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ARTICLE

Retinal defect in children with infantile spasms of varying etiologies

An observational study

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Abstract

Objective

To determine the prevalence of retinal defect in children with infantile spasms (IS) unrelated to treatment with vigabatrin and clarify if specific primary etiologies for IS are associated with retinal defect more than others.

Methods

This was an observational cohort study including 312 patients (176 male, 136 female) with IS who were vigabatrin-naive. Participants ranged from 1.7 to 34.7 months of age (mean 8.8 months). Electroretinograms (ERGs) were performed according to the International Society for Clinical Electrophysiology of Vision. Retinal defect was identified as abnormal if the 30-Hz flicker ERG amplitude was lower than the age-corrected normal 95% prediction interval. The primary etiology for IS, as determined by the treating pediatric neurologist(s), was obtained from patient health records and classified into 1 of 9 etiologic subgroups: (1) genetic disorders alone, (2) genetic-structural disorders, (3) structural-congenital, (4) structural-acquired (perinatal), (5) structural-acquired (postnatal), (6) metabolic disorders, (7) immunologic disorders, (8) infectious, and (9) unknown causes.

Results

Fifty-nine of the 312 vigabatrin-naive children (23.3%) showed retinal defect and the prevalence of retinal defect was highest (24.4%) in the structural-acquired (perinatal) subgroup, which included hypoxic-ischemic defect. Retinal function compared across subgroups showed no significant difference.

Conclusions

Care is required in diagnosing retinal toxicity, which would be enhanced by baseline flicker ERG in children with IS prior to starting vigabatrin.

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Glossary

ANOVA = analysis of variance; **ERG** = electroretinogram; **IS** = infantile spasms; **ISCEV** = International Society for Clinical Electrophysiology of Vision; **IVH** = intraventricular hemorrhage; **NISC** = National Infantile Spasms Consortium; **PVL** = periventricular leukomalacia.

In infantile spasms (IS), flexor or extensor spasms occur and neurodevelopmental regression is typical.[1] IS have been referred to as one of the catastrophic childhood epilepsies[2] because of the potential of IS to lead to drug-resistant epilepsy, severe to profound global developmental delay, or death.[3] Vigabatrin (Sabril; Lundbeck, Deerfield, IL) is one of the first-line treatments for IS, but retinal toxicity is known to occur in some patients treated with this drug.[4,5] Vigabatrin-associated retinal toxicity is diagnosed through clinical ophthalmology examinations and results from visual field assessment,[6] electroretinogram (ERG) assessment,[7–11] or optical coherence tomography.[12–14] The young age of children with IS (typically under 3 years of age) and likely developmental delay makes the ophthalmologic assessment difficult.[15,16] In a 2011 editorial, Good[17] wrote "In defense of ophthalmologists who follow these children, we have been placed in a challenging position with regard to detection of visual field changes associated with vigabatrin."

An additional confound concerning the diagnosis of vigabatrin-induced retinal toxicity in IS is the understanding that some children with IS have preexisting visual or retinal defects that are unrelated to vigabatrin.[7,18,19] The current study investigated whether children with IS had preexisting retinal defect before vigabatrin treatment and if specific etiologies of IS are more associated with retinal defect.

Methods

Objective

To determine the prevalence of retinal defect in children with IS that are unrelated to vigabatrin, we conducted electroretinography before vigabatrin treatment in children diagnosed with IS. Secondarily, to determine if specific primary etiologies of IS are more associated with retinal defect than others, we used a one-way analysis of variance (ANOVA) to compare results across etiologic subgroups.

Study population

In this observational cohort study, 333 children ≤3 years of age, diagnosed with IS, had visual electrophysiology assessment at The Hospital for Sick Children (SickKids) between October 1998 and April 2017. We estimate that from October 1998, 75%–90% of children with IS treated with vigabatrin by the Neurology department at SickKids received baseline ERG testing; this increased to 90% by 2003. The inclusion criteria were diagnosis with IS by a treating pediatric neurologist and vigabatrin-naive at ERG testing. Specifically, the children had either not started vigabatrin or had been on the anticonvulsant for ≤4 weeks, as baseline ERG monitoring is considered within 4 weeks after starting vigabatrin.[20] All patients had a history of flexor or extensor spasms and an EEG showing hypsarrhythmia.

Standard protocol approvals, registrations, and patient consents

This study was approved by the Research Ethics Board at The Hospital for Sick Children and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from parents or guardians.

Clinical ophthalmology evaluation

Full-field ERG was recorded in all patients according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards.[21] ERGs were performed under chloral hydrate sedation (80 mg/kg up to a maximum of 1 gram). Pupillary dilation was achieved by using 1% tropicamide (Mydriacyl; Alcon Laboratories, Inc., Fort Worth, TX) and 2.5% phenylephrine (Mydfrin; Alcon Laboratories, Inc.). After administration of a topical anesthetic, a contact lens electrode (Burian Allen ERG Electrode; Hansen Ophthalmic Development Laboratory, Iowa City, IA; or since 2016, ERG-JET; Fabrinal Eye Care, La Chaux-de-Fonds, Switzerland) was placed on the cornea. A Ganzfeld stimulator provided stimulus flashes and background luminance (Espion E2 ColorDome; Diagnosys LLC, Lowell, MA). The 30-Hz flicker ERG response reflects the function of both photoreceptors and other neuronal structures of the retina and the 30-Hz flicker amplitude is the most sensitive ERG marker for vigabatrin toxicity.[10,22] The light-adapted 30-Hz flicker ERG amplitude was analyzed for the current study.

Etiology data collection and classification

The study evaluated defined etiologies of IS recorded in the patients' health records. Children at The Hospital for Sick Children diagnosed with IS have an extensive diagnostic evaluation including a metabolic and genetic workup and an MRI scan of the brain. The primary etiology for IS, as determined by the treating pediatric neurologist(s) in the patient's health record, was recorded for each patient. Primary etiologies for IS were classified into 9 subgroups for analysis by Wirrell et al.,[23] who prospectively evaluated the etiologies of new-onset IS and included data from the National Infantile Spasms Consortium.[23] These subgroups included (1) genetic disorders alone (not associated with structural brain changes); (2) genetic-structural disorders (resulting in structural brain changes); (3) structural-congenital (resulting in brain changes without a documented genetic cause); structural-acquired (brain changes resulting from an injury or tumor; in this study, further divided into [4] perinatal structural-acquired and [5] postnatal structural

acquired); (6) metabolic disorders; (7) immunologic disorders; (8) infectious (documented or suspected brain infection resulting in epilepsy); and (9) unknown causes. Any medications taken before or at the time of testing were reported.

Data analysis

Retinal defect identified by abnormal 30-Hz flicker ERG amplitude prevalence was calculated in the study population and within the 9 etiologic subgroups studied. In each patient, 30-Hz flicker ERG amplitude data were averaged between the 2 eyes, or if data were only available for one eye, data from one eye were used. After taking an average of the 2 eyes or using data from one eye, the resultant 30-Hz flicker ERG amplitude was classified as abnormal if it was outside the 95% prediction interval of the age-expected distribution for typically developing children.[24] The normal 95% prediction interval is ±0.21 log microvolts from the age-expected ERG amplitude.[24] The 30-Hz flicker ERG amplitude was also expressed as a *z* score of the age-adjusted 30-Hz flicker ERG amplitude and compared across etiologic subgroups using a one-way ANOVA (Statistical Package for Social Studies software, IBM, Chicago, IL).

Data availability

All data are within this article.

Results

A total of 312 patients met the inclusion criteria. Of the 21 patients who did not meet the inclusion criteria, 18 patients had no recordable ERG in both eyes, 2 patients had more than one primary etiology for IS in their health records according to their treating pediatric neurologist(s), and one patient had an etiology for IS listed in the health record but information was lacking regarding whether the etiology was perinatal or postnatal. Demographic data for patients are shown in table 1. The mean age of children with IS was 8.8 months (SD 4.9 months, range 1.7–34.7) and 176 patients were male. The mean delay between performing the ERG and initiation of vigabatrin treatment was 1.9 weeks (SD 6.5 weeks, range 33.6 weeks before the start of vigabatrin treatment to 4.0 weeks after the start of vigabatrin treatment).

Of the 312 vigabatrin-naive children with IS who came for ERG testing, 58.7% of patients had a known etiology for IS (table 2).

The prevalence of etiologies for IS was genetic disorders alone, 11.5%; genetic-structural, 17.6%; structural congenital, 7.7%; structural acquired, 18.9%; metabolic, 2.2%; and infection, 0.6% (figure 1). The group with the structural acquired etiologies was broken down further into structural acquired perinatal (13.1% of the total cohort) and structural acquired postnatal (5.8%). Down syndrome was the most common purely genetic cause (n = 19/36, 52.8%), accounting for half of genetic etiologies that have no association with structural brain changes. Tuberous sclerosis accounted for more than half (n = 31/55, 56.4%) of the genetic-structural etiologies. Over a third of patients in the structural-congenital group (n = 8/24, 33.3%) had focal cortical dysplasia. The most prevalent structural acquired cause was hypoxic-ischemic encephalopathy (n = 14/59, 23.7%), accounting for almost a quarter of all structural-acquired etiologies for IS. Hypoxic-ischemic encephalopathy (n = 14/41, 34.1%) and stroke (n = 7/18, 38.9%) were the most common perinatal and postnatal structural acquired etiologies of IS, respectively. There were few patients with metabolic (n = 7) and infection etiologies (n = 2) for IS and no patients were identified from patient records with an immune cause for IS.

Table 1 Demographic data of 312 vigabatrin-naive children with infantile spasms

	Values
Age at testing, mo, mean (SD; range)	8.8 (4.9; 1.7 to 34.7)
Sex, male/female	176/136
Time on vigabatrin, wk, mean (SD; range)	−1.9 (6.5; −33.6 to 4.0)

Prevalence of retinal defect in vigabatrin-naive children

Fifty-nine of the 312 vigabatrin-naive children (23.3%) showed a retinal defect identified as an abnormal 30-Hz flicker ERG amplitude when compared with an age-normative dataset. An abnormal 30-Hz flicker ERG was most common in the structural-acquired perinatal group, with 10 out of 41 of the children (24.4%) showing an abnormal 30-Hz flicker ERG amplitude. The structural-congenital group, in which 5 out of 24 vigabatrin-naive children (20.8%) showed flicker abnormalities, and the genetic-structural group, where 11 out of 55 of the children (20.0%) showed flicker abnormalities (table 3), closely followed this.

Comparison of retinal function across etiologic subgroups

Retinal function expressed as a *z* score of the age-adjusted 30-Hz flicker ERG amplitude was compared across etiologic subgroups using a one-way ANOVA. The infection subgroup was excluded from the ANOVA analysis, as this group only had 2 patients. A one-way ANOVA showed no significant difference ($p = 0.75$, df 6) in the *z* scores of the age-adjusted 30-Hz flicker ERG amplitude between the etiologic subgroups. A boxplot shows the distribution of age-adjusted 30-Hz flicker ERG amplitudes expressed as a *z* score across subgroups (figure 2).

No vigabatrin vs short-term treatment (less than 4 weeks vigabatrin treatment)

The data show no evidence that children receiving short-term vigabatrin treatment had more cases of abnormal ERGs than those who had never received vigabatrin. For example, out of the 24 children with unknown etiology, 14 had never taken vigabatrin and 10 had short-term treatment (<4 weeks

Table 2 Primary etiologies of infantile spasms in a vigabatrin-naive cohort (n = 312)

Etiology subgroup	No. (%) of patients	Specific etiologies
Genetic	36 (11.5)	
	19	Trisomy 21
	5	*CDKL5* mutation
	3	*STXBP1* mutation
	2	*SCN2A* mutation
	2	1p36 deletion syndrome
	5 (1 of each from list)	15q11 gene triplication; *SPTAN1* mutation; *SCN8A* mutation; 10p deletion and 3p duplication; tetrasomy 15q
Genetic-structural	55 (17.6)	
	31	Tuberous sclerosis
	15	Lissencephaly
	7	Neurofibromatosis
	2 (1 of each from list)	*SETBP1* (Schinzel Giedion); Toriello-Carey syndrome
Structural-congenital	24 (7.7)	
	8	Focal cortical dysplasia
	3	Aicardi syndrome
	3	Polymicrogyria
	3	Agenesis of corpus callosum alone
	3	Linear sebaceous/epidermal nevus syndrome
	4 (1 of each from list)	Sturge-Weber syndrome; cerebral dysgenesis (malformation of corpus callosum, fused thalami, and cerebral heterotopias); left frontal arachnoid cyst; agenesis of corpus callosum, periventricular cyst, and areas of polymicrogyria
Structural-acquired	59 (18.9)	
Structural-acquired (perinatal)	41 (13.1)	
	14	HIE alone
	13	PVL/IVH alone
	12	Stroke
	2	HIE and IVH/PVL
Structural-acquired (postnatal)	18 (5.8)	
	7	Stroke
	5	CNS infection (3 bacterial meningitis, 2 meningitis of unknown type)
	4	Brain trauma (3 shaken baby syndrome, 1 other)
	2 (1 of each from list)	IVH/PVL alone; brain tumor (1 atypical teratoid rhabdoid tumor)
Metabolic	7 (2.2)	
	2	Leigh disease
	5 (1 of each from list)	Complex 1 deficiency; congenital disorder of glycosylation type IL (*ALG13* mutation); congenital disorder of glycosylation type 1p (*ALG11-CDG* mutation); neonatal hypoglycemia; *ALDH7A1* gene mutation

Continued

Table 2 Primary etiologies of infantile spasms in a vigabatrin-naive cohort (n = 312) *(continued)*

Etiology subgroup	No. (%) of patients	Specific etiologies
Immune	0 (0)	
Infection	2 (0.6)	TORCH
Unknown	129 (41.3)	

Abbreviations: HIE = hypoxic-ischemic encephalopathy; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; TORCH = toxoplasmosis, other (syphilis, varicella-zoster, parvovirus b19), rubella, cytomegalovirus, and herpes.

vigabatrin treatment). In 2 groups (genetic-structural and structural-acquired), there were more children with abnormal ERGs in the group who had never been treated with vigabatrin than in the group on short-term treatment.

Other medications taken before or at time of ERG testing

In the 59 vigabatrin-naive children who had abnormal ERGs, 24 (41%) were on no other medication before or at the time of the ERG. Among those patients taking medications, the most prevalent were 20 patients (34%) treated with phenobarbital and 6 patients (10%) treated with clobazam. In the 253 patients with normal ERGs, 78 patients (31%) were taking no other medication before or at the time of the ERG. A total of 66 (26%) were treated with phenobarbital and 29 (11%) were treated with clobazam.

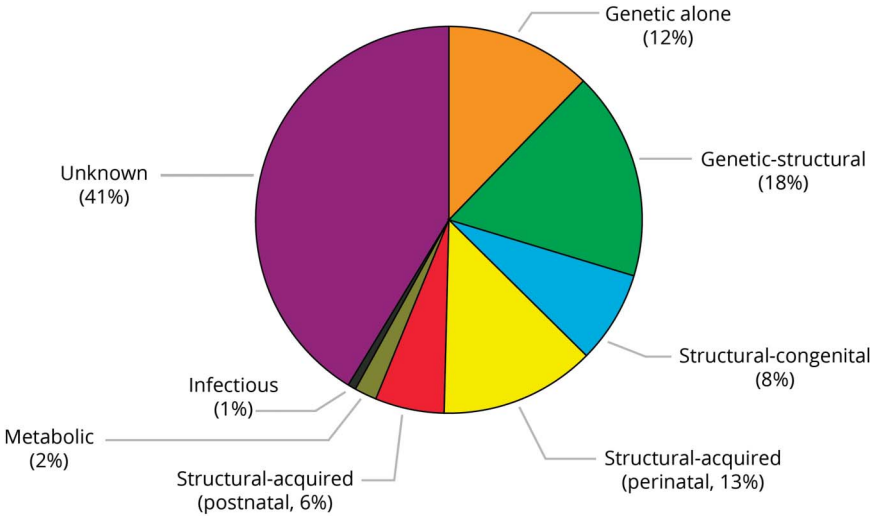
Discussion

To our knowledge, this is the first study to investigate the prevalence of retinal anomalies in a large cohort of children with IS that is unrelated to vigabatrin treatment and its association with etiologies of IS. We found that nearly a quarter of vigabatrin-naive children (before treatment with vigabatrin or <4 weeks of vigabatrin treatment) with IS showed evidence of a retinal defect on the 30-Hz flicker ERG. Nearly a quarter of children in this study had a structural-acquired perinatal cause for their spasms.

Abnormal 30-Hz flicker ERG amplitude data (<2 SD of laboratory normal data) before the start of vigabatrin treatment has been demonstrated previously by our laboratory in a longitudinal study of 33 children with IS.[7] Mirabella et al.[18] have also showed a reduced mean contrast sensitivity in vigabatrin-naive children with IS compared with normally developing children. However, these data have limited relevance to the current study since Mirabella et al. did not measure retinal function. Rather, visual cortical activity was assessed using a sweep visual evoked potential technique. The visual evoked potential might in itself be affected by seizures.

To our knowledge, published studies of retinal function in children with IS that is unrelated to vigabatrin treatment are limited. The reasons for an abnormal 30-Hz flicker ERG finding in vigabatrin-naive children with IS might be threefold. The first putative mechanism could involve GABA-mediated inhibition in the retina. Visual processing starts in the retina. Within only 2 synaptic layers, a large number of parallel information channels emerge, each encoding a highly processed

Figure 1 Prevalence of primary etiologies of infantile spasms (IS) in 312 vigabatrin-naive children with IS



Numbers rounded to nearest whole number.

Table 3 Prevalence of abnormal 30-Hz flicker electroretinogram (ERG) in vigabatrin-naive children

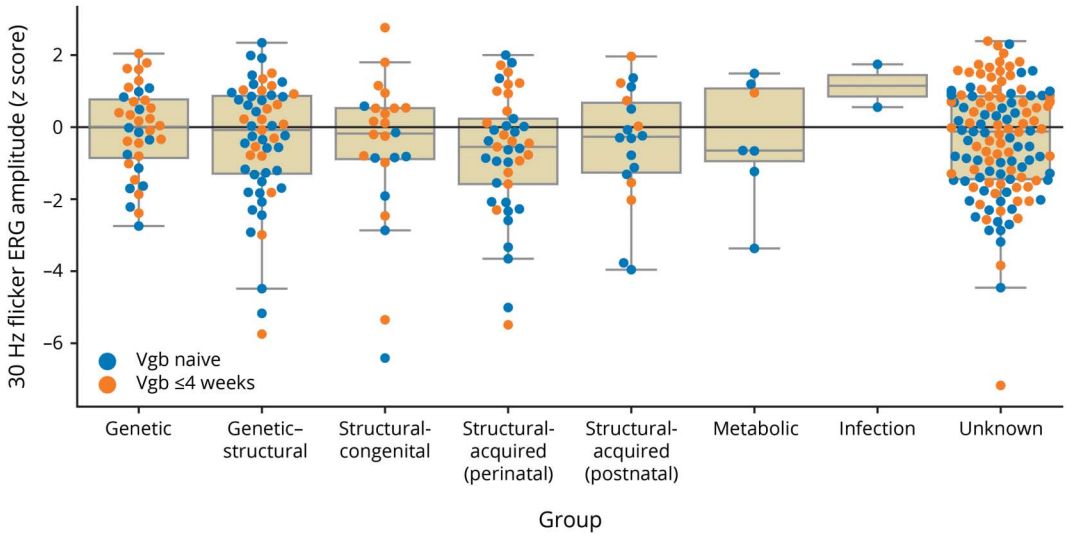
Etiologic subgroup	No. of children with abnormal 30-Hz flicker ERGs	No. of children with normal 30-Hz flicker ERGs	Percentage total
Genetic	5	31	13.8
Genetic-structural	11	44	20.0
Structural-congenital	5	19	20.8
Structural-acquired perinatal	10	31	24.4
Structural acquired postnatal	3	15	16.7
Metabolic	1	6	14.3
Infection	0	2	0
Unknown	24	105	18.6
Totals	59	253	23.3

Abnormality of the 30-Hz flicker ERG was based on case-by-case comparison with an age-normative dataset.

feature like edges or the direction of motion. Much of this functional diversity arises in the inner plexiform layer, where amacrine cells modulate the excitatory signal of bipolar and ganglion cells via GABA-mediated mechanisms.[25] GABA is involved in neuronal differentiation and maturation[26]; specifically, GABA is involved in regulating the maturation of cone pathways by influencing the development of the structure of synapses in the photoreceptor triad as well as the regulation of the extent of bipolar cell receptors. Of note, the disruptive effects of reduced GABAergic transmission on photoreceptor synapses are small compared to the effect of loss of glutamate transmission, which is markedly greater.[26] Therefore, inadequate GABA-mediated neurotransmission at an early age may impede normal retinal function in young children with IS. Children with IS have decreased levels of GABA in CSF,[27] suggesting that there may be a decrease in GABA transmission in this age-specific seizure type.

Second, the 30-Hz flicker ERG may be abnormal in vigabatrin-naive children with IS because the brain insults that led to IS also resulted in functional impairment of the retina. The evidence in support of this hypothesis is that children with a perinatal structural-acquired cause for their spasms (hypoxic-ischemic encephalopathy, periventricular leukomalacia [PVL]/intraventricular hemorrhage [IVH], and stroke) showed the highest prevalence of retinal defect among vigabatrin-naive children. In such cases, retinal damage may occur because of direct hypoxic-ischemic injury to the retina. There are experimental data that lend credence to this hypothesis as well. Jung et al.[28] showed that functional and structural abnormalities occur in the retina in an animal model of neonatal hypoxic-ischemic encephalopathy. Specifically, reductions in the b-wave amplitude of the scotopic and photopic ERG occur with sparing of the a-wave amplitude, and retinal histology shows damage to the inner layers of the retina with sparing of the photoreceptors.[28] These findings are corroborated by studies that show that the developing retina is highly sensitive to changes in oxygen levels.[29] Damage to the retinal vasculature in children born prematurely with PVL, a type of white matter brain injury,

Figure 2 Thirty-Hertz flicker electroretinogram (ERG) amplitude data in vigabatrin-naive children across etiologic subgroups



The black solid line represents no difference between patient and control. Orange data points represent data from children with short duration vigabatrin treatment (<4 weeks) and blue circles are those with a true baseline (no vigabatrin).

and IVH may occur through a similar mechanism involving hypoxia, but also relative hyperoxia in the extrauterine environment.[30,31] In regard to the latter, IVH is associated with retinopathy of prematurity[32–34] and a recent report has shown that PVL is associated with retinal vascularity changes similar to retinopathy of prematurity, which include delayed growth of the deep vascular plexus in the retina and increased numbers of local vascular pathology.[30] In some children, there may be indirect damage to the neuronal retina subsequent to cortical damage.[35] Previously we found that children with a history of IS have reduced vision that is associated with IS rather than vigabatrin treatment.[19] Abnormal cortical electrical activity from seizures may injure the visual cortex. In the current cohort, fewer than 10% of children were diagnosed with cerebral vision impairment; these data were in the structural-acquired (perinatal) and the unknown group. In some of these cases, retrograde degeneration may have contributed to the ERG defect. Perhaps retinal defect in neurofibromatosis and optic pathway gliomas may contribute minimally to the ERG defect as the retinal nerve fiber layer and the ganglion cell/inner plexiform layers thinning has been observed using optical coherence tomography.[36,37]

Finally, other medications or antiepileptic drugs, other than vigabatrin, were sometimes administered to patients in our cohort before ERG testing. This is an unlikely explanation for our findings because assessment of other medications or antiepileptic drugs revealed similar proportions of patients with ERG defect and those without who had been treated with phenobarbital and clobazam. Phenobarbital is not associated with visual effects,[38] although benzodiazepines (which include clobazam) may be associated with some attenuation of the ERG.[38] However, the effect of clobazam is unlikely to explain the prevalence of abnormal 30-Hz flicker ERG in vigabatrin-naive children because of the nearly equal proportions of patients with and without ERG defect taking clobazam.

The proportions of primary etiologies for IS identified in our cohort of children are consistent with recent results published by Wirrell et al.[23] using data from the National Infantile Spasms Consortium (NISC) database, which includes data from 21 US pediatric epilepsy centers. Similar to findings from the NISC, 58.7% of patients in our cohort compared to 64.4% in the Wirrell et al.[23] study had a known etiology for their spasms. Down syndrome and tuberous sclerosis remained the most common genetic and genetic-structural causes, respectively, although a greater number of tuberous sclerosis cases were identified in this cohort (n = 31/55, 56.3%) in comparison to the Wirrell et al.[23] study (n = 12/25, 48.0%), which led to a larger proportion of genetic-structural primary etiologies in the current study (17.6% vs 10.0%). Of the structural-congenital causes for IS, a greater proportion of children in our cohort had focal cortical dysplasia (n = 8/24, 33.3% in comparison to the Wirrel et al.[23] study [n = 1/27, 3.7%]), making it the leading cause of structural-congenital causes for IS in this cohort. In terms of the structural-acquired causes for IS, the current study investigated perinatal and postnatal structural-acquired causes for IS in separate subgroups for further specificity. In our cohort, 41 out of 59 (69%) structural-acquired causes for IS were due to perinatal brain injury. This is consistent with the Wirrel et al.[23] study (n = 33/56, 58.9%), although a higher proportion of perinatal brain injury occurred in our cohort. Fewer patients with metabolic (2.2% vs 4.8%) and infectious (0.6% vs 2.0%) causes were identified in our cohort compared to the Wirrel et al.[23] study as a primary etiology of IS; however, no patients with an immune cause for their spasms were identified in either cohort. The current study did not find any significant associations between the 30-Hz flicker ERG and the etiologic subgroups studied.

In the current study, ERGs were performed under chloral hydrate sedation. Sometimes a Bell phenomenon occurs in sedated children. When this happens, the eye rolls up and the corneal electrode may not always be centered. The result is an artificial lowering of the amplitude of the 30-Hz flicker ERG. In our experience, Bell phenomenon occurs more frequently in one eye than both. We mitigated this problem to some degree by taking the average from the left and right eye recordings when available (>90% children tested). However, in a few cases, an artifact might contribute to a reduction of the ERG 30-Hz flicker amplitude. Other limitations may be reduction in 30-Hz ERG amplitude as a result of the undiagnosed hereditary retinal dysfunction; although all children received a full ISCEV standard ERG and clinical ophthalmology examination, this possibility cannot be completely ruled out. Although our population includes a large number of children tested over the 19-year period, all referrals are from a single center and may not be representative of a wider population. However, our etiology classifications are comparable to those of Wirrell et al.[23] in regard to the proportion of children with different etiologies of IS. The Wirrell et al.[23] database was extensive and included data from 21 US pediatric epilepsy centers. Numbers for some etiologies, particularly metabolic and infectious causes, are limited. This study may not adequately represent the range of retinal function in these groups.

The 30-Hz flicker ERG response is reduced in almost 24% of children under 3 years of age with IS who are naive to vigabatrin. It is unlikely that other anticonvulsant drugs, that is, phenobarbital or clobazam, caused this retinal dysfunction in IS. Further, nearly a quarter of the children with IS and retinal dysfunction that antedated vigabatrin use had a structural-acquired perinatal cause for their spasms, suggesting a common etiology for both. We do not know whether preexisting retinal dysfunction makes the retina more vulnerable to vigabatrin-induced retinal toxicity in children with IS. Therefore, it is important to establish baseline retinal function with clinical ERG within 4 weeks of starting vigabatrin therapy in children with IS both to identify those children with retinal dysfunction unrelated to vigabatrin and to follow more carefully for vigabatrin-induced retinal toxicity.

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Appendix Authors

Name	Location	Role	Contribution
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Tom Wright, PhD	Kensington Eye Institute, Toronto, Canada	Author	Major role in acquisition of data, data analysis, revised manuscript
Blathnaid McCoy, MD	The Hospital for Sick Children, Toronto, Canada	Author	Interpreted data, revised manuscript for intellectual content
O. Carter Snead III, MD	The Hospital for Sick Children, Toronto, Canada	Author	Interpreted data, revised manuscript for intellectual content
Carol A. Westall, PhD	The Hospital for Sick Children, Toronto, Canada	Author	Designed study and conceptualized study, analyzed data, wrote manuscript for intellectual content

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