



The Tuberous Sclerosis Association

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It reports on a presentation at a meeting of the TS Alliance in San Diego in July 2001.

Vigabatrin: Pros, Cons and Constricted Field of Vision

Dr Donald Shields, Professor of Neurology and Paediatrics at UCLA School of Medicine

Dr Rima Nabbout-Tarantino, consultant in Neuro=Paediatrics at Necker Enfant Malades in Paris.

Dr Shields gave the first part of the presentation. He explained that infantile spasms (IS) are really hard to control and if they are not controlled they are much more likely to result in significant learning disabilities. He pointed out that a lot of people have TS without actually knowing it, and this is usually because they don't have seizures or other problems. If someone develops seizures later on in early childhood, they may have some developmental problems, but not too many. However, if there are very early onset seizures, usually infantile spasms, there is a high probability of disturbed development. So, if you want to change developmental outcome, he stressed that you must improve seizure control.

The goal is to change the way the child will develop and this is done this by controlling the seizures.

There are several drugs which are reported to be useful for infantile spasms, but none is approved for IS by the FDA in the USA. ACTH is the most used drug in the USA for IS, although it was actually approved for endocrine use. Subsequently it was withdrawn, and it is now only available on special protocol and cannot be obtained from pharmacies. ACTH has a good response rate, but a high relapse rate, too, and children cannot be on it for more than a very brief period. Clonazepam, nitrazepam, sodium valproate and topiramate all have a reasonable success rate initially, (possibly 10-40%) but they also have a high relapse rate.

These drugs all have side effects, too. ACTH suppresses the immune system and makes children very hungry. Clonazepam makes children excessively sleepy. Nitrazepam is thought to have a higher mortality rate. Sodium valproate is not recommended for children under 2 due to the possibility of liver problems.

Dr Shields described a study he ran in the USA to look at vigabatrin and IS. Children who took part were under 2 years old, weighed at least 9 lb, and must not have been treated with ACTH, valproic acid or any other drug for IS. They were put on a low dose for 2 weeks, after which it was then increased. A patient had to be seizure free for 7 days

starting in the first 14 days for the treatment to be regarded as positive response and an EEG was needed after 3 days following those 7 days to confirm this. 11% of those children responded at a low dose, and they were mainly TS children. 36% responded at a higher dose. Of the TS children, more than half responded by 2 weeks. By 30 days, 40% of the others responded, but 75% of TS children responded! As time went on, 90% of the TS children responded, meaning they were seizure free.

Dr Shields stated that there is absolutely no question that children with TS and IS should be treated with vigabatrin since 90% will respond favourably.

What happens to these children who do respond? They are coming along really well developmentally as oppose to those who didn't respond well.

Of those children who didn't respond to vigabatrin, they were all on phenobarbitone. When they were taken off phenobarbitone, the seizures stopped. In children who were on no medication at all before starting on vigabatrin, 65% responded within one month. In children who were already on tegretol or phenobarbitone, there was a 50% response rate. If they were on tegretol and phenobarbitone, the response rate fell to 20%.

This is a huge difference.

If a child with TS and IS is on tegretol or phenobarbitone, you are not going to get the same response rate as those who are on vigabatrin.

Phenobarbitone is very popular in the UA and is usually tried first, so it's unlikely that those children will do well.

Vigabatrin was developed in the mid-80s and there were a couple of reports that in rats fluid cysts developed in the white matter of the brain. The FDA stopped human trials, but the Europeans carried on. They hadn't seen these cysts. Around the time the FDA had been about to approve the drug, there were reports from England that there were some visual field defects (VFD), a peripheral visual field loss.

Evidence shows that 25-50% patients will develop VFD on this medicine. If on it for a long time, you are likely to develop the problem. It does seem that there is a time and dose response: the higher the dose and the longer it is taken, the more likely that visual field defects will develop. The first 2-3 months seem to be problem free. Most patients don't even realise that they have a visual field problem. Does the problem go away when the medication is stopped? Reports say no, although some are now doubting this.

What does vigabatrin do in the brain? The brain is an electrical-chemical system, where electrical impulses are sent to the end of the neurons, where a chemical drops off the end onto the next neuron and says that it wants to become more or less excited. Vigabatrin works on GABA, an inhibitory neuro-transmitter, which wants to get less excited. When GABA drops off, an enzyme transmitter splits off and sends it back to be reabsorbed.

Vigabatrin locks on to that enzyme and makes the GABA level go up, so that the brain becomes more inhibited – called the suicide inhibitor.

It stays on that enzyme until that enzyme is destroyed and a new one made – and this takes 3 days. There is probably a receptor in the retina that this enzyme is locking onto and is blocking its action in the periphery of the visual field. It probably turns over eventually but may sit there for 2-3 years. We may find out one day.

- So, vigabatrin is the drug of choice for infantile spasms in TS.
- The only way to achieve good development is by stopping the infantile spasms.
- They mustn't be using phenobarbitone or tegretol.
- Controlled infantile spasms change developmental outcome drastically.
- Visual field defects are common and possibly irreversible.
- You can't test VFD in a child, so assume that the child WILL have VFD and that it WILL be permanent.
- But if you consider the developmental outcome, then you must TREAT REGARDLESS.
- Epilepsy surgery can cause VFD, but if the surgery results in seizure control it is worth it.
- Is vigabatrin useful for other seizures in TS? 75% of those treated for IS go on to develop other seizure types, sometimes focal., and vigabatrin isn't that helpful in these cases.

Dr Rima Nabbout-Tarantino, consultant in Neuro-Paediatrics at Necker Enfant Malades in Paris

Dr Rima Nabbout-Tarantino had better results when using vigabatrin for focal/partial seizures in her study . She noticed good control of partial seizures in 75% children, although few of these children had TS. She felt that vigabatrin may still be useful for young children with partial seizures since partial seizures may evolve into IS. She also felt that whilst carbamazepine may trigger IS, vigabatrin does not.

She quoted a number of studies in Europe where vigabatrin was very helpful for IS , especially in TS.