

Contrast Sensitivity Is Reduced in Children with Infantile Spasms

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PURPOSE. To investigate whether visual deficits in children with infantile spasm (IS) are the result of seizure activity or of treatment with the anticonvulsant drug vigabatrin (VGB).

METHODS. Vision function was determined in three experiments by determining peak contrast sensitivity (CS) and grating acuity (GA) with the sweep visual evoked potential. Cross-sectional study A: 34 children, including 11 patients with childhood epilepsy with exposure to VGB for at least 6 months, 10 with childhood epilepsy exposed to antiepileptic drugs other than VGB, and 13 normally developing children. Cross-sectional study B: 32 children, including 16 with IS naïve to VGB and 16 normally developing children. Longitudinal study: seven children with IS naïve to VGB, with subsequent follow-up 5 to 10 months after starting VGB.

RESULTS. In cross-sectional study A, the median CS was reduced by 0.5 log units ($P = 0.025$) in children with epilepsy exposed to VGB compared with those exposed to other antiepileptic drugs and normally developing children. In cross-sectional study B, the median CS was reduced by 0.25 log units ($P = 0.0015$) in children with IS (VGB naïve) compared with normally developing children. Longitudinal assessment showed no decrease in CS in children with IS who were followed up 5 to 10 months after starting VGB. There was no difference in GA among groups in any of the experiments.

CONCLUSIONS. Patients with IS have CS deficits, but a sparing of GA. This deficit is present before VGB treatment and does not worsen with treatment onset. Results suggest that visual dysfunction is largely the result of the seizures themselves. (*Invest Ophthalmol Vis Sci.* 2007;48:3610-3615) DOI:10.1167/iov.06-0755

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West syndrome (WS) is a childhood seizure disorder that occurs in 2 to 5 of every 10,000 births,¹ although the incidence varies widely by region.² The initial onset of seizure usually occurs before the end of the first year, most typically between 4 and 6 months. The syndrome is characterized by the clinical manifestation of infantile spasm (IS), an abnormal EEG pattern known as hypsarrhythmia and physical and neurodevelopmental arrest or regression, almost always leading to mental delay and retardation. In addition to IS, up to half of children with WS display other seizure types that manifest before or during the onset of spasms.³

IS occurs with high frequency, with as many as 100 episodes a day, typically lasting from 1 to 5 seconds.^{4,5} Clinical manifestations of IS are bilateral symmetrical muscle contractions of the neck, trunk and limb extremities and can involve eye movement anomalies including deviations or nystagmus.^{6,7} IS represents a specific clinical manifestation of epileptic activity associated with WS.

In Canada and the United Kingdom, the first-line treatment for these seizures and associated hypsarrhythmia in children with WS is vigabatrin (VGB). VGB is an anticonvulsant drug that is often used to treat drug-resistant seizures in adults and children.⁸⁻¹⁰ It is a structural analog of the inhibitory neurotransmitter γ -aminobutyric acid (GABA), and it selectively and irreversibly binds to and inhibits the enzyme that breaks down GABA, GABA transaminase. The reduction of active enzymes results in an increase in GABA levels in the retina and the brain.¹¹

VGB is an effective therapy for seizures and is known to be effective particularly in children with IS. However, the drug is not without serious side effects. Of particular concern is that 30% to 40% of adults taking the drug have severe visual side effects¹²⁻¹⁴ suggestive of retinal toxicity, including retinopathy, optic disc pallor, maculopathy, and reduced retinal nerve fiber layers.¹⁵⁻¹⁸ Visual function is impaired, producing deficits in visual fields, contrast sensitivity, visual acuity, and color vision.¹⁹⁻²² Electrophysiological abnormalities have also been reported.²³

Determining whether VGB produces similar side effects on the developing visual system has been difficult. In adults, visual field measurement by static and kinetic perimetry has been a reliable means of confirming retinal toxicity, since a common manifestation of VGB-induced damage is a concentric visual field deficit.^{12,14,24} In children, visual field testing is largely dependent on cooperation from the child and is particularly challenging, especially in those younger than 3 years.²⁵ Thus, a significant hurdle in understanding the effects of VGB on the developing retina has been to find age-appropriate methods that reliably assess retinal health in these infants and children.

In a previous study we found that contrast sensitivity, assessed with the sweep visual evoked potential (sVEP), is reduced in VGB-treated children with IS compared with VGB-treated children with other seizure disorders and normally developing control subjects.²² Our previous study found that children with IS had significantly reduced contrast sensitivity compared with the other groups. We concluded from these findings that the VEP abnormalities most likely resulted from

retinal and cortical abnormalities associated with IS. Because children with IS not taking VGB were never assessed, this conclusion was never demonstrated directly. Thus, it remains an open question whether the deficits were the result of IS or VGB-induced toxicity or GABA insufficiency.^{26,27}

In the present study, we addressed this question in three experiments that compared visual function in epileptic children. In *cross-sectional study A*, a group of children with seizure disorders treated with VGB was compared with another seizure group treated only with other antiepileptic drugs and also with a group of normally developing children. In *cross-sectional study B*, children with IS who were naïve to VGB were compared with a group of normally developing children to determine whether visual deficits were present before VGB therapy began. The third experiment, a *longitudinal study* compared visual function in a subgroup of children with IS before and after VGB therapy. As in our previous study, two measures of visual function, contrast sensitivity and grating acuity, were assessed by sVEP.

METHODS

Patients

Thirty-five patients with epilepsy, some of whom were taking VGB or were about to begin VGB treatment, were recruited from The Hospital for Sick Children in Toronto, Canada, from January 2002 to June 2003. Twenty-one normally developing children were recruited from the community. Exclusion criteria for both groups included heritable eye disease, suspected cortical visual impairment, nystagmus, and prematurity. Cortical visual impairment was suspected in the presence of clinically poor vision in the absence of sufficient ocular abnormality and was confirmed by the examining clinician. This research adhered to the tenets of the Declaration of Helsinki and was approved by The Hospital for Sick Children Research Ethics Board. Informed consent was obtained from all parents of participants under the age of 16 years. Consent was obtained after careful explanation of the nature of the research and all possible associated benefits and risks.

Patients with epilepsy, who had been exposed to or prescribed VGB, underwent a full ophthalmic assessment and electroretinogram (ERG). All remaining subjects underwent a full ophthalmic examination. No progressive visual disorders were found.

Cross-sectional Study A. Contrast sensitivity (CS) and grating acuity (GA) were assessed in 11 patients with childhood epilepsy with exposure to VGB for at least 6 months, 10 with childhood epilepsy exposed to antiepileptic drugs (AEDs, such as phenobarbital, clobazam, and carbamazepine) other than VGB and 13 normally developing children (control subjects). Within the VGB group, all but two patients

had IS. The children in the control group had a median age of 24 months (minimum, 9; maximum, 216).

Children in the AED group may have been exposed to VGB for 2 weeks or less. These children were included, because, of the 206 children followed up at The Hospital for Sick Children (Sickkids) over the past 5 years, there had been no suspected cases of VGB-related visual defects in those taking VGB for less than 2 weeks. To the best of our knowledge, this is true of similar children treated at other centers. Thus, this subset of children was appropriately placed in the AED group.

Age of seizure onset ranged from birth to 3.75 years, with a median age of onset of 6 months. The duration of VGB therapy ranged from 9 to 64 months with a median duration of 25 months. Cumulative doses ranged from 22.8 to 98.4 g/kg, with a median cumulative dose of 48.22 g/kg. Demographic variables of the VGB and AED groups are shown in Tables 1 and 2, respectively.

Cross-sectional Study B. The second experiment compared children with childhood epilepsy naïve to VGB ($n = 16$) with normally developing children ($n = 16$). The ages of the epilepsy group ranged from 3 to 25 months, with a median age of 9 months. Ages of the control subjects ranged from 3 to 24 months, with a median age of 7 months. Demographic variables in the childhood epilepsy group are shown in Table 3. The VGB-naïve group consisted of nine children with IS tested before initiation of VGB and six tested within 2 weeks of starting VGB treatment. At the time of testing, five patients were on other AEDs. Age of seizure onset ranged from birth to 18 months of age, with a median age of 6 months.

Longitudinal Study. In the final study we assessed 7 of the 15 patients in the VGB naïve group from cross-sectional study B who were later prescribed VGB. These children returned for follow-up testing either at 5 months ($n = 2$) or 10 months ($n = 5$) to compare visual function before and after VGB treatment.

Sweep VEP Technique

Procedure. The sweep (s)VEP technique is described elsewhere.²² In brief, patients were seated either independently or on a parent's lap, depending on age. To ensure that the display was able to present age-appropriate stimuli to participants, those younger than 7 months were seated 70 cm from the display, and those older than 7 months were seated 150 cm away. Five gold cup electrodes (Grass-Telefactor, West Warwick, RI) were positioned on the scalp at O₂, O₁, O₂, P₂, and C₂, according to the International 10-20 Electrode Placement System. All patients were tested binocularly.

Five sweep conditions, two contrast and three spatial frequency, were presented with sinusoidal gratings, modulated in counterphase, in a pseudorandom order. These conditions were used to plot a contrast sensitivity function where the peak CS was derived. Patients

TABLE 1. Group Demographics of Children Taking VGB: Cross-sectional Study A

Subject	Age at Testing (mo)	Sex	Age at Seizure Onset (mo)	Other Health Problems	Seizure Type
C04v	9	M	3	Polycythemia, hyperbilirubinemia	IS
C09v	24	M	6	Trisomy 21, delayed visual maturation	IS
C08v	26	M	7	Encephalocele, abnormal corpus callosum, hypotonia, deafness	IS
C07v	30	M	Birth	Hypoxic ischemic encephalopathy	IS
C10v	33	M	1.5	Schinzel-Giedion syndrome, Dysmorphic syndrome, agenesis of corpus callosum, small right choroidal cyst	IS
C03v	36	M	9	Trisomy 21	IS
C14v	36	F	6	Developmental delay	IS
C01v	40	F	4	Neurofibromatosis-1	IS
C02v	42	F	7	Lissencephaly	IS
C16v	156	M	45	Hypopituitarism, partial agenesis of corpus callosum	Seizures
C15v	204	M	3	Developmental delay	Focal with secondarily generalized seizures
Median	36	—	6	—	—

TABLE 2. Group Demographics of Children Taking other AEDs: Cross-sectional Study A

Subject	Age at Testing (mo)	Sex	Age at Seizure Onset (mo)	Other Health Problems	Seizure Disorder
C09n	9	F	1	Renal abnormality, hypotonia, developmental delay	Focal
C11v	20	F	4.5	Mild developmental delay	IS
C13n	152	M	72	Developmental delay, autism spectrum disorder	Generalized tonic-clonic
L09v	34	M	8	Mosaic trisomy 21	IS
C08n	36	F	2	Diffuse periventricular white matter loss, nephrocalcinosis	Generalized tonic-clonic
C07n	48	F	Birth	Microcephaly, Erb's palsy, cerebral palsy	Complex partial
C06n	60	M	9	Hydrocephalus, precocious puberty, developmental delay	Generalized clonic
C12n	72	M	48	Attention deficit hyperactivity disorder	Complex partial
C05n	96	M	Birth	Mild developmental delay	Complex partial, generalized tonic-clonic
C11n	144	M	120	Autism spectrum disorder	Complex partial, generalized
Median	54	—	6.3	—	—

were presented with either an 80% spatial frequency sweep condition or a 0.5-cycle-per-degree (cyc/deg) contrast sweep condition. These two conditions represent the outer points of the function and were therefore collected first. Once these two thresholds were obtained, the remaining conditions were presented randomly: A minimum of two trials per condition were required for the thresholds of each condition to be entered in the analysis.

The patients were instructed to watch the screen for each trial presented. A small toy was used to attract younger patients' attention to the screen. Testing time, including electrode placement and removal, was approximately 45 minutes.

Display. A vertical sinusoidal luminance grating, alternating in counterphase at a temporal frequency of 6 Hz, was presented to participants. This stimulus was displayed on a 17-in. (43-cm) monitor (Power Mac G3 Pegasus MT; Apple Computer, Cupertino, CA). The space-average screen luminance was 100 cd/m².

VEP Recording. A differential amplifier (model 12 Data Acquisition System 12C-8-32; Grass Telefactor) was used to amplify the cortical response. Amplifier bandwidth was 1 to 100 Hz, and the EEG was digitized to 16-bit accuracy.

Contrast. For the 0.5-cyc/deg condition, contrast was swept logarithmically from 0.5% to 20% over the 10-second period. At higher

spatial frequencies, contrast was swept logarithmically from 1% to 40%.

Spatial Frequency. For patients 7 months of age or older, spatial frequency was swept linearly from 3 to 35 cyc/deg over the 10-second period. For patients younger than 7 months, spatial frequency was swept from 1 to 15 cyc/deg. These spatial frequency sweeps were performed at two fixed contrasts: 80% and 33%. Grating acuity was defined as the frequency threshold obtained from sweeping spatial frequency at 80% contrast.

Signal Analysis. The amplitude and phase of the evoked response were calculated by the recursive least squares (RLS) method. Contrast and spatial frequency thresholds were estimated by a linear extrapolation of VEP response to 0 amplitude. These extrapolations are derived completely by software based on fixed signal-to-noise ratios (Power Diva, The Smith-Kettlewell Eye Research Institute, San Francisco, CA), phase, and the T²-circ statistic. Trials were removed by the experimenter if it was deemed that the infant was not looking at the screen for the duration of the trial. Threshold values obtained from these sweep trials were used to fit a contrast sensitivity function using a negative exponential model.^{28,29} Peak CS values were derived from this model. Repeatability of grating acuity and contrast sensitivity using the sweep VEP has been described,^{30,31} and a single case demonstrat-

TABLE 3. Group Demographics of Patients with Childhood Epilepsy at Baseline: Cross-sectional Study B

Subject ID	Age at Testing (mo)	Age at Seizure Onset (mo)	Other Medications at Testing	Other Health Problems	Date of Sweep VEP Test	Date of VGB Initiation
L14V	3	Birth	None	Developmental delay, microcephaly	10-8-02	10-5-02
L12V	5	4	None	Mitochondrial disease, Leigh disease	8-13-02	NA
L13V	5	5	None	Delay in motor development	9-11-02	9-17-02
L10V	5	Birth	Phenobarbital, ranitidine, clobazam, vitamin B	Developmental delay, Complex I deficiency	4-25-02	NA
L06V*	5	5	None	None	2-19-02	2-19-02
L11V*	7	6	None	None	6-11-02	6-11-02
L15V	7	6	None	Developmental delay	1-21-03	1-23-03
L02V*	9	15	Phenobarbital, carbamazepine	Tuberous sclerosis, hypothyroidism, developmental delay	12-20-01	12-6-01
L01V*	9	8.5	None	Large right sided occipitoparietal cyst	3-1-01	3-15-01
L16V	9	Birth	Lorazepam, phenobarbital	Developmental delay	1-28-03	1-21-03
L05V*	11	7	None	Trisomy 21 syndrome	2-8-02	2-11-02
L08V*	11	7	None	Mild delay in mental and motor development	3-19-02	3-15-02
L09V	12	8	Phenobarbital	Trisomy 21: mosaic type	4-16-02	4-3-02
L07V	19	11	Carbamazepine	Tuberous sclerosis	2-26-02	2-27-02
L04V*	25	18	None	None	2-19-02	2-8-02

* Also tested in the longitudinal study.

ing repeatable peak CS values on two visits separated by 4 months in a 30-month-old child has been published by the SickKids group.³²

Statistical Analysis

Because of unequal variances between groups, nonparametric tests were used to assess differences in the three studies. In cross-sectional study A, a Kruskal-Wallis analysis was used to assess differences among children exposed to VGB for more than 6 months, children exposed to other AEDs, and normally developing children. For cross-sectional study B, the Mann-Whitney test was used to compare peak CS and GA in children with IS naïve to VGB and normally developing children. For the longitudinal study, the Wilcoxon signed ranks test was used to assess possible changes in peak CS and GA in children after being on VGB for 5 or 10 months.

RESULTS

Cross-sectional Study A

Patients exposed to VGB showed significantly lower peak CS values than did the AED group and normally developing children ($P = 0.025$; Fig. 1). Median peak log CS in patients exposed to VGB was 1.7, compared with 2.2 in the AED group. Median peak CS in the group of normally developing children was 2.1. There were no significant differences in GA among these groups ($P = 0.30$). Median values for the VGB, AED, and control groups were 19.5, 20, and 17 cyc/deg, respectively.

Cross-sectional Study B

Patients with IS naïve to VGB (baseline) had significantly lower peak CS than did normally developing children ($P = 0.0009$; Fig. 2). GA between these two groups was found to be statistically nonsignificant ($P = 0.68$) with a median value of 11.36 cyc/deg in the IS group and a median of 13.2 cyc/deg in the control group.

Longitudinal Study

Mean peak CS decreased over time ($P = 0.078$) in children taking VGB for 5 or 10 months when compared with their respective peak CS values before VGB administration. A closer look at individual changes, however, showed that CS was reduced over 0.5 log units in only two of the seven children

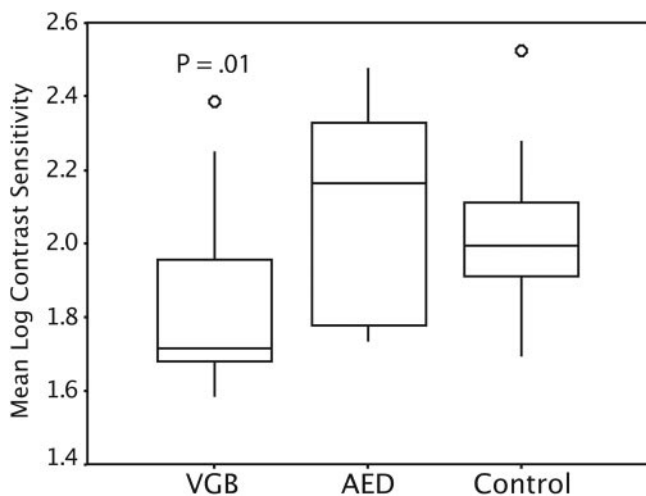


FIGURE 1. Box plots comparing CS in children in the VGB group with control subjects and children in the AED group. VGB group (maximum CS, 2.4; median, 1.7; minimum, 1.6); AED group (maximum CS, 2.5; median, 2.2; minimum, 1.7); and control group (maximum CS, 2.5; median, 2.1; minimum, 1.9). (○) Outliers.

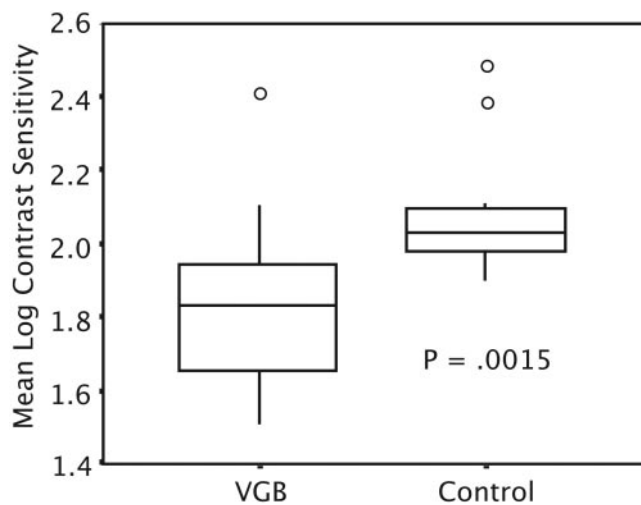


FIGURE 2. Box-plots comparing CS in VGB naïve children and the control group. VGB naïve (baseline) group (median, 1.8; minimum CS, 1.5) and control group (maximum CS, 2.5; median, 2.05; minimum value, 1.9). (○) Outliers.

(Table 4). Thus, the overall reduction in CS appears to be driven by the data from these two children. The change in CS was -0.29 log units, which was within the 95% confidence interval for changes over two visits in normal infants from two published reports,^{31,33} suggesting that the observed changes were random and not due to treatment effects.

DISCUSSION

VGB is an antiepileptic drug effective in treating children with IS.³⁴ As such, this medication is commonly administered as a first line of treatment to pediatric patients. However, the potential consequences of this drug on the developing visual system remain under investigation.

Our findings suggest that peak contrast sensitivity was significantly reduced in a group of children with IS who are taking VGB compared with children with seizure disorders taking other AEDs and with normally developing children. No differences in GA were found in any of the groups. This finding supports the conclusions of our previous paper suggesting that CS is a reliable indicator of visual deficits in children with IS.

The results of cross-sectional study B show that children with IS have deficits in CS before VGB treatment, compared with age-matched, normally developing children. This further suggests that reductions in CS are the result of brain abnormalities associated with IS. These types of IS-associated visual cortical deficits have been found in previous research. Rando et al.³⁵ assessed visual function in 25 children with WS, about

TABLE 4. Contrast Sensitivity Results in the Longitudinal Study

Subject ID	Sex	Age (mo)	Log CS Baseline	Log CS 5 Mo/10 Mo	Log CS Change
L06V	F	5	2.05	2.02	0.03
L11V*	F	7	1.84	1.31	0.53
L02V	F	9	1.71	1.55	0.16
L01V*	M	9	2.11	1.34	0.76
L05V	F	11	1.65	1.53	0.12
L08V	F	11	1.95	1.92	0.04
L04V	M	25	1.73	1.78	-0.05
Median		9	1.84	1.55	0.12

* Reduction in contrast sensitivity >0.5 log units.

half of whom were taking VGB. The study found abnormalities in cortically mediated aspects of visual function such as visual fields, Teller acuity, and attention. Guzzetta et al.³⁶ also assessed visual attention in 3-month-old infants who had symptomatic WS but who did not yet have developed IS. Visual attention was assessed with a fixation-shift test that demonstrated low attention in these children before the onset of spasms. This deficit remained during the acute stage of WS, and at a 2-year follow-up. This impairment occurred before the onset of seizures and thus before any AEDs were administered. This suggests that visual abnormalities and abnormal occipital EEG discharge during infancy may be predictive of the onset of WS.²³

The longitudinal study revealed a slight decrease in peak CS in children taking VGB for 5 or 10 months when compared with baseline. This longitudinal effect was not significant because the decrease primarily occurred in only two children. However, the effect should be investigated further. Overall, there is little evidence from the present study to suggest that VGB has a significant effect on visual function across the board in children with IS.

Taken together, these findings suggest that the occurrence of seizures, and not VGB treatment, largely affect cortical visual processing. Although children with WS in this study showed no evidence of cortical visual impairment in the eye examination, the reduction of peak CS by cortical evoked potentials indicates that the seizures are associated with impaired cortical visual function. There is the possibility that these abnormalities are due to an early deficiency in the GABA levels in these patients. Children with IS may have diminished GABA levels in their cerebral spinal fluid, suggesting a reduction in GABA transmission.^{37,38} Inadequate GABA transmission during critical developmental periods may hinder development of visual function. Studies looking at GABA-mediated inhibition and its effects on the visual system showed that having absent GABA-mediated inhibition during critical windows prevented development of ocular dominance, whereas increased GABA-mediated inhibition resulted in very sharp anatomic segregations.^{39–41} Thus, the visual deficits associated with IS may be due to developmental disruption associated with a decrease in GABA production during the early postnatal period rather than systemic neuronal damage as a consequence of seizure activity.

CONCLUSIONS

Children with WS have baseline visual deficits in peak contrast sensitivity that appear to be related to disease-associated IS. At least in the short term, there is no evidence that visual deficits are the results of treatment with VGB.

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