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Original Article

Electrophysiological Evidences of Visual Field Alterations in Children Exposed to Vigabatrin Early in Life

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ABSTRACT

BACKGROUND: We assessed central and peripheral visual field processing in children with epilepsy who were exposed to vigabatrin during infancy. **METHODS:** Steady-state visual evoked potentials and pattern electroretinograms to field-specific radial checkerboards flickering at two cycle frequencies (7.5 and 6 Hz for central and peripheral stimulations, respectively) were recorded from Oz and at the eye in seven school-age children (10.1 ± 3.5 years) exposed to vigabatrin early in life, compared with children early exposed to other antiepileptic drugs ($n = 9$) and healthy children ($n = 8$). The stimulation was made of two concentric circles (0 to 5 and 30 to 60 degrees of angle) and presented at four contrast levels (96%, 64%, 32%, and 16%). **RESULTS:** Ocular responses were similar in all groups for central but not for the peripheral stimulations, which were significantly lower in the vigabatrin-exposed group at high contrast level. This peripheral retinal response was negatively correlated to vigabatrin exposure duration. Cortical responses to central stimulations, including contrast response functions in the children with epilepsy in both groups, were lower than those in normally developing children. **CONCLUSIONS:** Alteration of ocular processing was found only in the vigabatrin-exposed children. Central cortical processing, however, was impaired in both epileptic groups, with more pronounced effects in vigabatrin-exposed children. Our study suggests that asymptomatic long-term visual toxicity may still be present at school age, even several years after discontinuation of drug therapy.

Keywords: visual evoked potential, electroretinogram, field-specific, epilepsy, vigabatrin, children

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Introduction

Vigabatrin is a ɣ-aminobutyric acid (GABA) transaminase inhibitor that results in an accumulation of the inhibitory neurotransmitter in the brain and, at higher concentrations, in the retina.[1] This antiepileptic drug is used either in monotherapy or in add-on therapy with proven efficacy in the treatment of infantile spasms (IS) and focal seizures in children.[2,3] It is often considered the first choice in the treatment of IS in tuberous sclerosis complex because it has demonstrated a high rate of IS control (95%).[4,5] However, an important proportion (20% to 70%) of adult patients undergoing vigabatrin therapy show deleterious secondary effects on peripheral visual fields, which are usually asymptomatic.[6-8] Potential visual toxic effects of vigabatrin in infants and young children represents a substantial challenge because of the difficulty of testing peripheral vision (perimetry) in pediatric populations, which is often considered unreliable under the developmental age of 9 years old.[9,10]

Electroretinogram (ERG) abnormalities occur in children treated with vigabatrin, including reduced cone response b-

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wave, decreased amplitude of the 30-Hz flicker response, and abnormalities in oscillatory potentials; however, some recovery after discontinuation of the therapy is typically observed.[11-15] These effects are mainly driven by cones and amacrine cells, which are not specific to the clinical vigabatrin-related field loss. Furthermore, a reduction of rod b-wave amplitude was also found in patients exposed to vigabatrin, either in adults[16-18] or in children.[19]

Very few studies have been conducted on the integrity of the visual processing in children exposed to vigabatrin. Contrast sensitivity and grating acuity were measured by Mirabella et al.[20] using the sweep visual evoked potential (VEP) technique in children exposed to vigabatrin, in children exposed to other antiepileptic drugs (AEDs), and in normally developing children. Patients who were exposed to vigabatrin showed significantly lower contrast sensitivity than did the other AED group and normally developing children. No significant difference in grating acuity was found among the groups. Interestingly, deficits in contrast sensitivity in patients before vigabatrin treatment compared with normally developing children were also observed, suggesting that reduction in contrast sensitivity was primarily associated with IS, not vigabatrin. However, visual functions investigated by Mirabella et al.[20] did not consider peripheral and central visual fields independently, which is an important variable with regards to vigabatrin toxicity.

To distinguish the integrity of central and peripheral visual fields, field-specific VEPs can be used.[21,22] In comparison with either Goldmann or Humphrey perimetry responses in children exposed to vigabatrin, VEPs can achieve good sensitivity (75%) and specificity (85%) for identifying peripheral visual field impairment.[23,24] Although this approach is interesting, its current clinical application is not optimal because seminal works using field-specific VEPs did not assess contrast sensitivity and used transient VEPs, which require a relatively high number of trials to ensure reliable responses. We have recently validated, in adults and children, an improved field-specific method by using steady-state VEPs to assess visual function processing in a short period (on the second scale rather than the minute scale), making it a valuable tool for probing visual function in individuals of limited attention span and/or in clinical settings.[22] We also showed that the recording from a single electrode (Oz) is sufficient to adequately track the cortical responses of the central and peripheral visual stimulations.

Our goal was to investigate the long-term toxicity of vigabatrin in children at school age ($\approx$10 years old) using a central and peripheral field-specific electrophysiological method, including contrast sensitivity. Field-specific steady-state VEPs and pattern ERGs (PERG) at different contrast levels were compared in children exposed to vigabatrin, in children exposed to other AEDs, and in healthy participants.

Materials and Methods

Participants

The vigabatrin-exposed group included seven children (three girls) aged from 4 to 15 years old (mean = 10.12; standard deviation [SD] = 3.49) with epilepsy and exposed to the medication within the first two years of life for at least six months (Table 1). All participants in this group were tested off medication at school age and showed no sign of toxicity through their clinical visual examination follow-ups during the medication intake including 30-Hz flicker ERGs, as recommended by Sergott and Westall.[25] The vigabatrin-exposed group was compared with two control groups. The first control group comprised nine children with epilepsy (five girls) exposed to AEDs other than vigabatrin and aged from five to 17 years of age (mean = 11.37; SD = 3.18; Table 2). The second control group comprised eight healthy participants (five girls) recruited in the community (mean age = 8.72; SD = 3.94). All participants had normal or corrected vision. Both epileptic groups were recruited from the neurology division at Sainte-Justine's Hospital. Informed consent was obtained in writing from all participants or their guardians, or assent from the participants themselves when possible. This study was approved by the Ethics Committee of the Sainte-Justine's Hospital Research Center.

Stimuli

Two radial checks with a central stimulation at 0 to 5 degrees diameter and a peripheral stimulation at 30 to 60 degrees radius, varying

TABLE 1.
Sociodemographic Data of Epileptic Children Exposed to Vigabatrin (VGB)

Patient (Sex)	Age at Testing (yr)	Age at Seizure Onset (mo)	Age at VGB Onset (mo)	Mean Dose (mg/kg)	Exposure Duration (mo)	Off-VGB Since (mo)	Other Health Problems	Seizure Type
1 (F)	11.1	8	8	56.9	15	76	TS	CP
2 (M)	9.8	5	6	108.0	12	111		IS
3 (M)	9.8	5	6	108.9	12	111		IS
4 (M)	13.2	6	7	108.8	29	123	WS	IS
5 (F)*	15.1	17	22	48.6	30	123	TS	CP
6 (F)	4.8	5	5	64.9	7	45		IS
7 (M)	7.1	12	12	106.4	9	67	WS	IS
Mean	10.1	8.29	9.4	86.1	16.3	93.7		
Median	9.8	6	7	106.4	12	111		

Abbreviations:
CP = complex partial
F = female
IS = infantile spasm
M = male
TS = tuberous sclerosis
WS = West syndrome
* The only participant with additional drug exposure (valproic acid and lamotrigine).

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