

# **VIGABATRIN-ASSOCIATED VISUAL FIELD LOSS (VAVFL): WHAT YOU NEED TO KNOW**

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## INTRODUCTION

Vigabatrin is used to treat infantile spasms and partial seizures that are common in tuberous sclerosis complex (TSC). First developed in 1975, vigabatrin potentiates the action of an important, protective neurotransmitter in the brain called  $\gamma$ -aminobutyric acid (GABA). Human clinical trials began in 1979 and first regulatory approval occurred in the United Kingdom in 1989, followed by Australia (1993) and Canada (1994). It wasn't until 8 years after the initial approval that the first reports of possible vigabatrin-associated visual field loss (VAVFL) appeared.<sup>1</sup> Citing VAVFL concerns, approval in the United States by the Food and Drug Administration (FDA) was denied in 1998. Meanwhile, the European Medicines Evaluation Agency (EMA) reviewed available evidence at the time and concluded that the benefits of vigabatrin treatment outweighed the risk of VAVFL and thus vigabatrin remained available outside the United States despite the VAVFL risk. In 2009, vigabatrin finally was approved by the FDA for use in the United States to treat pediatric patients one month to two years of age with infantile spasms and to treat adult patients with medically refractory complex partial seizures.

Multiple published studies have demonstrated the efficacy of vigabatrin for the treatment of infantile spasms and partial-onset seizures in TSC.<sup>2-8</sup> Yet persistent concern among patients and clinicians regarding VAVFL risk remains a significant barrier to widespread vigabatrin use in the United States. There have been numerous studies published since the original reports of VAVFL in 1997 with the aim of better understanding of VAVFL incidence, severity, timing, course, and contributing risk factors. However, large differences in results from the various studies have generated additional confusion due to significant differences in study design, such as variation in VAVFL definition, study population inclusion/exclusion criteria, and vision assessment methodology.<sup>9,10</sup> More importantly, most of these studies did not assess baseline visual function. Given these differences, estimating the true incidence of VAVFL is difficult and published reports range from less than 1% to more than 90%.<sup>11</sup> Most likely, the true incidence is somewhere between.

## WHAT IS VAVFL AND HOW IS IT DIAGNOSED?

Commonly, VAVFL is referred to by a variety of terms, including vision constriction, visual field constriction, narrowed field of vision, peripheral constriction of the visual fields, peripheral field vision loss, or simply vision loss. Although some at times refer to VAVFL as blindness, this latter description is inaccurate and misleading. Vigabatrin-treated patients do not go blind—things looked at directly (central vision) are unaffected and appear as clearly as ever. Rather, patients experiencing VAVFL demonstrate a reduced ability to see things around the edges of the field of vision (peripheral vision) (Figure 1). The underlying cause of VAVFL is thought to be attributable to damage that occurs in the retinal nerve fiber layer of the eye. The onset of VAVFL is typically gradual and minor such that most affected patients are unaware of any change in peripheral vision. If minor, VAVFL is unlikely to have any significant clinical impact on activities and quality of life. But if the VAVFL is progressive or significant, peripheral vision can be reduced to the point that seemingly simple tasks may be negatively impacted, such as surveying a large area quickly to find a person in a crowd or operating a

motor vehicle safely by being able to react to traffic or pedestrians approaching from the side. Additional concern arises from observation that in many patients, VAVFL persists even after vigabatrin is discontinued.

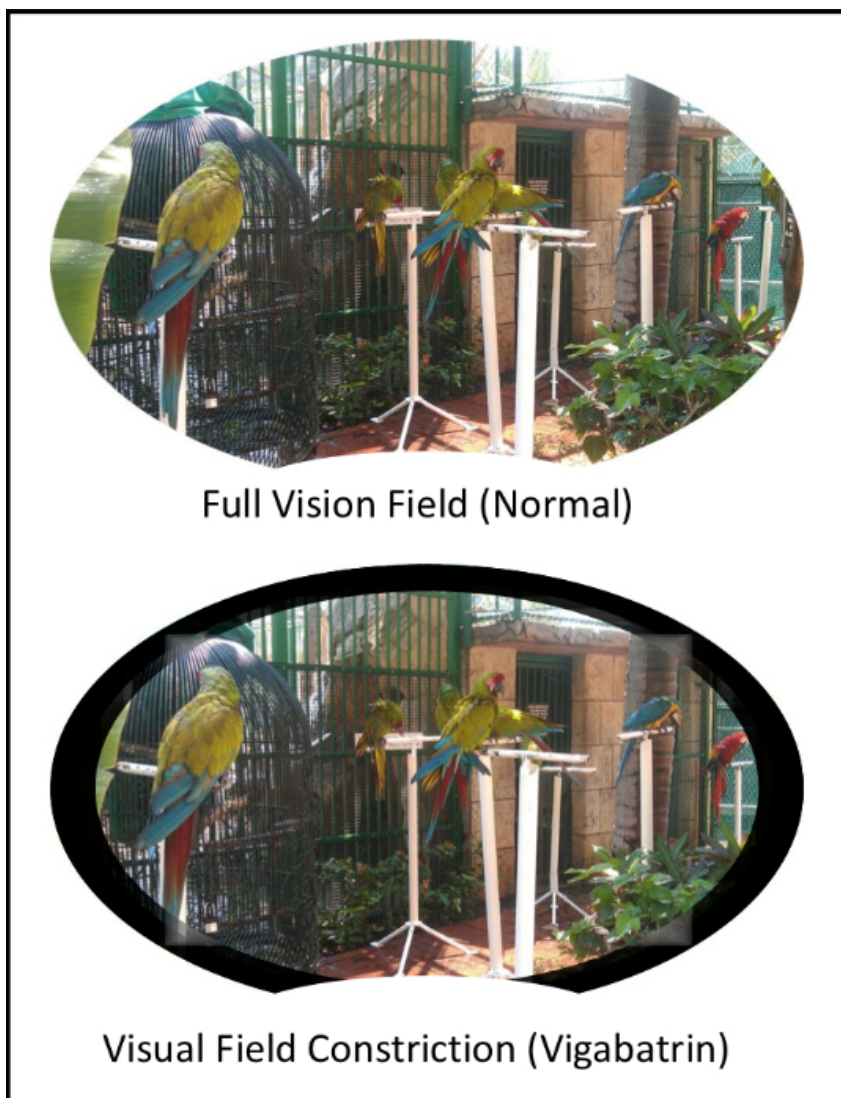


Figure 1: Comparison of normal visual field to constricted visual field caused by vigabatrin

In the majority of cases, VAVFL diagnosis is made by a clinical evaluation performed by a neurologist or ophthalmologist. The clinician may use additional specialized tests or tools to detect or confirm the presence of VAVFL, such as automated perimetry testing (there are other types of perimetry testing, but automated testing is most commonly used today), electroretinography (ERG), or optical coherence tomography (OCT). Each type of assessment has advantages and limitations that both patients and clinicians need to take into account when determining what tests to obtain and how to interpret results. A detailed visual history at baseline is helpful.

Clinical evaluation by the neurologist or ophthalmologist is the easiest and most simple means of assessment for VAVFL. This involves the clinician presenting objects at the edge of the visual field

and asking if the patient can see them (such as counting fingers held to the side of the patient while the patient looks straight ahead). For patients too young or with cognitive disabilities that prevent cooperation or the ability to respond verbally, the clinician may instead simply present an object or movement peripherally and see if the patient reacts or turns toward the stimulus. The advantages of clinical evaluation are that it requires no special equipment, can be performed on a wide range of patients, and most closely mimics typical situations that would be encountered in everyday life. Disadvantages, however, are that it is highly subjective, and not very precise or sensitive enough to detect early stages or mild types of VAVFL.

In automated perimetry, the patient rests his chin on a resting plate located in front of a curved screen where a small circle of light is flashed at various points on the screen that correspond to specific areas of central and peripheral vision. During testing, the patient must reliably look directly ahead and also remain attentive to accurately indicate when the light stimulus is seen. The advantages of automated perimetry are that testing is non-invasive, relatively inexpensive, and directly assesses visual function. Disadvantages of automated perimetry are that it cannot be performed in very young, cognitively disabled, or autistic/inattentive patients that are incapable of the cooperation needed to obtain reliable results. There may also be significant amounts of patient to patient and repeat testing variability with automated perimetry, meaning patients may show decline or improvement with repeated testing that is reflective of the degree of familiarity and cooperation with the test rather than reflective of any change in actual vision. Thus any abnormality detected with perimetry must be demonstrated on repeat testing to be considered reliable.

ERG measures the electrical responses of the retina to flashes or patterns of light. A recording electrode measures the amplitude and timing of the electrical response following the light stimulus. Normal retina responses have a specific range of amplitude and timing that can be abnormal in patients with VAVFL. The advantages of ERG are that testing is very reproducible and may be performed regardless of age or cognitive ability. In younger or uncooperative patients, however, restraint, sedation, or anesthesia may be required because such patients resist or refuse having the recording electrode placed directly on the eye. The unwanted consequence of sedation or anesthesia is that ERG responses may be reduced artificially by as much as 50%.<sup>12</sup> Various seizure medications may also negatively impact ERG results. Abnormal ERG responses may also arise from retinal lesions such as hamartomas that are common in TSC and have nothing to do with VAVFL. It is important also to remember that ERG results are correlative with visual function but not a direct measure of visual function like clinical assessment or automated perimetry testing. Like automated perimetry testing, any abnormality detected with perimetry or ERG must be demonstrated on repeat testing to be considered reliable.

OCT is a newer technology that uses near-infrared light to map and measure the thickness of individual cell layers that comprise the retina. It was first developed in the 1990s and is gaining increasingly popularity due to its ease of use and reproducibility of results. Scans take typically only take a couple minutes to obtain in cooperative patients. Unlike ERG, there is no direct contact to the patient's eye to perform the test. Sedation is less likely to be required for OCT, but if needed results

are not affected. Like ERG, a disadvantage of OCT is that results correlate with visual function but do not measure visual function directly. Another disadvantage is that normative values for TSC patients and parameters to define VAVFL are still in the process of being established due to the relatively new nature of OCT.

Regardless of the methodology used to monitor for the development of VAVFL in patients treated with vigabatrin, there is no consensus on how often surveillance examinations and/or tests should be performed. When the FDA approved vigabatrin for use in the United States, this approval was accompanied by a recommendation for ophthalmologic assessment within the first month of treatment, every 3 months thereafter while on treatment, and at least one additional assessment after treatment is discontinued. Strong evidence supporting such frequent assessments is lacking and many TSC experts recommend longer intervals, typically only once or twice annually unless additional concerns or risk factors are present to warrant evaluation on a more frequent basis.<sup>13</sup>

## **WHAT IS THE LIKELIHOOD OF VAVFL OCCURRING IN TSC PATIENTS TREATED WITH VIGABATRIN?**

While VAVFL certainly occurs in vigabatrin-treated patients, the true incidence rate is unknown. The reason for this ambiguity is different study populations (some studies only evaluated adults, whereas others only children), disease inclusion (patients with any cause for their seizures vs. patients without disorders such as TSC), study design (retrospective vs. prospective or cross-sectional), assessment methodology (clinical exam vs. perimetry vs. ERG or OCT), and lack of baseline assessment. What degree of abnormal result qualified as VAVFL also can differ significantly from study to study. As a result, comparing results of different studies is difficult, if not impossible.

After VAVFL was first reported in 3 patients in 1997, Wilton *et al.* (1999) analyzed questionnaires from more than 10,000 vigabatrin-treated patients to estimate the prevalence of self-reported vision-related problems or difficulties.<sup>14</sup> Only 4 patients were found to have objective evidence of visual field defects. A follow-up observational study involving an additional 4700 patients revealed another 10 cases.<sup>15</sup> All together, these two studies of self-detected, self-reported VAVFL identified a prevalence of less than 1%.

When formal ophthalmologic assessment includes perimetry testing and/or ERG, the estimated prevalence of VAVFL is much higher. Kinirons *et al.* provide an excellent systematic review of previous VAVFL-related studies involving adults, including their own experience with 93 additional patients.<sup>11</sup> In total, 23 studies between 1999 and 2006 involving 943 patients were included. No overall estimate of VAVFL was calculated, but reported prevalence was between 19-92% for the various studies. Plant *et al.* performed a similar meta-analysis but limited it to studies with less selection bias. In 16 studies involving a total of 790 patients, VAVFL was present in 34%.<sup>10</sup> Another large, prospective, multicenter study that was recently published found a slightly lower prevalence (in 398 patients over the age of 12 years with adequate ophthalmologic evaluations, VAVFL was found in 26%).<sup>16</sup> Thus the probable true prevalence of VAVFL detected with dedicated perimetry, ERG, or OCT testing is more likely between 25-35% in adults. Interestingly, the prevalence of VAVFL in

pediatric populations appears to be significant lower than that reported in adults. Consistently among multiple studies, the prevalence in children seems to be about half that reported for adults. For example, the same 2009 prospective multicenter study revealed VAVFL in only 13% (17/126) of patients under the age of 12 years.<sup>16</sup> Another study by Maguire *et al.* reported visual field defects in 33% of subjects in studies involving children, compared to 55% in adults.<sup>17</sup> A more recent retrospective analysis of 160 children detected VAVFL in only 11% of patients over a 10 year period.<sup>18</sup>

Few studies have attempted to assess VAVFL risk specifically for patients with TSC. To date, the majority of vigabatrin-related studies in TSC have focused primarily on efficacy. However, two more recent papers reported on VAVFL prevalence specifically in patients with TSC. Campasano *et al.* evaluated 46 patients using ERG, visual field testing, or both.<sup>3</sup> Of those tested with ERG, only 1/20 (5%) was discovered to have abnormal responses after being treated with vigabatrin for 1 year. Visual field testing was abnormal in 8/25 (32%), although in all cases but one the abnormalities were attributed to extensive tuber involvement resulting in cortical vision impairment rather than being related to vigabatrin treatment. A second study by Greiner *et al.* analyzed ophthalmologist reports for 63 TSC patients treated an average duration of 31 months.<sup>8</sup> Most patients were evaluated by clinician assessment only due to cognitive impairments that prevented additional evaluation. While 49% of the TSC patients were found to have visual abnormalities of one type or another, the vast majority were related to the underlying diagnosis of TSC and not vigabatrin treatment. ERG abnormalities were noted in only one of four patients (25%) that VAVFL was not completely excluded as a contributing factor.

## **ONCE DETECTED, WHAT IS THE LIKELIHOOD OF VAVFL BEING SEVERE?**

The discrepancy between self-reported vision disturbances and formal testing results via perimetry testing, ERG, or OCT highlights an important factor in the consideration of VAVFL risk. The vast majority of patients with VAVFL are unaware of any problems or difficulties because the impact on daily function and typical activities is in most cases minimal. VAVFL was detected by vision assessment in 34% but only 4% of the same patients demonstrated any symptoms.<sup>10</sup> More recently, a combined analysis of 341 pediatric and adult patients evaluated the severity of visual field constriction detected by perimetry testing and compared this to surveys of functional impairment.<sup>19</sup> Overall, visual field defects were detected in 72% of vigabatrin-treated patients compared to 45% of controls. The prevalence of moderate or severe visual field constriction, where symptoms may be noticeable, was much lower (19% and 5%, respectively) with only 1-2% in either group severely affected (binocular visual field reduced to 60 degrees, or roughly 30% of normal). Thus vision defects in the vast majority were so mild to the degree that normal daily activities, including obtaining a driver's license, would not be impacted. Other studies that have looked at this have reached similar conclusions and all agree that in a practical sense the likelihood of significant, relevant VAVFL is less than 5% and possibly less than 1%.

## ONCE DETECTED, WHAT IS THE LIKELIHOOD OF VAVFL GETTING WORSE?

When the first reports of VAVFL were first made in 1997, vigabatrin had been in use for nearly 10 years at the time. To go a decade without discovery of this magnitude is indicative not only the fact that most cases are mild and undetected by the patient, but also highlights another important characteristic of VAVFL: onset is slow and typically a process that takes several years to develop. While case reports exist suggesting VAVFL can be detected in as few as 3 months after treatment initiation, most studies indicate that most cases of VAVFL develop only after a year or more of treatment.

A common concern is whether or not VAVFL, once present, worsens over time. In 41 adult patients undergoing multiple eye examinations while continuing treatment with vigabatrin an average duration of 2 years (range 0.5-5.6 years), 24 had normal visual fields at both initial assessment and follow-up.<sup>11</sup> Of the remaining 17, the majority showed no progression of VAVFL; only 4 (24%) patients demonstrated any worsening and most of these were only mildly changed compared to baseline (no significant clinical change). A smaller study involving 16 patients with follow-up between 1.5-3.5 years, only 1 patient who continued vigabatrin treatment showed progression of VAVFL.<sup>20</sup> Collectively, we can conclude that most patients with detectable VAVFL who elect to continue treatment with vigabatrin will not significantly worsen in the short term. Much less is known about VAVFL in patients who are treated with vigabatrin over longer periods of time, but a recent study in 14 patients treated with vigabatrin for an average of 10 years (range 8.7-12.3) found that over the interval more than half (8/14) exhibited some degree of worsening, 1 of which rated as severe.<sup>21</sup> Thus while not every patient with extended exposure to vigabatrin will have worsening VAVFL, concern that worsening could occur over longer treatment periods remains.

Attempts to identify specific doses, treatment durations, or total life exposures that convey highest risk to vigabatrin-treated patients have yielded mixed results. In one of the largest analysis performed to date, Wild *et al* looked at the differences in patients with (n=120) and without (n=404) VAVFL.<sup>16</sup> In the largely adult-aged population (average 29-33 years), they found that those with VAVFL were more likely to be treated at higher doses (2200 mg/day) for a longer duration of time (5 years) when compared to those without VAVFL (1200 mg/day and 2 years, respectively). In contrast, a study involving 93 adult patients from Ireland who were treated with vigabatrin a minimum of 6 months found that maximum daily vigabatrin dose, duration of treatment, or lifetime cumulative exposure had no correlation with VAVFL.<sup>11</sup> Numerous case reports and small studies support one position or the other, including patients treated 5-10 years or longer without any detectable VAVFL. These data suggest that vigabatrin dose and duration of treatment may be important but are by no means definitive or exclusive in determining VAVFL risk for each individual patient. For example, a recent study suggested that combination of vigabatrin with additional anti-seizure medications may be a separate risk factor for developing VAVFL.<sup>18</sup>

## **ONCE DETECTED, WHAT IS THE LIKELIHOOD OF VAVFL BEING PERMANENT?**

A more often cited reason that leads clinicians or parents to not consider or decline treatment with vigabatrin is the possibility that VAVFL, once present, may be permanent. When VAVFL was first reported in 1997, the visual field abnormalities were still detectable more than a year after vigabatrin had been stopped.<sup>1</sup> Studies that have evaluated VAVFL after discontinuation of vigabatrin treatment support this conclusion, including the larger studies by Wild and Kinirons already discussed. VAVFL does not appear to get any worse after discontinuing vigabatrin, but rather remains stable as far out as investigators have continued assessment, typically between 1.5-3 years. However, several case reports and studies have noted exceptions where patients with VAVFL demonstrated improvement after treatment was discontinued. This appears particularly true for children,<sup>10</sup> although there may be alternative explanations for the improvement that have nothing to do with vigabatrin or VAVFL such as performing poorly on initial assessment because they do not understand initially how to perform the test or gain maturity that over time that makes testing more reliable and reproducible.

## **DOES TAURINE SUPPLEMENTATION LOWER THE RISK OF VAVFL?**

Taurine is a naturally occurring amino acid that is important for normal development and function of rod photoreceptors in the retina of the eye. While the link between taurine and retina health was established in 1975,<sup>22</sup> only more recently was it learned that vigabatrin treatment artificially causes taurine deficiency in mice and humans.<sup>23</sup> More importantly, retinal degeneration thought to be similar to that occurring in VAVFL could be prevented simply by providing extra taurine supplementation to the diet of at-risk mice.<sup>24, 25</sup> Dietary supplementation with extra taurine was able to largely reverse the damage already present as a result of the taurine deficiency in these animal models. Studies demonstrating similar prevention of VAVFL with taurine supplementation in humans have yet to be done.

## **CONCLUSIONS AND RECOMMENDATIONS**

Any pharmacological treatment of epilepsy is associated with expected benefits and known risks. It is in this context, when considering various treatment options for infantile spasms or epilepsy in TSC, that vigabatrin should be evaluated. There is no question that vigabatrin can be very effective for the treatment of epilepsy in patients with TSC. It is recommended first line treatment for infantile spasms in this population,<sup>13</sup> and is often very effective for many other seizure types in TSC.<sup>3, 7, 8</sup> This is even true when other currently available anticonvulsants have been tried and failed to adequately control seizures. VAVFL, while a valid concern, is often overemphasized despite established evidence regarding efficacy and low prevalence of significant functional impact on vision. Clinicians and parents also need to consider the consequences of continued seizures should alternative treatment choices prove less effective than what might be achieved with vigabatrin. Repeated studies have showed that delayed or inadequate seizure control, especially for infantile spasms, is associated with



much greater risk of negative long-term outcomes such as autism, cognitive difficulties, and medically-refractory epilepsy.

There is considerable variability at this time in practice approaches to vigabatrin treatment in patients with TSC. Some clinicians, once the determination to treat with vigabatrin has been made, will treat for a set amount of time (i.e., 3 or 6 months), and then discontinue treatment even if seizures are well-controlled. Too often, this inflexible approach leads to recurrence of seizures and subsequent courses of alternative anti-seizure medications fail to provide similar level of seizure control that was previously achieved with vigabatrin. A better approach, followed by many TSC specialists, is to initiate vigabatrin treatment early after onset of significant EEG epileptiform activity or first seizure and adjust dosage as needed over the following weeks.<sup>26</sup> If seizures fail to respond to adequate dosing, vigabatrin will be discontinued and alternative treatment strategies explored. But for those patients in whom vigabatrin is shown to be effective, treatment is typically continued for another 1-2 years before attempting to wean. In those patients in whom EEG abnormalities persist or in whom attempts to wean vigabatrin are associated with seizure recurrence or worsening, treatment may be continued much longer, even years, if necessary.

Like treatment duration and dosing, there is also much variability in practices to monitor and manage VAVFL risk. When vigabatrin was approved by the US Food and Drug Administration in 2009, a companion risk evaluation and mitigation strategy (REMS) was imposed that included mandatory evaluations by a vision specialist every 3 months. ERG or OCT may be included in these evaluations but are not required. There is limited evidence to suggest that performing evaluations every 3 months provides any added benefit to the patient for detection or management of VAVFL. This is particularly true for patients with cognitive or developmental disabilities common in TSC that prevent any reliable perimetry testing. Collectively, these factors have led to the recent recommendation by the International TSC Consensus Group in 2012 against ophthalmologic evaluations every 3 months.<sup>13</sup> Instead, annual evaluations are considered more than adequate for most individuals. Only when VAVFL is identified or suspected are more detailed or frequent assessments indicated. However, in the United States this evaluation is still mandated every 3 months, except in exempted individuals (i.e., patient is blind, has a general neurological or medical condition precludes the need for or ability to safely obtain visual assessments), and ultimately this accumulating cohort of patients will provide the best data regarding the true incidence of VAVFL.

The role of taurine supplementation remains to be determined for TSC epilepsy patients treated with vigabatrin. Studies to date are preliminary and do not provide any direct evidence that taurine prevents or reverses VAVFL. Given that taurine is natural and already present in the human body and already a commonly used supplement popular with body builders without significant adverse effects at high doses, it may be appropriate to provide taurine supplementation while awaiting results of such studies. Indeed, it is routine practice in our clinic to offer taurine supplementation to our patients when initiating vigabatrin. Standard dosing is not available, so we treat infants with 250 mg once/day, preschool- and school-aged children with 250 mg twice/day, and adults with 500 mg

twice/day. Taurine supplementation, however, does not prevent the need for continued ophthalmological assessments.

In conclusion, VAVFL concern alone should not preclude treatment of infantile spasms and other seizure types in patients with TSC. The risks and benefits should be carefully reviewed and discussed with patients/caregivers when considering starting treatment with vigabatrin. The overall risk of significant VAVFL is low, much lower than the risks associated with inadequate or poor seizure control. Many a parent has presented to our clinic with the argument that the very real and present risk of long-term cognitive impairment and poor seizure control should outweigh a theoretical risk of mild peripheral vision impairment. I have to agree, and vigabatrin continues to be a frequently utilized treatment option for our patients. While VAVFL risk remains a valid concern, in this context VAVFL alone is not a valid reason for withholding this potentially effective treatment option when appropriate for the patient.

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