

# Infantile Spasms: Opportunities to Improve Care

Ricka Messer, MD, PhD<sup>1</sup>  Kelly G. Knupp, MD, MSCS<sup>1</sup>

<sup>1</sup>Department of Pediatrics and Neurology, University of Colorado, Aurora, Colorado

Semin Neurol 2020;40:236–245.

Address for correspondence Kelly G. Knupp, MD, MSCS, Department of Pediatrics and Neurology, University of Colorado, Anschutz Campus, 13123 E 16th Avenue, Box 155, Aurora, CO 80045 (e-mail: Kelly.Knupp@childrenscolorado.org).

## Abstract

Infantile spasm (IS) is a distinct epilepsy syndrome characterized by epileptic spasms (the clinical seizure type) and hypsarrhythmia (the electrographic abnormality). IS is frequently accompanied by impaired neurodevelopment and is often associated with structural, genetic, or metabolic etiologies. Prompt treatment of this severe epileptic encephalopathy improves long-term outcomes but remains elusive in many situations. Despite common misconceptions, even patients with identified etiologies or preexisting developmental delay benefit from proven standard therapies, including adrenocorticotropic hormone (ACTH), oral corticosteroids, or vigabatrin. Treatment efficacy should be assessed with electroencephalography at 2 weeks, and an alternative therapy is indicated if epileptic spasms or hypsarrhythmia have not resolved. Collaboration with primary care providers is critical to mitigate the potentially serious adverse effects of standard treatments and also to provide developmental interventions. Although new approaches are on the horizon, addressing current challenges and opportunities now can dramatically improve patient outcomes.

## Keywords

- ▶ infantile spasms
- ▶ West syndrome
- ▶ adrenocorticotropic hormone
- ▶ prednisolone
- ▶ vigabatrin

Infantile spasm (IS) is a severe epileptic encephalopathy of early childhood that was first described in 1841.<sup>1</sup> Historically, the classic triad of West syndrome included clinical seizures (epileptic spasm, ES), an abnormal interictal electroencephalogram (EEG) pattern (hypsarrhythmia), and developmental issues. However, developmental delay and hypsarrhythmia are not always present at onset, which the International League Against Epilepsy (ILAE) seizure classification and West Delphi Consensus Statement recognized with broader definitions of IS, West syndrome, ES, and hypsarrhythmia (▶ **Table 1**).<sup>2,3</sup> The diagnosis of IS requires both a high index of suspicion and a prolonged EEG, and many resources are available to educate the public and providers about this unusual seizure type (▶ **Fig. 1**). Perhaps more than any other epilepsy syndrome, short- and long-term outcomes are influenced by time to treatment and choice of treatment. This review will highlight several opportunities for improvements in the care of children with IS (▶ **Table 2**).

Though one of the most common epilepsies of early childhood, IS has an incidence of only 0.01 to 0.58/1,000 live births.<sup>4–7</sup> IS predominately affects children less than 2 years

of age, with a peak onset of 3 to 7 months and only rare reports of age of onset up to 4 years of age.<sup>8–12</sup> The epidemiology of IS has been evaluated in several different populations, and a recent meta-analysis suggests that latitude may impact the incidence, but importantly, data from lower latitudes are scarce.<sup>5</sup> Gender differences have also been debated, though most studies suggest a slight preponderance in boys compared with girls.

## Seizure Description

Like other seizure types, ESs are paroxysmal, involuntary, repetitive, abnormal movements. The semiology is unique, with sudden contraction of the trunk and extremities lasting less than 1 second, but often occurring in clusters (▶ **Table 3**). ESs are frequently associated with sleep–wake transitions. Consciousness is not impaired, but the child may briefly cry or appear distressed after each spasm. Mimickers of ES include normal baby movements, exaggerated startle reflex, Sandifer syndrome (abnormal movements provoked by gastroesophageal reflux), benign sleep myoclonus, myoclonic seizures, focal seizures, and tonic seizures.<sup>13,14</sup>

Issue Theme Pediatric Neurology; Guest Editors, Kendall B. Nash, MD, and Nilika Shah Singhal, MD

Copyright © 2020 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.  
Tel: +1(212) 760-0888.

DOI <https://doi.org/10.1055/s-0040-1705121>.  
ISSN 0271-8235.

**Table 1** Proposed definitions of terms, modified from West Delphi Consensus and ILAE<sup>3,92</sup>

Term	Definition	Additional information
Infantile spasm (IS)	The epilepsy syndrome—children younger than 2 y with epileptic spasms, with or without hypsarrhythmia	Within the ILAE 2017 epilepsy classification, IS is an epileptic encephalopathy caused by various etiologies
West syndrome (WS)	The constellation of epileptic spasms and hypsarrhythmia, with or without developmental issues	Historically, developmental issues were a defining feature of WS, named after the first person to recognize the constellation of symptoms which were affecting his own child
Epileptic spasm (ES)	The seizure type	The term “ES” is preferable to the term IS when referring to the clinical seizures. ES can have focal motor onset, generalized motor onset, or unknown motor onset, but do not require a specified awareness
Hypsarrhythmia (“hyps”)	The abnormal interictal EEG pattern	This random, high-voltage pattern was first described by Gibbs and Gibbs in 1952

Abbreviations: EEG, electroencephalogram; ILAE, International League Against Epilepsy.

**Electroencephalogram Findings**

Prolonged EEG is required for the diagnosis of IS and helps differentiate between IS mimics. The characteristic EEG background pattern is hypsarrhythmia (►Fig. 2)—chaotic, asynchronous, and high-amplitude activity (often greater than 200 microvolts) with intermixed multifocal spikes.<sup>15</sup> Although hypsarrhythmia is considered a biomarker of IS, disagreement about the defining characteristics continues,<sup>3,16</sup> despite standardized grading tools focusing on quantifiable features such as the Burden of Amplitudes and Epileptiform Discharges (BASED) score (►Table 4).<sup>17</sup> The BASED score creates an objective scale to determine the features of hypsarrhythmia and has been shown to improve inter-rater reliability. Hypsarrhythmia is most likely to be seen during non-REM sleep. Most, but not

all, children with ES have hypsarrhythmia; studies report 52%<sup>18</sup> to 100%.<sup>8,19–21</sup> This variation is primarily due to inclusion of variants of hypsarrhythmia.<sup>22</sup> When hypsarrhythmia is not present, the EEG pattern is still markedly abnormal. If spells are not captured on the EEG, repeat EEG may be warranted if concerning spells continue to occur. Parental video of the spells may also help clarify the diagnosis.

During the seizure, the ictal EEG has a distinctive, diffuse high-amplitude slow wave with superimposed fast activity, followed by electrodecrement (diffuse attenuation), which may appear to be more normal activity (►Fig. 3). This “pseudo-normalization” can last for several seconds, even minutes. In addition to IS, other epilepsy syndromes, such as Ohtahara syndrome or early infantile myoclonic epilepsy, may have ES as



**Fig. 1** Pneumonic developed by the Infantile Spasms Action Network to improve awareness of infantile spasms.

**Table 2** Key opportunities and goals for improving the care of patients with IS

Opportunity	Goal
1. Make the diagnosis early <sup>a,b,c,d</sup>	Evaluate with prolonged EEG within 1–2 wk of symptom onset
2. Initiate treatment early <sup>a,b,c,d,e</sup>	Initiate treatment within 1 wk of diagnosis
3. Investigate the etiology <sup>a,c,d</sup>	Perform brain MRI within 4 wk of diagnosis; consider tiered genetic/metabolic testing
4. Choose a standard first-line treatment <sup>a,b,c,d,e,f,g</sup>	Treat with ACTH, oral corticosteroids, or vigabatrin (see ► <b>Table 5</b> )
5. Mitigate adverse side effects of treatments <sup>a,c,e,g</sup>	Monitor for hypertension and infection at least weekly (ACTH, OCS); obtain ophthalmologic evaluation every 3 mo (vigabatrin); see ► <b>Table 6</b>
6. Assess treatment efficacy <sup>a,b,c,d,e,g</sup>	Confirm that both clinical spasms <i>and</i> hypsarrhythmia have resolved with follow-up EEG at 2–3 wk
7. Change treatments if response is incomplete <sup>a,c,d</sup>	Switch to an alternative standard treatment. For IS refractory to two standard treatments, consider surgery and/or additional treatments (pyridoxine, ketogenic diet, typical antiseizure medications)
8. Monitor developmental outcomes <sup>c,d,e,g</sup>	Refer to early intervention services; assess every 6 mo

Abbreviations: ACTH, adrenocorticotropic hormone; EEG, electroencephalogram; ILAE, International League Against Epilepsy; IS, infantile spasm.

Sources for opportunities:

<sup>a</sup>U.S. Consensus Report.<sup>29</sup>

<sup>b</sup>AAN/CNS Guideline.<sup>37</sup>

<sup>c</sup>Quality of Care Indicators.<sup>27</sup>

<sup>d</sup>ILAE Recommendations.<sup>30</sup>

<sup>e</sup>AAN Quality Measures.<sup>28</sup>

<sup>f</sup>Cochrane Review.<sup>38</sup>

<sup>g</sup>AAN/CNS Practice Parameter MacKay.<sup>36</sup>

**Table 3** Distinguishing features of various types of clinical spasms

Clinical spasm type	Distinguishing features
Flexor spasms (“Jackknife seizures”)	The child may appear to do an abdominal “crunch”—the neck and trunk suddenly flex, the knees are pulled up, and the arms either come in toward the chest or, more commonly, stiffen and are flung outward
Extensor spasms	The child may throw the head back, arch the back, and stiffen and extend the arms and legs
Mixed extensor–flexor spasms	The child may show features of both types
Hemi-spasms	Only one side of the body is affected
Asymmetric spasms	These may mimic the asymmetric tonic posture reflex or otherwise affect the two sides of the body differently
Subtle spasms	The child may demonstrate isolated forceful head bobs, facial grimace, eye rolling, eye deviation, or brief staring

a seizure type, but these disorders have other EEG features, as well as a more concerning prognosis.

## Early Diagnosis and Treatment Impact Developmental Outcomes—Opportunities 1 and 2

Onset of ES is frequently preceded by developmental delays, plateau, or regression. A recent study found 90% of infants with IS had developmental delay at the time of presentation.<sup>23</sup> More than half had impaired social responsiveness, such as absent social smile, as well as auditory impairments, including poor response to voice. In addition, 44% displayed visual inattention, which caregivers may notice as a decrease in eye contact or tracking. Over time, the developmental

impact becomes more pronounced, and the child may lose head control, stop sitting, and become less interactive.

Fortunately, timely treatment, particularly within 7 to 30 days of ES onset, is associated with improved response to treatment and neurodevelopmental outcomes.<sup>13,24–26</sup> Thus, consensus quality improvement guidelines strongly recommend evaluation with prolonged EEG and treatment initiation as soon as possible, certainly within 1 to 2 weeks of presentation.<sup>27–30</sup>

## Take a Step-Wise Approach to the Etiologic Investigation—Opportunity 3

After the diagnosis of IS has been established, the etiology should be investigated, particularly since some causes may

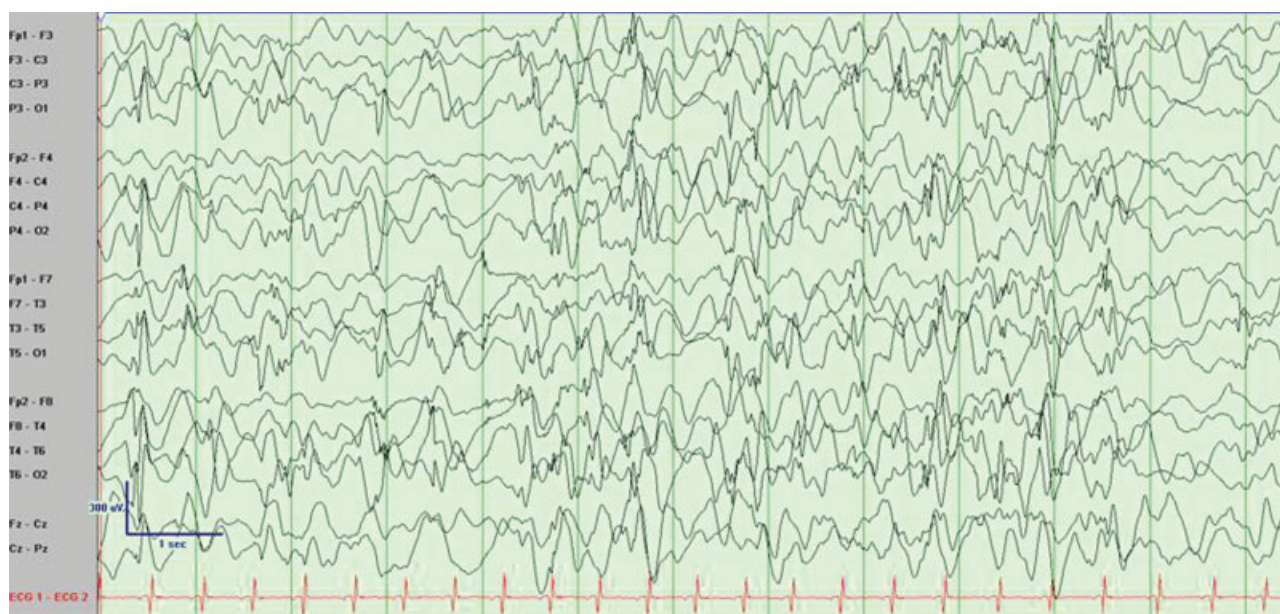


Fig. 2 Example of hypsarrhythmia.

Table 4 BASED score<sup>17</sup>

BASED score	Description
0	Normal
1	Any definite nonepileptiform abnormality
2	<3 spike foci and no common background slow waves $\geq 200 \mu\text{V}^{\text{a,b}}$
3	MFS <50% of one second bins <sup>c</sup> and no common background slow waves $\geq 200 \mu\text{V}^{\text{a,b}}$ or no MFS but common background slow waves $\geq 200 \mu\text{V}^{\text{a,b}}$
4 (Hyps <sup>d</sup> )	MFS <50% of one second bins <sup>c</sup> and common background slow waves $\geq 200 \mu\text{V}^{\text{a,b}}$
5 (Hyps <sup>d</sup> )	MFS $\geq 50\%$ of one second bins, <sup>c</sup> or Common background slow waves $\geq 300 \mu\text{V}^{\text{a,e}}$ in two or more bilateral head regions

Abbreviations: BASED, Burden of Amplitudes and Epileptiform Discharges; MFS, multifocal spikes—at least three different foci;  $\mu\text{V}$ , microvolts.

<sup>a</sup>Peak-to-peak amplitude on a longitudinal bipolar montage, refers to background slow waves and excludes (1) the slow wave associated with a preceding spike, (2) hypnagogic patterns, and (3) arousal rhythms.

<sup>b</sup>May be one or more head regions, must be a common finding, may be regional (e.g., left posterior), and may exist in the presence of other lower amplitude background activities.

<sup>c</sup>The percentage of one second bins that include one or more spikes in the most severely abnormal 5-minute epoch (i.e., the epoch that gives the highest BASED score).

<sup>d</sup>To determine the presence or absence of hypsarrhythmia, findings should be representative of the most severely abnormal 5-minute epoch of the study (i.e., the epoch that gives the highest BASED score); a score of 4 or 5 suggests electrographic evidence of hypsarrhythmia.

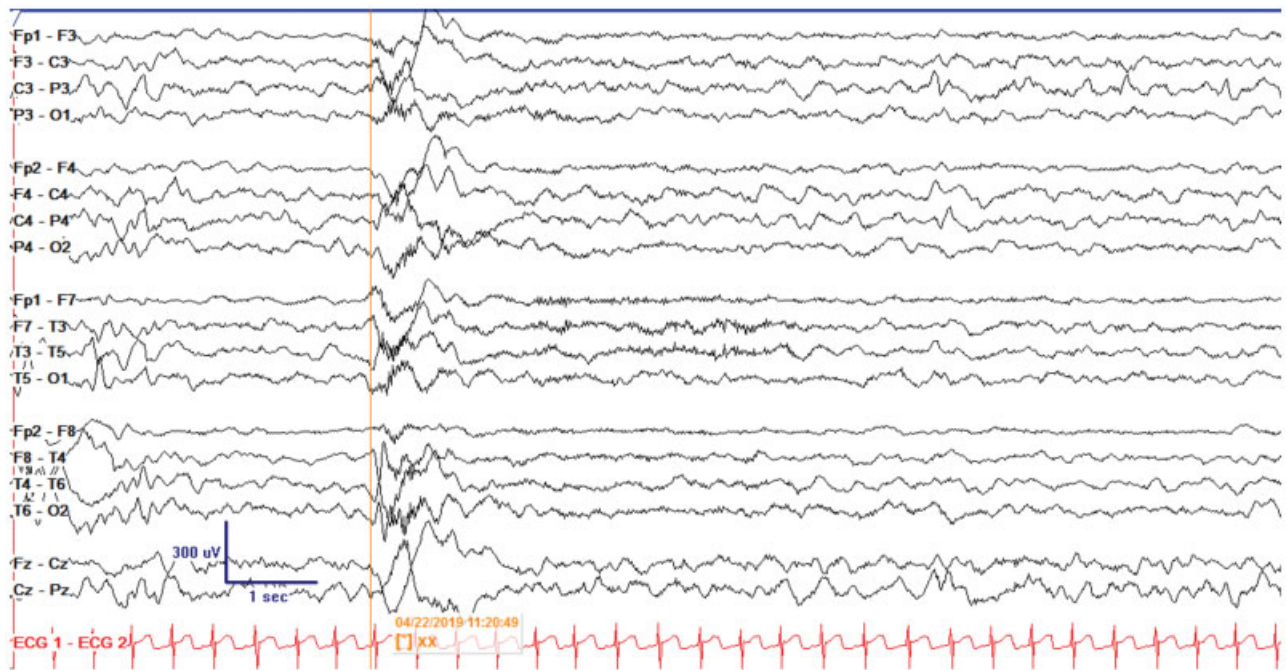
<sup>e</sup>Must be two of the following: bilateral frontal, bilateral temporal, bilateral parietal, and bilateral occipital; must be a common finding.

benefit from specialized treatment (► Table 5).<sup>27,29–31</sup> Many speculate that brain dysfunction from essentially any cause early in life may converge into a “final common pathway” that ultimately results in the development of IS. Indeed, more than 200 conditions are known to be associated with IS.

The combination of history, physical exam, and early imaging yields a diagnosis in 40 to 55% of cases.<sup>32,33</sup> Patients with disorders such as tuberous sclerosis complex, Trisomy 21, and Menkes disease have high rates of IS, and may have notable physical exam findings, such as ash leaf spots (identified most easily with a Wood’s lamp), syndromic facies, or unusually brittle hair. Structural causes, such as brain malformations, traumatic brain injury, hypoxic-ischemic encephalopathy, and congenital cytomegalovirus account for roughly 40% of cases,

including 20% with acquired brain injury.<sup>32–34</sup> Thus, brain MRI is strongly recommended for the initial diagnostic evaluation of patients with IS, and additional testing can be deferred, unless syndromic features, concerning symptoms, or metabolic derangements are also present.

If imaging is uninformative, chromosomal microarray/comparative genomic hybridization, followed by an epilepsy gene panel if needed, as well as serum lactate, serum amino acids, and urine organic acids are recommended. Genetic testing demonstrates an etiology in 23% of those without imaging findings.<sup>32</sup> Various inborn errors of metabolism, including GLUT1 deficiency, pyridoxine-dependent seizures, phenylketonuria, nonketotic hyperglycinemia, and methylmalonic aciduria continue to be reported as rare but potentially treatable



**Fig. 3** Example of electroencephalogram findings during an epileptic spasm.

**Table 5** Comparison of standard first-line IS treatments

Treatment	Efficacy	Logistics	Side effects (see ▶Table 6)
ACTH	ILAE: "preferred treatment" Short-term response: 76–87% 3-mo response: 55% Risk of relapse: likely less	Cost: \$\$\$ + admission Dosing: intramuscular injections, 150 units/m <sup>2</sup> /d for 2 wk, 2-wk taper Other: specialty pharmacy	Mild-moderate: irritability, increased appetite, weight gain, poor sleep, stomach ulcers, hypertension, hyperglycemia Severe: infection, cardiomyopathy, adrenal crisis
Oral corticosteroids (prednisolone)	ILAE: "probably effective" Short-term response: 63–80% 3-mo response: 39% Risk of relapse: possibly higher than ACTH	Cost: \$, no admission Dosing: oral liquid, 4–8 mg/kg/d (max 60 mg) for 2 wk, 2-wk taper Other: any retail pharmacy	
Vigabatrin	ILAE: "possibly effective, especially for TSC" Short-term response: 35–54% 3-mo response: 36% Risk of relapse: higher than ACTH	Cost: \$\$ +/- admission Dosing: powder mixed into oral liquid, increased from 50 to 150 mg/kg/d over 7–14 d, then 3–12 mo Other: specialty pharmacy and REMS enrollment	Mild-moderate: poor sleep, drowsiness, hypotonia, behavioral changes, irreversible MRI changes Severe: irreversible peripheral vision loss

Abbreviations: ACTH, adrenocorticotropic hormone; ILAE, International League Against Epilepsy; REMS, Risk Evaluation and Mitigation Service; TSC, tuberous sclerosis.

causes of IS, although patients with the newly recognized "IS-associated gene" disruptions, such as ARX (Aristaless-related homeobox) and CDKL5 (cyclin-dependent kinase-like 5), and STXBP1 (syntaxin-binding protein 1), may be much more likely to develop IS.<sup>31,35</sup> Third/fourth tier testing could include novel gene testing or repeat brain MRI, since advances in genetic technology occur rapidly, and ongoing myelination may permit visualization of small abnormalities. Despite exhaustive evaluations, a definitive etiology is not found in 30 to 50% of children.

### Offer an Effective Standard Treatment—Opportunity 4

Unlike other epilepsy types, the efficacy of IS treatment is determined with an "all-or-none" approach that requires

both cessation of ES and resolution of hypsarrhythmia, thus requiring a repeat EEG within 2 to 3 weeks of treatment initiation.<sup>3,27,36</sup> Partial reduction of ES frequency or cessation of ES with persistence of hypsarrhythmia is considered treatment failure.

IS responds poorly to typical antiseizure medications. Currently, adrenocorticotropic hormone (ACTH), oral corticosteroids (OCS), and vigabatrin are the only identified "possibly" or "probably effective" therapies for IS (▶Table 5).<sup>28,30,37</sup> Importantly, comparing treatment efficacy has been confounded by evolving dosing regimens and outcome measures, and most guidelines were published prior to several recent clinical studies. Although the 2012 American Academy of Neurology/Child Neurology Society guidelines found insufficient evidence to support short-term efficacy of OCS, they agreed with the ILAE

consensus and Cochrane review that hormonal treatment with either ACTH or OCS improved long-term outcomes compared with vigabatrin, particularly for children with an unknown etiology.<sup>30,37,38</sup> Furthermore, increasing the percentage of children with IS who receive ACTH, OCS, or vigabatrin as a first-line agent was identified as a key quality improvement metric by the 2018 Child Neurology Quality Measurement Set Workgroup.<sup>28</sup> The 2016 National Infantile Spasms Consortium (NISC) observational study of more than 230 patients found that the most important determinant of response to treatment was utilizing any one of these three treatments as the first-line agent, regardless of etiology, prior developmental delay, or presence of hypsarrhythmia.<sup>20,39</sup>

### Steroid/Hormonal Treatments (ACTH and OCS)

Steroid/hormonal medications, including ACTH and OCS, have been used since the 1950s.<sup>40,41</sup> Some speculate that the hypothalamic–pituitary–adrenal axis is dysregulated in the pathophysiology of IS, possibly due to stress, and that ACTH may have additional neuromodulatory properties compared with OCS.<sup>42,43</sup> Synthetic and naturally derived ACTH have similar efficacy, with 2-week response rates of 76 to 87% in controlled trials, though a direct comparison has not occurred.<sup>44,45</sup> The high cost and poor availability of ACTH have fueled the pursuit of alternative hormonal treatments, including OCS, though the comparative efficacy between ACTH and OCS is debated. Early studies using low-dose OCS (1–2 mg/kg/day) demonstrated inferior efficacy compared with ACTH,<sup>45,46</sup> whereas recent studies of high-dose OCS (4–8 mg/kg/day) have found response rates of 63 to 80%, similar to ACTH.<sup>44,47–49</sup>

### Vigabatrin

Vigabatrin is a specific inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for metabolizing GABA at the synapse. Short-term response rates to vigabatrin range from 35 to 54%, significantly lower than hormonal treatments; however, the 14-day assessment point of most studies may not sufficiently account for the longer titration period of vigabatrin.<sup>44,50–53</sup> Although long-term outcomes were similar between vigabatrin and hormonal treatments across all etiologies, hormonal therapies were associated with improved development in children with unknown etiologies.<sup>54</sup> Interestingly, in patients with tuberous sclerosis complex, vigabatrin is more efficacious than steroids and is, therefore, the treatment of choice.<sup>51,55</sup>

### Alternative Treatments

Although other IS treatments have been investigated, in general, these studies have small sample sizes, inadequate primary outcome measures, or lack of randomization. Some therapies show promise as first-line treatment when standard treatment options are not possible. A small prospective study of the ketogenic diet as initial treatment for IS demonstrated a 2-week clinical response rate of 56%, all of whom had normal EEGs at 6 months.<sup>56</sup> The efficacy of pyridoxine as a first-line agent has not been clearly established, despite frequent use at some centers. Early studies with topiramate showed a 28 to

45% response rate at 3 months; however, a newer study found only a 9.7% response rate, and all relapsed.<sup>57–59</sup> Interestingly, a recent randomized controlled study of zonisamide found a 20% clinical and electrographic response rate at 2 weeks.<sup>60</sup> Other typical antiseizure medications have been trialed throughout the years. Two small prospective studies found levetiracetam was effective in 14 to 40% of patients.<sup>61,62</sup> A retrospective study of sodium valproate with or without a benzodiazepine demonstrated ES cessation in 45.8%,<sup>63</sup> though use of valproate acid is often avoided in young children due to concern for POLG pathogenic variants. Overall, the NISC study grouped all non-standard treatments, including the ketogenic diet, topiramate, zonisamide, clobazam, clonazepam, valproic acid, phenobarbital, oxcarbazepine, and levetiracetam, into a single “other” category, and found response rates of 22% at 2 weeks and only 9% (3/32) at 3 months.<sup>39</sup>

### Mitigate the Side Effects of Treatments—Opportunity 5

All three standard treatments carry significant risk of serious side effects (▶ **Table 5**).<sup>36</sup> The Children’s Hospital Colorado clinical pathway outlines one institution’s approach to recommended surveillance and treatment (▶ **Table 6**). In some studies, more than half of patients with IS treated with steroid/hormonal medications experienced adverse effects, such as irritability, hypertension, and infection, which may require medical intervention.<sup>48,64</sup> Although 34 to 52% of all patients treated with vigabatrin were found to have permanent visual field loss, the incidence of clinically significant visual impairment may be less than 4% in the IS population.<sup>65–67</sup> Nonetheless, in the United States, vigabatrin initiation requires enrollment in a Risk Evaluation and Mitigation Service (REMS) program, and frequent ophthalmologic evaluations are recommended. Some concerns remain about the clinical significance of vigabatrin-associated reversible MRI changes, though these have not been definitively associated with any symptom, including movement disorders.<sup>64,68,69</sup>

### Assess Treatment Efficacy and, if Needed, Switch to an Alternative Treatment—Opportunities 6 and 7

Prolonged repeat EEG 2 to 3 weeks after treatment initiation is strongly recommended.<sup>27,29</sup> If ES or hypsarrhythmia persists, then the first medication should be weaned while a second medication is started.<sup>27</sup> The NISC study found that children who failed an initial standard treatment had a 55% response rate when given another standard treatment with a different mechanism of action.<sup>26</sup> A similar approach is likely warranted for IS recurrence, defined as recurrence of ES, which occurs in 30 to 50% of patients.

The best approach after two standard medications have failed is not clear, but in general, additional therapy trials and ongoing reassessment of efficacy are recommended.<sup>30,70</sup> The ketogenic diet is another important consideration, with one study demonstrating a 37% clinical response rate at 6 months, most of who had failed standard treatments.<sup>56</sup> Typical

**Table 6** Strategies for mitigating side effects of hormonal treatments and vigabatrin

Hormonal treatments	
Irritability, increased appetite, and poor sleep	Provide anticipatory guidance and coping strategies
Complex treatment plan and high risk of side effects	Neurology nurse phone call within 1 wk Primary care provider monitors weight, blood/urine glucose, and hypertension (defined as SBP > 95th% × 3 d) twice a week
Stomach irritation/ulcer	Prescribe histamine blockers (such as ranitidine) or proton pump inhibitors (such as omeprazole) for duration of treatment
Infection—Part 1: Pretreatment screening	Assess for any signs/symptoms of infection. If the patient has tuberculosis risk factors, place purified protein derivative skin test (Quantiferon gold is not accurate in infants)
Infection: Part 2—During treatment and for 2–3 mo after	Avoid live vaccines; defer other vaccines if possible. Prescribe antibiotic prophylaxis (sulfamethoxazole/trimethoprim) × 8 wk. Counsel caregivers to avoid sick contacts and monitor for thrush. Evaluate child immediately for any sick symptoms
Adrenal suppression	Consider stress dose steroids for any illness, surgery, or other physical stressor. Provide caregivers with a letter explaining possible need for stress dose steroids during treatment and for 2–3 mo after
Hypertension management—Part 1: Electrolyte disturbances	Obtain electrolyte levels within 24 h of HTN diagnosis. If hypokalemia, alkalosis, or hypernatremia is found, obtaining endocrinology input, evaluation for cardiac arrhythmia, and initiation of a diuretic (rather than propranolol) may be needed
Hypertension management—Part 2: Risk of cardiomyopathy	Initiate propranolol within 24 h of diagnosis of HTN and refer patient to nephrology for further HTN management. Obtain ECHO within 1 wk. If ECHO is abnormal, urgent cardiology evaluation is warranted. Weaning steroids is typically not recommended
Hyperglycemia management	Refer to endocrinology for possible initiation of insulin
Vigabatrin	
Irritability, poor sleep	Provide anticipatory guidance and coping strategies
Sedation, lethargy, hypotonia	Evaluate child immediately if feeding is impacted or caregivers are concerned. Consider increasing the vigabatrin dose more slowly
Risk of permanent vision loss	Enroll child in the REMS program. Obtain ophthalmology evaluation within 4 wk of treatment initiation, every 3 mo during treatment, and 3 mo after completing treatment. Monitor for signs of worsening vision, such as being easily startled
Reversible MRI abnormalities	Counsel caregivers about the potential risk; report possible associated symptoms to REMS

Abbreviations: ECHO, echocardiography; HTN, hypertension; MRI, magnetic resonance imaging; REMS, Risk Evaluation and Mitigation Service; SBP, spontaneous bacterial peritonitis.

anticonvulsants, such as topiramate, zonisamide, or clobazam, are often utilized as third- and fourth-line agents. One study evaluated whether topiramate or zonisamide could prevent IS recurrence when given for several months after initial treatment with standard therapies, but found that neither was effective.<sup>71</sup> Epilepsy surgery has been used with great success in appropriately chosen children with focal etiologies for seizures, but is not recommended as first-line therapy due to the lengthy surgical evaluation process and risks associated with surgical intervention.<sup>72,73</sup> Children with focal findings on imaging, EEG, and/or asymmetric clinical spasms might be considered as a candidate for surgical evaluation. Corpus callosotomy maybe an option in children without focal imaging abnormalities.<sup>74</sup> Careful evaluation should occur urgently in an appropriate epilepsy center, as outcome may be improved with earlier treatment.

### Improving Long-Term Outcomes—Opportunity 8

Although short-term efficacy focuses on resolution of ES and hypsarrhythmia, ultimately, the goal of therapy is to improve

long-term outcomes, such as neurodevelopment and subsequent epilepsy. Several studies indicate that 11 to 60% of patients experience other seizure types later in life,<sup>19,75–80</sup> with almost one-third presenting by the age of 1 year. Evolution into Lennox–Gastaut syndrome has been reported in approximately 25% of infants with IS; identifying any etiology and children of older age at diagnosis both are known risk factors.<sup>10,81,82</sup>

Intellectual impairment is often the primary concern for both parents and providers. Fewer than 10% of children with prenatal and perinatal etiologies have normal intellectual outcomes,<sup>83</sup> compared with 41 to 57% of those without prior developmental delay and unknown etiologies.<sup>19,82,84</sup> One long-term study evaluated specific developmental domains, and found 30% with visual impairment and severe cerebral palsy in 45%, though 42% of children were able to ambulate.<sup>19</sup> Psychiatric disorders and autism as long-term outcomes have not been well studied, but one study found psychiatric disorders in 28% of children.<sup>19</sup> Autism has been reported in 13 to 33%.<sup>85,86</sup> All children with IS should be referred for early intervention evaluation, and many children may benefit from multidisciplinary care from rehabilitation providers, neuropsychologists,

social work, and developmental pediatricians.<sup>87</sup> Ongoing improvements in supportive care have already impacted mortality rates in children with IS, which historically reached 15% by 11 years, but more recent cohorts have reported 5 to 8%.<sup>4</sup>

### Recent Updates and Future Directions

Ongoing research focuses on several aspects of the disease, including identification of IS risk factors, determining best treatment paradigms with current medications, evaluating new treatments, understanding risk factors for poor outcomes, and determining the full spectrum of long-term outcomes. An exciting recent study evaluated the efficacy of combination treatment with hormonal therapy (ACTH or OCS) and vigabatrin, finding that short-term outcomes were improved in those receiving combination therapy.<sup>64</sup> A second study investigating combination treatment is currently enrolling in the United States (NCT03347526), though some centers have already adopted dual treatment approaches.<sup>88</sup> A team science approach to developing new animal models for IS was recently an initiative of Citizens United for Research in Epilepsy (CURE; <https://www.cureepilepsy.org>), leading to several new animal models. Ongoing studies seek to determine if transcranial direct stimulation,<sup>89</sup> cannabidiol (CBD; NCT034211496), AQB-565 (a novel fusion peptide derived from ACTH),<sup>90</sup> or CPP-115 (a vigabatrin analogue)<sup>91</sup> could be effective. Future research may also address treatment of subpopulations, such as those without hypsarrhythmia, or hypsarrhythmia without clinical spasms, and also to determine the appropriate duration of treatment. A consistent theme in the research to date is that the most important opportunity to improve outcomes is rapid treatment with appropriate medication.

#### Conflict of Interest

K.G.K. reports other funding from Zogenix, West Therapeutics, Biomarin, Biocodex, and GW Pharma, and grants from Pediatric Epilepsy Research Fund, and Colorado Department of Public Health and Environment, outside the submitted work. R.M. reports grants from West Therapeutics, Inc and Pediatric Epilepsy Research Consortium (PERC), during the conduct of the study.

### References

- 1 West W. On a particular form of infantile convulsions. *Lancet* 1841;1:724–725
- 2 Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58(04):522–530
- 3 Lux AL, Osborne JP. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group. *Epilepsia* 2004;45(11):1416–1428
- 4 Trevathan E, Murphy CC, Yeargin-Allsopp M. The descriptive epidemiology of infantile spasms among Atlanta children. *Epilepsia* 1999;40(06):748–751
- 5 Jia JL, Chen S, Sivarajah V, Stephens D, Cortez MA. Latitudinal differences on the global epidemiology of infantile spasms: systematic review and meta-analysis. *Orphanet J Rare Dis* 2018;13(01):216

- 6 Cowan LD, Hudson LS. The epidemiology and natural history of infantile spasms. *J Child Neurol* 1991;6(04):355–364
- 7 Riikonen R. Epidemiological data of West syndrome in Finland. *Brain Dev* 2001;23(07):539–541
- 8 Kurokawa T, Goya N, Fukuyama Y, Suzuki M, Seki T, Ohtahara S. West syndrome and Lennox-Gastaut syndrome: a survey of natural history. *Pediatrics* 1980;65(01):81–88
- 9 Riikonen R, Donner M. ACTH therapy in infantile spasms: side effects. *Arch Dis Child* 1980;55(09):664–672
- 10 Bednarek N, Motte J, Soufflet C, Plouin P, Dulac O. Evidence of late-onset infantile spasms. *Epilepsia* 1998;39(01):55–60
- 11 Donat JF, Wright FS. Simultaneous infantile spasms and partial seizures. *J Child Neurol* 1991;6(03):246–250
- 12 Talwar D, Baldwin MA, Hutzler R, Griesemer DA. Epileptic spasms in older children: persistence beyond infancy. *Epilepsia* 1995;36(02):151–155
- 13 Auvin S, Hartman AL, Desnoux B, et al. Diagnosis delay in West syndrome: misdiagnosis and consequences. *Eur J Pediatr* 2012;171(11):1695–1701
- 14 Hussain SA, Lay J, Cheng E, Weng J, Sankar R, Baca CB. Recognition of infantile spasms is often delayed: the ASSIST study. *J Pediatr* 2017;190:215–221.e1
- 15 Gibbs FA, Gibbs EL. *Atlas of Electroencephalography*. Reading, MA: Addison-Wesley; 1952
- 16 Hussain SA, Kwong G, Millichap JJ, et al. Hypsarrhythmia assessment exhibits poor interrater reliability: a threat to clinical trial validity. *Epilepsia* 2015;56(01):77–81
- 17 Mytinger JR, Hussain SA, Islam MP, et al. Improving the inter-rater agreement of hypsarrhythmia using a simplified EEG grading scale for children with infantile spasms. *Epilepsy Res* 2015;116:93–98
- 18 Granström ML, Gaily E, Liukkonen E. Treatment of infantile spasms: results of a population-based study with vigabatrin as the first drug for spasms. *Epilepsia* 1999;40(07):950–957
- 19 Riikonen R. A long-term follow-up study of 214 children with the syndrome of infantile spasms. *Neuropediatrics* 1982;13(01):14–23
- 20 Demarest ST, Shellhaas RA, Gaillard WD, et al; Pediatric Epilepsy Research Consortium. The impact of hypsarrhythmia on infantile spasms treatment response: observational cohort study from the National Infantile Spasms Consortium. *Epilepsia* 2017;58(12):2098–2103
- 21 Howitz P, Platz P. Infantile spasms and HLA antigens. *Arch Dis Child* 1978;53(08):680–682
- 22 Hrachovy RA, Frost JD Jr, Kellaway P. Hypsarrhythmia: variations on the theme. *Epilepsia* 1984;25(03):317–325
- 23 Sumanasena SP, Wanigasinghe J, Arambepola C, Sri Ranganathan S, Muhandiram E. Developmental profile at initial presentation in children with infantile spasms. *Dev Med Child Neurol* 2019;61(11):1295–1301
- 24 O'Callaghan FJ, Lux AL, Darke K, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. *Epilepsia* 2011;52(07):1359–1364
- 25 O'Callaghan FJK, Edwards SW, Alber FD, et al; International Collaborative Infantile Spasms Study (ICISS) investigators. Vigabatrin with hormonal treatment versus hormonal treatment alone (ICISS) for infantile spasms: 18-month outcomes of an open-label, randomised controlled trial. *Lancet Child Adolesc Health* 2018;2(10):715–725
- 26 Knupp KG, Leister E, Coryell J, et al; Pediatric Epilepsy Research Consortium. Response to second treatment after initial failed treatment in a multicenter prospective infantile spasms cohort. *Epilepsia* 2016;57(11):1834–1842
- 27 Wang CJ, Jonas R, Fu CM, Ng CY, Douglass L. Quality-of-care indicators for infantile spasms. *J Child Neurol* 2013;28(01):13–20
- 28 Patel AD, Berg AT, Billingshurst L, et al. Quality improvement in neurology: Child neurology quality measure set: executive summary. *Neurology* 2018;90(02):67–73



- 29 Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. *Epilepsia* 2010;51(10):2175–2189
- 30 Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. *Epilepsia* 2015;56(08):1185–1197
- 31 Paciorkowski AR, Thio LL, Dobyns WB. Genetic and biologic classification of infantile spasms. *Pediatr Neurol* 2011;45(06):355–367
- 32 Wirrell EC, Shellhaas RA, Joshi C, Keator C, Kumar S, Mitchell WG; Pediatric Epilepsy Research Consortium. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. *Epilepsia* 2015;56(04):617–625
- 33 Poulat AL, Lesca G, Sanlaville D, et al. A proposed diagnostic approach for infantile spasms based on a spectrum of variable aetiology. *Eur J Paediatr Neurol* 2014;18(02):176–182
- 34 Osborne JP, Lux AL, Edwards SW, et al. The underlying etiology of infantile spasms (West syndrome): information from the United Kingdom Infantile Spasms Study (UKISS) on contemporary causes and their classification. *Epilepsia* 2010;51(10):2168–2174
- 35 Salar S, Moshé SL, Galanopoulou AS. Metabolic etiologies in West syndrome. *Epilepsia Open* 2018;3(02):134–166
- 36 Mackay MT, Weiss SK, Adams-Webber T, et al; American Academy of Neurology; Child Neurology Society. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. *Neurology* 2004;62(10):1668–1681
- 37 Go CY, Mackay MT, Weiss SK, et al; Child Neurology Society; American Academy of Neurology. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2012;78(24):1974–1980
- 38 Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. *Cochrane Database Syst Rev* 2013;(06):CD001770
- 39 Knupp KG, Coryell J, Nickels K, et al; Pediatric Epilepsy Research Consortium. Response to treatment in a prospective national infantile spasms cohort. *Ann Neurol* 2016;79(03):475–484
- 40 Low NL. Infantile spasms with mental retardation. II. Treatment with cortisone and adrenocorticotropin. *Pediatrics* 1958;22(06):1165–1169
- 41 Sorel L, Dusaucy-Bauloye A. [Findings in 21 cases of Gibbs' hypsarrhythmia; spectacular effectiveness of ACTH]. *Acta Neurol Psychiatr Belg* 1958;58(02):130–141
- 42 Brunson KL, Eghbal-Ahmadi M, Baram TZ. How do the many etiologies of West syndrome lead to excitability and seizures? The corticotropin releasing hormone excess hypothesis. *Brain Dev* 2001;23(07):533–538
- 43 Jaseja H, Jaseja B, Badaya S, Tonpay P. Superior therapeutic efficacy of adrenocorticotrophic hormone (ACTH) in infantile spasms: emerging evidence. *Epilepsy Behav* 2012;25(02):250
- 44 Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. *Lancet* 2004;364(9447):1773–1778
- 45 Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. *Pediatrics* 1996;97(03):375–379
- 46 Hrachovy RA, Frost JD Jr, Kellaway P, Zion TE. Double-blind study of ACTH vs prednisone therapy in infantile spasms. *J Pediatr* 1983;103(04):641–645
- 47 Hussain SA, Shinnar S, Kwong G, et al. Treatment of infantile spasms with very high dose prednisolone before high dose adrenocorticotrophic hormone. *Epilepsia* 2014;55(01):103–107
- 48 Yi ZS, Wu HP, Yu XY, Chen Y, Zhong JM. Efficacy and tolerability of high-dose prednisone in Chinese children with infantile spasms. *Brain Dev* 2015;37(01):23–28
- 49 Gonzalez-Giraldo E, Stafstrom CE, Stanfield AC, Kossoff EH. Treating infantile spasms with high-dose oral corticosteroids: a retrospective review of 87 children. *Pediatr Neurol* 2018;87:30–35
- 50 Chiron C, Dulac O, Beaumont D, Palacios L, Pajot N, Mumford J. Therapeutic trial of vigabatrin in refractory infantile spasms. *J Child Neurol* 1991(Suppl 2):S52–S59
- 51 Vigeveno F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study. *Epilepsia* 1997;38(12):1270–1274
- 52 Appleton RE, Peters AC, Mumford JP, Shaw DE. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. *Epilepsia* 1999;40(11):1627–1633
- 53 Elterman RD, Shields WD, Mansfield KA, Nakagawa J; US Infantile Spasms Vigabatrin Study Group. Randomized trial of vigabatrin in patients with infantile spasms. *Neurology* 2001;57(08):1416–1421
- 54 Lux AL, Edwards SW, Hancock E, et al; United Kingdom Infantile Spasms Study. The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *Lancet Neurol* 2005;4(11):712–717
- 55 Chiron C, Dumas C, Jambaqué I, Mumford J, Dulac O. Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. *Epilepsy Res* 1997;26(02):389–395
- 56 Hong AM, Turner Z, Hamdy RF, Kossoff EH. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. *Epilepsia* 2010;51(08):1403–1407
- 57 Glauser TA, Clark PO, Strawsburg R. A pilot study of topiramate in the treatment of infantile spasms. *Epilepsia* 1998;39(12):1324–1328
- 58 Zou LP, Lin Q, Qin J, Cai FC, Liu ZS, Mix E; Topiramate Study Group. Evaluation of open-label topiramate as primary or adjunctive therapy in infantile spasms. *Clin Neuropharmacol* 2008;31(02):86–92
- 59 Weber A, Cole JW, Mytinger JR. Infantile spasms respond poorly to topiramate. *Pediatr Neurol* 2015;53(02):130–134
- 60 Angappan D, Sahu JK, Malhi P, Singhi P. Safety, tolerability, and effectiveness of oral zonisamide therapy in comparison with intramuscular adrenocorticotrophic hormone therapy in infants with West syndrome. *Eur J Paediatr Neurol* 2019;23(01):136–142
- 61 Gümüş H, Kumandaş S, Per H. Levetiracetam monotherapy in newly diagnosed cryptogenic West syndrome. *Pediatr Neurol* 2007;37(05):350–353
- 62 Mikati MA, El Banna D, Sinno D, Mroueh S. Response of infantile spasms to levetiracetam. *Neurology* 2008;70(07):574–575
- 63 Auvichayapat N, Tassniyom S, Treerophon S, Auvichayapat P. Treatment of infantile spasms with sodium valproate followed by benzodiazepines. *J Med Assoc Thai* 2007;90(09):1809–1814
- 64 O'Callaghan FJ, Edwards SW, Alber FD, et al; Participating Investigators. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. *Lancet Neurol* 2017;16(01):33–42
- 65 Maguire MJ, Hemming K, Wild JM, Hutton JL, Marson AG. Prevalence of visual field loss following exposure to vigabatrin therapy: a systematic review. *Epilepsia* 2010;51(12):2423–2431
- 66 Westall CA, Wright T, Cortese F, Kumarappah A, Snead OC III, Buncic JR. Vigabatrin retinal toxicity in children with infantile spasms: an observational cohort study. *Neurology* 2014;83(24):2262–2268
- 67 Schwarz MD, Li M, Tsao J, et al. A lack of clinically apparent vision loss among patients treated with vigabatrin with infantile spasms: the UCLA experience. *Epilepsy Behav* 2016;57(Pt A):29–33
- 68 Hussain SA, Tsao J, Li M, et al. Risk of vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent. *Epilepsia* 2017;58(04):674–682
- 69 Fong CY, Osborne JP, Edwards SW, et al. An investigation into the relationship between vigabatrin, movement disorders, and brain magnetic resonance imaging abnormalities in children with infantile spasms. *Dev Med Child Neurol* 2013;55(09):862–867

- 70 Fedak EM, Patel AD, Heyer GL, Wood EG, Mytinger JR. Optimizing care with a standardized management protocol for patients with infantile spasms. *J Child Neurol* 2015;30(10):1340–1342
- 71 Rajaraman RR, Lay J, Alayari A, Anderson K, Sankar R, Hussain SA. Prevention of infantile spasms relapse: zonisamide and topiramate provide no benefit. *Epilepsia* 2016;57(08):1280–1287
- 72 Chipaux M, Dorfmüller G, Fohlen M, et al. Refractory spasms of focal onset—a potentially curable disease that should lead to rapid surgical evaluation. *Seizure* 2017;51:163–170
- 73 Chugani HT, Ilyas M, Kumar A, et al. Surgical treatment for refractory epileptic spasms: the Detroit series. *Epilepsia* 2015;56(12):1941–1949
- 74 Baba H, Toda K, Ono T, Honda R, Baba S. Surgical and developmental outcomes of corpus callosotomy for West syndrome in patients without MRI lesions. *Epilepsia* 2018;59(12):2231–2239
- 75 Glaze DG, Hrachovy RA, Frost JD Jr, Kellaway P, Zion TE. Prospective study of outcome of infants with infantile spasms treated during controlled studies of ACTH and prednisone. *J Pediatr* 1988;112(03):389–396
- 76 Primec ZR, Kopac S, Neubauer D. Epidemiologic features of infantile spasms in Slovenia. *Epilepsia* 2002;43(02):183–187
- 77 Dulac O, Plouin P, Jambaqué I. Predicting favorable outcome in idiopathic West syndrome. *Epilepsia* 1993;34(04):747–756
- 78 Ito M, Aiba H, Hashimoto K, et al. Low-dose ACTH therapy for West syndrome: initial effects and long-term outcome. *Neurology* 2002;58(01):110–114
- 79 Hwang YS; Korean Child Neurology Society. National survey on West syndrome in Korea. *Brain Dev* 2001;23(07):565–569
- 80 Matsuo A, Matsuzaka T, Tsuru A, et al. Epidemiological and clinical studies of West syndrome in Nagasaki Prefecture, Japan. *Brain Dev* 2001;23(07):575–579
- 81 Lombroso CT. A prospective study of infantile spasms: clinical and therapeutic correlations. *Epilepsia* 1983;24(02):135–158
- 82 Rantala H, Putkonen T. Occurrence, outcome, and prognostic factors of infantile spasms and Lennox-Gastaut syndrome. *Epilepsia* 1999;40(03):286–289
- 83 Matsumoto A, Watanabe K, Negoro T, et al. Infantile spasms: etiological factors, clinical aspects, and long term prognosis in 200 cases. *Eur J Pediatr* 1981;135(03):239–244
- 84 Sidenvall R, Eeg-Olofsson O. Epidemiology of infantile spasms in Sweden. *Epilepsia* 1995;36(06):572–574
- 85 Riikonen R, Amnell G. Psychiatric disorders in children with earlier infantile spasms. *Dev Med Child Neurol* 1981;23(06):747–760
- 86 Askalan R, Mackay M, Brian J, et al. Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms. *J Child Neurol* 2003;18(03):165–170
- 87 Wheless JW, Gibson PA, Rosbeck KL, et al. Infantile spasms (West syndrome): update and resources for pediatricians and providers to share with parents. *BMC Pediatr* 2012;12:108
- 88 Hussain SA. Treatment of infantile spasms. *Epilepsia Open* 2018;3 (Suppl 2):143–154
- 89 Yang D, Du Q, Huang Z, et al. Transcranial direct current stimulation for patients with pharmacoresistant epileptic spasms: a pilot study. *Front Neurol* 2019;10:50
- 90 Chern CR, Chern CJ, Velišková J, Velišek L. AQB-565 shows promise in preclinical testing in the model of epileptic spasms during infancy: head-to-head comparison with ACTH. *Epilepsy Res* 2019;152:31–34
- 91 Doumlele K, Conway E, Hedlund J, Tolete P, Devinsky O. A case report on the efficacy of vigabatrin analogue (1S, 3S)-3-amino-4-difluoromethylenyl-1-cyclopentanoic acid (CPP-115) in a patient with infantile spasms. *Epilepsy Behav Case Rep* 2016;6:67–69
- 92 Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58(04):512–521