Published in final edited form as:
Epilepsia. 2003 August ; 44(8): 993–994.

Treatment of Infantile Spasms: The Ideal and the Mundane

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Over 150 years after the description of infantile spasms (IS, 1), fifty years after the delineation of hypsarrhythmia (2), and forty years after the coining of the term “west syndrome” (3), there is little progress in understanding and effectively treating this disorder.

This may not be surprising, because there is little consensus about most features of this enigmatic syndrome: is it a generalized seizure disorder, as classified by the ILAE (4), or focal seizures arising from “hidden” limbic (5) or brainstem (6) regions? Are the spasms truly seizures, or does the pervasive hypsarrhythmia signify a state of virtual status epilepticus? Some of the least defined aspects of infantile spasms remain in the treatment arena. Indeed, even the need for treatment has been debated (7), particularly in view of the fact that IS seems to remit spontaneously in most affected infants (8, but see 9). However, a broad consensus does exist on the merits of therapy for IS. This is particularly true because of often clear regression of an affected infant—whether or not his/her development had been normal prior to the onset of spasms (10,11). Further, successful treatment may lead to dramatic improvements in cognition and function. Therefore, a quest for effective, well tolerated therapies for IS has been the Golden Fleece of the clinical Argonauts in the field.

The relative ineffectiveness of conventional anticonvulsants for IS had been established by the mid 20th century (reviewed in 10,11). The pioneering work of Sorel (12) suggested that the neuropeptide corticotropin (ACTH), acting directly within the brain (13–15) might suppress IS. Early anecdotal clinical success with ACTH (12,16) was confirmed by blinded controlled studies, although the rate of ACTH efficacy varied from ~40 to 88% (17,18). Whereas the rapid and robust effects of ACTH in eradicating IS and the hypsarrhythmia reported in these studies were impressive, the underlying mechanisms remained unclear. Actions directly within the brain were suggested by concurrent work in animals (13,19), but the lack of efficacy of analogs that do not release endogenous steroids (14,15) led to the conclusion that ACTH acted on IS by releasing endogenous glucocorticoids, a view supported by the (more limited) efficacy of the latter hormones (19,20). The notion that ACTH and glucocorticoids share a hormonal action that alters immune (20), stress (21), inflammatory or other derangements in IS became prevalent, to the point that both classes of compounds are commonly referred to as “steroids” (20). In addition, the rationale for the use of one is often based on efficacy and side effects of the other.

More recently, unique mechanisms of action of ACTH, entering the CNS and acting on melanocortin receptors (MCRs) to reduce an excitatory neuropeptide in limbic structures has been put forth (22). These data suggest that analogs of ACTH that bind MCRs but do not release steroids might constitute the longed-for Golden Fleece—the successful, hypothesis-driven therapy that is free of severe systemic side effects of ACTH and high dose steroids (21,22).

Whereas this ethereal goal might be realized in the future, much effort has been directed over the past 50 years to evaluate the role of available anticonvulsants for IS, and each new promising drug has been tested on these seizures (e.g., 23,24). The discovery of vigabatrin in particular raised tremendous hope: The drug controlled the spasms and improved or

eliminated hypsarrhythmia initially in uncontrolled (25), then in larger controlled trials (26,27), and particularly in IS associated with tuberous sclerosis (28). Whereas the precise efficacy of vigabatrin has not been fully defined (27,29), the medication has rapidly gained prominence as a key step forward in the Argonauts' quest for optimal IS therapy.

The use of vigabatrin for IS has more recently been significantly curtailed by the emergence of apparently irreversible retinal changes and altered peripheral vision upon its use. While these side effects have diminished the likelihood of the drug's approval in the U.S., vigabatrin remains an important mainstay in the treatment of IS in Europe, together with earlier anticonvulsants with some established efficacy, such as nitrazepam (30). In addition, among the emerging crop of new anticonvulsant medications, none has shown exceptional efficacy for the disorder. Based on all of this, how should a clinician treat an infant with IS?

Whereas the optimal therapy for this disorder remains elusive, the paper by Capovilla and colleagues in this issue describes some of the approaches that are being utilized in Europe. The paper discusses the use of nitrazepam and vigabatrin, and addresses specifically the issue of treatment duration: when is it safe to discontinue the medication? Using a collaborative multicenter approach, the authors demonstrate that at least in some infants, treatment may be stopped, without seizure recurrence, after several months. This information should be significantly helpful to clinicians who are facing these issues.

Other related questions continue unanswered: How many infants with IS were seen? How many were treated with these drugs and did not respond, or were excluded for a variety of reasons?—in other words, what is the likelihood that a clinician treating an infant with nitrazepam or vigabatrin will be successful in controlling the spasms and in discontinuing therapy. These answers are still shrouded in mists, as are those for the cardinal questions of which drugs to use and how to evaluate their efficacy. Still, while the optimal therapy for IS, based on the understanding of its pathophysiology, remains our Golden Fleece, the paper by Capovilla et al., provides useful hints for practical management of the disorder.

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