

# Catastrophic epilepsies: Clinical controversies of infantile spasms

<sup>1,2,4</sup>Yoshimi Sogawa, <sup>1-4</sup>SL Moshé

<sup>1</sup>The Saul R. Korey Department of Neurology, <sup>2</sup>Department of Pediatrics, <sup>3</sup>The Dominick P. Purpura Department of Neuroscience and <sup>4</sup>the Montefiore/Einstein Epilepsy Center, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA.

## Abstract

Infantile spasms is an age-specific epilepsy syndrome, often associated with a grim prognosis in terms of epilepsy and cognitive outcome. Major obstacles to achieve significant progress in treating these patients are: the relative rarity of the syndrome, their heterogeneous etiologies and variable evolutions that limit the reported cases to small numbers with different follow up periods. This article addresses some of the clinical controversies that are critical when considering future studies and treatment trials of infantile spasms.

## INTRODUCTION

Infantile spasms is an age-specific epilepsy syndrome, characterized by brief clustering seizures (spasms) accompanied with pathognomonic EEG patterns (hypsarrhythmia and electrodecremental responses) and often associated with a grim prognosis.<sup>1,2</sup> The majority of patients present before one year of age with an incidence of 2.5 per 10,000 live births with a slight male predominance.<sup>3,4</sup> The causes of infantile spasms are diverse, but can be classified into symptomatic and cryptogenic groups for diagnostic/prognostic purposes. Symptomatic infantile spasms are considered the consequence of an identified central nervous system (CNS) disorder and comprise 60-80% of cases. In the cryptogenic group, growth and development prior to the onset of infantile spasms are normal, and a CNS abnormality is suspected but remains unidentified. In both symptomatic and cryptogenic groups, the emergence of the spasms is often associated with developmental regression and subsequently, children may become mentally retarded with or without autistic features.<sup>5,6</sup> Many will develop other seizure types including Lennox-Gastaut syndrome and partial epilepsy.<sup>6-8</sup> Since the initial description by West<sup>9</sup>, there is an extensive literature. However, there still many questions left unresolved and several controversial issues.

## CLINICAL CONTROVERSIES

The clinical controversies of infantile spasms are listed in Table 1.

**Table 1: Clinical controversies in infantile spasms**

- Are infantile spasms a form of an encephalopathy?
  - Are infantile spasms and hypsarrhythmia a form of non-convulsive status epilepticus?
  - Does hypsarrhythmia alone have negative impact on cognition?
  - Where is their proper place within the classification of the epilepsy?
- Why only some and not all patients with a disease (associated with spasms) will develop spasms?
  - Is there a common substrate that allows the expression of spasms in various diseases?
  - Can a heterogeneous condition be regarded as a single entity?
  - Is the traditional separation into “symptomatic” and “cryptogenic” groups justified?
- What influences the epilepsy and cognitive outcomes?
  - What influences the transition to other epileptic syndromes?
  - How high is the rate of spontaneous remission and when?
  - What determines the cognitive outcome?
- What is the optimal treatment?
  - Should the choice and duration of treatment be tailored by etiologies?
  - How do we assess treatment outcome in short- and long-term?

Address correspondence to: Yoshimi Sogawa, MD, Montefiore Medical Center, Department of Neurology, 111 E 210<sup>th</sup> Street, Bronx, NY 10467, Tel: 718-920-4378. e-mail: YSogawa@montefiore.org

Although clustering spasms with electrodecremental responses on EEG are the hallmark of the clinical manifestations in infantile spasms, it is difficult to assess whether there is an “interictal” period defined as “return to the baseline EEG”. Since the EEG continuously contains epileptiform discharges and ictal events, infantile spasms could be regarded as a form of non-convulsive status epilepticus. Viewing infantile spasms as a form of non-convulsive status epilepticus may lead to more aggressive medical interventions not to stop or decrease spasms, but to eliminate hypsarrhythmia and electrodecremental responses on the EEG. To assess the severity of EEG abnormalities as a potential biomarker for prognosis and its temporal change in response to the treatment, it is important to develop strict EEG criteria for hypsarrhythmia.<sup>10</sup>

Infantile spasms are not one actual disease and better viewed as “a final common pathway” of non-specific, often a time-limited response that can result from lesions in widespread locations cortical or subcortical, present at the appropriate maturational stage.<sup>11</sup> Most of symptomatic infantile spasms are a rare manifestation of unrelated diseases such as tuberous sclerosis, genetic mutations (Trisomy 21, ARX gene mutation), inborn errors of metabolism, cerebral dysgenesis or hypoxic ischemic encephalopathy. It is largely unknown why only some and not all patients with each disease associated with spasms will develop spasms but is likely that infantile spasms may have a common substrate that goes across the various etiologies.

Early recognition of infantile spasms and rapid control of spasms with normalization of EEG has been suggested as a good prognostic factor for long-term outcome, especially in patients with cryptogenic infantile spasms.<sup>12</sup> It is not yet clear if the rapid and complete response is a function of underlying pathology, but these data suggest that prompt control of spasms within a short period from the infantile spasms onset may be beneficial. However, it has been difficult to compare the treatment response between the trials, because of the variable outcomes at different follow-up periods on each trial. Also, the long-term outcomes in terms of epilepsy and cognitive function are significantly influenced by underlying etiology, which is variable among the studied populations.<sup>13,14</sup> Infants in the cryptogenic group do better than infants in the symptomatic group, and the trials with high ratio of cryptogenic cases tend to report better treatment response and long-term outcomes. Overall, 25% of patients with

infantile spasms recover fully and remain seizure free and one third of patients will transform into Lennox-Gastaut Syndrome, another epileptic encephalopathy with onset in early childhood.<sup>8</sup> The mechanisms responsible for the variable evolution of the seizure patterns are unknown and spontaneous remissions have been reported.<sup>15,16</sup> These factors make correct assessment of treatment efficacy difficult. Infantile spasms are often refractory to conventional anti-epileptic drugs. The most widely accepted treatment is ACTH and its response rate varies from 40 to 100%.<sup>17,18</sup> The appropriate doses and duration of ACTH have not been determined for the specific disease categories that comprise infantile spasms and the doses range from 5 IU/m<sup>2</sup>/day synthetic ACTH to 150IU/m<sup>2</sup>/day of natural ACTH. Vigabatrin is effective in some cases too, especially in infantile spasms associated with tuberous sclerosis.<sup>19</sup> There is no clear consensus if the choice and duration of treatment be tailored by etiologies except for vigabatrin as an alternative first choice in tuberous sclerosis.

Irrespective of the underlying etiology, many patients with infantile spasms begin losing developmental milestones and, subsequently may become mentally retarded with or without autistic features, as the infantile spasms progresses. Although infantile spasms may spontaneously remit, cognitive deficits persist. Few studies have evaluated the incidence of autism in children with infantile spasms, but has been reported in 15% of children and is much higher than in general population.<sup>5,6</sup> Many of these children had tuberous sclerosis as the underlying etiology for infantile spasms. Indeed, the likelihood of autism is greater if the child has early-onset infantile spasms that are difficult to control in children with tuberous sclerosis.

## CONCLUSION

There has been a significant progress in recognizing infantile spasms, making the diagnosis, and identify the underlying etiology. However, treatment options are still limited either because of toxicity or lack of efficacy. Information about the factors influencing long-term cognitive outcomes, including autism and the occurrence of intractable epilepsy is needed. Our understanding of the mechanisms underlying the spasms will be augmented by the recent development of promising animal models.<sup>20,21</sup> In addition, multi-institutional and perhaps international collaborations are needed

to obtain data with enough statistical power and to answer some of the long-standing questions in this overwhelmingly poor prognosis epileptic syndrome that presents in infancy.

## ACKNOWLEDGEMENTS

Supported by NINDS grants NS-20253, NS48856, NS058303 and the Heffer Family Medical Foundation. YS is a NSADA trainee. SLM is the recipient of the Martin A. and Emily L. Fisher fellowship in Neurology and Pediatrics.

## REFERENCES

1. 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; 45:1416-28.
2. Hrachovy RA, Frost JD, Jr. Infantile spasms. *Pediatr Clin North Am* 1989; 36:311-29.
3. Primec ZR, Kopac S, Neubauer D. Epidemiologic features of infantile spasms in Slovenia. *Epilepsia* 2002; 43:183-7.
4. Riikonen R. Decreasing perinatal mortality: unchanged infantile spasm morbidity. *Dev Med Child Neurol* 1995; 37:232-8.
5. 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; 18:165-70.
6. Riikonen R. Long-term outcome of patients with West syndrome. *Brain Dev* 2001; 23:683-7.
7. Ito M, Kumagai T, Yamazaki Y, et al. Long-term prognosis of patients with West syndrome in Japan: medical aspects. *Brain Dev* 2001; 23:692-4.
8. Yamatogi Y, Ohtahara S. Age-dependent epileptic encephalopathy: a longitudinal study. *Folia Psychiatr Neurol Jpn* 1981; 35:321-32.
9. West W. On a peculiar form of infantile convulsions. *Lancet* 1841; 1:724-5.
10. Kramer U, Sue WC, Mikati MA. Hypsarrhythmia: frequency of variant patterns and correlation with etiology and outcome. *Neurology* 1997; 48:197-203.
11. Lado FA, Moshe SL. Role of subcortical structures in the pathogenesis of infantile spasms: what are possible subcortical mediators? *Int Rev Neurobiol* 2002; 49:115-40.
12. Kivity S, Lerman P, Ariel R, Danziger Y, Mimouni M, Shinnar S. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotrophic hormone. *Epilepsia* 2004; 45:255-62.
13. Matsumoto A, Watanabe K, Negoro T, et al. Long-term prognosis after infantile spasms: a statistical study of prognostic factors in 200 cases. *Dev Med Child Neurol* 1981; 23:51-65.
14. Lombroso CT. A prospective study of infantile spasms: clinical and therapeutic correlations. *Epilepsia* 1983; 24:135-58.
15. Hrachovy RA, Glaze DG, Frost JD, Jr. A retrospective study of spontaneous remission and long-term outcome in patients with infantile spasms. *Epilepsia* 1991; 32:212-4.
16. Hattori H. Spontaneous remission of spasms in West syndrome--implications of viral infection. *Brain Dev* 2001; 23:705-7.
17. Hancock E, Osborne JP, Milner P. Treatment of infantile spasms. *Cochrane Database Syst Rev* 2002; CD001770.
18. Mackay MT, Weiss SK, Adams-Webber T, et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. *Neurology* 2004; 62:1668-81.
19. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: literature review. *J Child Neurol* 1999; 14:71-4.
20. Lee CL, Frost JD, Jr., Swann JW, Hrachovy RA. A new animal model of infantile spasms with unprovoked persistent seizures. *Epilepsia* 2008; 49:298-307.
21. Mares P, Velisek L. N-methyl-D-aspartate (NMDA)-induced seizures in developing rats. *Brain Res Dev Brain Res* 1992; 65:185-9.