Reduced Grating Acuity Associated with Retinal Toxicity in Children with Infantile Spasms on Vigabatrin Therapy

Sivan Durbin,[1,2] *Giuseppe Mirabella,*[1,2,3] *J. Raymond Buncic,*[1,2,3] *and Carol A. Westall*[1,2,3]

Purpose. To determine whether visual functions are decreased in children with infantile spasms and vigabatrin-attributed retinal toxicity.

Methods. Contrast sensitivity and grating acuity were measured by using sweep visual evoked potential (VEP) testing in 42 children with infantile spasms (mean age, 29.23 ± 18.31 months). All children had been exposed to vigabatrin (VGB) for a minimum of 1 month. These children were divided into retinal toxicity and no toxicity groupings based on 30-Hz flicker amplitude reductions on the full-field electroretinogram. A multivariate analysis of variance (MANOVA) compared visual functions between children with and without retinal toxicity.

Results. The MANOVA showed that visual function was significantly affected by VGB retinal toxicity. Further univariate analysis revealed that grating acuity was significantly reduced in children with toxicity. No differences in contrast sensitivity were found between children with toxicity and those without.

Conclusions. Reduced visual functions from VGB-attributed retinal toxicity can be detected in children with infantile spasms with the sweep VEP. (*Invest Ophthalmol Vis Sci.* 2009; 50:4011–4016) DOI:10.1167/iovs.08-3237

West Syndrome is a catastrophic childhood epilepsy affecting infants at an incidence of 2 to 5 per 10,000 births.[1] The syndrome is characterized by the clinical manifestation of infantile spasms (IS), a chaotic and disorganized EEG pattern known as hypsarrhythmia, and physical and neurodevelopmental arrest or regression. It is associated with severe mental retardation, developmental delay, psychomotor regression, and cerebral palsy.[1,2] The seizures are of high frequency and disrupt normal maturational processes within the central nervous system. IS represent a specific clinical manifestation of epileptic activity associated with West syndrome.

Treatment for IS is initiated rapidly and aggressively to abolish seizures and associated hypsarrhythmia. An effective treatment is the antiepileptic drug vigabtrin,[2] especially when used as an initial therapy.[3] In cases of IS caused by tuberous sclerosis, vigabatrin (VGB) is the drug of choice.[3,4] VGB (Sabril; Ovation Pharmaceuticals, Deerfield, IL) is a γ-amino butyric acid (GABA) enhancer, and is used as a first-line therapy in Canada and Europe. VGB enhances GABA transmission by selectively and irreversibly binding GABA-transaminase, the enzyme responsible for recycling GABA. It is particularly effective in patients with an etiology of tuberous sclerosis,[2] where it has up to 95% effectiveness in abolishing spasms and normalizing the EEG.[5]

Although VGB is better tolerated than other treatments, a major side effect in a substantial proportion of adult patients is the emergence of retinal toxicity, eventually leading to visual field deficits. Visual field constriction has been noted in 30% to 50% of adult patients and in children prescribed the drug.[4,6–8] Studies in rodents have shown that retinal insult is associated with an accumulation of VGB within retinal cells and elevated retinal GABA levels at the synapse.[9,10] Human[11–13] and animal[14] studies have shown that the cone rather than the rod system is more affected by VGB toxicity. Specifically, ERG reductions in the 30-Hz flicker amplitude have been associated with VGB retinal toxicity.[13] Recent evidence using ocular coherence tomography (OCT) demonstrates peripheral retinal nerve fiber layer thinning in patients with VGB-attributed field loss.[15,16] These OCT data substantiate previous findings of clinically detectable atrophy in the peripheral retinal nerve fiber layer by photography and/or direct funduscopy.[17]

The use of OCT measures in children taking VGB may in time prove to be useful for monitoring these patients; however, despite the wider availability of OCT for use in children over 3 years of age, this technology is not yet as available for infant testing. In infants and children, retinal function can be assessed reliably using the electroretinogram (ERG).[18] Our laboratory has extensive experience using the ERG to monitor retinal function in infants taking VGB.[12,17,19,20]

The sweep VEP is recorded using surface electrodes rather than contact lens electrodes required for ERG testing. If vision function assessed using sweep VEP recording is found to be sensitive in the detection of retinal toxicity, the VEP marker could provide a less invasive alternative in identifying the effects of toxicity. Previous studies using the sweep VEP have effectively demonstrated that contrast sensitivity in children with IS is reduced, although this effect occurs independently of drug therapy.[21–23] This reduction is seen at baseline (before starting VGB therapy) and is specific to children with IS.[21–23]

The following study compares visual function in a group of children with IS and retinal toxicity to children with IS with no toxicity. The 30-Hz flicker of the photopic ERG response was used to identify VGB attributed toxicity. Cortical visual function was assessed by measuring contrast sensitivity and grating acuity using the sweep VEP.

Methods

Patient Population

We investigated the effects of retinal toxicity on visual function in children with IS who were taking or had taken VGB. To be included in the analysis, subjects had to be older than 9 months and exposed to VGB for a minimum of 1 month. All the children tested had IS, as identified by a hypsarrhythmic EEG.

From the [1]Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, Toronto, Canada; the [2]Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Canada; and the [3]Brain and Behavior Program, Sick Kids Research Institute, Toronto, Canada.

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Corresponding author: Carol A. Westall, Department of Ophthalmology and Vision Sciences, Sick Kids, 555 University Avenue, Toronto, ON M5G 1X8, Canada; carol@sickkids.ca.

Complete eye examinations were performed on all children with IS taking VGB as part of their clinical assessment. This included behavioral grating acuity (Teller cards, Cardiff Acuity Test, or logMAR crowded-letter chart), confrontation visual fields (see Ref. 23) ocular motility, refraction, fundus examination, and ERG testing. Fundus examination classified the retinal picture into one of three groups: (0) a normal retina, (1) mild and diffuse tissue loss of the nerve fiber layer with an optic disc change, and (2) a more severe change of an identifiable pattern of peripheral retinal tissue loss at the level of the optic nerve head, previously described as VGB attributed "inverse" optic atrophy.[17] Refractive corrections were worn during sweep VEP testing. Exclusion criteria included children with progressive eye disorders, cortical visual impairment, nystagmus, amblyopia or refractive errors thought to affect the VEP recordings. Cortical visual impairments were identified by author JRB, a neuro-ophthalmologist at The Hospital for Sick Children in Toronto, Canada, based on poor visual responsiveness with few other cerebral deficits, absence of anterior disease, absence of nystagmus, and normal pupillary responses.

All children underwent ERG testing. The 30-Hz flicker has been used in several studies to determine VGB-related retinal toxicity.[12,17,19,20,24] In our study, toxicity was defined by continuous reduction in photopic flicker amplitudes compared with that measured before VGB therapy. All data were corrected for age. The reduction was required to be greater than that allowed for by intervisit variability (0.3 log units), and the reduced amplitude was required to be present on at least two consecutive visits.

Parents or primary caregivers received a full description of the study and explanation of the testing procedures. Informed consent was obtained. The study and its testing procedures were approved by the Sick Kids Research Ethics Board and were in accordance with the Declaration of Helsinki.

Sweep VEP Testing

Sweep VEP thresholds were recorded with the child placed either in the parent's lap facing the video monitor or seated alone in a chair. Children under 1 year of age were seated 100 cm from the monitor. Children older than 1 year of age were seated at 150 cm.

All testing was binocular. Electrode placement was in accordance with the International 10-20 electrode placement system.[25] Five gold cup electrodes were placed on the scalp. Three active electrodes were placed over the occipital cortex (O_1, O_z, and O_2). The other two electrodes served as the reference (C_z) and the ground (P_z). The electroencephalographic response was amplified 50,000 times with a differential amplifier (Model 12 Data Acquisition System; Grass Technologies, West Warwick, RI) and digitized to 16-bits accuracy with an analog-to-digital converter. Electrode impedance was kept below 10 kΩ.

Contrast sensitivity and grating acuity thresholds were estimated with a sinusoidal grating presented on a 16-in. (40.6 cm) monitor. The stimulus was phase-alternated at 6 Hz (12 reversals per second). The mean luminance was 80 cd/m^2. PowerDiva software (ver.1.8.5; Smith Kettlewell Eye Research Institute, San Francisco, CA) was used to record sweep VEPs.

The sweep VEP estimates thresholds by tracking the response of a changing (swept) grating over a 10-second trial interval and then extrapolating this response to 0 amplitude. For the grating acuity condition, the spatial frequency of an 80% contrast grating was increased linearly from 2 to 23 cyc/deg. For the contrast sensitivity condition, the grating with a contrast of 0.5 cyc/deg was increased in logarithmic steps from 0.5% to 20%. A minimum of three trials per condition was collected, and the responses averaged, with the amplitude and phase of the response being separately measured for each second of the 10-second trial. The second harmonic amplitude at 12 Hz was calculated for each epoch for the extrapolation. McKeefry et al.[26] showed that the greatest signal generated by the achromatic phase-reversing sweep VEP stimulus occurs at the second harmonic. The signal was compared with a noise estimate that was obtained by averaging the amplitudes at neighboring frequencies of the second harmonic: 11 and 13 Hz. The amplitude and phase of the evoked response were calculated using recursive least squares.[17]

To determine the visual threshold, the highest spatial frequency or lowest contrast peak meeting all scoring criteria was chosen for extrapolation using the following criteria: (1) The peak amplitude of the response had to exceed the average noise by a factor of three. Norcia et al.[27–29] showed that this signal-to-noise ratio gives a conservative false alarm rate of 0.3% for any one bin of measurement. (2) The phase of the response was constant (synchronized) with stimulus onset. Alternatively, the phase could also progressively increase with spatial frequency sweeps or decrease with contrast sweeps, due to latency changes in the visual system.[27–29] (3) Signal peaks produced by broadband artifacts, such as those produced by muscle contractions and eye blinks were rejected.[27–29]

A linear regression line was fitted between this peak to the point of 0 amplitude.[30] The spatial frequency or contrast at which the regression line crossed 0 mV was taken as the grating or contrast threshold estimate.[27–29,31–33]

Data Analysis

To facilitate judgment of the degree of grating acuity difference between the subject populations and age-matched control data all grating acuity scores were converted from cycles per degree to log minimum angle of resolution (logMAR). To control for the effects of development, measured thresholds for grating acuity and contrast sensitivity were converted into a difference score that was based on a normative data set collected at the Hospital for Sick Children. This data set contains values from 172 typically developing infants ranging from 3 to 228 months (0.25–19 years) of age. A natural logarithmic function was fitted to these normative data, with each estimate from the present study being expressed as the difference between the obtained and expected value for a given age.

Commercial software (SAS System, ver. 8; SAS, Cary, NC) was used to analyze the data. The Shapiro-Wilkinson test validated the use of parametric data analysis methods. Log contrast sensitivity and linear grating acuity were found to have normal distributions ($P = 0.7047$ and $P = 0.890$, respectively) using the Shapiro-Wilkinson test. Student's *t*-tests and Fisher exact tests were used to determine whether any differences were found between the two groups (retinal toxicity and nonretinal toxicity) for nondependent variables. Wilk's λ, a multivariate analysis of variance (MANOVA), was used to determine whether grating acuity and contrast sensitivity were affected by retinal toxicity. Univariate analyses of variance (ANOVAs) were used to test for differences in specific visual functions. Finally, sensitivity and specificity were calculated for significant visual measures.

A portion of the data used in this manuscript was previously collected by Sharon Morong and Adena Perron. Some of the data have been published elsewhere.[22,23]

Results

A total of 42 subjects were included in the analysis (Table 1). Subject ages at testing ranged from 9 to 82.2 months, with a mean of 29.1 months (SD 18.5). There were 17 girls and 25 boys included in the sample. Onset of seizure activity ranged from 0.8 to 22 months, with a median of 5 months and mean of 6.8 months (SD 4.5).

Only three patients of the 10 classified as having toxicity according to ERG parameters had evidence of typical retinal nerve fiber loss at the level of the optic nerve head.[9] No patients without toxicity defined by the ERG had evidence of VGB attributed retinal nerve fiber loss. Several patients in both groups showed evidence of mild retinal nerve fiber defect not attributed to VGB: four in the group with toxicity and six in the larger group without toxicity.

TABLE 1. Patient Characteristics and Sweep VEP Results

Subject	Known Retinal Toxicity	Age at Test Date (mo)	Log Peak CS	Grating Acuity (logMAR)	Seizure Onset (mo)	Taking VGB at Test Date	Taking Other AED	Sex	Cumulative Dosage (g/kg)	Days on VGB	Fundus Exam Grade
1	Yes	27.8	1.54	0.49	9	Yes	No	M	15.28	236	0
2	Yes	17.0	2.12	0.53	11	Yes	Yes	M	24.70	176	1
3	Yes	20.4	1.74	0.30	0.8	Yes	No	F	49.08	478	2
4	Yes	22.0	1.53	0.39	11	Yes	Yes	M	44.90	326	2
5	Yes	25.1	1.77	0.15	4	Yes	Yes	M	53.52	590	1
6	Yes	28.3	1.87	0.50	2	Yes	No	M	79.72	653	1
7	Yes	33.0	2.39	0.66	1.5	Yes	No	M	100.4	540	2
8	Yes	34.0	1.8	0.30	5	No	Yes	M	48.88	473	1
9	Yes	37.7	1.25	0.59	5	No	No	M	60.01	543	0
10	Yes	82.2	2.49	0.31	5	No	No	M	60.01	543	0
11	No	9.0	1.71	0.51	8	Yes	Yes	F	4.80	49	0
12	No	10.0	1.79	0.22	5	Yes	Yes	M	17.96	139	0
13	No	11.0	2.48	0.36	5	No	Yes	M	1.17	137	0
14	No	11.0	1.92	0.25	5	Yes	Yes	M	17.90	178	1
15	No	12.0	1.31	0.10	5	Yes	Yes	M	19.27	151	0
16	No	13.0	1.65	0.18	4	Yes	No	F	14.88	148	0
17	No	16.0	1.57	0.16	7	Yes	Yes	M	10.62	143	0
18	No	16.0	2.02	0.32	5	Yes	Yes	M	37.03	328	1
19	No	16.4	2.25	0.01	5	Yes	No	F	35.39	247	0
20	No	17.2	2.22	0.34	2	Yes	Yes	M	43.04	255	0
21	No	17.2	1.4	0.19	4	Yes	No	F	29.79	435	0
22	No	17.2	1.4	0.35	6	Yes	No	F	38.73	539	0
23	No	17.4	2.15	0.26	5	Yes	Yes	M	35.52	349	0
24	No	19.0	1.34	0.56	8	Yes	Yes	F	54.06	384	0
25	No	21.6	1.71	0.12	6	No	No	M	4.62	240	1
26	No	22.0	1.92	0.29	7	Yes	Yes	M	27.12	323	0
27	No	23.7	2.21	0.31	11	Yes	No	F	51.32	376	0
28	No	25.5	1.77	0.45	6	No	Yes	F	28.20	407	1
29	No	26.6	1.01	0.12	7	Yes	Yes	F	55.44	582	0
30	No	30.0	1.32	0.41	18	Yes	Yes	F	12.79	165	0
31	No	30.2	2.13	0.16	8	No	Yes	M	61.53	533	0
32	No	34.2	2.01	0.40	2	No	No	F	19.03	475	1
33	No	35.0	1.62	0.24	22	No	Yes	M	27.47	221	0
34	No	35.0	1.78	0.19	18	Yes	Yes	F	23.75	300	0
35	No	38.2	1.24	0.40	5	Yes	No	M	119.6	974	0
36	No	41.5	1.38	0.33	13	No	No	M	36.76	327	0
37	No	42.0	1.91	0.23	7	Yes	Yes	F	97.36	1034	0
38	No	54.9	2.64	0.11	6	No	No	F	46.12	1393	NA
39	No	56.6	2.4	0.21	2	Yes	Yes	F	114.8	1640	1
40	No	66.6	1.8	0.41	1	No	No	M	17.74	1794	0
41	No	68.2	1.59	0.03	2	No	Yes	M	61.67	1785	0
42	No	76.1	1.71	0.31	7	Yes	Yes	F	181.00	2063	0

Fundus examination grades: 0, normal; 1, mild, diffuse nerve fiber layer defect and/or mild optic disc change; and 2, nerve fiber loss at the level of the optic nerve head consistent with vigabatrin toxicity.[9] CS, contrast sensitivity; AED, antiepileptic drugs.

Twenty-nine (69%) subjects were taking VGB at the time of the testing. Twenty-six (59.5%) of these subjects were taking other antiepileptic medications concurrently with VGB. Other antiepileptic medications included phenobarbital, phenytoin, carbamazepine, valproic acid, and gabapentin.

The days on VGB ranged from 31 to 2063 with a mean of 475.1 days (SD 469.4). Cumulative dosage ranged from 1.171 to 472.62 g/kg with a mean of 57.43 g/kg (SD 77.50). There were 10 (24%) cases of retinal toxicity.

t-Tests were conducted to check for differences between the two groups for nondependent linear variables (Table 2). There were no significant differences found between the groups for age at testing (in months), seizure onset (in months), cumulative dosage (in grams per kilogram), and number of days on VGB. Fisher's exact tests were conducted to check for differences between the two groups for categorical variables (see Table 3). There were no differences found between the two groups for those taking medications other than

TABLE 2. *t*-Tests Showing No Significant Differences between the Two Groups for Nondependent Values

	Age at Test (mo)	Seizure Onset (mo)	Cumulative Dosage (g/kg)	Days on VGB
Mean				
No retinal toxicity	29.07	6.94	42.08	566.06
Retinal toxicity	32.75	5.43	53.65	455.8
t-Test *P*	0.59	0.31	0.27	0.33

TABLE 3. Fisher's Exact Tests Showing Differences between the Two Groups for Nondependent Values

	Sex	Taking Other Medications	Taking VGB at Test Date
Fisher's Exact Test	$P = 0.031$	$P = 0.27$	$P = 0.71$

VGB, and for those taking VGB at test date. A significant difference between the sexes was seen in the two groups.

Grating acuity results were converted from cycles per degree into logMAR scores [$\log_{10}(30/\text{cpd})$]. LogMAR scores are used in standard acuity charts.

The multivariate analysis showed that visual measures using the sweep VEP were different between retinal toxicity and no toxicity groups ($P = 0.048$). Univariate analyses indicated a significant difference in grating acuity, where the patients with no retinal toxicity had better mean acuity differences (compared with normative values) than those with toxicity ($P = 0.02$; Fig. 1). Overall, infants with no toxicity had an average of 0.032 logMAR score lower than age-matched control data (better VA), whereas those with toxicity had an average logMAR score of 0.144 higher than age-matched norms (poorer VA). The difference between retinal toxicity and no retinal toxicity was less than two lines on the standard chart. Univariate analyses showed no differences in contrast sensitivity between the groups; however, both groups showed reduced contrast sensitivities compared with those of normally developing children.

Although there was a significant overall difference in grating acuity between the toxicity and no-toxicity groups, we calculated sensitivity and specificity to determine whether grating acuity alone could effectively discriminate the presence of toxicity in these patients. We used a criterion value of 0.23 logMAR and lower as a measure of normal acuity, which was equal to the 33rd percentile value of the total distribution of grating acuity scores for both groups. Using this criterion, we found a sensitivity of 0.90, suggesting that grating acuity was indeed a highly effective measure for determining the presence of toxicity in the absence of other indicators. However, we also found a specificity of 0.424, suggesting that using grating acuity would also errantly identify a large proportion of patients as having toxicity when none was present.

DISCUSSION

Deficits in visual functions were evident on sweep VEP assessments in children with VGB-attributed retinal toxicity. The multivariate analysis, which included both grating acuity and contrast sensitivity, was sensitive for detecting differences ($P = 0.048$) between the toxic and nontoxic groups. The multivariate analysis of visual function is a more comprehensive assessment of vision as it incorporates both grating acuity and contrast sensitivity in an age-dependent manner. Our results demonstrated that overall visual function was reduced in children with retinal toxicity compared with those without. These reductions demonstrate how vision as a whole is affected by VGB-attributed retinal toxicity.

The univariate analysis demonstrated a reduction in age-corrected grating acuity in children with retinal toxicity compared with those without toxicity. Contrast sensitivity was poorer in both groups compared with that in the age-matched control group, although there were no significant differences between the toxic and nontoxic groups. Contrast sensitivity has been shown to be reduced in children with IS,[22,23] which our previous data showed to be related to IS, not to VGB.[22] This may be related to findings that children with seizure disorders often have diffuse retinal nerve fiber loss unrelated to VGB. In these cases, some visible optic atrophy is apparent.[9] In the group with toxicity, the clinical fundus examination did not regularly identify or parallel the ERG-based toxicity, as evidenced by the random distribution of retinal examination appearance among the group regardless of the decrease in grating acuity, suggesting that the ERG criteria for identification of early toxicity are more sensitive than the purely clinical ones.

Reduced grating acuity in children with IS with toxicity is present. Grating acuity was within normal limits in those with IS and no toxicity. Therefore, the reduction can be attributed to the effects of drug toxicity rather than the effects of disease.

Although there is now strong evidence suggesting significant visual function abnormalities in children with IS, sensitivity and specificity analyses suggest that grating acuity alone is not a specific measure. Low grating acuity was present in 90% of children with toxicity, but also in almost 58% of children with no toxicity. Thus, individual visual measurements are less effective in definitively identifying patients who have retinal toxicity.

Differences between the sexes were also demonstrated in our analysis. A previous study by Wild et al.,[34] demonstrated a 2.1-fold increased relative risk of VGB-associated visual field loss for adult male patients.[34] Our study demonstrates a similar trend, with 9 of 10 patients with VGB-associated retinal toxicity being male; however, our sample number is too low to draw a similar conclusion.

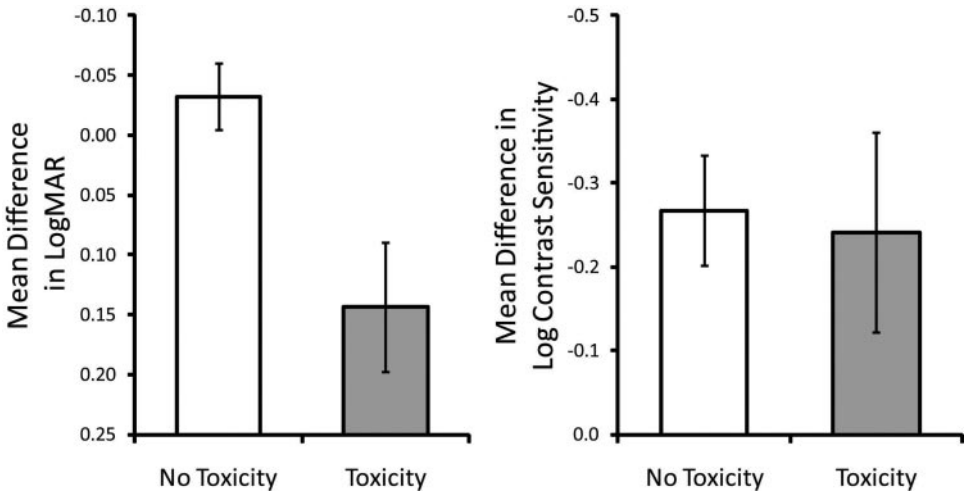

FIGURE 1. Mean VEP difference scores between retinal toxicity and nonretinal toxicity groups. The *y*-axis denotes the difference between log obtained and log age expected values for a given age. Compared with age-corrected control data, poorer grating acuity is represented by increasing positive values, whereas poorer contrast sensitivity is represented by increasing negative values.

VGB-Attributed Toxicity

An appearance of visual field narrowing associated with VGB therapy was first reported in adults by Eke et al. in 1997.[35] Since then, visual field deficits have been reported in 40% to 50% of adult cases and more recently in children. Continuation of VGB therapy during adulthood can be associated with progressive and irreversible peripheral visual field loss.[8,36–38] However, to our knowledge, there have been no reports of total blindness in adults taking VGB.

In the adult population, the evidence as to whether central retinal defects such as grating acuity are associated with VGB therapy is equivocal. Studies have found grating acuity defects in some patients taking VGB.[39] Others, for example McDonagh et al.,[40] found no significant differences in grating acuity or color vision in patients with epilepsy, regardless of whether they were taking VGB.

Central and/or Peripheral Retina Defect Attributed to VGB

VGB works as an antiepileptic drug by increasing levels of inhibitory γ-amino butyric acid (GABA) in the brain. VGB enhances GABA inhibition by selectively and irreversibly binding GABA-transaminase (GABA-T), the enzyme responsible for recycling GABA.[41,42] VGB crosses the blood–retina barrier[41–43]; consequently, there is a very high accumulation of VGB molecules in the retina. In a rat model, VGB concentration was found to be 5 to 18.5 times higher in the retina than in the brain.[42] Toxicity may result from accumulation of VGB in the retina or as a result of higher levels of GABA in the retina.

Why is the peripheral retina affected more than the central portion? GABA accumulation occurs in multiple retinal cell types: amacrine, bipolar, horizontal, and Müller cells.[41,43] As Müller cell density is lower in the periphery than in the central retina (6000 cells/mm^2 versus 30,000 cells/mm^2), it has been suggested[44] that diffuse Müller cell damage would be evident first in the periphery. This scenario would provide the pathophysiology for the frequently found peripheral visual field loss. If, on the other hand, progressive density accumulation of VGB molecules causes toxicity, then VGB may preferentially accumulate in the GABA-ergic amacrine cells in the central retina[45,46] providing some pathophysiological basis for suggested central retinal defects. Central retinal morphologic changes have been identified clinically in toxicity cases in children.[9]

VGB in the Developing Retina

The subjects in the present study are young. VGB therapy may affect the developing retina differently than it affects the mature retina; retinal maturation involves cellular migration, foveal formation, cone proliferation, and growth. During the period of seizure onset (0.8–22 months) and consequent VGB use, migrating retinal cells may mask the preponderance of peripheral versus central cellular toxicity and visual defects found later in the adult retina. During the first 45 months of life, the inner retinal layers move away from the fovea. By approximately postnatal month 5, the ganglion cells move away from the center thereby forming the foveal pit.[47,48] By 12 months of age, the diameter of the foveola decreases to half its size, with subsequent tighter cone packing.[49] Between 15 and 45 months, the fovea reaches adult size.

In addition to the role of migrating inner retinal cells, the cones themselves are developing. From birth to 45 months there is a 2.5 times increase in cone density and a further 35% increase to adulthood.[50] By 15 months, the cone outer segments are seven times longer than at birth, but are still shorter than in the adult. By 45 months they are still 30% to 50% shorter than adult outer segments.[51]

Grating acuity development follows the anatomic development. It increases from 4.5 cyc/deg at 1 month of age to between 20 and 30 cyc/deg by 6 to 8 months of age[27,32,52] and reaches an asymptote at adult levels by 6 years of age.[52]

All children who developed VGB-attributed toxicity were taking VGB during the first year of life. This is the time of rapid development and high plasticity; retinal neurons in the cone pathways engaged in cellular proliferation, migration, and differentiation are likely to be more susceptible to insult during this time. Unlike the adult retina, the infant retina may be more susceptible to damage in the more central, rapidly maturing, foveal pathways. Indeed, some children show subtle involvement of the macular retina in the presence of toxicity, identified clinically as wrinkling.[9]

Limitations

A limitation of the present study is the small size of the sample. Only 10 patients with toxicity were represented. Larger samples with more cases of retinal toxicity may uncover a reduction in contrast sensitivity measurements along with the acuity reductions presented in this study.

Conclusion

The results suggest that children with IS who are identified as having retinal toxicity have reduced overall visual functioning compared with those with no identifiable toxicity. Retinal toxicity in patients exposed to VGB is a common concern for ophthalmologists and neurologists. In the IS population, visual functions are known to be reduced, independent of VGB exposure. This reduction has presented a problem in identifying patients with IS who have toxicity, because reductions due to the disease are difficult to separate from reductions due to VGB toxicity. However, the results of this study demonstrate that overall visual functions in children with IS are further reduced in those with retinal toxicity compared to those with no identifiable toxicity.

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