



VIGABATRIN'S COMPLICATED JOURNEY—TO BE OR NOT TO BE?

Visual Fields at School-Age in Children Treated with Vigabatrin in Infancy. Gaily E, Jonsson H, Lappi M. *Epilepsia* 2009;50(2):206–216. **PURPOSE:** The use of vigabatrin (VGB) as an antiepileptic drug (AED) has been limited by evidence showing that it causes vigabatrin-attributed visual field loss (VAVFL) in at least 20–40% of patients exposed at school age or later. VGB is an effective drug for infantile spasms, but there are no reports on later visual field testing after such treatment. Our aim was to investigate the risk of VAVFL in school-age children who had received VGB in infancy. **METHODS:** Visual fields of 16 children treated with VGB for infantile spasms were examined by Goldmann kinetic perimetry at age 6–12 years. Normal fields were defined as the temporal meridian extending to more than 70°, and mild VAVFL between 50 and 70°. Abnormal findings were always confirmed by repeating the test. Exposure data were collected from hospital charts. **RESULTS:** Vigabatrin was started at a mean age of 7.6 (range, 3.2–20.3) months. The mean duration of therapy was 21.0 (9.3–29.8) months and cumulative dose 655 g (209–1,109 g). Eight children were never treated with other AEDs, five received only adrenocorticotropic hormone (ACTH) in addition to VGB, and three children had been treated with other AEDs. Fifteen children had normal visual fields. Mild VAVFL was observed in one child (6%) who had been treated with VGB for 19 months and who received a cumulative dose of 572 g. **CONCLUSIONS:** The risk of VAVFL may be lower in children who are treated with VGB in infancy compared to patients who receive VGB at a later age.

Magnetic Resonance Imaging Abnormalities Associated with Vigabatrin in Patients with Epilepsy. Wheless JW, Carmant L, Bebin M, Conry JA, Chiron C, Elterman RD, Frost M, Paolicchi JM, Donald Shields W, Thiele EA, Zupanc ML, Collins SD. *Epilepsia* 2009;50(2):195–205. **PURPOSE:** Vigabatrin used to treat infantile spasms (IS) has been associated with transient magnetic resonance imaging (MRI) abnormalities. We carried out a retrospective review to better characterize the frequency of those abnormalities in IS and in children and adults treated with vigabatrin for refractory complex partial seizures (CPS). **METHODS:** Medical records and 332 cranial MRIs from 205 infants (aged ≤ 24 months) with IS treated at 10 sites in the United States and Canada were collected. Similarly, 2,074 images from 668 children (aged 2–16 years) and adults (aged > 16 years) with CPS were re-reviewed. Prespecified MRI abnormalities were defined as any hyperintensity on T2-weighted or fluid-attenuated inversion-recovery (FLAIR) sequences with or without diffusion restriction not readily explained by a radiographically well-characterized pathology. MRIs were read by two neuroradiologists blinded to treatment group. The incidence and prevalence of MRI abnormalities associated with vigabatrin were estimated. **RESULTS:** Among infants with IS, the prevalence of prespecified MRI abnormalities was significantly higher among vigabatrin-treated versus vigabatrin-naive subjects (22% vs. 4%; $p < 0.001$). Of nine subjects in the prevalence population with at least one subsequent determinate MRI, resolution of MRI abnormalities occurred in six (66.7%)—vigabatrin was discontinued in four. Among adults and children treated with vigabatrin for CPS, there was no statistically significant difference in the incidence or prevalence of prespecified MRI abnormalities between vigabatrin-exposed and vigabatrin-naive subjects. **DISCUSSION:** Vigabatrin is associated with transient, asymptomatic MRI abnormalities in infants treated for IS. The majority of these MRI abnormalities resolved, even in subjects who remained on vigabatrin therapy.

COMMENTARY

Vigabatrin is both a new and an old drug. For physicians in Europe, Canada, and many other countries except the United States, vigabatrin has been used as an antiepileptic drug since 1989, when it was first approved in the United Kingdom. With the realization in 1997 that vigabatrin could cause irreversible peripheral visual field deficits (1), the prescribing of vigabatrin has waned, and it now is essentially used in most

countries only for infantile spasms and patients with very resistant partial seizures.

From the largest prospective study on irreversible peripheral visual field deficits, based on 563 patients stratified into different treatment groups, it is now known that there are three major risk factors of vigabatrin-induced peripheral visual field deficits: male gender, extended treatment duration, and the cumulative dose of vigabatrin given (2). Data gathered so far suggest that: 1) the cumulative incidence increases rapidly during the first 2 years of treatment and within the first 2 kg of vigabatrin intake and 2) it stabilizes at 3 years and after a lifetime total vigabatrin dose of 3,000 mg (2,3). Patients with irreversible

peripheral visual field deficits who are withdrawn from vigabatrin do *not* show improvement in their visual fields. Until now, however, little was known about the possibilities of ophthalmological damage in infants and young children—the study by Gaily et al. fills this knowledge gap. Although a small study, all the children ($n = 16$) were treated for infantile spasms with vigabatrin, and the automated visual fields assessments were performed as soon as the children were old enough to be able to cooperate. The studies were carried out after at least 4 years on vigabatrin and are encouraging, as only one child had a slight peripheral visual field deficit and 15 others tested normal.

There is an important historical lesson regarding visual field deficits in humans: at the time vigabatrin was new and undergoing clinical trials, the FDA was the most skeptical of the agencies involved in assessing the drug, especially when it was realized that vigabatrin first, could cause retinopathy in rats and then that it was associated with reversible intramyelinic edema in the brains of rodents and dogs but not of monkeys (4). After extensive testing of patients in clinical trials and from autopsy reports, the intramyelinic edema concern for humans was laid to rest (2). Next, just when the FDA was reconsidering approving vigabatrin in the 1990s, the first confirmed reports of visual field deficits appeared. Now, 12 years later, vigabatrin has been exhumed in the United States, as the FDA again is deciding if it should be made available. On the heels of the FDA review, new articles about long-term vigabatrin use are being published in an attempt to better understand and calculate its risks and benefits. In other countries throughout the world, vigabatrin has proven to be an invaluable and effective treatment for infantile spasms (5). Very few side effects are reported among children, and vigabatrin seems to be extremely well tolerated in this patient population. Aware of this favorable profile, most pediatric neurologists in the United States await with enthusiasm the pending approval of vigabatrin.

Vigabatrin is an irreversible GABA-transaminase inhibitor and can increase whole GABA in the brain by 300% in a predictable, dose–response manner (6). There has never been another mechanism of action found for this drug that is of significance. Therefore, vigabatrin for the most part is considered to be a disease-specific compound, as GABA is an inhibitory neurotransmitter that is effective in inhibiting excitatory reactions, such as seizures (7).

How does vigabatrin cause peripheral visual field deficits? The retina is not protected by the blood–brain barrier, and 10% of vigabatrin in the blood will pass through the blood brain barrier to the brain (8). Far greater amounts of the drug are able to enter the retina, which has no significant barriers for vigabatrin; thus, vigabatrin and subsequent GABA levels are even higher in the ocular region. The most viable hypothesis to date, however, is that it is not GABA itself that affects the

cones of the retina, but rather vigabatrin. One study showed that when the retina is exposed to light, vigabatrin reacts to cause retinopathy—at least in rats (9). However, it has not been shown that the retinopathy in rats is the same as peripheral visual field deficits found in humans.

There may be several reasons why infants do not develop visual field deficits. Although the cause is not definitively known, developmental differences in cones (most affected in animals) and the specific stage of development of the optic nerve may prevent the deficits in infants. In addition, small children are not exposed to bright lights as often as older children and adults, which may impact the incidence. Yet, even in adult patients with partial onset seizures, for whom vigabatrin may be an effective last resort treatment, the total amount of vigabatrin ever taken is the most important factor in development of visual field deficits. Thus, one treatment strategy would be to treat a patient for 6 months, evaluate for efficacy, and if there is no beneficial effect, stop the treatment. If treatment is effective, continue it, while every 3–6 months closely monitor the visual fields with automated perimetry and discuss with the patient whether or not to carry on. The Gaily et al. study is valuable in demonstrating that the risk of field deficits is not as great for children as for adults; thus, therapy can be started in infants with minimal risk. However, as noted, therapy for infants needs to be continually reevaluated and attempts to stop the drug should be made after a year or so of successful therapy.

What does previous and current MRI analysis tell us about intramyelinic edema? Until recently, the changes in the intramyelinic edema and microvacuolization were not known to occur in humans. Because of the existence of intramyelinic edema in rodents and dogs, many MRI studies were done with patients who participated in the previous clinical trials (1990–1998), but no pathology was ever found (10). The first publication of intramyelinic edema and microvacuolization MRI changes in humans was in the form of an abstract, and a complete report was published in 2009 (11). The abnormalities were picked up by T₂-weighted MRIs, with increased signals on diffusion-weighted imaging (DWI) and fluid-attenuated inversion-recovery (FLAIR) studies. These studies were retrospective, with no control group, and the link between vigabatrin and intramyelinic edema on MRI still could not be firmly established.

The study by Wheless and colleagues presents the data of all known cases of suspect intramyelinic edema associated with vigabatrin-treated patients (mostly infantile spasms) as well as a review of all previous studies using MRI for children and adults. The analysis from this review suggests that intramyelinic edema and microvacuolization changes do occur in the immature brain but not that of older children and adults. The mechanisms underlying this finding are unknown, but the changes

seem to be largely reversible whether or not the drug is stopped. One speculation is that the harmful effects are caused by GABAergic neurotoxicity (12). The clinical consequences also are unknown, although many infants have been treated with vigabatrin without unusual events. However, these children often have other serious comorbidities, and it is unclear if any of the mental or physical disabilities are associated in any way with intramyelinic edema, as the clinical causes and associations could be hidden in the plethora of their disabilities and not be determined. Only a long-term prospective, placebo-controlled study of infants being treated with vigabatrin that uses MRI for the clinical assessment can answer this question (a study that the authors do suggest).

So, should infants be offered vigabatrin when faced with intractable infantile spasms? Maybe. However, it does seem unethical not to offer a chance at seizure freedom from this catastrophic form of epilepsy, which likely is equated with non-convulsive status epilepticus. A solution to the concern about prescribing vigabatrin could be to closely study all infants, follow the clinical efficacy, side effects, and MRI, and act immediately to cease the drug if T₂ abnormalities appear that were not present at baseline. The benefits of seizure freedom in these children may outweigh the unknown risks of reversible intramyelinic edema, but it is also important not to continue treatment when vigabatrin does not rapidly achieve a beneficial effect.

The controversy with vigabatrin continues, as it is a drug with excellent efficacy but unusual and disturbing side effects, which have limited its use for the last 12 years. Hopefully, the information gained from these two articles as well as by other recent studies on vigabatrin toxicity will shed some light on how it can still be used without causing harm, but rather only benefit, to the patient.

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References

1. Eke T, Talbot JF, Lawdden MC. Severe persistent visual field constriction associated with vigabatrin. *BMJ* 1997 Jan 18;314:180–181.
2. Wild JM, Hyo-sook A, Baulac M, Burszty J, Chiron C, Gandolfo E, Safran AB, Schiefer U, Perucca E. Vigabatrin and epilepsy: lessons learned. *Epilepsia* 2007;48:1318–1327.
3. Kalviainen R, Nousiainen I. Visual field defects with vigabatrin: epidemiology and therapeutic implications. *CNS Drugs* 2001;15:217–130.
4. Gibson JP, Yarrington JT, Loudy DE, Gerbig CG, Hurst GH, Newberne JW. Chronic toxicity studies with vigabatrin, a GABA-transaminase inhibitor. *Toxicol Pathol* 1990;18:225–238.
5. Willmore LJ, Abelson MB, Ben-Menachem E, Pellock JM, Shields WD. Vigabatrin: 2008 update. *Epilepsia* 2009;50:163–173.
6. Ben-Menachem E, Persson LI, Schechter PJ, Haegele KD, Huebert N, Hardenberg J, Dahlgren L, Mumford JP. The effect of different vigabatrin treatment regimens on CSF biochemistry and seizure control in epileptic patients. *Br J Clin Pharmacol* 1989;27:79S–85S.
7. Schechter PJ, Tranier Y. Effect of elevated brain GABA concentrations on the actions of bicuculline and picrotoxin in mice. *Psychopharmacology* 1977;54:145–148.
8. Ben-Menachem E, Persson L, Schechter PJ, Haegele KD, Huebert N, Hardenberg J, Dahlgren L, Mumford J. Effects of single doses of vigabatrin on CSF concentrations of GABA, homocarnosine, homovanillic acid and 5-hydroxyindolacetic acid in patients with complex partial seizures. *Epilepsy Res* 1988;2:96–101.
9. Izumi Y, Ishikawa MBenz AM, Izumi M, Zorumski CF, Thio LL. Acute vigabatrin retinotoxicity in albino rats depends on light but not GABA. *Epilepsia* 2004;45:1043–1048.
10. Cohen JA, Fisher RS, Brigell MG, Peyster RG, Sze G. The potential for vigabatrin-induced intramyelinic edema in humans. *Epilepsia* 2000;41:148–157.
11. Pearl P, Vezina LG, Saneto RP, McCarter R, Molloy-Wells E, Heffron A, Trzcinsk S, McClintock WM, Conry JA, Elling NJ, Goodkin HP, Sotero de Menezes M, Ferrie R, Gilles E, Kadom N, Gailard WD. Cerebral MRI abnormalities associated with vigabatrin therapy. *Epilepsia* 2009;50:184–194.
12. Ben-Ari Y. Basic development rules and their implications for epilepsy in the immature brain. *Epileptic Disord* 2006;8:91–102.