Fig. 1)**.

Electroencephalography (EEG)

An EEG (preferably video-EEG) is the most important tool in diagnosis and management of epileptic spasms, and the following protocol may be followed:



[1]In low resource settings, CT may be considered as initial investigation, especially if the etiology is likely perinatal asphyxia; [2]If initial MRI normal, consider repeating after the age of 2 years, with MRS, if unknown etiology and persisting spasms. In case of refractory spasms, especially if asymmetric, consider FDG PET to look for focal cortical dysplasia, in consultation with expert; [3]Detailed pedigree should be drawn although family history may or may not be contributory as many variants are de novo; IEM: Inborn error of metabolism, EIEE: Early infantile epileptic encephalopathy; TMS: Tandem mass spectrometry; GCMS: Gas chromatography mass spectrometry; SGOT: Serum glutamic oxaloacetic transaminase.

Fig. 1 Diagnostic algorithm for child with West syndrome.

Basic level: Recording for sufficient length to capture sleep is strongly recommended and if achieved, further recording for at least 10 minutes after awakening should be attempted, as epileptic spasms occur very often in that period. The EEG should be planned preferentially during spontaneous sleep and after feeding. This may require planning arrangements with parents. In infants whose EEG is abnormal and the epileptic spasms have not been captured during the EEG, a home video is suitable to establish presence of clinical spasms.

Advanced level: If there is diagnostic uncertainty e.g. if EEG is not diagnostic or spasms are not observed, a prolonged overnight inpatient video EEG recording for 24 hours with polygraphic (with neck and bilateral deltoid EMG) parameters is desirable as it will capture awake as well as all sleep stages and possibly also capture spasms. However, if inpatient facilities are not available, a prolonged EEG record for 2-4 hours to capture stage 2 of non-REM sleep followed by 30 minutes after awakening should be considered [5]. Long term video EEG may also pick up other coexisting seizure types, as noted in 22% of infants with epileptic spasms in a study; especially in those who had etiology of preterm birth or birth asphyxia [6].

Depending on the clinical and EEG findings, the level of diagnostic certainty can be classified as confirmed, probable and possible WS according to following criteria [1,5]:

a) *Confirmed WS:* When interictal EEG shows hypsarrhythmia (or its variants) along with either electroclinical documentation (ictal EEG showing electrodecremental response) or home video showing cluster of spasms.

b) *Probable WS (High diagnostic certainty):* When clinical history is suggestive of spasms but EEG shows multifocal discharges but not hypsarhythmia or its variants.

c) *Possible WS (Low diagnostic certainty):* When history of spasms is doubtful, and EEG shows multifocal discharges and not hypsarhythmia or its variants

Depending on the clinical and EEG findings, the level of diagnostic certainty can be classified as confirmatory, probable and possible WS [1,5]. In probable or possible cases, parents should be encouraged to bring home video of the spasms. Repeat EEG at advanced level can be planned to record hypsarrhythmia or spasms.

Following the initiation of any first line treatment, the efficacy of therapy should be assessed within 2-3 weeks; in terms of cessation of spasms and resolution of hypsarrhythmia on EEG [4]. If no/partial response to treatment is seen, a repeat EEG may be considered to plan the next level of treatment. EEG should also be repeated after 2 weeks if the first EEG **is** normal or inconclusive, or if there is a suspicion of additional/change in seizure type, which may occur in 12-42.3% of cases [6]. If focal abnormalities are identified in infants with additional focal seizures, further investigations like high resolution multi-modality magnetic resonance imaging (MRI)/ positron emission tomography (PET) can be planned to search for a resectable lesion [6].

2. *Consensus statement: EEG for Suspected West Syndrome*

- EEG evaluation with standard 10-20 system of electrode placement with preferably 3 additional surface EMG electrode channels (over the neck and bilateral deltoids) is recommended within 24-48 hours of suspected diagnosis. Video-EEG recording of at least 30 minutes of sleep followed by brief awake state should be attempted to capture hypsarrhythmia and ictal correlate of spasms.
- Prolonged video EEG recording may be required if the EEG is not diagnostic or the spasms are not observed or there is uncertainty regarding the diagnosis.
- Sleep may be induced using chloral hydrate, triclofos, or melatonin; although, natural sleep is preferred. The diagnostic patterns include inter-ictal pattern of hypsarrhythmia or its variants and ictal patterns of spasms.
- Repeat EEG may be considered:
  - After clinical cessation of spasms, to document resolution of hypsarrhythmia on EEG;
  - If the first EEG was normal/ inconclusive;
  - If there is suspicion of additional/change in seizure type; and
  - If the there is no/partial clinical improvement.

EEG Patterns of WS

EEG background is mostly abnormal during both wakefulness and sleep. The inter-ictal patterns vary according to the underlying pathology, age and stage of sleep.

Inter-ictal patterns:

a. Hypsarrhythmia: This term describes a characteristic high voltage, completely disorganized and chaotic pattern consisting of random high voltage slow waves and spikes. These spikes vary from moment to moment,

both in location and duration. At onset, hypsarrhythmia may be present only during drowsiness and light sleep, but soon becomes abundant during wakefulness. During stage 2 and 3, there is an increase in the spikes and polyspikes; which become more synchronous, causing fragmentation of the hypsarrhythmic activity, giving a quasi-periodic appearance [5,7]. The hypsarrhythmia pattern usually attenuates in REM sleep. Capturing wakefulness after sleep is crucial to demonstrate the chaotic background activity considered typical of hypsarrhythmia.

b. Hypsarrhythmia variants/ modified hypsarrhythmia: Up to 33% patients do not show hypsarrhythmia [7]. Several variants have been described: rapid, slow, asymmetric, unilateral and even suppression burst like patterns [8]. Many of these variations correlate with neuropathology. Asymmetric hypsarrhythmia constituted 23% of cases with hypsarrhythmia in a study and indicates the importance of identifying focal hemispheric abnormalities like cortical dysplasia; more so if in infants with asymmetric spasms [9]. Also, hypsarrhythmia may not be seen in late onset spasms [9].

Ictal EEG pattern (during spasms): The most common pattern seen in 72% of the attacks is a brief duration (1-5 sec) three phased pattern: *a*) diffuse high amplitude slow wave, *b*) low amplitude fast activity, and *c*) short lasting diffuse flattening of ongoing activity (electro-decremental response) [10]. In asymmetric spasms, there may be focal discharges preceding, during or following it; indicating the side with focal cortical lesion.

Evolution of EEG: On effective treatment, rapid improvement in EEG is seen, which may even completely normalize. However, resolution of hypsarrhythmia with persistence of background abnormalities occurs more frequently, as a reflection of underlying abnormalities. In most symptomatic cases, there is return of spike wave discharges with development of other seizure types [11]. The chaotic pattern gradually becomes more organized and disappears by 2-4 years and may evolve into other abnormal patterns [12].

Neuro-imaging Studies

If available and feasible, MRI is preferred over Computed Tomography (CT) scan in view of higher yield of abnormalities. Early MRI (T2, T1, FLAIR) with epilepsy protocol should be considered to reach an etiologic diagnosis. However, treatment should not be delayed if MRI cannot be done immediately due to lack of availability or need of anesthesia.

One third of cases considered idiopathic on clinical assessment enter the symptomatic category of structural-metabolic following the MRI scan. In the National Infantile Spasms Consortium, a causal abnormality was identified in 40.9% of infants who underwent MRI with epilepsy protocol, making it the highest yield test [13]. Common abnormalities picked up in Indian scenario include sequelae of perinatal asphyxia and hypoglycemia.

Timing of MRI: Ideally MRI should be obtained prior to initiation of therapy, as Adrenocorticotropic hormone (ACTH) therapy may cause transient abnormalities that may be falsely misinterpreted as brain atrophy. Also, Vigabatrin (VGB) can induce T2 signal abnormalities [14]. On the other hand, MRI done in early infancy may miss cortical dysplasias in view of immature myelination [15].

Repeat MRI: If initial MRI is normal, and seizures persist, MRI may be repeated after 6 months, and certainly at 24-30 months age when myelination is more mature [11].

Additional neuroimaging studies: Magnetic resonance spectroscopy (MRS) can help to delineate a possible metabolic or mitochondrial cause. Areas of hypo metabolism on a Positron emission tomogram (PET) may indicate a cortical malformation. PET may be important in a child with asymmetric spasms, focal EEG changes and a normal MRI of the brain. Positive PET localization has led to seizure remission following the resection surgery done (based on the PET finding) even with a normal MRI [16]. Ictal and interictal single photon emission computed tomography (SPECT) has been used to aid in the localization of the epileptic focus in children with asymmetric infantile spasms who are being evaluated for surgery.

3. *Consensus Statement: Neuroimaging in WS*

- MRI is the neuroimaging modality of choice, and should be considered for etiologic diagnosis in children with WS. However, if it is delayed for any reason, treatment should be started without waiting for the imaging.
- In low-resource settings, if there is clear history of perinatal asphyxia or neonatal hypoglycemia, an initial CT scan may suffice. However, if the CT is normal, an MRI must definitely be considered.
- If the first MRI is normal, repeat MRI (preferably 3 Tesla, with epilepsy protocol incorporating 3D FLAIR, STIR, SPGR sequences and optionally diffusion weighted MRI with post processing) should be considered after the age of 24 months (when the myelination is complete) to pick up any cortical dysplasia missed on early MRI or any additional findings which may help to suspect a genetic/ metabolic etiology.

- If previous MRI with epilepsy protocol is normal, additional studies like MRS, PET and SPECT may be considered if there are asymmetric spasms, focal features on EEG with spasms refractory to treatment, especially in children with tuberous sclerosis. However, the patient should be referred to an expert for planning these studies.

Metabolic Evaluation of West Syndrome

More than 25 IEM have been found to be associated with WS, with frequency of metabolic disorders in epileptic spasms estimated to be 4.7% [13]. A wide range of metabolic disorders, including mitochondrial disorders, such as Leigh's disease, aminoacidopathies, such as non-ketotic hyperglycinemia, can present with infantile spasms. Other metabolic conditions include glucose transporter defects, pyridoxine deficiency, pyridoxal-5-phosphate deficiency, disorders of cerebral folate metabolism, Menkes' disease, and biotinidase deficiency. At the very least, disorders treatable at low cost-e.g. pyridoxine dependency and biotinidase deficiency should be ruled out, if required, by a therapeutic trial.

Clues to the presence of IEM include a positive family history, consanguinity, previous sibling deaths, failure to thrive, fluctuating course, deterioration after a period of apparent normalcy, tone abnormalities or movement disorders. Ophthalmological examination, unusual odors and visceromegaly may provide other clues. MRI may show non-specific or specific patterns (for few disorders). However, if none of these features are present, the yield of metabolic investigations is very low [17].

4. *Consensus Statement: Metabolic Testing*

- Metabolic evaluation should be considered if
  - No specific etiology can be identified on examination and MRI; or
  - Clinical clues to the presence of underlying metabolic etiology including coexistent movement disorder, failure to thrive; or systemic findings; or
  - There is poor response to conventional treatment.
- First tier investigations:
  - Blood: Glucose, blood gas, biotinidase, Serum glutamate oxaloactetate Transaminase (SGOT), serum ammonia, creatine kinase, uric acid, lactate, plasma amino acids and acylcarnitines (Tandem Mass Spectrometry) total homocysteine
  - Urine: Ketones, reducing sugar, organic acids (Gas Chromatography Mass Spectrometry)
- Second tier investigations: Depending on the results of the first-tier tests and clinico-radiological clues.
  - Blood: Lysosomal enzymes, very long chain fatty acids,
  - Urine: oligosaccharides,
  - CSF: glycine, lactate/pyruvate, neuro-transmitters.
- Plasma / CSF glucose ratio after a 4 hour fast is a low-cost test to diagnose a treatable disorder (Glucose transporter defect), hence it can be done even as a first line test.

Genetic Evaluation

Genetic causes are being increasingly recognized in epileptic encephalopathies of unexplained etiology. A timely genetic diagnosis has potential for precision treatment decisions, which can improve seizure and development outcomes. It also helps to counsel the parents regarding prognosis and recurrence risk in future pregnancies. A combination of genetic tests provided a definitive diagnosis in more than 40% of children presenting with new-onset spasms without an obvious cause after clinical evaluation and MRI [4,13,18].

Copy number variants (CNVs) are deletions and duplications of stretches of DNA ranging from 1 kb to an entire chromosome. These CNVs can be detected by chromosomal microarrays (CMA) which include comparative genomic hybridization (CGH). Pathogenic CNVs were detected in 3.6-11.8% of children with epileptic encephalopathies [17]. The yield is likely to be higher in case of associated dysmorphism, intellectual disability, developmental delay disproportionate to seizure etiology/frequency, and presence of behavioral issues including autism in non-consanguineous families.

The applications of NGS include targeted gene panel, whole exome (WES) and whole genome sequencing (WGS). However, WES has shown to have higher diagnostic yield compared to gene panels, as it sequences the entire coding genome. The current diagnostic yield of genetic tests is below 60%; and a substantial number of patients may still remain undiagnosed.

In one Indian study, in 36 patients with WS with presumed genetic etiology, genetic causes were identified in 17 children [4]. In a multicentric study, out of 100 infants with epileptic spasms of unknown cause undergoing whole exome sequencing, pathogenic mutations were identified in 15 [19]. Etiology was more

likely to be identified in those children who had abnormal development (32.5%) vs. those with normal development (8.3%) [19].

5. *Consensus Statement: Genetic Testing*

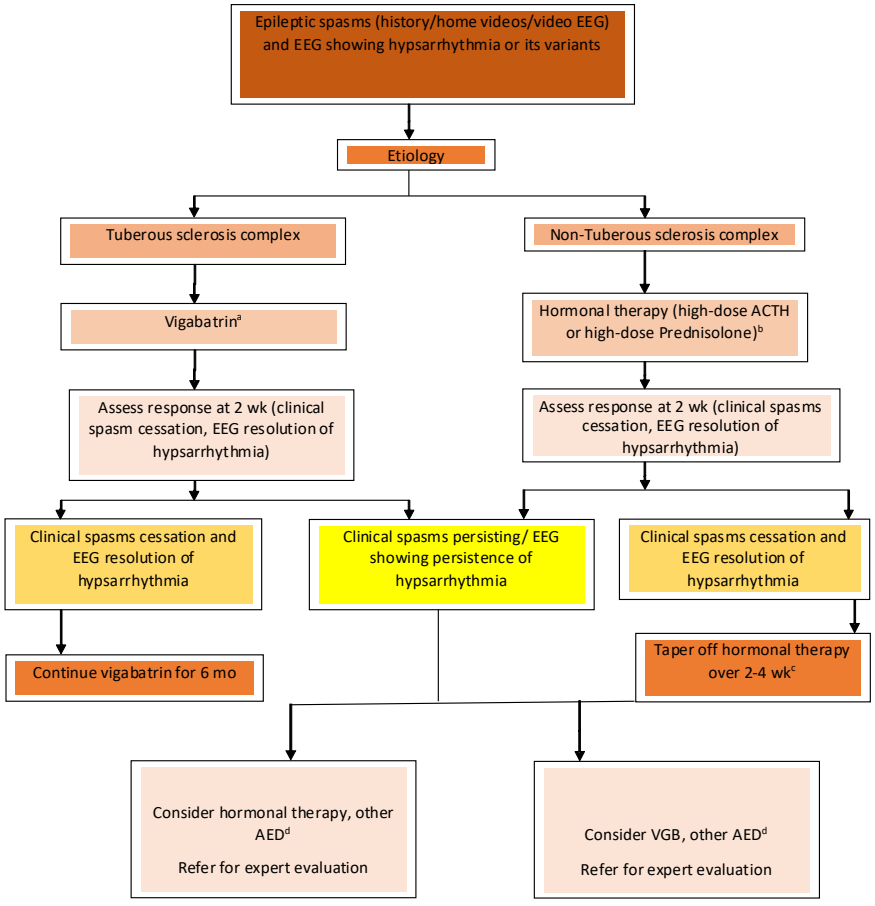
- Genetic testing should be considered if history, clinical examination or MRI suggests an unknown or a known genetic etiology.
- It should also be considered in children with dysmorphism
- Pre and post-test counselling of parents to explain what to expect from the test and the implications of pathogenic/ likely pathogenic/VUS/negative results is recommended.
- In children with dysmorphism, karyotype and CGH microarray florescent in-situ hybridization (FISH) should be the first-line tests.
- WES in trios with parental samples to enable variant segregation should be done if first line tests are negative. American College of Medical Genetics and Genomics (ACMG) criteria should be used in consultation with a geneticist to ascertain the pathogenicity of an identified variant [20].
- In children without dysmorphism, clinical/whole exome sequencing trio testing should be the first line genetic testing.

Treatment

The treatment algorithm for WS is shown in **Fig. 2**.

First-line Treatment Options

High-quality evidence is available for hormonal therapy (adrenocorticotropic hormone or oral steroids), VGB and combination of hormonal therapy with VGB in the treatment of WS. The United Kingdom Infantile Spasms



[a]Vigabatrin dose: Start with 50 mg/kg/d and hike by 50 mg/kg every 3-7 d interval as tolerated to a maximum dose of 150 mg/kg/d; [b]ACTH Dose: 150 IU/m^2 or 6 IU/Kg IM daily for 2 wk, Oral Prednisolone dose: 4 mg/kg/d for 2 wk; [c]If EEG shows continued presence of epileptiform abnormalities despite the resolution of hypsarrhythmia, consider starting sodium valprote, topiramate or zonisamide for 12-24 mo; [d]Other AEDs which may be considered include topiramate, zonisamide, benzodiazepines, or sodium valproate. Pyridoxine trial may be considered in cases with unknown etiology.

Fig. 2 Treatment algorithm for West syndrome.

Study compared hormonal treatment with VGB for epilepsy and development outcome at short-term (14 months and four years of age). It was observed that hormonal therapy was superior in terms of an initial cessation of epileptic spasms, but not at 14 months and four years of age [21]. However, successful initial control of epileptic spasms was associated with better long-term developmental outcome [22].

Recently, the effectiveness of the combination of hormonal therapy with VGB was studied in comparison with hormonal therapy alone [23,24]. Initial results demonstrated that the combination therapy was significantly superior to the hormonal therapy for the cessation of epileptic spasms as a short-term response. However, the combination therapy did not significantly improve epilepsy or neurodevelopmental outcome at 18 months of age. Pyridoxine, as an adjunct with steroid therapy was not been found superior to steroid therapy alone [25].

6. *Consensus Statement: First-line treatment for WS*

The first-line treatment options are hormonal therapy (adrenocorticotropic hormone or oral steroids) and VGB. Hormonal therapy should be preferred for cases other than tuberous sclerosis complex and VGB should be the first choice for tuberous sclerosis complex. Regarding combination treatment, in view of limited literature, the group suggested the need for more data, before recommending as it as routine first line treatment.

Hormonal Therapy

Hormonal therapy in the form of ACTH and oral steroids has been widely used. ACTH has disadvantages of parenteral route and cost. Oral steroids have advantages of ease in administration due to oral route and low-cost. It is difficult to summarize evidence comparing these two modalities of treatment, as different preparations (synthetic and natural ACTH), different doses of ACTH and prednisolone, and different regimens have been used in various studies. Also, many of the studies were underpowered or used varying outcomes. The most important outcomes would be electroclinical resolution and neurodevelopmental outcomes. However, many studies have only used clinical spasm cessation, or surrogate markers such as EEG improvement.

In the 2004 United Kingdom Infantile Spasms study, spasm freedom was achieved in 70% of children taking high dose oral prednisolone (40-60 mg/day) and 76% of children taking ACTH (40 IU/alternate day) [21]. A few recent studies [26,27]used high-dose oral steroids as initial management of WS, and subsequent treated failed cases with ACTH and demonstrated a response rate of 40% and 33% respectively, with high-dose ACTH therapy among non-responders with high-dose oral steroids [26,27]. Two recent systematic reviews have suggested equivalent efficacy of high dose prednisolone as ACTH [28,29].

Dosage schedule for ACTH: Typically, in the high dose schedule, 150 IU/m^2/BSA has been used, and in the low dose schedule, 20-30 IU/day has been used [30]. There is a need of high-quality studies and evidence to conclude the optimum dosing protocol of ACTH.

Dosage schedule for prednisolone: In the previously mentioned UK Infantile spasms study, 40-60 mg/day of oral prednisolone was used [21]. However this dose may be too high for our smaller size infants. Chellamuthu et al have studied high dose (4 mg/kg) vs. 2 mg/kg daily oral prednisolone in a randomized controlled trial and demonstrated the higher effectiveness (52% versus 25%) of high-dose prednisolone with similar adverse event profile [31]. Some centers advocate very high 8mg/kg/day as initial dosing protocol [26]. There are concerns of infection and tolerability issues with very high dose of oral steroids.

7. *Consensus Statement: Hormonal therapy in WS*

- Both ACTH and high-dose prednisolone have reasonably similar efficacy and adverse effect profile for the treatment of WS.
- The initial choice depends on the preference of the treating pediatrician/neurologist and family, based on factors of cost, availability of infrastructure and personnel for daily intramuscular injections.
- High-dose ACTH therapy may also be considered in cases who failed to response with oral steroids.
- High-dose ACTH is a preferred therapeutic option as compared to low-dose ACTH. Suggested dose is 150U/m^2/BSA or 6U/kg intramuscular once daily for two weeks to assess therapeutic response.
- High dose prednisolone (4 mg/kg/day) is recommended in view of better efficacy and similar tolerability to the usual dose (2 mg/kg/day). This treatment should be given for 2 weeks to assess response.
- If there is clinical spasms cessation, EEG should be performed to look for resolution of hypsarrhythmia. If there is EEG resolution as well, i.e. electroclinical cessation, then the first line drug (ACTH/prednisone) should be tapered off over 2-4 weeks.
- In case there is no clinical spasms cessation or persistence of hypsarrhythmia on EEG, then the first line drug should be tapered off and second line treatment should be started.

Further treatment after electroclinical resolution

There is no published evidence on what treatment the child should be started after there is clinical cessation of spasms and EEG resolution of hypsarrhythmia or its variants. There is no evidence that anti-epileptic drug treatment will prevent relapses or further development of epilepsy.

8. *Consensus Statement: Further Treatment After Electroclinical Resolution*

After clinical cessation of spasms, if the EEG shows resolution of hypsarrhythmia, the following actions are recommended:

- If the EEG is normal, or shows background abnormalities such as slowing but no epileptiform abnormalities, then the hormonal therapy can be tapered off and there is no need to start any other anti-epileptic drug treatment.
- If the EEG shows epileptiform abnormalities such as multifocal or focal spike wave discharges, the patient may be started on an anti-epileptic drug such as topiramate, sodium valproate and/or zonisamide for a period of 12-24 months (there is no evidence to prefer any one of these AEDs).

Treatment of Relapses

Relapse of epileptic spasms is frequent and constitute major challenge as it is an adverse prognostic variable for long-term epilepsy and neurological outcome [32]. There is a paucity of evidence on how to manage these patients. Options include a second trial of hormonal therapy or starting VGB.

9. *Consensus Statement: Treatment of Relapses*

The treatment of children who have initially responded with hormonal therapy should be individualized. Options include a repeat trial of hormonal therapy or vigabatrin.

Monitoring and Precautions on Hormonal Therapy

There are no published guidelines or recommendations on the plan of investigations before and during steroid or ACTH therapy in children with WS. The dwelling environment and socioeconomic strata would determine the risk of exposure to pathogens and subsequent infection.

Both ACTH and oral steroid treatment are commonly associated with adverse effects such as irritability, increased appetite, hypertension, weight gain, hyper-pigmentation and risk of infections. Adverse effects are associated with high dose and longer duration of therapy. It is routine to monitor blood pressure, blood sugar and urine sugar. There is variability in frequency of monitoring for these adverse effects.

10. *Consensus Statement: Pre-Hormonal Therapy Investigations, Monitoring and Precautions on Hormonal Therapy*

- Screening with chest *X* ray and Mantoux test is recommended in children at high risk, i.e. positive family history of contact and suspected immunodeficiency.
- Children with WS on hormonal therapy should be monitored for adverse effects. Parents should be counseled regarding the adverse effects.
- Clinical surveillance for infections should be done.
- At least weekly blood pressure monitoring needs to be done while the child is on therapy.
- No live vaccines (e.g. oral polio or measles) should be given while child is on hormonal treatment and for 1 month after stopping the therapy.
- Children on systemic corticosteroids for more than 2 consecutive or 3 cumulative weeks within last 6 months are at risk for adrenal insufficiency. Hence in case of inter-current illness, oral intolerance or surgical procedures, hydrocortisone should be administered in a stress dose of 25-100 mg/m^2 in divided doses.

Vigabatrin

Vigabatrin (VGB) is a GABA agonist that acts by inhibiting 4-aminobutyrate transaminase, the enzyme for catabolism of GABA. VGB is the drug of choice for epileptic spasms in tuberous sclerosis [18]. VGB is less effective that hormonal therapy as first line drug in treatment of infantile spasm. In terms of short term efficacy, cessation of spasm ranges from 27.3-55.3% with the use of VGB [21]. However, there is a considerable variation in the definition of spasm cessation among various studies. Apart from TSC, there are few etiological predictors of favorable response to VGB. Data from the International Collaborative Infantile Spasms Study (ICISS) [23] study revealed that children with stroke and infarcts responded well to combination of VGB and steroids when compared to those with other etiology. However, there is limited data on predictors of clinical response to VGB among non-TSC patients with epileptic spasms.

There is limited number of studies on long term efficacy of VGB in infantile spasms. The United Kingdom Infantile Spasms Study (UKISS) included non-tuberous sclerosis infants aged 2–12 months who were

followed up to determine the long term developmental outcome at 12-14 months of age. It was observed that mean Vineland adaptive behaviour scales (VABS) score were comparable between the high dose steroid group and VGB group [22].

There is a considerable variation in the dose and regimen for treatment of children with epileptic spasms. Doses from 18 mg/kg/day to 150 mg/kg/day have been used by many authors for infantile spasm. The dose is increased by 50 mg/kg/day every 3-7 days, to a maximum of 150 mg/kg/day [33].

Visual field defects have been reported with use of VGB [34]. Other side effects reported with use of VGB include sedation, irritability, and hypotonia. There are no standard methods to detect visual field loss among young children. A 30 HZ flicker electroretinography (ERG) has been used to monitor ocular toxicity. The proportion of patients with visual field defects in adults (52%) was noted to be higher than children (34%) in a systematic review of 1678 exposed patients to VGB [34].

11. *Consensus Statement: Vigabatrin in WS*

- VGB is the first line treatment among infantile spasm with tuberous sclerosis complex.
- Among patients with infantile spasm (non-tuberous sclerosis), VGB should be considered for treatment where hormonal therapy/steroids are either contraindicated or has failed.
- VGB is started at a dose of 50 mg/kg/day and hiked by 50 mg/kg every 3-7 days interval as tolerated to a maximum dose of 150 mg/kg (max within 14 days) or cessation of clinical and electrophysiological spasm has been achieved, whichever is earlier.
- If effective, the duration of therapy should generally be limited to six months.
- Parents should be explained the risk of possible visual side effects with use of VGB, and its minimal risk in infants and among those with less than six months of drug.
- Baseline and six-monthly ophthalmological evaluation including fundus examination is recommended for all children on VGB.
- Electroretinography (ERG) is optional at 6 monthly intervals in case of prolonged VGB therapy.

Treatment After Failed Hormonal Therapy and VGB

Other antiepileptic drugs which may be tried in children with epileptic spasms who have failed hormonal therapy and VGB include topiramate, sodium valproate, zonisamide, levetiracetam, and benzodiazepines such as nitrazepam, clobazam and clonazepam. Nitrazepam has been approved by Central Drugs standard Organization (India) for its use in epilepsy. There have also been small studies on the use of pyridoxine (other than when treating pyridoxine-dependent seizures), thyrotropin releasing hormone (TRH), hydrocortisone, sulthiame, and magnesium sulphate. However, considering limited literature with insufficient evidence, none of these drugs are deemed effective in treatment of infantile spasms [35].

12. *Consensus Statement: Treatment After Failure of Hormonal Therapy and Vigabatrin*

- Among children who failed hormonal therapy and VGB, use of benzodiazepines, sodium valproate, topiramate, or zonisamide may be considered.
- A trial of pyridoxine, pyridoxal phosphate, folinic acid and biotin may be considered for a minimum duration of seven days among those with epileptic spasms of unknown etiology and failed response to first line agents.

Dietary Therapies

The ketogenic diet (KD) is a high-fat, low-carbohydrate, and restricted protein diet that has been found useful in the management of WS [36]. KD administration in infants needs hospitalization, monitoring and availability of a trained dietician as the diet must be carefully titrated to achieve seizure reduction and provide calories and proteins for growth [37]. This may be difficult to achieve in a low resource setting. Also, ketogenic formula, which makes KD administration easier for infants, is not easily available in India, and is costly. The modified Atkins diet, which is a simpler and easier to administer version of the KD, has also been found to be effective and well-tolerated in children with infantile spasms [38].

13. *Consensus Statement: Dietary therapies for WS*

- Dietary therapy should be considered in children with WS after the failure of hormonal therapy and/or vigabatrin and one more AED, provided a center providing this therapy is accessible.
- KD is preferable, but in low resource settings, the modified Atkins diet may be used.
- Considerations while starting the diet include family education/motivation, and availability of a trained dietician.
- For infants <18 months of age, in-patient initiation is recommended, lower fat: protein ratios should be used, fine tuning of the diet is needed to maintain growth

- Dietary therapy should be tried for at least 3 months before considering it ineffective
- If effective in controlling spasms, it should be continued for a period of at least 2 years

Epilepsy Surgery

In the recent years, there have been studies on epilepsy surgery in refractory epileptic spasms [25]. The various surgeries reported include total hemispherectomy, subtotal hemispherectomy, multilobar resection, lobectomy and tuberectomy. Curative epilepsy surgery has the best outcomes with EEG-concordant lesional abnormalities on MRI [25]. The advances in neuroimaging and invasive monitoring have facilitated patient selection, presurgical evaluation, and ultimately, resection planning [39].

14. *Consensus Statement: Epilepsy Surgery in WS*

Children should be evaluated for epilepsy surgery after failure of the first line treatments (hormonal treatment and/or vigabatrin), if there is presence of surgically resectable lesions e.g., cortical dysplasias, hemimegalencephaly, Sturge Weber syndrome, tuberous sclerosis, and if there is presence of focal features on clinical semiology of spasms and EEG.

EARLY DIAGNOSIS

As mentioned earlier, the diagnosis of WS is significantly delayed in India, adversely impacting the treatment response and neurodevelopmental outcome [3,4]. In one study, the mean age at diagnosis was 13.1 months and the mean lead time to treatment was 7.9 months [3].

Pre-Symptomatic Diagnosis and Treatment of WS

Certain populations are at high risk of developing WS, such as infants with perinatal brain injury and tuberous sclerosis. There is evidence that asymptomatic infants with tuberous sclerosis complex at high risk of developing spasms and epilepsy can be identified in the pre-symptomatic stage using serial surveillance EEGs. All pre-symptomatic patients with tuberous sclerosis showing epileptiform abnormalities detected on serial surveillance EEGs went on to develop epilepsy [40]. Presence of epilepsy in tuberous sclerosis is an important association for mental retardation/intellectual disability. Antiepileptic treatment with VGB in this high-risk group, identified on serial EEGs, can significantly reduce the rates of evolution of asymptomatic EEG abnormalities to epilepsy and give a much better neuro-developmental outcome (nearly 80% normal development vs 20%, with standard treatment) Furthermore, the rates of drug resistant epilepsy were 7 % vs 42 % in the preventive vs standard groups [40].

There are also a few retrospective studies with small numbers of patients on the EEG findings preceding the onset of epileptic spasms and hypsarrhythmia in infants with perinatal asphyxia and periventricular leukomalacia. More evidence is needed before routine serial surveillance EEGs are recommended for presymptomatic diagnosis of WS in at-risk infants with perinatal brain injury.

15. *Consensus Statement: Early Diagnosis*

- Health professionals dealing with follow up and early intervention of high-risk infants should be trained to ask about and recognize epileptic spasms.
- Parents of high-risk infants should be made aware about the risk of epileptic spasms and educated to recognize spasms and report to a health facility early in case spasms occur.
- In every infant with developmental delay, the presence of epileptic spasms must be enquired for, especially at the 10 week and 14 week immunization visit.
- If spasms are suspected, an EEG should be urgently obtained within 24-48 hours.
- Infants diagnosed with tuberous sclerosis complex antenatally or at birth should be referred to a pediatric neurologist for consideration of surveillance EEGs, monthly from 2 mo of age, and presymptomatic treatment with VGB.

Supportive Care

Key facets of supportive care in WS include issues pertaining to nutrition, sleep, dental care, behavior, cognition and schooling.

16. *Consensus Statement: Supportive care in WS*

Anticipatory evaluation and appropriate management of co-morbidities (specifically related to feeding, oral hygiene, neuromotor delays, constipation, sleep, and growth retardation) should be ensured. Schooling, as per cognitive abilities, should be ensured. Disability certification, if eligible as per government guidelines, should be proactively arranged, so as to facilitate financial and other support.

CONCLUSION

In this article, the guidelines for the diagnosis and management of West syndrome are provided. These are based on the current evidence and where-in the evidence is insufficient, expert opinion. The neurodevelopmental outcomes of children with West syndrome are likely to improve with timely diagnosis and early appropriate management. As there is on-going research on the many facets of treatment, and there are still many unanswered

questions, an update of these guidelines will be provided when new evidence emerges.

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Contributors: SS and RM: conceptualized the idea; SS, JSK, KS, JS, JNG, RM, KPV: constituted the writing committee and drafted the manuscript; JSK devised and conducted Delphi process. All the authors approved the final version of the manuscript.

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Annexure 1

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