

Dear ILAE committee,

The Pediatric Epilepsy Research Consortium (PERC) is a group of 50+ pediatric epilepsy programs in the United States. PERC's mission is to provide a network and infrastructure to facilitate collegial, collaborative practice-changing research that will provide answers needed to improve the care of children with epilepsy. PERC supports several special interest groups, each of which consist of clinician researchers who meet regularly to discuss active projects and opportunities to collaborate.

The PERC Infantile Spasms Special Interest Group (PERC ELE SIG) reviewed the ILAE's recent document regarding the Proposed Classification of Syndromes in Neonates and Infants. This submission pertains only to the syndromic classification/criteria for children with infantile spasms.

### **I Syndrome name: "Infantile spasms syndrome"**

#### **Comment#1:**

The term *infantile spasms* has been used inconsistently within the medical literature for decades, with different authors referring to a seizure type and others referring to an epilepsy syndrome. (Mytinger, 2021) The original intent of Gibbs and Gibbs, and carried forward by Gastaut in the 1970 ILAE classification of seizures, was that the term infantile spasms referred to a particular type of seizure. (Gastaut, 1970; Gibbs FA, 1952) In subsequent decades, however, without additional clarification from the ILAE, many authors used the term infantile spasms to refer to an epilepsy syndrome. Clarification came in 2017 from the ILAE. Within the "Instruction Manual for the ILAE 2017 Operational Classification of Seizure Types" Fisher and colleagues clarified that the "term infantile spasms remains suitable for epileptic spasms occurring at infantile age." (Fisher et al., 2017) Thus, within this framework, infantile spasms are seizures and not an epilepsy syndrome. Without further clarification from the ILAE, the use of the seizure type "infantile spasms" within the syndrome name "infantile spasms syndrome" may perpetuate the uncertainty in terminology.

#### **Recommended text to be added to page 23, seizures types:**

The term infantile spasms remains suitable to describe a seizure type, the most common form of epileptic spasms occurring in infancy. (Fisher et al., 2017) When the word *syndrome* is added, the syndrome designation is "Infantile Spasms Syndrome."

#### **Comment#2:**

The new name "Infantile Spasms Syndrome" created significant discussion within our group. Some members strongly preferred to keep the West syndrome as the syndrome name and to simply clarify criteria for diagnosis. The group consensus, however was that we do not find fault in the designation of West syndrome as the syndrome name, nor do we necessarily oppose the new syndrome name "Infantile Spasms Syndrome." The major issue impacting care is the historically unsuitable criteria for West syndrome. Particularly problematic is the overreliance on

coexisting hypsarrhythmia as a criterion for diagnosis. Only about 60% of children with infantile spasms have hypsarrhythmia on presentation (Gaily et al., 2001; Vendrame et al., 2012) thus excluding many children from receiving a diagnosis of Infantile Spasms Syndrome and being enrolled in a clinical trial. Of great concern is the fact that some clinicians inappropriately withhold standard therapy in children with infantile spasms who do not have hypsarrhythmia despite the fact the presence or absence of this finding on the diagnostic EEG has no impact on the response to treatment (Demarest et al., 2017) or later outcome. (Vendrame et al., 2012) In addition, the determination of hypsarrhythmia and modified hypsarrhythmia have poor inter-rater reliability, which limits their use for clinical and research purposes. (Hussain et al., 2015) Finally, resource limited regions may be unable to perform a long-term EEG to capture sleep when hypsarrhythmia is more often present.

### **Recommended text to be added to page 23/24, EEG:**

Many children with infantile spasms do not have hypsarrhythmia and the determination of hypsarrhythmia and modified hypsarrhythmia has poor inter-rater reliability. (Hussain et al., 2015) The diagnosis of Infantile Spasms Syndrome does not require the presence of hypsarrhythmia or modified hypsarrhythmia. Clinicians should not withhold standard therapy for children with infantile spasms who do not have hypsarrhythmia or modified hypsarrhythmia.

## **II Diagnostic criteria for Infantile Spasms Syndrome**

We applaud efforts to emphasize the importance of early diagnosis and treatment. To that end, we recommend criteria for Infantile Spasms Syndrome that are inclusive. We believe this will promote the use of standard therapy (defined as high-dose prednisolone, adrenocorticotropic hormone, and/or vigabatrin). Restrictive criteria that are not supported by evidence may have negative consequences for children with infantile spasms (e.g., the inappropriate withholding of standard therapy). The current proposal largely addresses the greatest shortcoming in the prior syndrome criteria – the over-reliance on the presence of hypsarrhythmia. However, we have the following other recommendations:

1. Although clustering of infantile spasms is often present, children with single infantile spasms should be included in the syndrome diagnosis. The requirement for clustering spasms, without the inclusion of children with single spasms, is not supported by available evidence. For example, there is no evidence to suggest a differential treatment response among children with clustered vs. single intermittent infantile spasms. Furthermore, the clustering nature of infantile spasms can be clinically difficult to detect or remain undetected in resource-limited regions without long-term EEG. Excluding children with isolated infantile spasms from a syndrome diagnosis may delay or prevent children from receiving standard therapy.
2. We agree that many children with infantile spasms present without evidence of developmental slowing. Yet, infantile spasms that occur with EEG findings consistent with an epileptic encephalopathy (e.g., background slowing and disorganization and abundant epileptiform discharges) suggest imminent developmental slowing or regression. The requirement for developmental slowing may delay treatment or prevent

some children from receiving standard therapy. Please remove this mandatory requirement. We propose an alternative (see Table).

- Given the range of EEG findings proposed by the ILAE, the EEG section could be simplified to “epileptiform EEG.” However, we propose an alternative (see Table).

### Guidance for the diagnosis of Infantile Spasms Syndrome

Mandatory Features:	EEG	Exclusionary Features:
<ul style="list-style-type: none"> <li>• Epileptic Spasms</li> <li>• Onset age 2 months to 2 years</li> </ul>	<p>Epileptic spasms captured on EEG: Any Epileptiform EEG</p> <p><b>OR</b></p> <p>If epileptic spasms not captured on EEG, then one of the follow two conditions are met:</p> <ul style="list-style-type: none"> <li>• Developmental abnormalities<sup>^</sup> with epileptiform EEG</li> <li>• No developmental abnormalities but with EEG findings consistent with EE</li> </ul>	<ul style="list-style-type: none"> <li>• Presence of alternative age-dependent DEE such as:               <ul style="list-style-type: none"> <li>-- Early Infantile DEE</li> <li>-- Late Infantile DEE*</li> <li>-- Lennox-Gastaut syndrome</li> </ul> </li> </ul>

EE, epileptic encephalopathy; DEE, developmental and epileptic encephalopathy

\*(Nordli, 2012)

<sup>^</sup>Developmental slowing, stagnation or regression

### III “EEG”

Comment#1: The ILAE has previously recommended that “The term modified hypsarrhythmia should be discarded and atypical features should be specified if present.”(ILAE, 1992) As noted above, modified hypsarrhythmia has poor inter-rater reliability.

Recommendation: We strongly recommend the removal of “modified hypsarrhythmia” as currently used within the proposal.

Comment#2: The requirement for hypsarrhythmia for those without captured infantile spasms (Table 8) is unnecessarily restrictive. First, only about 60% of children have hypsarrhythmia on initial presentation for infantile spasms.(Gaily et al., 2001; Vendrame et al., 2012) Second, most regions of the world do not have access to long-term monitoring to capture events. Where EEG is available, either a home video of typical infantile spasms or history of clustering spasms, *plus* an epileptiform interictal EEG is adequate for the diagnosis of infantile spasms.

Recommendation: We recommend the removal of the hypsarrhythmia requirement in children without spasms captured on EEG.

#### **IV “Genetics:”**

Comment: After the MRI, the highest yield diagnostic test is a comprehensive gene panel and whole exome sequencing.(Helbig et al., 2016; Ko et al., 2018; Yuskaitis et al., 2018) The yield of these tests exceed routine karyotype and chromosomal microarray.(Wirrell et al., 2015) The gene panel, in particular, is increasingly available.

Recommendation: Note the high yield of the gene panel and/or whole-exome. However, genetic testing may not be available in many regions of the world.

#### **V “Metabolic and Other lab Studies:”**

Comment: We agree that metabolic etiologies are a rare cause of infantile spasms and that metabolic testing should be considered when the etiology is not identified by examination or MRI.

Recommendation: Emphasize that metabolic studies should be considered on an individual basis and that testing should not delay standard therapy.

#### **VI Clarification regarding age of onset**

Comment: The ILAE commission uses different ages for the age of onset within the proposal:

“Infantile Spasms Syndrome is characterized by onset of epileptic spasms between 3 and 12 months of age, although later onset may occur.”

“Infantile Spasms Syndrome typically has onset between 3-12 months, with a range of 1-24 months.”

Recommendation: Syndrome diagnosis for children age 2 months to 2 years.

#### **VII “Differential Diagnosis:”**

Recommendation: Please expand the list to include

-reflux/Sandifer syndrome

-startle

-Fejerman syndrome (as a separate entity from benign myoclonus of infancy)

#### **VIII Contributors:**

John R. Mytinger

Sonam Bhalla

Sonal Bhatia  
Fiona Baumer  
Harini Chellamani  
Krista Eschbach  
Erin M. Fedak Romanowski  
Zachary Grinspan  
Shaun Hussain  
Kelly Knupp  
John J. Millichap  
Sunil Naik  
Adam Numis  
Debopam Samanta  
Renee Shellhaas  
Rani Singh  
Deepa Sirsi  
Emily Spelbrink  
K. Liu Lin Thio  
Steven Wolf  
Christopher Yuskaitis  
Daniel Shrey

## References:

- Demarest, S.T., Shellhaas, R.A., Gaillard, W.D., Keator, C., Nickels, K.C., Hussain, S.A., Loddenkemper, T., Patel, A.D., Saneto, R.P., Wirrell, E., Sanchez Fernandez, I., Chu, C.J., Grinspan, Z., Wusthoff, C.J., Joshi, S., Mohamed, I.S., Stafstrom, C.E., Stack, C.V., Yozawitz, E., Bluvstein, J.S., Singh, R.K., Knupp, K.G., Pediatric Epilepsy Research, C., 2017. The impact of hypsarrhythmia on infantile spasms treatment response: Observational cohort study from the National Infantile Spasms Consortium. *Epilepsia* 58, 2098-2103.
- Fisher, R.S., Cross, J.H., D'Souza, C., French, J.A., Haut, S.R., Higurashi, N., Hirsch, E., Jansen, F.E., Lagae, L., Moshe, S.L., Peltola, J., Roulet Perez, E., Scheffer, I.E., Schulze-Bonhage, A., Somerville, E., Sperling, M., Yacubian, E.M., Zuberi, S.M., 2017. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia* 58, 531-542.
- Gaily, E., Liukkonen, E., Paetau, R., Rekola, R., Granstrom, M.L., 2001. Infantile spasms: diagnosis and assessment of treatment response by video-EEG. *Dev Med Child Neurol* 43, 658-667.
- Gastaut, H., 1970. International League Against Epilepsy: Clinical and Electroencephalographical Classification of Epileptic Seizures. *Epilepsia*, 102-113.
- Gibbs FA, G.E., 1952. Atlas of electroencephalography. Addison-Wesley, Cambridge, MA.
- Helbig, K.L., Farwell Hagman, K.D., Shinde, D.N., Mroske, C., Powis, Z., Li, S., Tang, S., Helbig, I., 2016. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genet Med* 18, 898-905.
- Hussain, S.A., Kwong, G., Millichap, J.J., Mytinger, J.R., Ryan, N., Matsumoto, J.H., Wu, J.Y., Lerner, J.T., Sankar, R., 2015. Hypsarrhythmia assessment exhibits poor interrater reliability: a threat to clinical trial validity. *Epilepsia* 56, 77-81.

ILAE, 1992. Commission on Pediatric Epilepsy of the International League Against Epilepsy: Workshop on Infantile Spasms. *Epilepsia* 33, 195.

Ko, A., Youn, S.E., Chung, H.J., Kim, S.H., Lee, J.S., Kim, H.D., Kang, H.C., 2018. Vigabatrin and high-dose prednisolone therapy for patients with West syndrome. *Epilepsy Res* 145, 127-133.

Mytinger, J., 2021. Definitions and diagnostic criteria for infantile spasms and West syndrome – Historical Perspectives and Practical Considerations. *Seminars in Pediatric Neurology* In Press.

Nordli, D.R., Jr., 2012. Epileptic encephalopathies in infants and children. *J Clin Neurophysiol* 29, 420-424.

Vendrame, M., Guilhoto, L.M., Loddenkemper, T., Gregas, M., Bourgeois, B.F., Kothare, S.V., 2012. Outcomes of epileptic spasms in patients aged less than 3 years: single-center United States experience. *Pediatr Neurol* 46, 276-280.

Wirrell, E.C., Shellhaas, R.A., Joshi, C., Keator, C., Kumar, S., Mitchell, W.G., Pediatric Epilepsy Research, C., 2015. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. *Epilepsia* 56, 617-625.

Yuskaitis, C.J., Ruzhnikov, M.R.Z., Howell, K.B., Allen, I.E., Kapur, K., Dlugos, D.J., Scheffer, I.E., Poduri, A., Sherr, E.H., 2018. Infantile Spasms of Unknown Cause: Predictors of Outcome and Genotype-Phenotype Correlation. *Pediatr Neurol* 87, 48-56.