

# Current trends in the treatment of infantile spasms

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**Abstract:** Infantile spasms are an epilepsy syndrome with distinctive features, including age onset during infancy, characteristic epileptic spasms, and specific electroencephalographic patterns (interictal hypsarrhythmia and ictal voltage suppression). Adrenocorticotrophic hormone (ACTH) was first employed to treat infantile spasms in 1958, and since then it has been tried in prospective and retrospective studies for infantile spasms. Oral corticosteroids were also used in a few studies for infantile spasms. Variable success in cessation of infantile spasms and normalization of electroencephalograms was demonstrated. However, frequent significant adverse effects are associated with ACTH and oral corticosteroids. Vigabatrin has been used since the 1990s, and shown to be successful in resolution of infantile spasms, especially for infantile spasms associated with tuberous sclerosis. It is associated with visual field constriction, which is often asymptomatic and requires perimetric visual field study to identify. When ACTH, oral corticosteroids, and vigabatrin fail to induce cessation of infantile spasms, other alternative treatments include valproic acid, nitrazepam, pyridoxine, topiramate, zonisamide, lamotrigine, levetiracetam, felbamate, ganaxolone, liposteroid, thyrotropin-releasing hormone, intravenous immunoglobulin and a ketogenic diet. Rarely, infantile spasms in association with biotinidase deficiency, phenylketonuria, and pyridoxine-dependent seizures are successfully treated with biotin, a low phenylalanine diet, and pyridoxine, respectively. For medically intractable infantile spasms, some properly selected patients may have complete cessation of infantile spasms with appropriate surgical treatments.

**Keywords:** infantile spasms, adrenocorticotrophic hormone, oral corticosteroids, vigabatrin

## Introduction

Infantile spasms are an age-specific epilepsy syndrome characterized by flexor, extensor, and mixed flexor-extensor spasms which often occur in clusters and onset during first 2 years of life.<sup>1</sup> Most of the infantile spasms are symptomatic and 9% to 15% of the cases were cryptogenic.<sup>2</sup> West syndrome is diagnosed when infantile spasms, hypsarrhythmia and mental retardation are present.

## Epidemiology

The incidence of infantile spasms is estimated at 0.20 to 0.60 per 100.<sup>3-8</sup> The prevalence is 0.15 to 0.20/1000 children age 10 or younger.<sup>8,9</sup>

## Clinical features and long-term outcome

The peak onset of infantile spasms is between 3 and 7 months, 93% before age 2 years; however, onset at birth and at 4.5 years has been reported.<sup>10</sup> The spasms are bilateral

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sudden muscle contractions involving neck, trunk, and four extremities, and may be flexor, extensor, or mixed types. The spasms may be single, but often occur in clusters. The majority of the infantile spasms are symptomatic and may be associated with prenatal, perinatal, and postnatal causes, including brain dysgenesis; neurocutaneous syndromes such as tuberous sclerosis; metabolic disorders; chromosomal syndrome such as Down syndrome or gene abnormalities such as ARX gene mutations; hypoxic ischemic encephalopathy; brain tumor; neonatal bacterial meningitis; and herpes simplex encephalitis, among others.<sup>1,10–12</sup> Cryptogenic cases, characterized by lack of obvious evidence of brain damage or known etiology, comprise 9% to 15% of infantile spasms.<sup>2</sup> The typical interictal electroencephalogram is hypsarrhythmia and classical ictal correlates may consist of fast wave bursts, high voltage slow waves, and generalized voltage attenuation or electrodecremental response.<sup>13,14</sup> About 10% to 25% of the patients with infantile spasms recover spontaneously.<sup>11,15,16</sup> In the pre-adrenocorticotrophic hormone (ACTH) era, long-term follow-up in 103 patients with infantile spasms, at age 5 years or older, showed that 11% of children still had infantile spasms, 45% had other seizure types, and 55% were seizure-free; 13% over 1 year of age had normal intellectual capacity, and mortality was 11% by age 2 years.<sup>17</sup>

In a prospective study of the outcome of 64 infants with infantile spasms treated during controlled studies of ACTH and prednisone, mean duration of follow-up was 50 months, and there was a 5% mortality rate in symptomatic patients; 2 of 8 cryptogenic patients were cognitively normal, compared with 1 of the 56 symptomatic patients; infantile spasms persisted in 42% of children, whereas 53% of patients developed other seizure types and 47% were seizure-free; no difference in long-term intellectual outcome or epilepsy was associated with delay in treatment >5 weeks from onset of infantile spasms.<sup>18</sup> However, in another prospective study of 102 infants with infantile spasms, with follow-up beyond 6 years, 50% of ACTH-treated patients were developmentally normal, 62% were seizure-free, and 39% had a normal EEG; better neurodevelopmental outcome was seen with early therapy of <1 month.<sup>19</sup> Two other studies also revealed favorable long-term outcome of ACTH treatment within 1 month of onset for cryptogenic infantile spasms.<sup>20,21</sup> Some studies reported equal efficacy of infantile spasms treatment in both symptomatic and cryptogenic groups,<sup>22</sup> but other studies found a better response of treatment in the cryptogenic group.<sup>23,24</sup> Additionally, the effect of hormonal therapy on long-term neurodevelopmental

outcome is unclear, with some studies reporting a positive association between initial responsiveness to ACTH and improved long-term intellectual development,<sup>19,23,25</sup> but other studies found no significant difference in prognosis between initial responders and nonresponders to hormonal therapy.<sup>18,26</sup> Of patients with infantile spasms, 20% to 50% eventually evolve into Lennox-Gastaut syndrome.<sup>7,8,19,27</sup> The patients with cryptogenic infantile spasms have 30% to 50% mental retardation compared with 80% to 95% for patients with symptomatic etiology.<sup>4,8,20,25–28</sup>

## Treatment

The treatment of infantile spasms remains very challenging throughout the world. Over the years, the treatment choices have been surveyed and evaluated in the United States, Japan, the United Kingdom, and Europe.<sup>29–34</sup> For example, in 1994, the survey report in the Child Neurology Society revealed ACTH as the first choice for the treatment of the infantile spasms, followed by valproic acid and oral corticosteroids as second and third choices, respectively.<sup>30</sup> In another example, in 2000, a survey of the treatment of infantile spasms by the Japanese Epilepsy Society showed that vitamin B6 was the preferred first-line drug, followed by the combination of vitamin B6 and valproate or monotherapy with valproate; corticotropin was the third choice.<sup>31</sup> Other surveys will be discussed later in the paper.

## ACTH (adrenocorticotrophic hormone)

### Mechanism of ACTH and prednisone

ACTH may reduce neuronal excitability in infantile spasms by two mechanisms of action: (1) inducing steroid release and (2) a direct, steroid-independent action on melanocortin receptors. These combined effects may explain the robust, established clinical effects of ACTH in the therapy of infantile spasms.<sup>35</sup> Additionally, suppression of corticotropin-releasing hormone (CRH), an excitant neuropeptide, by ACTH/steroids was proposed as another mechanism for ACTH treatment of infantile spasms.<sup>36</sup> However, there is considerable debate about the reasons why ACTH and prednisone are useful in infantile spasms, their mechanism of action, and their long-term effects on brain development.<sup>37</sup>

The therapeutic effect of ACTH in infantile spasms was initially reported in a series of children with infantile spasms and hypsarrhythmia.<sup>38</sup> Since then, both prospective and retrospective studies with ACTH have been conducted for the treatment of infantile spasms.

In one prospective study, 26 patients receiving the high-dose therapy were treated as follows: 150 U/m<sup>2</sup>/day for 3 weeks, 80 U/m<sup>2</sup>/day for 2 weeks, 80 U/m<sup>2</sup> every other day for 3 weeks, and 50 U/m<sup>2</sup>/day every other day for 1 week, with the dosage then tapered to zero during a 3-week period; the 24 patients assigned to the low-dose therapy group received 20 to 30 U/day for 2 to 6 weeks; the dosage was then tapered to zero during a 1-week period.<sup>39</sup> The response was defined as cessation of infantile spasms and disappearance of hypsarrhythmia. Among 26 patients treated with the high-dose therapy, 13 (50%) responded; of the 24 patients treated with the low-dose therapy, 14 (58%) responded. No significant difference in the cessation of infantile spasms and improvement of the electroencephalogram was demonstrated in the two groups. Additionally, no difference in the relapse rate between the two groups was noted. Furthermore, the side effects seen in both treatment groups were similar, except that hypertension occurred more frequently in the high-dose group. In another report, there is no evidence that high-dose ACTH treatment (150 U/m<sup>2</sup>/day) is more effective than low-dose ACTH (20–30 U/day).<sup>23</sup> The relapses of the infantile spasms often occur in one third to one half of patients, and a second course of ACTH is often effective.<sup>22</sup> In another prospective randomized controlled study, low-dose ACTH (0.005 mg/kg/day = 0.2 IU/kg/day) or high-dose (0.025 mg/kg/day = 1 IU/kg/day) synthetic ACTH therapy showed no difference in the initial and long-term seizure and developmental outcomes in the 17 responders who were followed up for longer than 1 year after the completion of ACTH therapy.<sup>40</sup> The optimal dose of ACTH is still unknown based on the above studies.

In the report of the American Academy of Neurology and the Child Neurology Society on the medical treatment of infantile spasms, 14 studies on ACTH including 5 randomized controlled studies, 4 prospective, open-label trials, and 5 retrospective studies were reported.<sup>11</sup> ACTH dosage ranged from 0.2 IU/kg to 150 IU/m<sup>2</sup>, the duration of treatment was from 4 to 12 weeks, the rate of cessation of infantile spasms was from 42% to 87%, time from initial treatment to cessation of infantile spasms was from 7 to 12 days, and the relapse rate of infantile spasms varied from 15% to 33%.<sup>11</sup>

## Oral corticosteroids

Five studies including 2 randomized controlled studies, 2 prospective open-label studies and 1 retrospective study with 2 to 3 mg/kg prednisone or prednisolone from 2 to 32 weeks.<sup>11</sup> The cessation rate of infantile spasms varied from 29% to 59%.

## ACTH versus oral corticosteroids

A prospective randomized single-blinded study with 2-week ACTH 150 IU/m<sup>2</sup> was compared with 2-week oral prednisone 2 mg/kg, revealing superior efficacy of high-dose ACTH in the cessation of infantile spasms and disappearance of hypsarrhythmia.<sup>41</sup> Of 15 infants randomized to ACTH, 13 responded by EEG and clinical criteria (86.6%); 4 of the 14 patients given prednisone responded (28.6%). A double-blind, placebo-controlled, crossover study to compare the therapeutic effectiveness of ACTH (20 to 30 units/day) with that of prednisone (2 mg/kg/day) showed no difference in the cessation of infantile spasms and disappearance of hypsarrhythmia between ACTH and prednisone.<sup>22</sup> High-dose ACTH 150 IU/m<sup>2</sup> was superior to prednisone 3 mg/kg in the cessation of infantile spasms with 100% in ACTH versus 59% in prednisone, 97% disappearance of hypsarrhythmia in ACTH versus 50% in prednisone.<sup>24</sup> However, some patients who do not initially respond to ACTH may respond to prednisone and vice versa.<sup>22</sup>

## Side effects of ACTH and oral corticosteroids

Hypertension 0% to 37% (4 studies), irritability 37% to 100% (3 studies), infection 14% (1 study), cerebral atrophy 62% (1 study), 5 deaths in 304 cases (2 were associated with sepsis attributed to ACTH) were seen in randomized controlled studies.<sup>11</sup>

## Vigabatrin

Vigabatrin, a structural analogue of gamma-aminobutyric acid (GABA), is an irreversible inhibitor of GABA transaminase and increases the GABA levels, an inhibitory neurotransmitter, in the brain.<sup>42</sup> In a randomized, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms, compared with baseline, the patients treated with vigabatrin had a 78% reduction in infantile spasms compared with 26% in the group treated with placebo, at the end of the double-blind phase.<sup>29</sup> In a randomized trial of vigabatrin in patients with infantile spasms, resolution rate of infantile spasms was 23% at 2 weeks after treatment, and 65% at the end of a 3-month open-label period; the efficacy and safety of vigabatrin in patients with infantile spasms, particularly among those with infantile spasms secondary to tuberous sclerosis, was demonstrated.<sup>43</sup> In other open-label uncontrolled prospective studies, the response rate was better in cryptogenic infantile spasms (50% to 100%) compared with the symptomatic cases (0% to 59%), the time from initiation of therapy to cessation of infantile spasms varied

from 12 to 35 days, and the vigabatrin dosages ranged from 18 to 200 mg/kg/day.<sup>11</sup> Additionally, the treatment response of infantile spasms to vigabatrin in the infants with tuberous sclerosis was uniformly favorable, with cessation of infantile spasms varying from 91% to 100%.<sup>43–49</sup>

Vigabatrin 100 to 150 mg/kg/day was compared with ACTH in the treatment of infantile spasms and the resolution rate of infantile spasms was similar for both vigabatrin and ACTH; however, the improvement of hypsarrhythmia was better for ACTH.<sup>48,50</sup> In the United Kingdom, ACTH treatment induced complete cessation of infantile spasms better than vigabatrin initially, but not at 12 to 14 months of age; better initial cessation of infantile spasms by ACTH treatment in those with no identified underlying etiology may lead to improved developmental outcome.<sup>51</sup>

### Side effects of vigabatrin

In both randomized controlled studies and open-label uncontrolled studies, sedation, irritability, insomnia and hypotonia were reported in vigabatrin treatment.<sup>11</sup> Concentric visual field defects and abnormalities in electroretinograms were also demonstrated in children; however, the incidence in infants under 1 year of age is unknown currently.<sup>11,52–54</sup>

### Valproic acid

Valproic acid enhances GABA-ergic inhibitory system at the cortical and subcortical levels and blocks neuronal firing by blocking voltage-gated sodium channels.<sup>42</sup> In an uncontrolled, open-label, prospective study, cessation of infantile spasms in 73% and resolution of hypsarrhythmia in 91% of 22 patients (18 with symptomatic infantile spasms and 4 with cryptogenic infantile spasms) were reported after 6 months of therapy with valproic acid 40 and 100 mg/kg/day.<sup>55</sup> However, relapse of infantile spasms in 23% of patients was seen in the first 7 months of treatment. In another open-label, uncontrolled, prospective study, cessation of infantile spasms was seen in 72% of the patients with infantile spasms after 3 months of treatment with valproic acid.<sup>56</sup>

Common side effects of valproic acid include weight gain, nausea, vomiting, hair loss, easy bruising, tremor; rare idiosyncratic effects consist of agranulocytosis, Stevens–Johnson syndrome, aplastic anemia, hepatic failure, dermatitis–rash, serum sickness, and pancreatitis.<sup>42,57</sup>

### Nitrazepam

Mechanism of nitrazepam in the treatment of infantile spasms may be related to their effect in modification of the sensitivity of GABA receptors.<sup>58</sup> In the retrospective case series,

nitrazepam 0.5 to 3.5 mg/kg/day was reported to induce resolution of infantile spasms from 30% to 54% and disappearance of hypsarrhythmia from 15% to 46%.<sup>59,60</sup> Another prospective randomized multicenter study comparing corticotropin with nitrazepam revealed no difference in efficacy in the treatment of infantile spasms.<sup>61</sup>

Nitrazepam was associated with excess sedation, hypersalivation, swallowing difficulty, high incidence of aspiration pneumonia, and several deaths.<sup>62,63</sup>

### Pyridoxine

Pyridoxine is a coenzyme of glutamic acid decarboxylase and enhances GABA synthesis.<sup>64</sup> Low levels of GABA in cerebrospinal fluid of infants with infantile spasms were reported.<sup>65</sup> Pyridoxine is the first treatment of choice for infantile spasms in Japan.<sup>31,32,66</sup> Two uncontrolled prospective open-label studies in infantile spasms revealed efficacy for infantile spasms.<sup>67,68</sup> At dosages of pyridoxine >1 g/day (usual dose of pyridoxine 10 to 50 mg/kg/day), a complete control of infantile spasms was reported in 35% to 40% of cryptogenic cases but only 10% of symptomatic cases.<sup>67</sup> Side effects of high-dose pyridoxine include loss of appetite, irritability and vomiting.<sup>68</sup>

Pyridoxine-dependent seizures are characterized by intractable seizures including infantile spasms that are not controlled with anticonvulsants but that respond both clinically and electrographically to 100 to 500 mg of intravenous pyridoxine.<sup>69</sup> Pyridoxine-dependent seizures, an autosomal recessive disorder, is caused by mutations in the ALDH7A1 gene on chromosome 5q31.<sup>69</sup> The patients require lifetime treatment with pyridoxine at 15 to 20 mg/kg/day.<sup>69</sup>

### Zonisamide

Zonisamide blocks repetitive firing of voltage-sensitive sodium channels, reduces voltage-sensitive T-type calcium currents without affecting L-type calcium currents, and is a weak carbonic anhydrase inhibitor.<sup>70</sup> In one add-on nonblind study, zonisamide 4 to 20 mg/kg/day in 27 children with infantile spasms (25 symptomatic and 3 cryptogenic cases) induced cessation of infantile spasms and resolution of hypsarrhythmia in 33%; however, a 50% recurrence rate was also reported.<sup>71</sup> In another add-on nonblind study, 16 patients with infantile spasms (13 symptomatic and 3 cryptogenic cases) were treated with 4 to 8 mg/kg/day zonisamide after failing to respond to pyridoxine and valproic acid. Only 2 patients showed cessation of infantile spasms but no recurrence of infantile spasms after 26 months of follow-up.<sup>72</sup> Zonisamide monotherapy 3 to 10 mg/kg/day was administered



in 11 patients with newly diagnosed infantile spasms (cryptogenic 3, symptomatic 8) as the second-choice drug that failed to respond to high-dose vitamin B6. The cessation of infantile spasms and disappearance of the hypsarrhythmia in 4 symptomatic patients (36%) were achieved after 1 to 5 days of treatment, however there were two relapses (50%) 4 to 6 weeks after cessation of seizures.<sup>73</sup> In another study, the long-term effectiveness of zonisamide was evaluated in 11 patients with West syndrome (7 symptomatic) who had cessation of spasms with zonisamide monotherapy. During the follow-up period (24 to 79 months), this response was maintained in 7 patients (relapse rate = 36%).<sup>74</sup> Recently, 6 of 23 (26%) patients with symptomatic infantile spasms became spasm-free on zonisamide.<sup>75</sup>

Common side effects of zonisamide in children include anorexia, dizziness, ataxia, fatigue, somnolence, and confusion; rare idiosyncratic effects consist of nephrolithiasis, oligohydrosis, and hyperthermia.<sup>57</sup>

## Topiramate

Topiramate blocks voltage-sensitive sodium channels, enhances the activity of GABA, an inhibitory neurotransmitter, blocks the action of glutamate, an excitatory neurotransmitter, and is also a weak carbonic anhydrase inhibitor.<sup>42,76</sup> In a nonblind add-on pilot study with topiramate 25 mg daily up to 24 mg/kg/day on 11 children with refractory infantile spasms, 5 (45%) became spasm-free during the study, with absence of infantile spasms and hypsarrhythmia.<sup>77</sup> Eleven children with infantile spasms who completed the pilot study entered an 18-month study in which the dosages of topiramate and other anticonvulsants were adjusted to optimal response (maximum, 50 mg/kg/day). Four (50%) children were spasm-free, 7 (88%) had experienced a  $\geq 50\%$  reduction in spasms, and 3 (38%) were able to achieve topiramate monotherapy.<sup>78</sup> Topiramate was well tolerated in that no patients discontinued because of adverse events. In a prospective, 2-month study with topiramate 3 to 27 mg/kg/day in 15 children with recently diagnosed infantile spasms, 3 patients became spasm-free (20%), 5 had  $>50\%$  reduction, 3 had at least 25% reduction, 4 patients did not respond, and 3 of 15 patients had cessation of hypsarrhythmia.<sup>79</sup> Topiramate treatment in children with West syndrome was reported in a retrospective multicenter evaluation of 100 patients: 17.5% of patients became free of seizures, and in 47%, the seizure frequency decreased by at least 50%; additionally, hypsarrhythmia remitted in 18 of 83 cases.<sup>80</sup>

Common side effects of topiramate include anorexia, weight loss, word-finding disturbance, cognitive slowing,

ataxia, poor concentration, dizziness, fatigue, paresthesia, somnolence; rare side effects consist of nephrolithiasis, hypohidrosis, acute angle closure glaucoma.<sup>42,57</sup>

## Felbamate

Felbamate potentiates GABA-mediated inhibition, blocks voltage-dependent sodium channels, and the ionic channel at the N-methyl-D-aspartate receptor.<sup>42</sup> In one nonblind add-on study, felbamate 15 to 45 mg/kg/day resulted in cessation of infantile spasms in 3 of 4 patients, all refractory to conventional antiepileptic drugs.<sup>81</sup> In another nonblind study for refractory infantile spasms, in which 4 of 6 patients were refractory to both corticosteroids and new antiepileptic drugs (vigabatrin and lamotrigine), felbamate 15 to 45 mg/kg/day treatment decreased seizure frequency by 75%.<sup>82</sup>

Felbamate common side effects consist of nausea, vomiting, anorexia, weight loss, insomnia, dizziness, headache and ataxia; rare serious idiosyncratic effects include aplastic anemia, and hepatic failure.<sup>42,57</sup>

## Lamotrigine

Lamotrigine has been shown to act at voltage-sensitive sodium channels, stabilizing neural membranes and inhibiting the release of excitatory neural transmitters.<sup>42</sup> The dosage of lamotrigine can be titrated slowly up to 5 mg/kg/day when combined with valproate, but can be gradually increased to 15 mg/kg/day when not combined with valproate. In a single-blind, placebo-controlled, add-on study, 30 patients with infantile spasms refractory to conventional antiepileptic drugs and to vigabatrin and corticotropin were treated with lamotrigine, 9 patients showing  $>50\%$  decrease in infantile spasms, 5 of these with complete cessation of spasms.<sup>83</sup> Three infants affected with symptomatic West syndrome, unresponsive to vigabatrin and to ACTH, were successfully treated with very small doses of lamotrigine.<sup>84</sup> Common side effects of lamotrigine include rash, nausea, dizziness, and somnolence; rare idiosyncratic effects include Stevens-Johnson syndrome and hypersensitivity syndrome.<sup>42,57</sup>

## Levetiracetam

Levetiracetam binds to synaptic vesicle protein, has actions on neuronal GABA- and glycine-gated currents, as well as voltage-dependent potassium currents, however, its exact mechanism of action is unknown.<sup>57</sup> In an open-label add-on study of levetiracetam 10 to 60 mg/kg/day in refractory childhood epilepsy syndromes, efficacy was demonstrated in one patient's infantile spasms.<sup>85</sup> Refractory infantile spasms in another infant were responsive to levetiracetam

15 mg/kg/day, resulting in cessation of infantile spasms for 6 months.<sup>86</sup> Treatment with levetiracetam 30 mg/kg/day for cryptogenic West syndrome resulted in cessation of infantile spasms in 2 patients, a 50% reduction in seizure frequency in 2 patients, but no improvement in seizure frequency in another patient. There were no relapses in the two patients at 6 months after the cessation of seizures.<sup>87</sup>

Common side effects of levetiracetam include somnolence, headache, anorexia, and nervousness. Less frequent side effects consist of agitation, aggression, anxiety, or depression.<sup>57</sup>

## Thyrotropin-releasing hormone

A daily dose of thyrotropin-releasing hormone 0.5 to 1 mg was administered intravenously or intramuscularly for 1 to 4 weeks. The follow-up periods were 3 to 12 months (mean 6 months). Complete cessation of spasms was achieved in 7 of 13 (53.7%) of those with infantile spasms, and marked improvement of electroencephalograms was observed in 8 of 13 (61.5%) of these.<sup>88</sup> Thyrotropin-releasing hormone was shown to increase cerebrospinal fluid kynurenine level.<sup>89</sup> Thyrotropin-releasing hormone may act as an anti-epileptic through a kynurenine mechanism, considering that kynurenic acid acts as an antagonist on the N-methyl-D-aspartate receptor complex.<sup>90</sup> Additionally, thyrotropin-releasing hormone-mediated increase in GABA release has also been demonstrated and may contribute to its anti-epileptic effects.<sup>91</sup> The effectiveness of thyrotropin-releasing hormone was also reported in West syndrome, Lennox-Gastaut syndrome, and early infantile epileptic encephalopathy that were intractable to anticonvulsants and adrenocorticotrophic hormone.<sup>90,92</sup>

## Ganaxolone

Ganaxolone is an allosteric modulator of GABA receptors acting through binding sites, which are distinct from the benzodiazepine binding site.<sup>93,94</sup> In a multicenter, open-label, add-on trial, investigating the safety and efficacy of ganaxolone up to 36 mg/kg/day in children with refractory infantile spasms, infantile spasm frequency was reduced by at least 50% in 33% of these subjects, with an additional 33% experiencing some improvement (25% to 50% reduction in spasm frequency); ganaxolone was well tolerated, and adverse events attributed to ganaxolone were generally mild, consisting of somnolence, diarrhea, nervousness, and vomiting.<sup>95</sup> In another add-on nonblind study, ganaxolone treatment in 20 children with infantile spasms refractory to corticosteroids, lamotrigine and vigabatrin, only 1 patient had

cessation of infantile spasms and >50% decrease in seizure frequency in 50% of the patients.<sup>58</sup>

## Liposteroid

Dexamethasone palmitate (liposteroid) was used for the treatment of West syndrome and compared with adrenocorticotrophic hormone (ACTH) therapy.<sup>96</sup> A single intravenous injection of liposteroid (0.25 mg/kg) was administered seven times in 3 months (total dosage = 1.75 mg/kg) to 5 symptomatic patients with West syndrome, aged 4 to 11 months. ACTH (0.025 mg/kg/day) was administered intramuscularly for 6 weeks (total dosage = 0.625 mg/kg) to 5 symptomatic patients with West syndrome, aged 6 to 10 months. Infantile spasms and hypsarrhythmia on EEG disappeared in all 5 patients in the liposteroid therapy group within 4 doses; in the ACTH therapy group, infantile spasms and hypsarrhythmia on EEG similarly disappeared during treatment in all 5 patients, but infantile spasms reappeared 2 months after therapy in 2 patients. No notable adverse reactions occurred in the liposteroid group, but transient dysfunction of the thyroid and anterior pituitary gland and increased levels of serum cortisol were experienced in the ACTH group.<sup>96</sup> In another study, a single intravenous injection of liposteroid (0.25 mg/kg) was administered 12 times in 1 month (total dosage 3.0 mg/kg) to 4 patients with West syndrome. All 4 patients previously had daily seizures uncontrolled by conventional antiepileptic drugs, such as valproic acid, clonazepam or zonisamide. Infantile spasms and hypsarrhythmia on EEG disappeared in 1 patient within 4 doses; a greater than 50% decrease in seizures, and EEG improvement, were found in another 2 patients; no notable effects were seen in the other 2 patients. There were no clinically significant adverse reactions throughout the therapy.<sup>97</sup>

## Sulthiame

Sulthiame is a carbonic anhydrase inhibitor that is widely used to treat partial and myoclonic seizures. Sulthiame (5 to 10 mg/kg/day) was studied in a randomized double-blind placebo-controlled add-on trial on baseline pyridoxine medication for the primary therapy of West syndrome and was found to have a positive effect in the primary therapy of West syndrome. Based on the intention to treat, 6 (30%) of 20 patients responded to sulthiame, reaching complete cessation of infantile spasms and resolution of hypsarrhythmia, while no patients on placebo responded ( $p < 0.025$ ).<sup>98</sup> Side effects of sulthiame occurred in 48% of patients, including vomiting in 38%, somnolence in 20%, restlessness in 16%, loss of appetite in 5.5%, and diarrhea in 3%.<sup>98</sup>

## Intravenous immunoglobulin (IVIg)

In one study, 6 children with cryptogenic infantile spasms and 5 with symptomatic infantile spasms were treated with IVIg at 100 to 200 mg/kg of body weight at intervals of 2 or 3 weeks (6 to 10 administrations). All 6 patients with cryptogenic West syndrome showed complete remission in accordance with normalized electroencephalogram. Of the 5 patients with symptomatic West syndrome, 1 showed cessation of clinical spasms in agreement with EEG improvement and 2 others revealed transient cessation of spasms with recurrence.<sup>99</sup> Five of 23 patients with infantile spasms experienced cessation of infantile spasms with 1 g/kg of IVIg for 2 days, repeated every 3 weeks for 6 months.<sup>100</sup>

## Ketogenic diet

Since the early 1920s, the ketogenic diet has been used successfully to treat patients with intractable epilepsy; however, the mechanism by which the diet protects against seizures is unknown. The ketogenic diet is a calorie-restricted diet in which the fat:carbohydrate plus protein ratio ranges from 2:1 to 5:1. During a 4-year period, 23 children with infantile spasms, aged 5 months to 2 years, were started on the ketogenic diet; at 3, 6, 9, and 12 months, 38%, 39%, 53%, and 46%, respectively, of all patients currently on the diet were > 90% improved (3 were seizure-free at 12 months); 67%, 72%, 93%, and 100% were >50% improved.<sup>101</sup> In another retrospective study, the ketogenic diet achieved the spasm-free state in 53.5% (23/43) of patients and a greater than 90% reduction of spasms in 62.8% (27/43) of patients; the spasm outcomes were highly concordant with improvements in EEG findings and development.<sup>102</sup> In a retrospective study, a case-control evaluation was performed for the ketogenic diet versus ACTH for new-onset infantile spasms, including 13 patients on the ketogenic diet and 20 patients on high-dose ACTH. Eight of 13 (62%) infants treated with the ketogenic diet were spasm-free within 1 month, compared with 18 of 20 (90%) treated initially with ACTH; ACTH-treated infants were more likely to have a normal EEG at 1 month; side effects (31% vs 80%,  $p = 0.006$ ) and relapse rate after initial success (12.5% vs 33%,  $p = 0.23$ ) were lower with the ketogenic diet.<sup>103</sup>

Early side effects in the initial 4 weeks of treatment may consist of transient dehydration, nausea, vomiting, diarrhea, constipation, lethargy, hypoglycemia, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, hypoproteinemia, hypomagnesemia, hyponatremia, low concentrations of high-density lipoprotein, hepatitis, acute pancreatitis,

metabolic acidosis, hemolytic anemia, and Fanconi renal tubular acidosis; later side effects include osteopenia, renal stones, cardiomyopathy, secondary hypocarnitinemia, and iron-deficiency anemia.<sup>104–106</sup>

## Combination therapies

Nine infants with an underlying static encephalopathy and newly diagnosed infantile spasms were treated in an open study with ACTH and vigabatrin. The ACTH was discontinued after 4 to 6 weeks and the infants were maintained on vigabatrin alone. Following an initial response with complete cessation of infantile spasms in all 9 patients, a long-term spasm cessation for a mean of 19.2 months was reported in all but one child.<sup>107</sup> Ninety-four patients with West syndrome were treated with sodium valproate and steroids, starting with hydrocortisone orally for 2 weeks. If spasms stopped, hydrocortisone was withdrawn, if spasms persisted, tetracosactrin (synthetic ACTH) was administered for another 2 weeks, and then hydrocortisone was slowly withdrawn. Spasms cessation was 72% for cryptogenic and 60% for symptomatic infantile spasms at 31-month follow-up.<sup>108</sup> In 4 patients with cryptogenic and 1 patient with symptomatic (tuberous sclerosis) West syndrome, the combined therapy with topiramate and vigabatrin achieved a rapid and complete cessation of infantile spasms, and in 3 patients with cryptogenic West syndrome, the EEG also became normal.<sup>109</sup>

## Rare treatable symptomatic infantile spasms

Rarely, infantile spasms occur in association with biotinidase deficiency, which can be treated with biotin successfully.<sup>110</sup> Children with infantile spasms associated with phenylketonuria have been reported and were treated successfully with low phenylalanine diet and valproic acid or nitrazepam.<sup>111</sup>

## Surgical treatment

In 4 infants with cryptogenic infantile spasms, positron emission tomography effectively identified unsuspected focal cortical dysplasia and all 4 patients were spasm-free after resective surgery.<sup>112</sup> In another study, 23 infants and children underwent cortical resection ( $n = 15$ ) or hemispherectomy ( $n = 8$ ) for intractable infantile spasms; convergence between electroencephalogram and neuroimaging localization was a prerequisite to surgery; at follow-up (range 4 to 67 months; mean 28.3 months), 15 children were spasm-free, 3 had 90% spasm reduction, 1 had 75% spasm reduction, and 4 failed

to benefit from surgery in terms of seizure frequency.<sup>113</sup> Twenty-four children receiving resection surgery for medically intractable infantile spasms showed a significant increase in developmental level at 2 years post surgery compared with presurgical levels.<sup>114</sup> A favorable outcome of multiple sub-pial transection in 2 patients who had intractable atypical infantile spasms preceded by partial seizures, without any lateralized magnetic resonance imaging abnormalities, was recently reported.<sup>115</sup> Infantile spasms associated with cortical dysplasia requiring treatment with lesionectomy in the right perirolandic area at 49 weeks conceptional age in one infant and left temporo-occipital disconnection at 45 weeks in the other infant, resulted in Engel classification I and catch-up developmental progress.<sup>116</sup> For patients without a surgically resectable lesion, corpus callosotomy has been reported to improve dramatically infantile spasms, as well as other seizure types, such as drop attacks.<sup>117</sup> After complete callosotomy, infantile spasms disappeared in 80% of 17 cases; drop attacks were dramatically reduced or completely stopped in 90% of the children. However, the excellent response of callosotomy in infantile spasms would require more studies for confirmation.

## Conclusion

According to a 2008 Cochrane review,<sup>122</sup> hormonal treatment resolves infantile spasms in more infants than vigabatrin, but this may or may not translate into a better long-term outcome. If prednisone or vigabatrin are used, then high dosage is recommended. Vigabatrin may be the treatment of choice for infantile spasms associated with tuberous sclerosis. In the United States of America, ACTH is probably an effective agent in the short-term treatment of infantile spasms and vigabatrin is possibly effective as suggested by the practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society.<sup>11</sup> In Japan, the most recent survey in 2006 on treatment of infantile spasms reveals vitamin B6 as the first-choice drug, followed by valproic acid, zonisamide, and adrenocorticotrophic hormone; however, in cryptogenic patients, ACTH was used most frequently, usually within 1 month after disease onset, followed by valproic acid, vitamin B6, and zonisamide.<sup>32</sup> The 2004 National Institute for Clinical Excellence (NICE) Guidelines,<sup>118</sup> the 2005 Scottish Intercollegiate Guidelines Network (SIGN) Guidelines,<sup>119</sup> and the 2005 US Pediatric Epilepsy survey<sup>33</sup> all support the use of vigabatrin as first-line therapy for infantile spasms associated with tuberous sclerosis complex. However, only the NICE Guidelines support vigabatrin as the drug of

choice in symptomatic infantile spasms. In a recent survey in the United Kingdom, hormone treatment controlled infantile spasms better than vigabatrin initially, but not at 12 to 14 months of age. Better initial control of infantile spasms by hormone treatment in those with no identified underlying etiology may lead to improved developmental outcome.<sup>51</sup> In another recent survey, vigabatrin is the first choice for infantile spasms associated with tuberous sclerosis or symptomatic etiologies; ACTH and prednisone also are as good as other first-line options.<sup>34</sup>

When children fail to have complete cessation of infantile spasms after treatment with ACTH, vigabatrin, or prednisone, some other medications have been used to treat infantile spasms with variable success in cessation of infantile spasms. In uncontrolled studies, these include topiramate, zonisamide, valproic acid, nitrazepam, lamotrigine, levetiracetam, felbamate, high-dose pyridoxine, liposteroid, ganaxolone, and thyrotropin-releasing hormone. Other alternative treatment for infantile spasms may consist of intravenous immunoglobulin and a ketogenic diet. Some selective children with medically intractable infantile spasms may have excellent success in resolution of spasms with proper surgical treatment options.

More research is necessary on the pathophysiology of infantile spasms, such as that conducted for recent animal models of infantile spasms,<sup>120</sup> so that we can treat infantile spasms more successfully. Finally, infants with West syndrome could be identified several weeks before the occurrence of hypsarrhythmia by a typical EEG pattern, which may open the way for early intervention to prevent development of hypsarrhythmia and infantile spasms.<sup>121</sup>

## Disclosures

The author discloses no conflicts of interest.

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