Infantile Spasms

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Background: Infantile spasms (West syndrome) is an epilepsy condition affecting 1 in 2000 infants. Perhaps no more worrisome neurologic disorder exists because of its frequent association with delayed development and cognition at such a young age. Despite its existence in the literature since 1841, proven therapies are limited because of efficacy, tolerability, at times even availability.

Review Summary: In this review, the clinical features, electroencephalogram (EEG) findings (hypsarrhythmia), prognostic factors, and myriad of treatment options for this condition will be discussed. Guidelines, surveys, and practice parameters have judged adrenocorticotropin hormone and vigabatrin to be the most proven treatments, with the latter indicated for tuberous sclerosis. However, potentially helpful therapies with fewer side effects have recently emerged including high-dose oral prednisolone, ketogenic diet, and topiramate. Additionally, advances in the past several years include the creation of viable animal models for testing new treatments.

Conclusions: At no other time since its first description in 1841 has the field of infantile spasms research been so rapidly changing. For the thousands of infants faced with this potentially devastating disorder, there is no time like the present.

Key Words: infantile spasms, hypsarrhythmia, vigabatrin, ACTH, ketogenic diet, prednisolone, West syndrome

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Perhaps no other epilepsy syndrome in existence engenders more dread among neurologists than infantile spasms. First described 165 years ago by Dr. William James West in an article in *Lancet* regarding his own son,[1] this condition presents after several months of age in infants with the abrupt onset and gradually worsening occurrence of clustering flexor and extensor arm and head movements. A sizeable minority of these children may be previously normal at the time, but rarely remain so, with most affected patients developing regression. Even in the approximately 70% with "symptomatic" infantile spasms (previously identified etiology); many will have worsening of prior developmental delay. The EEG is filled with the most chaotic pattern imaginable, and the spasms themselves are often both disturbing to the infant as well as their worried caregivers. Infantile spasms is not rare, seen in 1 in 2000 infants, with most large academic centers diagnosing approximately 1 new case per month.

One would expect that considerable and urgent progress has been made in the early identification and treatment of this devastating disease since 1841. Unfortunately, infants are still diagnosed only when the seizures begin and at times only after days of spasms because of potential misdiagnosis by pediatricians or neurologists. Additionally, treatments are very limited and incompletely effective, with the majority of the new anticonvulsants introduced in the past 20 years studied for complex partial seizures and in adults rather than for infantile spasms.

There is hope, however. Parents of children with certain high risk conditions that predispose to infantile spasms have organized and improved early recognition through the internet and other media. Several animal models have been recently studied and may offer a mechanism for testing novel anticonvulsant therapies specifically for infantile spasms.[2] Anticonvulsants (as well as the ketogenic diet and surgery) both currently in clinical use and in varying stages of development are being used increasingly for infantile spasms with optimistic preliminary results. Government agencies are hearing the message, and in 2009 the Food and Drug Administration reinstated the clinical availability of vigabatrin to children in the United States. This review will highlight the diagnosis, etiologies, and treatments for infantile spasms at this changing time in this history of infantile spasms.

DIAGNOSIS

Children between the ages of 3 and 10 months often present with the abrupt onset of second-long head and arm jerks, which can be both flexor and extensor.

Initially subtle, the seizures seen in infantile spasms will soon become worse and obvious to most neurologists. Children between the ages of 3 and 10 months often present with the abrupt onset of second-long head and arm jerks, which can be both flexor and extensor.[3] It is typically seen prior to the age of 1 year, but can occur beyond that age. A clustering of spasms is seen in the majority of patients and often occurs after sleep transition, with a gradual decreasing frequency as the cluster continues over several minutes. The infant may become upset and cry during the events which appear to only briefly interrupt consciousness. At times misdiagnosed as colic or gastroesophageal reflux, parents will often bring their infant for further medical attention when the jerks become more forceful or the child begins to lose developmental skills. Parents sometimes report a loss of babbling, verbalizations, or even head and trunk control.

The diagnosis of West syndrome is confirmed by EEG, and a 30-minute record is often sufficient. The classic pattern identified, hypsarrhythmia, describes the high voltage, chaotic nature of the epileptiform discharges.[3–5] The entire record in "classic" hypsarrhythmia is comprised of very high voltage (>200 uV), asynchronous, random, and typically independent, spike and sharp wave discharges.[3–5] Periods of electrodecrements lasting several seconds can be identified both interictally and during clinical spasms, almost

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mimicking a burst suppression pattern in some instances. The discharges may improve significantly during rapid-eye-movement sleep, but then worsen again in non-rapid-eye-movement sleep. It is generally advised that a period of sleep is important during an EEG obtained to rule out infantile spasms.

The entire record in "classic" hypsarrhythmia is comprised of very high voltage, asynchronous, random, and typically independent, spike and sharp wave discharges.

"Modified" hypsarrhythmia is defined as focal or asymmetric discharges, episodes of voltage attenuation, and some interhemispheric synchronization.[3] Modified hypsarrhythmia, often seen in older infants, may also have some normal background activity and relatively few electrodecrements. However, there is no evidence for a difference in either prognosis or treatments between classic and modified hypsarrhythmia; its occurrence should not preclude emergent treatment. In addition, experts will caution that infantile spasms can occur prior to or even in the absence of either classic or modified hypsarrhythmia.[3] In these cases, multifocal spike waves can be seen and may evolve into the hypsarrhythmic pattern over weeks. A normal EEG essentially rules out the diagnosis.

Once the diagnosis is made, prompt treatment should ensue. The neurologist's diagnostic task, however, is not completed at that point. Approximately 70% to 80% of cases of infantile spasms are eventually classified as "symptomatic," with an identified causative etiology.[6] Over 200 structural, metabolic, or genetic abnormalities that involve the central nervous system have been described as associated with infantile spasms. However, some conditions are more commonly seen, perhaps indicating a shared pathogenesis, and are listed in Table 1. A reasonable basic workup in "cryptogenic" cases includes magnetic resonance imaging (MRI), urine organic acids, plasma amino acids, lactate, pyruvate, ammonia, serum karyotype, and liver and kidney function tests. Many neurologists also recommend obtaining a screen for the SCN1A (sodium channel neuronal type 1 alpha subunit) mutation, cerebrospinal fluid analysis, comparative genome hybridization (gene array), urine sulfites, and transferrin electrophoresis. Pyridoxine is frequently administered during the EEG to look for spontaneous improvement (which can occur in pyridoxine-dependent seizures), however, these seizures are rare and are even more unlikely as a cause of infantile spasms specifically.

TABLE 1. Several Conditions That Appear to Be More Likely to Predispose to Infantile Spasms (Listed Alphabetically)

Aicardi syndrome
Cytomegalovirus (CMV) infection
Down syndrome (trisomy 21)
Hemimegalencephaly
Hypoxic-ischemic encephalopathy
Incontinentia pigmenti
Intercranial hemorrhage
Lissencephaly
Phenylketonuria
Sturge-Weber syndrome
Tuberous sclerosis complex

Approximately 70% to 80% of cases of infantile spasms are eventually classified as "symptomatic."

TREATMENT

Corticosteroids and vigabatrin remain the most commonly used treatments.

The treatment of infantile spasms remains enigmatic and often depends on the individual neurologist evaluating the child. In general, corticosteroids and vigabatrin remain the most commonly used treatments, but other therapies are also widely prescribed. An overview of the short-term efficacy rates for frequently used treatments is presented in Table 2.

Corticosteroids

Corticosteroids remain the gold standard compared with all others, with approximately 60% to 80% of infants becoming spasm-free.

One of the earliest treatments for infantile spasms has been the use of hormonal therapy, specifically corticosteroids. This treatment remains the gold standard compared with all others according to every published practice parameter and guideline (with the exception of vigabatrin for the infantile spasms associated with tuberous sclerosis complex, which will be discussed later) (Table 3).[33–36] The most recent to date, a 2008 Cochrane review,[36] concluded that "hormonal treatment resolves spasms faster than vigabatrin and in more infants." Unfortunately, corticosteroids also likely have the highest rate of side effects.

Adrenocorticotropin hormone (ACTH) has been the mainstay of hormonal treatment for several decades, and can be provided as an animal product produced from cows (ACTHar gel) in the United States or synthetic (Synthacten) in much of the rest of the world. ACTH is highly effective, with approximately 60% to 80% of infants becoming spasm-free.[7–13,33] Studies have shown that high dose (150 units/m^2/d initially) ACTH is equivalent to low dose (20–40 units/m^2/d) in terms of seizure suppression.[13] Parents are trained, often during a 1-day admission, to administer ACTH injections and infants are observed carefully by their pediatrician for adverse effects. High-dose ACTH is typically effective within sev-

TABLE 2. Spasm-Free Outcomes for New-Onset Infantile Spasms After 2 to 4 Weeks, Based on Published Trials for Major Therapies

Therapy	Percentage Spasm-Free	References
Corticosteroids		
ACTH	54%–87%	7–13
High-dose oral steroids	67%–76%	11,14
Low-dose oral steroids	29%–39%	12,13
Vigabatrin	16%–67%*	15–20
Ketogenic diet	62%	9
Valproate	72%–73%	21,22
Nitrazepam	30%–54%	23,24
Sulthiame	40%	25
Zonisamide	33%–36%	26,27
Topiramate	20%–30%	28–30
Pyridoxine	0%–29%	25,31,32

Larger and prospective studies are reported when available.
*Ninety-one percent to 100% for tuberous sclerosis complex.[33]
ACTH indicates adrenocorticotropin hormone.

TABLE 3. Opinions of Major Reviews and Meta-Analyses of the Infantile Spasm Literature

Review/Parameter	Recommendations
American Academy of Neurology and Child Neurology Society (2004)[33]	ACTH "probably" effective, vigabatrin "possibly." Vigabatrin best for tuberous sclerosis. Low-dose steroids not effective. All other treatments inconclusive.
National Institute for Health and Clinical Excellence (NICE) (2004)*	Both corticosteroids and vigabatrin are effective.
United States Expert Consensus (2005)[34]	ACTH and topiramate "usually" appropriate; zonisamide, vigabatrin, valproate, prednisone "sometimes" appropriate. Vigabatrin and ACTH "usually" appropriate for tuberous sclerosis.
European Expert Consensus (2007)[35]	Vigabatrin (best), ACTH, and prednisone "usually" appropriate, valproate "sometimes" appropriate. Vigabatrin the only "usually" appropriate treatment for tuberous sclerosis.
Cochrane Review (2008)[36]	Hormonal treatment (either high dose oral or ACTH) leads to a more rapid response than vigabatrin.

*Available at: http://guidance.nice.org.uk/CG20.
ACTH indicates adrenocorticotropin hormone.

eral days, and the dose is then gradually reduced until discontinuation; tapered over 4 to 8 weeks in a weekly or biweekly manner.

Adverse effects can be significant and may include edema, gastric bleeding, weight gain, irritability, hypertension, injection-site irritation or infection, increased susceptibility to illness, cortical atrophy, and death. Recurrence of spasms unfortunately occurs in about one-third of infants, but may respond to either a second course of ACTH or increasing the dose to the high dose (and gradually withdrawing it again).[33] Lastly, the 2007 decision by Questcor Inc., to increase the cost of ACTHar gel in the United States from approximately $2000 to $80,000 for a 1-month treatment course has been a subject of great concern and raised a confounding financial issue with this drug. The company does offer a support program (www.acthar.com) to help with insurance approval.

Alternative steroid formulations have been studied in a limited manner, likely as a result of the poor results seen with oral prednisolone in 2 studies from 1983 and 1996.[12,13] However, a low dose of prednisone (2 mg/kg/d) was used in those studies. A recent prospective study entitled the "UKISS" trial (United Kingdom Infantile Spasms Study) included high-dose (approximately 4 mg/kg/d) oral prednisolone as well as synthetic ACTH in the "hormonal treatment" arm.[11] Results were identical between both steroid groups and were superior initially to vigabatrin, with 19 of 25 (76%) responding by 2 weeks to oral steroids and 21 of 30 (70%) to ACTH.[11] Our group has recently replicated these findings with oral high-dose prednisolone, with 10 of 15 (67%) infants responding within 2 weeks.[14] Side effects appear to be also reduced (as is the cost, by a factor of 400). As a result of a positive response to oral prednisolone, reduced side effects, and a lower cost, ACTH is no longer recommended as the initial treatment of infantile spasms at our institution.

Vigabatrin

Vigabatrin appears to be highly effective for infantile spasms associated with tuberous sclerosis complex.

One of the most popular therapies for infantile spasms in Europe, Canada, Mexico, and other countries, vigabatrin is the subject of considerable attention as it is now Food and Drug Administration reapproved in the United States as of August 21, 2009.[37] Initially approved in 1994, gamma-vinyl GABA (vigabatrin) is an irreversible inhibitor of GABA, orally administered, and renally excreted.[37] Chiron et al first reported the efficacy of vigabatrin for infantile spasms in 1991,[15] but once it became available in the United States, its use for this indication grew rapidly.[15–19]

Vigabatrin is dosed initially at 50mg/kg/d divided twice daily, but if not effective, the dose is recommended to be increased every 3 days to up to a maximum of 150 mg/kg/d. It is available in 500 mg powder packets than can be dissolved in 10 mL of water to create a 50 mg/mL solution. In the United States, it is available through specialty pharmacies (1–888–45-SHARE). Reported spasm-free rates vary from as low as 16%[17] to 100%,[15] with an overall range approximately 50% to 60%.[15–19,37] One of the initial studies comparing vigabatrin to ACTH in the short-term found it to be inferior (48% vs. 74%)[19] and the UKISS study did as well (54% vs. 73%).[11] In a longer-term comparison (12–14 months), the UKISS study found no difference between steroids and vigabatrin (76% vs. 75%).[20] Vigabatrin appears to be highly effective for infantile spasms associated with tuberous sclerosis complex specifically.[33–35] Based on this, several practice parameters have highlighted this benefit as perhaps elevating the use of vigabatrin over corticosteroids for this single condition.[33–35]

The adverse effect profile of vigabatrin is significant, unfortunately. One of the most concerning is the effect of vigabatrin on retinal function,[38] with the occurrence in 15% to 31% of infants specifically of a peripheral visual field defect.[37]

This adverse effect is difficult to monitor, and serial sedated electroretinograms may be necessary for infants. The earliest reported changes in infants occurred after 3 months, therefore, it is recommended that visual field testing needs to be obtained after 3 months and every 3 months afterward.[37] It seems reasonable therefore to begin vigabatrin in infants with infantile spasms on a trial basis (2–4 weeks), obtaining an electroretinograms only if vigabatrin is continued and monthly weighing the risks of vigabatrin versus benefits once clinical spasms and hypsarrhythmia have resolved. Many centers will discontinue vigabatrin after 6 months if fully successful. Vigabatrin has also been associated with changes on MRI (T2-weighted changes in the thalamus, basal ganglia, corpus callosum, and midbrain) which appear to be reversible and asymptomatic, with uncertain clinical significance or cause.[39] Prospective studies of these MRI findings in patients exposed to vigabatrin are being planned. Psychosis and behavioral change have also been described.

Ketogenic Diet

In 62% the ketogenic diet completely stopped the spasms, normalizing the EEG within 2 months.

The ketogenic diet (KD) is a high fat, adequate protein, low carbohydrate diet used continuously for the treatment of intractable childhood epilepsy since 1921.[40] It can be easily provided as an infant formula and substituted for the current nutritional source (be it infant formula or breast milk) with excellent ketosis in infants readily achievable. First described as efficacious in 70% of cases of infantile spasms by Nordli et al in 2001 as part of a larger series of infants with epilepsy,[41] it was later specifically reported as effective in 72% of 23 cases of infantile spasms after 6 months of treatment by our institution.[42] In this series, the KD was typically used after other medications had failed, including 75% who had tried ACTH unsuccessfully.[42] Side effects were minimal and limited to constipation, kidney stones, weight loss, and gastroesophageal reflux. Perhaps most importantly, 57% had cognitive improvements reported, typically in conjunction with seizure control.[42] The most recent retrospective experience with the ketogenic diet in 43 infants was reported by Eun et al,[43] with even greater improvement, including a spasm-free response of 53.5% (27/43 infants).

Because the KD is very effective in recalcitrant infantile spasms, could it be used as a first-line therapy? In 2008, we reported our retrospective experience treating 13 infants aged 2 to 10 months with the KD for new-onset infantile spasms.[9] Families were offered the diet with the understanding that ACTH would be started if the diet was unsuccessful after 2 to 3 weeks. In 8 (62%), the KD completely stopped the spasms, normalizing the EEG within 2 months.[9] Recurrence was limited to only 1 in 8, and that child responded to diet modification. Four of the 5 infants who did not respond to the KD later responded to ACTH and had good outcomes. As of the writing of this review, we have now seen a spasm-free response within 2 weeks in a total of 11 of 19 infants (58%). We, therefore, strongly believe that this therapy has a role as a viable first-line treatment if an infant is brought to a medical center that offers the diet within 2 weeks of presentation. The current Johns Hopkins protocol is listed in Table 4.

TABLE 4. Johns Hopkins Hospital Ketogenic Diet Protocol for New-Onset Infantile Spasms

Baseline
Obtain complete blood count, comprehensive metabolic profile, fasting lipid profile. Registered dietitian familiar with the ketogenic diet discusses with the family the current nutritional intake (formula/breastfeeding, amount per d).
Diet initiation
Change any supplemental medications to carbohydrate-free preparations. Fast for 24 h (carbohydrate-free clear fluids allowed). Check finger-stick blood glucose every 8 h during fasting period. After 24 h, begin 4:1 ketogenic diet formula (50% of calculated daily calories first 24 h). Check urine ketones daily.
Two-wk assessment
Assess seizure response by phone. If spasm-free, begin oral citrates, multivitamin and calcium (if not included in ketogenic infant formula). If not, discontinue ketogenic diet and begin oral corticosteroids.
Four-wk assessment
Evaluate infant in clinic and obtain follow-up EEG to confirm improvement.
Twelve-wk assessment
Evaluate infant in clinic, repeat baseline laboratory studies, and can decrease ketogenic ratio to 3:1 if indicated or desired (based on growth and/or tolerability).
Twenty-four-wk (final) assessment
Evaluate infant in clinic and repeat EEG again. If EEG is normal discontinue the ketogenic diet gradually by reducing the ratio biweekly until 1:1 and then restart regular formula or milk.

Topiramate

The reported spasm-free rates with topiramate are approximately half of that of corticosteroids and vigabatrin.

Another increasingly popular anticonvulsant being used, especially in the United States, is topiramate. In a manner similar to vigabatrin and the KD, it is often started by centers who wish to avoid corticosteroid side effects for infants brought to medical attention quickly. This anticonvulsant is a feasible option as it is widely available, has a sprinkle formulation (which can be administered with applesauce or baby foods), is relatively well-tolerated in infants (adverse effects include primarily acidosis, weight loss, and sedation), and could be continued long-term without the duration-dependent side effects of corticosteroids and vigabatrin. Dosing is somewhat higher than for other forms of epilepsy, with 10 to 30 mg/kg/d typically described.[28–30,44–46]

The reported spasm-free rates with topiramate, however, are approximately half of that of corticosteroids and vigabatrin. There have been 3 recent prospective studies since 2006, with 3 of 15 (20%),[28] 6 of 20 (30%),[29] and 4 of 19 infants (21%)[30] responding to topiramate as a first-line therapy. In the most recent study, 2 of the successfully treated infants required as long as 8 and 69 months to see this effect.[30] Topiramate's efficacy appears higher in the refractory cases. In studies evaluating topiramate as an adjunct for intrac-

table infantile spasms, there was 18% to 45% spasm-freedom with its use.[44–46]

Pyridoxine (Vitamin B6)

Experience with pyridoxine (vitamin B6) therapy outside of pyridoxine dependency is also very limited, with most published reports and experience initially from Japan. Although relatively easy to provide (no prescription needed, in fact), the data suggests very poor efficacy, with 13% to 29% response in the first 2 formal studies.[31,32] The 2004 AAN/CNS practice parameter went as far as to comment that the response rate for pyridoxine is similar to the reported spontaneous remission rate.[33] A recent randomized, placebo-controlled trial of sulthiame began with an open-label, 4-day pyridoxine treatment for all 37 infants.[25] No child in this study responded to pyridoxine.[25] Many neurologists, however, especially in Japan provide vitamin B6 initially as a brief trial, despite this weak evidence, perhaps as a result of its safety and ease of use.

Other Anticonvulsants in Active Clinical Use

Several additional anticonvulsants have been used in limited studies. Valproate was reported to be efficacious in 72% to 73% of infants after 3 to 6 months in 2 prospective but uncontrolled studies in 1988 and 1992.[21,22] Interestingly, despite the surprisingly reported high efficacy, valproate has not been formally studied as monotherapy to my knowledge in the past 17 years. This may be due to the higher risk of hepatic dysfunction in children under age 2 years with metabolic disorders and absent elimination by glucuronidation at this age.

Nitrazepam has also been evaluated in 2 retrospective studies, with 30% to 54% spasm-freedom reported.[23,24] Zonisamide is quite popular in Japan, and occasionally used in lieu of topiramate for intractable infantile spasms. Reports describe 33% to 36% response to new-onset spasms.[26,27] In the single randomized, placebo-controlled study of sulthiame, 6 of 20 (30%) infants became spasm-free by 9 days.[25] Levetiracetam has been reported as effective for recalcitrant infantile spasms,[47] but never studied to my knowledge as a first-line therapy.

Ganaxolone

Ganaxolone is an agent of a novel class of compounds referred to as "neuroactive steroids" that affect the $GABA_A$ receptor.[48] Although it has no hormonal effects, it was developed after progesterone was identified as having anticonvulsant benefits. In a prospective, open-label study, ganaxolone was reported as efficacious in 5 of 20 (25%) children with mostly intractable infantile spasms using an intent-to-treat analysis.[48] No information currently exists regarding its use for new-onset infantile spasms. Ganaxolone is currently being studied in a multicenter clinical trial in the United States specifically for infantile spasms (Marinus Pharmaceuticals, Inc.) and is in phase III development at this time.

Epilepsy Surgery

Epilepsy surgery has been described as beneficial for children with intractable, infantile-onset epilepsy. Many epileptologists advocate operating early to theoretically improve the chances of normal development. There is limited information, however, regarding epilepsy surgery for children with infantile spasms specifically. One study described seizure-free outcomes in 15 (65%) of 23 infants treated for intractable infantile spasms.[49] Another more recent from the Cleveland Clinic reported 11 children with spasms who had surgery including hemispherectomy, but they were not differentiated in terms of outcome from the other 13 children.[50]

Although often considered a "last resort," if a focal lesion exists, it may be reasonable to proceed quickly toward surgery, perhaps after corticosteroids and vigabatrin have both been unsuccessful. Of course, the decision is ultimately up to the parents and the known and predictable loss of motor function that would occur after a hemispherectomy (for example) needs to be carefully considered in light of the often unknown and unpredictable developmental outcome of persistent infantile spasms. Similarly to the KD, epilepsy surgery should be considered and performed in a center familiar with its use in young infants to maximize its potential success.[51]

PROGNOSIS

Most children do poorly, with 80% to 90% having developmental delay, often profound.

Overall, most children do poorly, with 80% to 90% having developmental delay, often profound.[6,52] What factors influence the prognosis? For many years, it was often stated that the only factor influencing later cognitive outcome was the underlying etiology for the infantile spasms, with those having symptomatic etiologies doing poorly. Treatment had little influence on outcome.

This somewhat fatalistic concept has been recently challenged. Factors that have been reported to predict a good prognosis include a cryptogenic etiology, age at onset older than 4 months, absence of atypical spasms and partial seizures, no seizures prior to spasms, absence of asymmetric EEG abnormalities, rapid treatment, and a quick response without recurrence.[6,52] Children with infantile spasms due to Down syndrome, neurofibromatosis, and periventricular leukomalacia may have a more benign prognosis.[6]

In a thought-provoking study from Kivity et al in Israel, 22 infants with cryptogenic IS treated within 1 month of onset of infantile spasms with ACTH were compared with 15 treated after 1 to 6.5 months.[10] All of those treated within 1 month had normal cognition, compared with only 40% of those treated later, $P < 0.001$.[10] Several other studies have also commented on the improvement in development with early treatment,[53–55] although some have differentiated this response to occur only in those with cryptogenic infantile spasms.[56] The 2004 American Academy of Neurology/Child Neurology Society Practice Parameter concluded that the evidence for early treatment was "conflicting" and "insufficient."[33] Despite this, the majority of pediatric epileptologists feel that children with new-onset infantile spasms, regardless of the etiology, should be evaluated, diagnosed, and treated as promptly as possible.

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ANIMAL MODELS

One of the largest obstacles to developing new treatments for infantile spasms has been the historic lack of an appropriate animal

model. Previous attempts to develop animal models have been unable to mimic the clinical epileptic spasms, EEG findings, and unique response to nonconventional anticonvulsants seen in West syndrome. However, recent advances, especially since 2007, have led to new and exciting potential animal models.[2] These models, listed in Table 5, may provide a way to test novel therapies that would otherwise never see sufficient numbers of children for a feasible clinical trial.

FUTURE DIRECTIONS

What will the next decade see in regards to infantile spasms? Hopefully new parent support group and national organization initiatives will raise public awareness and improve early detection so that all pediatricians and parents are warned and educated at the 2-month well-child examination. Diagnostically, advances in neuroimaging (3 and 7 Tesla MRI, diffusion tensor imaging) and neurogenetics will continue to identify the etiology for more affected infants and reduce the percentage of idiopathic infantile spasms to effectively zero. As structural etiologies are increasingly found by MRI, those infants with a surgically approachable focus could be operated within weeks of diagnosis if corticosteroids are ineffective. New treatments will continue to be developed as animal models become widely available to test novel anticonvulsant compounds, including for specific etiologies and conditions responsible for infantile spasms. The primary outcome of clinical trials will be long-term intelligence and developmental outcomes, rather than clinical spasms or EEG currently. Oral prednisolone will be the gold standard of treatment but combination therapies will become increasingly used to approach 90% to 100% spasm-free rates. Already, vigabatrin is currently under further evaluation in combination with corticosteroids in England (International Collaborative Infantile Spasms Trial). These future combinations may include diet, supplements, anticonvulsants, and corticosteroids altogether, with stepwise weaning of individual treatments gradually when effective.

CONCLUSIONS

This is an exciting time for neurologists treating infantile spasms. Advances in diagnosis and treatment are occurring at a rapid pace. As these new tests and treatments continue to be widely available to infants, a cure for this devastating condition may be hopefully here after nearly 2 centuries of frustration.

TABLE 5. Animal Models of Infantile Spasms[2]

Model	How Model is Created
CRH/stress	CRH intraperitoneally.
Betamethasone/NMDA	Betamethasone intraperitoneally to dam on G15, followed by NMDA intraperitoneally to offspring on P15.
TTX	TTX intracerebral infusion by osmotic pump for 28 d, beginning on P10.
Multiple-hit	Doxorubicin intracerebroventricularly and lipopolysaccharide intracerebrally on P3, followed by p-chlorophenylalanine intraperitoneally on P5.
ARX knockout	Targeted deletion of *ARX* gene from cortical interneurons.
Down syndrome	$GABA_B$ receptor agonists intraperitoneally to Ts65Dn mice.

Adapted from *Epilepsy Curr.* 2009;9:75–81.

CRH indicates corticotropin-releasing hormone; TTX, tetrodotoxin; G, gestational day; P, postnatal day; *ARX*, Aristaless-related homeobox; GABA, gamma-aminobutyric acid.

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