



Infantile Spasms: The Devil Is in the Details, But Do We See the Forest for the Trees?

Seizure Outcome in Infantile Spasms—A Retrospective Study.

Basheer Peer Mohamed, Rod C. Scott, Nivedita Desai, Pranathi Gutta, Shekhar Patil. *Epilepsia* 2011;52(4):746–752.

PURPOSE: Prior to the United Kingdom Infantile Spasms Study (UKISS), our practice was to initiate vigabatrin for infantile spasms. However, since then we tend to use steroids as first-line agent for infantile spasms. Herein we compare seizure-free outcomes in children with infantile spasms on steroid therapy or vigabatrin therapy. **METHODS:** This was a retrospective case study over 8 years of children with infantile spasms who were treated at our center. A positive response to therapy was defined as a two-week spasm-free interval. **KEY FINDINGS:** Of the 98 children presenting to us, 75 were included for this study. The ratio of cryptogenic to symptomatic spasms was 24:51. The response rate for steroid therapy was 61.1% and 42.5% for vigabatrin. Cessation of spasms was achieved faster in the group receiving steroids. Both groups had similar relapse rates. Steroids had significantly better response in the cryptogenic group, whereas in the symptomatic group both the medications were equally effective. Cryptogenic spasms have a better neurodevelopmental outcome. Early introduction of therapy for spasms did not predict a good neurodevelopmental outcome. Seventy-eight percent of children with spasms had seizures of other types at 12 months follow-up. **SIGNIFICANCE:** At our center, steroids are now the preferred choice for initial therapy of infantile spasms. This is likely to have been a beneficial change, particularly for children with cryptogenic spasms. Spasms in 25% of the patients tend to be refractory, and the majority of patients from the cohort continue to have epilepsy with motor and cognitive disabilities.

Commentary

It is generally acknowledged that infantile spasms (IS) are a devastating disease with a poor prognosis. Hormonal preparations in the form of ACTH or oral corticosteroids, as well as vigabatrin, are well-established treatments (1–4). The cessation of spasms is achieved in 30 to 93 percent of patients and does not necessarily indicate a good developmental outcome (3–4). Several small and large prospective trials were conducted (3–4). Practice guidelines from 2004 concluded that ACTH is probably effective, but the evidence is too inconclusive to make recommendations about one treatment method over another. In the interim, a large prospective controlled trial, the United Kingdom Infantile Spasms Study (UKISS), demonstrated the superiority of steroids in spasm cessation but showed no difference in seizure or cognitive outcome at 1 year (1). This particular trial excluded children with tuberous sclerosis (TS). There is general agreement that tuberous sclerosis appears selectively responsive to vigabatrin (3). Cryptogenic spasms without proven etiology have a better prognosis than symptomatic spasms.

The study by Mohamed et al. retrospectively reviews treatment of IS in a single center. It confirms that cryptogenic IS

have a more favorable prognosis, and that oral steroids lead to a more rapid cessation of spasms than vigabatrin. However, overall responder rate and long-term outcome are similar regardless of treatment. Children whose spasms responded to treatment tended to have a better prognosis. They could not reproduce that treatment delay (>28 days after the onset of spasms) was associated with a worse prognosis (5).

Although many aspects of the study are confirmatory, retrospective studies of this type serve an important function. First, the study includes all comers and reflects more general neuropediatric practice. Prospective clinical trials enroll very selective populations. The study is useful to counsel parents about the prognosis and provides some guidelines for treatment. The investigators also examined second-line treatment, which is studied less frequently. Combination therapy did not have a synergistic effect. Second, such studies give us the opportunity to reflect upon our clinical practice and subsequent treatment decisions.

Controlled prospective trials influence what we do, as demonstrated in this study. UKISS had a significant influence on the treatment patterns of the investigators. However, only a few questions in neurology are truly settled by prospective studies, and we have to resort to the art of medicine, where the devil lies in the detail, such as preparations, dosages and subpopulation of patients.

Mohamed et al. treated patients with oral prednisolone at higher doses. Other important trials used high- or low-dose



ACTH injections. ACTH is available in a synthetic or natural form, depending on the country. Studies comparing ACTH to oral formulations of prednisone may have given only low doses of the latter (6). Dosing of ACTH is still a matter of debate. If vigabatrin is studied, there is no consensus about the dosing (7).

We cannot ignore other factors, which certainly influences our medical practice to an equal amount as controlled trials. The prevailing medical or institutional culture, healthcare systems and cost probably influence us more than we want to admit. The study was conducted in the United Kingdom, where oral prednisolone is well established for the treatment of spasms. Vigabatrin has been widely available in Europe since the early 1990s and has been a preferred treatment in many centers for the ease of use. It has only recently been approved in the United States and is not considered first-line therapy (3). In the United States, ACTH is widely used despite a considerable increase in cost over the last decade. However, just for financial reasons, oral formulations have become more commonplace. Natural ACTH is preferred in the United States and synthetic, in Europe. Some centers that have extensive expertise in the ketogenic diet advocate diet as a first-line treatment (8). Centers with extensive experience in one or the other will favor a certain treatment. We would not be honest if we denied that those factors do influence treatment decisions, and above that, the design of clinical trials.

Despite a differing response initially, Mohammed et al. again confirmed that steroid and vigabatrin do not differ in long-term seizure or neurodevelopmental outcome. It could be hypothesized that vigabatrin takes longer in its effectiveness. Do none of those interventions have an effect on cognition and we are just treating the symptoms of spasms? Then, the real problem is the underlying disease. But, undeniably, patients whose spasms cease and don't return do better in terms of seizures and development. Stopping the seizures should then be sufficient, shouldn't it?

Steroids and vigabatrin are both not innocent in regards to side effects. Steroids acutely cause hypertension, somnolence, adrenal dysfunction, and immunosuppression. Vigabatrin has a cumulative retinal toxicity, which is difficult to assess in infants and has not been studied long-term. Animal data suggest apoptosis, and ominous MRI changes with vigabatrin remain unexplained. Steroids and cognition represent another unexplored field. What are the neurodevelopmental effects of the administration of steroids in infancy? It is inconceivable that steroids, which have significant CNS effects on the adult brain, do not influence cognitive development in the immature brain. It is interesting that the neurocognitive outcome was better in children receiving lower doses of steroids for IS (9).

Besides pondering the details of how much, which hormone, and in what form, aren't we missing an important point? In this study, 87% of children had abnormal developmental outcome and 77% still had seizures after 12 months in the study. A report of 192 children 30 years ago reports an abnormal development in 88% (9). It seems we have not made big strides in more than a generation. Do we see the forest for the trees?

We certainly progressed in identifying subgroups of patients that do better, but the neurocognitive devastation with IS remains the largest burden for patients and parents (3). Are the spasms, the EEG changes, the underlying etiology, or possibly our treatment responsible for this dismal outcome? As with many things in nature, the answer will certainly not rest in one or the other, but probably in a combination of all those factors. We have focused our efforts over the last decades in treating spasms. Maybe it is time to shift our focus. We need to better understand the contribution of seizures to cognitive development without ignoring the underlying etiology. We need to also realistically evaluate the effects of our therapy. Extending studies beyond mere seizure cessation and developing strategies to enhance neurodevelopment are vital. More research and clinical trials in a multicenter fashion are urgently needed. Animal models can help in this quest (10), but they do not relieve us from applying what we learn to humans.

by Barbara C. Jobst, MD

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