Prevention of infantile spasms in tuberous sclerosis complex

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Since the ground-breaking work of Gomez in the 1970s and the later epidemiological studies of Webb and Osborne(1), the link between early onset epilepsy, especially infantile spasms (IS), and intellectual disability in tuberous sclerosis complex (TSC) has been accepted. This association raises the question of whether prevention of epilepsy in early life in TSC patients may improve the longer-term cognitive outcome.

One of the problems with pursuing a preventative approach is that not all TSC patients will develop epilepsy and it is debatable whether all TSC patients diagnosed before the onset of epilepsy should be exposed to a medication with significant side–effects. Vigabatrin - the the proposed prophylactic agent - is associated with visual field deficits in a significant proportion of patients and causes characteristic MRI brain changes in the basal ganglia, brain stem and cerebellum that may also be associated with adverse neurological outcomes. However, it has been shown that EEGs performed early in life in TSC patients accurately identifies those who are most at risk of developing future clinical seizures(2). In these patients, notwithstanding the possible side-effects of therapy, the balance perhaps shifts in favour of using prophylactic vigabatrin.

The question of whether prophylaxis does lead to improved outcomes is being explored. Previous open label non-randomised studies suggest that the prophylactic approach is associated both with better epilepsy and cognitive outcomes(3). These studies are possibly undermined by selection bias and the fact that there is comparison of a prospectively followed preventative group and a historical cohort who had different levels of care. In effect it was a comparison of two non-comparable groups.

The recently published EPISTOP trial addresses the question in a rigorous way(4). Although the numbers in EPISTOP included in the randomised controlled trial (n = 27) were small, it does show convincingly that the preventative approach delayed the onset of seizures. However, the EPISTOP trial is disconcerting for believers of the concept of an epileptic encephalopathy because it shows that despite preventative treatment delaying seizure onset, there was no difference in development between the two randomised groups. This result contrasted with the results from the Polish open-label study and perhaps underlines the need to be circumspect about the results of open-label studies using historical controls(3). In similar findings to the EPISTOP study, the ICISS study showed that despite the superiority of one treatment modality in treating IS, there was no difference in later developmental outcome(5). Is it possible that the infantile seizures are simply a marker (and not the cause) of something else that is determining developmental outcome? One argument against this may be the data on lead-time to treatment in IS being related to developmental outcome – suggesting that the longer the seizures are untreated, the worse the outcome.

Another limitation to the prophylactic approach in TSC patients, highlighted in Riikonen's paper in this edition, is that the vast majority of TSC patients will be diagnosed after seizure onset and therefore cannot benefit from a preventative approach(6). They can, however, be

treated rapidly once seizures occur. One explanation for no difference in development between the randomised groups in the EPISTOP study is that the conventionally treated group were being watched closely and were treated immediately upon seizure occurrence.

Riikonen's paper is a retrospective study of a historical cohort at the end of the last century. Ante-natal imaging, quality of EEG monitoring and awareness of TSC have all improved in the intervening years and it may be that a similar study today would show different results. However, it is still true that most cases of TSC are sporadic and are not diagnosed antenatally. A prophylactic approach will still only be available to a minority of cases.

This study also raises another tantalising question about treatment of IS in TSC. There is consensus amongst the paediatric neurology community that vigabatrin should be the treatment of choice for IS in TSC even though there is not an extensive high-quality evidence base for this belief. The data from Riikonen's paper demonstrates striking effectiveness of ACTH in their cohort and she speculates that this is due to the inflammatory activity of cortical tubers. This observation raises the question of whether a combination of vigabatrin and ACTH (or prednisolone) may be a more effective treatment modality than vigabatrin alone in IS associated with TSC and whether further trials of what may be the best treatment modality for spasms in TSC are now warranted.

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