

# Reduced Visual Function Associated with Infantile Spasms in Children on Vigabatrin Therapy

Dena S. Hammoudi,<sup>1,2</sup> Sophia S. F. Lee,<sup>3</sup> Adena Madison,<sup>1,2</sup> Giuseppe Mirabella,<sup>1,4</sup>  
J. Raymond Buncic,<sup>1,2,4</sup> William J. Logan,<sup>4,5,6</sup> O. Carter Snead,<sup>4,5,6</sup> and Carol A. Westall<sup>1,2,4</sup>

**PURPOSE.** To use visual evoked potential (VEP) testing to determine whether visual deficits are present in children with a history of vigabatrin use.

**METHODS.** Contrast sensitivity and visual acuity were assessed by visual evoked potential testing and compared between 28 children (mean age,  $4.90 \pm 4.92$  years) with seizure disorders who had taken vigabatrin and 14 typically developing children (mean age,  $3.14 \pm 1.70$  years). Exclusion criteria were heritable eye disease, suspected cortical visual impairment, nystagmus, and prematurity  $>2$  weeks. The effects of the following factors on contrast sensitivity and visual acuity were examined: type of seizure (infantile spasms versus other), ERG result, duration of vigabatrin therapy, cumulative dosage of vigabatrin, and other seizure medications (other versus no other medication).

**RESULTS.** Contrast sensitivity and visual acuity were reduced in vigabatrin-treated children with infantile spasms compared with vigabatrin-treated children with other seizure disorders and typically developing control subjects. The other factors examined had no significant effect on contrast sensitivity or visual acuity, with adjustment for seizure type.

**CONCLUSIONS.** Children with infantile spasms on vigabatrin may have compromised visual function, even in the absence of suspected cortical visual impairment. The children tested in the present study have reduced vision, probably associated with infantile spasms rather than vigabatrin. (*Invest Ophthalmol Vis Sci.* 2005;46:514–520) DOI:10.1167/iovs.04-0559

Infantile spasms is a type of seizure disorder with poor prognosis for seizure control and normal intellectual development.<sup>1</sup> They typically occur within the first 4 to 12 months

of life. Although medication may be necessary for only a limited period, infantile spasms have been difficult to control with conventionally used anticonvulsants. Vigabatrin ( $\gamma$ -vinyl-GABA) is an antiepileptic drug that is useful in the management of childhood seizures, including infantile spasms.<sup>2</sup> The anticonvulsant effect of vigabatrin is probably achieved by irreversible inhibition of the enzyme  $\gamma$ -aminobutyric acid (GABA)-transaminase, which breaks down the inhibitory neurotransmitter GABA and results in increased levels of GABA in the brain and in the retina.<sup>3</sup>

Vigabatrin has been associated with visual toxicity in the form of irreversible constriction of the visual field.<sup>4</sup> This visual field defect is associated with changes in electroretinogram (ERG) results. Specifically, vigabatrin-attributable visual field loss has been associated with evidence of reduced cone b-wave response,<sup>5,6</sup> decreased amplitude of the 30-Hz flicker response,<sup>7</sup> and abnormalities in photopic and scotopic oscillatory potentials.<sup>6–8</sup> Because of their young age, it is not possible to conduct formal visual field testing of most of the patients taking vigabatrin at The Hospital for Sick Children. We perform ERGs on this population. A variety of ERG parameters (amplitude and implicit time) change during vigabatrin treatment.<sup>9</sup> Changes that are nontoxic reverse after cessation of treatment.<sup>10,11</sup> For example, changes in oscillatory potential amplitude result, at least in part, from nontoxic changes.<sup>11</sup> The Hospital for Sick Children's ophthalmology protocol for children on vigabatrin treatment is that if the ERG, particularly the 30-Hz flicker response, decreases more than expected from intervisit variability, both the clinical assessment and the ERG are repeated within 3 months. If the reduction is maintained, the treating neurologist is informed of the likelihood of vigabatrin toxicity.

Nousiainen et al.<sup>12</sup> demonstrated a correlation between a *contrast sensitivity* deficit and the extent of visual field constriction in patients taking vigabatrin. In the present study, contrast sensitivity, assessed with visual evoked potentials (VEPs), was used as a measure of visual sensitivity. The purpose of the present study was to determine whether visual deficits, as assessed using the VEP, are present in children with a history of vigabatrin use.

## METHODS

### Patient Population

The study was cross-sectional, comparing VEP contrast sensitivity and visual acuity between a vigabatrin-treated group of children with seizures and a control group of normally developing subjects. The vigabatrin-treated group comprised 28 children: 15 boys and 13 girls (1.29–19.92 years of age; mean age, 4.90). At the Hospital for Sick Children, the largest group treated with vigabatrin as a first-choice drug is the subset of children with infantile spasms. In view of the predominance of children with infantile spasms, we grouped the subjects according to infantile spasms ( $n = 15$ ) or other seizure disorder ( $n = 13$ ; Table 1). Control subjects were 14 typically developing children: eight boys and six girls (1.25–5.92 years of age; mean age, 3.14). As

From the <sup>1</sup>Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, Toronto, Canada; the Departments of <sup>2</sup>Ophthalmology and Vision Sciences and <sup>3</sup>Public Health Sciences, University of Toronto, Toronto, Canada; the <sup>4</sup>Brain and Behavior Program, The Hospital for Sick Children Research Institute, Toronto, Canada; the <sup>5</sup>Division of Neurology, Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada; and the <sup>6</sup>Division of Neurology, Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada.

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

TABLE 1. Clinical Characteristics of Vigabatrin Treated Group

Subject	General Seizure Condition	Other Health Problems	Medications at Time of Test*	Ophthalmoscopy Abnormalities	
				OD	OS
1	IS, cryptogenic	None	Vigabatrin	N	N
2	IS	NF-1, optic gliomas (from radiology)	Vigabatrin	N	N
3	IS	DD, strab., microcephaly, LG	Depakane, carnitine, lamictal	N	N
4†	IS	Trisomy 21	Vigabatrin	Peripheral nerve fibre thinning	
5	IS	TS, DD	Vigabatrin, phenobarbital	Small astrocytoma	N
6	IS	Trisomy 21	Vigabatrin	N	N
7	IS	Mild DD	Vigabatrin	N	N
8	IS	DD		N	N
9	IS	None	Tegretol	N	N
10	IS, myoclonic	TS, DD	Vigabatrin, tegretol, depakene	N	N
11	IS	None		N	N
12†	IS, myoclonic	TS, DD	Vigabatrin, tegretol, topamax	Small hamartoma nasal to disc	Small hamartoma above maculae
13	IS	DD, microcephaly, ventral septal defect	Vigabatrin, fluradix, losec, domperidone, lamictal	N	N
14	IS, atonic seizures	TS, DD, rhab.	Clobazam, depakote sprinkles, carnitor	N	Three astrocytic hamartomas
15	IS, CPS	TS	Vigabatrin, tegretol	Several small depigmented spots	One small depigmented spot
16	Gen T/C	TS	Vigabatrin, tegretol, epival	Retinal cysts	
17	CPS	TS	Vigabatrin, tegretol, epival	Astrocytic nerve fiber hamartomas	
18	Epilepsy	TS, PDD, cardiac rhab.	Vigabatrin	N	N
19	LG, ES	DD, PDD	Depakote sprinkles, Ca <sup>++</sup> suppl.	N	N
20‡	Seizures	None	Depakene	Peripheral retinal atrophy with mild disc pallor	
21	Seizures (Aicardi syndrome)	DD, hypotonia	Vigabatrin, topamax	Small retinal lacuna adjacent to fovea	N
22	Tonic, intractable	DD, hypotonia	Vigabatrin, phenobarbital, budesonide, dilantin, ventolin	Mild decrease in NFL (atrophy), in area of macular mound	
23	Partial Gen T/C	TS, DD, cardiac rhab.	Vigabatrin, valium	N	N
24	Seizures, epilepsy	None	Vigabatrin, tegretol	N	N
25	Gen T/C	None	Tegretol, epival, topomax	N	N
26	CPS, Gen T/C	None	Epival, neurontin	N	N
27	GenT/C, complex partial secondary generalized	TS, DD, rhab.	Dilantin, ativan	Small astrocytomas	
28	Myoclonic seizures	DD, mild extraventricular obstructive hydrocephalus	Vigabatrin, clobazam, valproic acid	N	N

N, normal; NF-1, neurofibromatosis; DD, developmental delay; strab., strabismus; LG, Lennox-Gastault; TS, tuberous sclerosis; rhab., rhabdomyoma; CPS, complex partial seizures; Gen T/C, generalized tonic clonic; PDD, pervasive developmental disorder; ES, epileptic syndrome; suppl., supplement; NFL, nerve fiber layer.

\* Ten patients had discontinued vigabatrin at time of test.

† Subsequent development of clinical vigabatrin toxicity.<sup>11</sup>

‡ Peripheral (nerve fiber) atrophy consistent with vigabatrin toxicity.<sup>11</sup>

part of their clinical assessment, all vigabatrin-treated children had undergone a complete eye examination, including behavioral visual acuity, confrontation visual fields, ocular motility, refraction, and fundus examination. Behavioral acuity was measured according to each child's ability. The tests used were the Teller cards, Cardiff Acuity Test (both preferential-looking type tests) or logMAR (logarithm of the minimum angle of resolution) crowded-letter chart. Visual field testing was performed by confrontation, assessing the ability of the child to respond to a toy placed in each of four quadrants. Directed fixational eye movements were observed, to determine whether the child had

detected the target. There were no standard norms for confrontation visual fields, except those of general principal, in which the patient was or was not able to perceive the test object, as one would have expected him or her to. The tester can use his or her own ability to see the test object in the periphery as a comparative norm during the actual testing procedure, in which the tester faces ("confronts") the patient. Test results give only an approximation of the intactness of the visual field, which can be gained in no other way in populations such as that of the present study. Although it is not possible to pick up early visual field defect by the confrontation method, results have been

found to be abnormal in clinical patients who were identified as having vigabatrin toxicity.<sup>13</sup>

All children on vigabatrin had undergone electroretinogram (ERG) testing. As flicker ERG amplitude has been found to be the ERG outcome variable most associated with toxicity,<sup>7</sup> flicker amplitude, expressed as relative log amplitude (log microvolts increase or decrease from laboratory age-matched, normal control database),<sup>11</sup> was used as a predictor in the present study. Refractive corrections were worn during testing. Exclusion criteria were heritable eye disease, suspected cortical visual impairment, nystagmus, and prematurity >2 weeks. Cortical visual impairment was suspected in the presence of clinically poor vision in the absence of sufficient ocular abnormality to explain it and was a decision left to the discretion of the examining clinician. Informed consent was obtained, and a full debriefing of the procedure was provided to the parents or caregivers before testing, in accordance with the Declaration of Helsinki. The Hospital for Sick Children Research Ethics Board formally approved all procedures.

### VEP Testing

VEPs were performed with active electrodes placed at O<sub>1</sub>, O<sub>z</sub>, and O<sub>2</sub> and referenced to C<sub>z</sub>, with P<sub>z</sub> serving as the ground.<sup>14</sup> VEP methods and the software used (PowerDiva; developed by Vladimir Y. Vildavski, Infant Vision Laboratory, Smith Kettlewell Eye Research Institute, San Francisco, CA) have been described elsewhere.<sup>15-17</sup> Testing was binocular. In our experience, we have found that vigabatrin-attributable retinal toxicity is bilateral. Although the sensitivity of detecting a deficit may increase under monocular conditions, this was not possible in the study patient population. We found that children with seizures would not tolerate the increased test time required. Briefly, children viewed a 17-in. video monitor (Dynamic Displays, Eau Claire, WI) that displayed vertical sine wave gratings that reversed in contrast at a modulation frequency of 6 Hz. Responses evoked from the visual cortex were amplified and digitized. Five conditions were tested: two varying in spatial frequency (linear steps) with the contrast level fixed and three varying in contrast (log steps) at fixed spatial frequency. For each condition, the amplitude at twice the stimulus frequency (12 Hz) was tracked as the stimulus was swept through 10 varying spatial frequencies and contrasts over a 10-second trial, such that each response bin equaled 1 second. The rationale for linear and log steps for spatial frequency and contrast changes, respectively, is based on studies by Norcia et al.<sup>16</sup> and Tyler et al.<sup>18</sup> Tyler et al.<sup>18</sup> describe the linear extrapolation to zero voltage on a *linear* spatial frequency axis as providing a useful measure of visual acuity in infants. Contrast response functions, on the contrary, consist of a monotonically increasing function that is associated linearly with increase in *log contrast* over a range of near-threshold contrasts.<sup>16</sup> This relationship was reported initially by Campbell and Maffei.<sup>19</sup> In the present study, for each trial, log contrast or spatial frequency was increased by one step per second. The sweep ranges were age appropriate.<sup>16</sup> A minimum of five trials was tested for each condition to ensure that at least two response bins, representing the peak of the 10-second response, had a signal-to-noise ratio (SNR) exceeding 3:1. For these trials, the average amplitude of the response at the second harmonic was plotted against spatial frequency or log contrast, depending on the condition tested. Presentation of experimental conditions was randomized.

A linear regression line was fit from the peak of the averaged response (SNR >3) to the first data point where the signal crossed zero amplitude. These crossings were taken as visual thresholds (spatial frequency or contrast) for each condition. The visual threshold of the spatial frequency sweep at 80% contrast derived the visual acuity outcome measure. The second outcome measure was log<sub>10</sub> peak contrast sensitivity, which was derived from the visual thresholds for each condition, plotted as contrast sensitivity (1/contrast threshold) versus spatial frequency. The exponential model:  $y = ce^{-ax}$  was fit to these data, where  $y$  is the contrast sensitivity,  $x$  is the spatial frequency,  $c$  is the peak contrast sensitivity, and  $a$  is the rate at which contrast sensitivity changes as spatial frequency increased.

As VEP contrast sensitivity and VEP visual acuity had reached adult-like levels in all children, it was not necessary for either result to be age corrected. Sweep VEP acuity is adult-like by 8 months,<sup>20</sup> and contrast sensitivity by 9 months.<sup>21,22</sup>

### Data Analysis

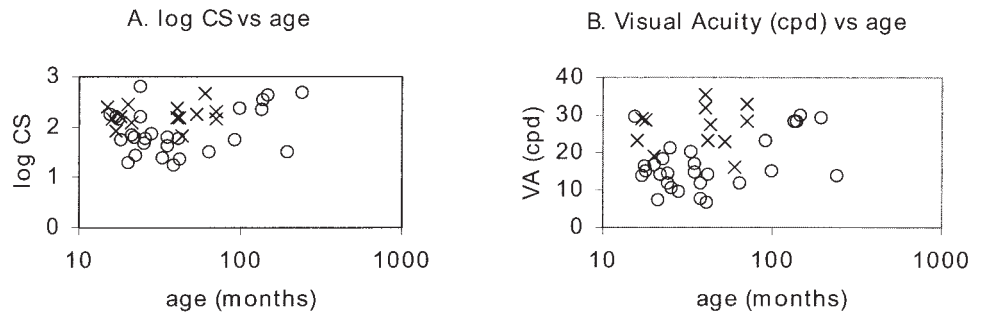
Due to the small number of patients participating in this study, all data analyses were performed using nonparametric approaches. Visual results were compared between the two treatment groups (vigabatrin versus control). The effects of ERG result, duration of vigabatrin, and the cumulative dosage of vigabatrin and other seizure medications were compared between the two seizure type groups (infantile spasms versus other) with Wilcoxon rank sum test, a nonparametric alternative to the two-sample *t*-test. Bootstrap, linear regression, and forward model selection were used to determine which factors were associated with visual function results. Bootstrap<sup>23</sup> is a resampling procedure that involves sampling with replacement from the original data. The bootstrap sample contains the same number of observations as the original data set. A statistic such as the parameter estimate for a variable in a linear regression model is calculated for the bootstrap sample. For linear regression models that include seizure type as a predictor, the bootstrap sample maintains the same number of observations in each seizure type group as in the original data set. The sampling and estimation steps are repeated a large number,  $B$ , of times, resulting in  $B$  replicates of parameter estimates. In this study  $B = 1000$ —that is, 1000 bootstrap samples were generated. The empiric 95% confidence interval of the parameter is constructed using the 2.5th and 97.5th percentiles of the replicates. The advantage of using the bootstrap method is that no distributional assumption is made about the data. However, the data are assumed to be representative of the population from which they were drawn. Moreover, bootstrapping small-sample data underestimates the true variability in the data, because there are only a few observations to select from. It has been suggested that data from a sample size <10 are too few to obtain reliable estimates and confidence intervals.<sup>23,24</sup> This problem did not arise in the present study, as the sample size was >10 in all treatment and seizure type groups.

Standard forward model selection is a variable selection method that begins with an empty model containing no variables. Univariate linear regression is fitted for each variable, and the most significant variable is selected to enter the model. Each subsequent step adds the variable that is most significant while adjusting for predictors already in the model. The procedure continues to add one variable at a time until no additional variable can significantly improve the model fit. When bootstrap and forward model selection are used concurrently, as in the current analysis, the standard forward model selection method is applied; however, the bootstrap method is implemented whenever a linear regression is fitted.

The Kruskal-Wallis test (nonparametric ANOVA) was used to test for differences in visual results between the group with infantile spasms (IS), the group with other seizure types (Other), and the control group. If the result was significant, Dunn's method of multiple comparisons using rank sums,<sup>25</sup> a nonparametric multiple comparison test, was used to determine which groups differed. Dunn's method combines the three groups, ranks the data from smallest to largest, and compares the mean rank between two of the groups. All tests were evaluated at a 0.05 significance level. Statistical analyses were performed on computer (S-plus 2000 software; Insightful Corp., Seattle, WA).

### RESULTS

Visual evoked potential results are shown for the seizure group and control group in Figure 1. Visual evoked potential results and outcome of the five factors compared between the two seizure groups are shown in Table 2. Table 3 shows visual evoked potential results of the control subjects.



**FIGURE 1.** (A) VEP contrast sensitivity (CS) results versus age in months. (B) VEP visual acuity versus age. (○) Data from children receiving vigabatrin treatment; (×) data from control subjects.

Twenty-two of the 28 children on vigabatrin had visual field assessment (confrontation). No abnormality was detected. Twenty-three children had behavioral visual acuity within the expected range for their age (laboratory databases of visual acuity scores of each test for different ages), whereas four had reduced visual acuity. The youngest child (1.29 years) had a Teller visual acuity score of 3.2 cyc/deg—0.4 logMAR lower than expected for her age—whereas the other three with reduced acuity had scores <0.3 logMAR below the acuity expected for the child’s age on the specific test. Visual acuity was not tested in one child. Refractive errors were between -0.75 and +6 D spherical equivalent (median, +1 D; mean, +0.58 D; SD, 1.54). Three children, one with infantile spasms and the others with other seizure types, had pale optic discs with some decrease in the nerve fiber layer.

Comparison of factors that were used as covariates in the subsequent univariate analysis revealed that duration on vigabatrin was significantly lower in the IS group than in the other seizure type group, and the proportion of children taking other

medication was higher in the other seizure type group (Table 4).

Contrast sensitivity and visual acuity were reduced in children with seizures treated with vigabatrin in comparison with control subjects (Wilcoxon rank sum test,  $W = 509$ ,  $P = 0.01$  for contrast sensitivity and  $W = 456$ ,  $P < 0.01$  for visual acuity). Bootstrap and univariate linear regressions revealed that seizure type had a significant effect on contrast sensitivity and visual acuity (Table 5). Cumulative dosage also had a significant effect on visual acuity, but the effect was small. For each gram of vigabatrin taken per kilogram body weight, visual acuity was estimated to increase by  $3.21 \times 10^{-3}$  cyc/deg, with an empiric 95% confidence interval of  $4.79 \times 10^{-4}$  to  $6.07 \times 10^{-3}$ . Using a cumulative dosage of 40 g/kg meant that visual acuity was estimated to increase by 0.13 cyc/deg, an effect that was not clinically meaningful; and thus cumulative dosage can be disregarded as affecting visual acuity.

However, after adjustment for seizure type, none of the other variables (duration of vigabatrin therapy, cumulative dos-

**TABLE 2.** Visual Evoked Potential Results of Vigabatrin-Treated Group and Clinical Variables Examined

Subject	Age (y)	VEP Acuity	Log Peak Contrast Sensitivity	Seizure Type	30-Hz ERG Flicker Amplitude	Cumulative Dose of Vigabatrin (mg/kg)	Duration on (Off) Vigabatrin*	Other Medication at Time of Test
1	1.42	13.8	2.22	IS	-0.0135	27	9 mo	No
2	1.88	18.41	1.44	IS	-0.09	39.05	9 mo	No
3	3.46	14.16	1.38	IS	-0.287	35.53	9 mo (16 mo)*	Yes
4	1.67	16.81	1.29	IS	-0.066	33.75	11 mo	No
5	2.00	14.66	2.21	IS	-0.069	56.25	1 y	Yes
6	2.08	21.37	1.68	IS	-0.101	69	1 y 11 mo	No
7	1.46	16.43	2.15	IS	0.15	17.65	11 mo	No
8	2.13	10.74	1.77	IS	0.036	43.66	1 y 1 mo (6 mo)*	No
9	2.92	17.24	1.62	IS	-0.094	33.13	9 mo (2 mo)*	Yes
10	1.83	14.17	1.80	IS	-0.133	44.49	10 mo	Yes
11	2.92	14.97	1.80	IS	-0.217	32.5	1 y 1 mo (3 mo)*	No
12	2.33	9.57	1.87	IS	-0.37	72.89	1 y 11 mo	Yes
13	1.50	15.11	1.74	IS	-0.117	64.62	1 y 4 mo	Yes
14	3.17	7.63	1.25	IS	-0.194	73.26	1 y 9 mo (13 mo)*	Yes
15	3.17	11.81	1.24	IS	-0.092	50.59	1 y 7 mo	Yes
16	11.13	28.38	2.35	O	0.033	73.23	2 y 7 mo	Yes
17	16.08	29.32	1.51	O	0.07	39.24	2 y 7 mo	Yes
18	8.25	15.23	2.37	O	-0.336	105.79	5 y 7 mo	No
19	3.42	6.63	1.78	O	-0.261	30.79	1 y 1 mo (17 mo)*	Yes
20	11.5	28.37	2.56	O	-0.234	54.55	5 y (14 mo)*	Yes
21	1.29	29.53	2.25	O	-0.329	43.09	9 mo	Yes
22	1.75	7.5	1.85	O	-0.144	19.43	1 y 7 mo	Yes
23	5.33	11.88	1.51	O	-0.241	55.04	4 y 9 mo	Yes
24	7.58	23.07	1.75	O	-0.282	26.25	2 y 4 mo	Yes
25	19.92	13.78	2.69	O	-0.157	29.22	2 y 6 mo (17 mo)*	Yes
26	12.17	30.15	2.65	O	0.073	39.87	3 y (14 mo)*	Yes
27	2.75	20.31	1.40	O	-0.031	10.06	11 mo (11 mo)*	Yes
28	2.00	11.98	2.81	O	-0.151	16.48	1 y	Yes

O, other seizure type.

\* Ten patients had discontinued vigabatrin at time of test.



TABLE 3. Visual Evoked Potential Results in the Control Group

Subject	Age (y)	VEP Acuity	Log Peak Contrast Sensitivity
C1	1.25	N/A	2.40
C2	3.38	31.88	2.18
C3	3.38	35.59	2.37
C4	1.5	28.66	2.21
C5	3.5	23.33	2.18
C6	3.58	27.27	1.84
C7	5	16.14	2.65
C8	1.75	N/A	2.08
C9	4.42	22.81	2.25
C10	1.33	23.2	2.17
C11	5.92	33.04	2.31
C12	5.92	28.5	2.16
C13	1.67	18.92	2.45
C14	1.42	29.03	1.92

N/A, not available.

age of vigabatrin, ERG flicker amplitude, and other seizure medications) had any significant effect on either contrast sensitivity or visual acuity. Thus, with bootstrap, forward model selection, and linear regression, only seizure type had a significant effect on contrast sensitivity and visual acuity. Contrast sensitivity was estimated to be 0.42  $\log_{10}$  units lower in the group with infantile spasms than those with other seizure types (bootstrap empiric 95% CI:  $-0.7$  to  $-0.11$ ). Visual acuity was estimated to be 5.24 cyc/deg lower for infantile spasms than other seizure types (bootstrap empiric 95% CI:  $-10.18$  to  $-0.11$ ).

As seizure type was found to be associated with contrast sensitivity and visual acuity, it was determined how visual function in each seizure group is affected relative to the control. The Kruskal-Wallis test confirmed significant differences in the medians of  $\log_{10}$  contrast sensitivity ( $P < 0.01$ ) and visual acuity ( $P < 0.01$ ) between infantile spasms, other seizure type, and the control (Fig. 2).  $\log_{10}$  contrast sensitivity and visual acuity results for children with infantile spasms were significantly lower than in the control group, based on Dunn's CIs ( $\log_{10}$  contrast sensitivity:  $-24.61$  to  $-6.74$ ; visual acuity:  $-26.21$  to  $-8.46$ ; Fig. 2). Children with other seizure types had visual acuity results lower than did the control, but there was no difference in the  $\log_{10}$  contrast sensitivity results ( $\log_{10}$  contrast sensitivity 95% CI:  $-12.64$  to  $+5.89$ ; visual acuity 95% CI:  $-19.43$  to  $-1.08$ ). The three children with mild optic nerve defect had contrast sensitivities within normal limits.

In this pediatric population, there was a fair correlation between visual acuity scores recorded in behavioral testing and

with the sweep VEP ( $r = 0.42$ ). The mean of the scores was similar: behavioral 15 cyc/deg (SD, 6.7) and sweep VEP 16.9 cyc/deg (SD, 6.9). The variability in the correlation probably reflects the slower maturational age for behavioral visual acuity assessment than for VEP visual acuity.

## DISCUSSION

The visual function deficit was most pronounced in the group with infantile spasms. The results of this study are consistent with the suggestion that the visual loss is related to the seizure disorder (infantile spasms). In other words, there is a possibility of compromised vision in infantile spasms.

Infantile spasms is a rare seizure disorder of infancy and early childhood with an onset typically within the first year of life. Characteristic features of infantile spasms, sometimes called West syndrome, include myoclonic seizures, hypsarhythmia (abnormal, chaotic EEG), and mental retardation. Visual impairment and abnormal VEP patterns in children with infantile spasms have been described.<sup>26-28</sup>

Several factors may be related to compromised vision in children with infantile spasms. First, the spatial arrangement of ON and OFF areas in receptive fields changes when GABA-mediated inhibition is decreased.<sup>29-31</sup> GABA, the major inhibitory neurotransmitter in the central nervous system, is reduced in the cerebrospinal fluid (CSF) of children with infantile spasms.<sup>32-34</sup> GABA-mediated inhibitory mechanisms act throughout the mammalian visual system on the retina,<sup>35</sup> lateral geniculate body,<sup>36</sup> and the visual cortex.<sup>29-31,37</sup> Important effects of GABA inhibition have been shown on the receptive field properties of cells in the visual cortex.<sup>29-31,37</sup> Administration of the GABA antagonist bicuculline methiodide (BIC) into the visual cortex causes an increase in the size of receptive fields of many cortical neurons in the cat.<sup>31</sup> Reduced CSF GABA levels in early infancy would change the spatial structure of receptive fields and may be responsible for reduced selectivity of cortical neural response to visual stimuli, affecting visual acuity and peak contrast sensitivity. This scenario may manifest as delayed visual development.

Reduced cortical plasticity due to low GABA levels at a critical period for visual development may prevent recovery of initially delayed visual development. GABA is essential for the cortical effects of ocular dominant plasticity that occur after monocular deprivation (MD) during the critical period. Inhibiting GABA by BIC infusion reduces the ocular dominance shift after MD.<sup>31</sup> Hensch et al.<sup>38</sup> demonstrated that gene-targeted destruction of an isoform of GAD (a GABA-synthesizing enzyme) prevents the competitive loss of responsiveness to an eye briefly deprived of vision.

TABLE 4. Comparison of Clinical Variables between the Infantile Spasms Group and the Other Seizure Type Group

Covariate	Median or Frequency of Each Covariate in Each Seizure Group		Test	Test Statistic	P
	IS	Other			
Duration (mo)	12	30	Wilcoxon Rank Sum	$-2.68^*$	0.01†
Cumulative dosage (g/kg)	43.66	39.24	Wilcoxon Rank Sum	239	0.34
Flicker amplitude (log relative amplitude)	$-0.09$	$-0.16$	Wilcoxon Rank Sum	240	0.32
Other medication					
No	7	1	Fisher's Exact	—	0.04†
Yes	8	12			

\* Rank sum normal statistic with correction.

† Significant.

TABLE 5. Bootstrap Empirical 95% Confidence Intervals for the Fitted Univariate Models

Bootstrap	Log <sub>10</sub> Contrast Sensitivity		Visual Acuity (cpd)	
	Lower CI	Upper CI	Lower CI	Upper CI
Seizure Type (IS vs. Other)	-0.72	-0.11	-10.18	-0.11
Duration (mos)	0.00	0.02	-0.04	0.38
Cumulative dosage (g/kg)	-1.13 × 10 <sup>-2</sup>	6.52 × 10 <sup>-3</sup>	4.79 × 10 <sup>-4</sup>	6.07 × 10 <sup>-3</sup>
Flicker amplitude (log relative microvolts)	-1.16	1.22	-8.90	36.42
Other medication	-0.13	0.21	-2.70	5.50

An additional factor associated with compromised visual function may relate to the abnormal electrical activity in the brain that results in the hypersarrhythmia pattern and seizures. The EEG patterns associated with infantile spasms are generalized and may involve the visual cortex, causing visual impairment. Brooks et al.<sup>26</sup> presented three cases of children with infantile spasms, in whom cortically mediated visual dysfunction developed near the onset of their seizures. Treatment of their infantile spasms improved visual function in all three cases. Iinuma et al.<sup>28</sup> showed that visual abnormalities associated with occipital slow-wave activity and irregular polyspikes on EEG are a strong risk factor for development of West syndrome in children with perinatal illness. Such focal occipital EEG abnormalities or dysrhythmia may precede the development of the generalized hypersarrhythmia and seizures in some children with infantile spasms. Other types of seizures, typically those of partial onset, originating in the occipital cortex, have also been associated with transient cortical visual deficits and blindness. In the present study, those with known cortical visual loss were not included in the study, although

some with mild cortically induced vision loss would have been included.

Shortcomings of the present study reside in the heterogeneity of the group of subjects. A larger sample size may have revealed an influence of duration of vigabatrin therapy, drug dosage, ERG flicker amplitude, other seizure medications, or other diagnoses on the tested visual responses. Despite this shortcoming, it is valid to assert that children with infantile spasms who are treated with vigabatrin have compromised visual systems. A subsequent study in our laboratory, in which we evaluated visual acuity and contrast sensitivity using the same VEP technique, demonstrated reduced visual function in children with infantile spasms before vigabatrin treatment was initiated<sup>39,40</sup> (Morong et al., manuscript in preparation).

CONCLUSIONS

Children with infantile spasms who are treated with vigabatrin may have compromised visual function, even in the absence of

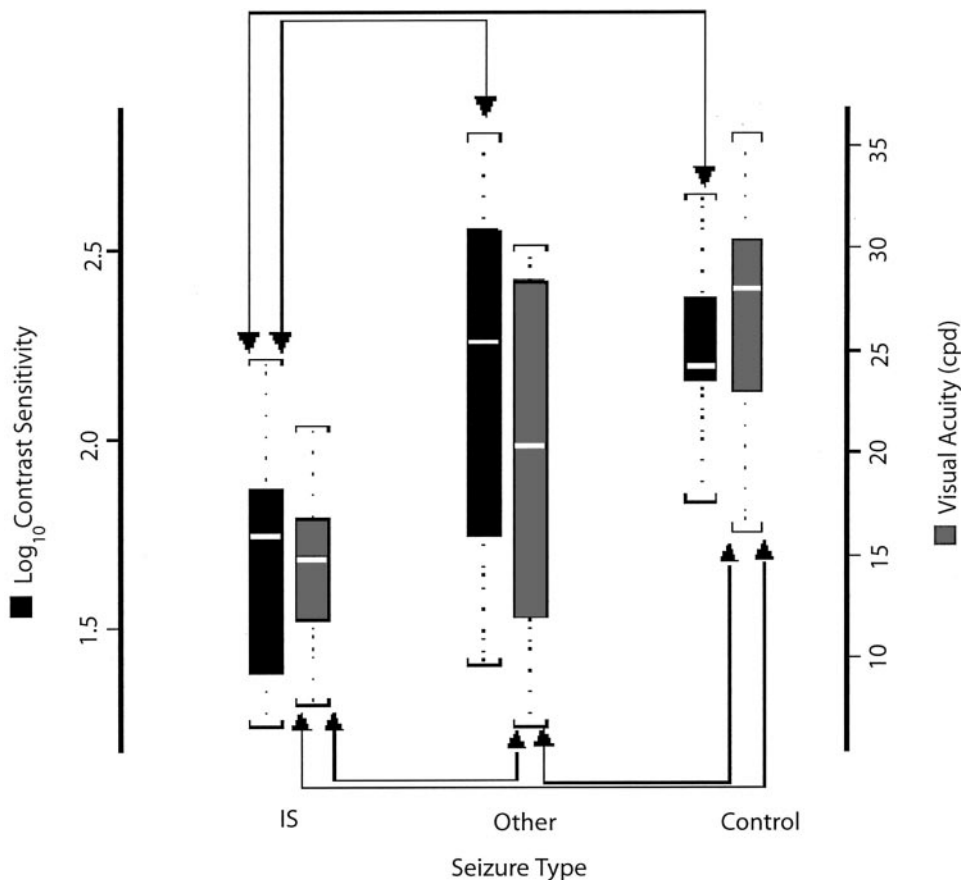


FIGURE 2. A box plot showing the distribution of log<sub>10</sub> contrast sensitivity (black) and of visual acuity (cpd; gray) in the infantile spasm, other seizure types, and control groups. The minimum, first quartile, median, third quartile and the maximum observation are shown from the bottom to the top. Arrows: significant difference, P ≤ 0.05. The three children with mild optic nerve defect—one with infantile spasms and two with other seizure types—had contrast sensitivities within normal limits (log CS = 1.80, 1.85, and 2.56, respectively).

suspected cortical visual impairment. In the group tested in the present study, reduced visual function was probably associated with infantile spasms rather than vigabatrin.

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