Epilepsy, cysticercosis, and toxocariasis: A population-based case-control study in rural Bolivia

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CME

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A. Nicoletti, MD; A. Bartoloni, MD; A. Reggio, MD; F. Bartalesi, MD; M. Roselli, MD; V. Sofia, MD; J. Rosado Chavez, MD; H. Gamboa Barahona, MD; F. Paradisi, MD; G. Cancrini, MD; V.C.W. Tsang, PhD; and A.J. Hall, PhD

Abstract—*Objective:* To assess the relationship between epilepsy and infection with *Taenia solium* and *Toxocara canis* with a case-control study, in the rural area of the Cordillera Province, Bolivia. *Methods:* A preliminary two-phase door-to-door prevalence survey determined the prevalence of epilepsy and identified cases and control subjects. At least two control subjects per case were selected, matching on sex, age, and community of residence. Cases and control subjects were assessed serologically for antibodies against *T. canis* by ELISA and against *T. solium* by enzyme-linked immunoelectrotransfer blot (EITB). *Results:* The prevalence survey found 130 confirmed cases of epilepsy, of which 113 were eligible for the case-control study (59 partial seizures and 54 generalized seizures). Two hundred thirty-three control subjects were selected. Multivariable analysis for a matched case-control study was carried out. There was an association between EITB positivity for *T. solium* and epilepsy with an OR of 1.85 (95% CI 0.99 to 3.4) for all cases. A stronger association was found in those with partial epilepsy with a late onset of disease (15 years and older), where the OR was 3.66 (95% CI 1.10 to 12.10). A positive association was also found with *T. canis* for all cases with an OR of 2.70 (95% CI 1.41 to 5.19). This increased for those with late-onset partial epilepsy to an OR of 18.22 (95% CI 2.10 to 158.10). *Conclusion:* This finding suggests that both neurocysticercosis and toxocariasis may in part explain the higher prevalence of epilepsy, particularly partial epilepsy, in developing countries.

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Cysticercosis is a systemic infection by the larval tissue stage of the pork tapeworm *Taenia solium*. Humans acquire cysticercosis by ingesting eggs of *T. solium* in food or water contaminated by feces of individuals who harbor the adult parasite in the small intestine or by auto-infection.[1] Although cysticercosis has a worldwide distribution, its prevalence is highest in developing countries. Neurocysticercosis (NCC), caused by infection of the CNS with the larval-stage *T. solium*, is considered the major cause of neurologic disease in developing countries of Latin America, Africa, and Asia.[2] NCC has a broad spectrum of clinical manifestations, with seizures being the most frequent, and is considered one reason for the higher incidence of epilepsy in developing vs industrialized countries.[3]

Human toxocariasis is another parasitic zoonosis caused by larval stages of *Toxocara canis*, the common roundworm of dogs, and probably by the roundworm of cats too. Humans are infected by ingestion of embryonated *T. canis* eggs present in the soil or on contaminated hands and fomites.[4] Most humans infected by *T. canis* do not develop overt clinical disease.[5] On the other hand, migrating *T. canis* larvae can cause, particularly in young children, inflammatory tissue reactions with multisystem involvement, leading to the clinical syndrome of visceral larva migrans. The larvae can locate in the CNS, leading to a variety of neurologic disorders.[4] Toxocariasis has been suggested as a co-factor for epilepsy.[6] How often *Toxocara* larvae provoke neurologic disorders in humans is not clear. Toxocariasis occurs whenever the human–soil–dog relationship is particularly close. High seroprevalence rates of *Toxocara* infection have been found in developing countries where the humid climate favors the survival of parasite eggs in the soil and poor hygiene increases the probability of human infection.[7-9]

We assessed, by a case-control study, the relationship between epilepsy and seropositivity for *T. solium* and *T. canis* in the rural area of the Cordillera Province, Bolivia. This area was chosen because epilepsy is a major health problem, with a prevalence of 12.3/1,000,[10] because of the anecdotal report of cases of human and porcine cysticercosis, and because a study had shown a high prevalence of *Toxocara* anti-

From the Institute of Neurological Science (Drs. Nicoletti, Reggio, and Sofia), University of Catania, Institute of Infectious Diseases (Drs. Bartoloni, Bartalesi, Roselli, and Paradisi), University of Florence, and Institute of Parasitology (Dr. Cancrini), University "La Sapienza," Rome, Italy; Health District (Drs. Rosado Chavez and Gamboa Barahona), Cordillera Province, Camiri, Bolivia; Centers for Disease Control and Prevention (Dr. Tsang), Atlanta, GA; and London School of Hygiene and Tropical Medicine (Dr. Hall), United Kingdom.

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Address correspondence and reprint requests to Dr. Alessandra Nicoletti, Istituto di Scienze Neurologiche, Università di Catania, Via S. Sofia no. 78, 95125 Catania, Italy; e-mail: anicol@dimtel.nti.it

bodies in the populations of two rural communities (27% in one community and 42% in the other).[11]

The study was conducted with the agreement of the National Department of Epidemiology of the Ministry of Social Welfare and Public Health and with the support of the Guaranì political organization (Asamblea del Pueblo Guaraní). Background and methods have been published.[12]

Methods. *Study area.* The study was carried out in the rural area of the Cordillera Province, Santa Cruz Department, in southeastern Bolivia. The Cordillera Province covers 86,245 km^2 and, by Bolivian National Census (Istituto Nacional de Estadistica, 1992) has a population of 88,628 inhabitants, 32,953 of whom live in urban and 55,675 in rural areas.[13] The province is administratively divided into 10 areas. Racially the population is a mixture of mestizos, descendants of intermarriages between Spanish colonists and the native tribes (the Guaraní-Chiriguanos), and approximately 30% pure Guaraní Indians. The majority of the population speaks both Spanish and Guaraní, while a minority speaks only Guaraní. Agriculture and animal husbandry are the major subsistence activities. The health-care infrastructure consists of a district hospital, nine area hospitals, and rural health centers.

Case ascertainment and control selection. A preliminarily door-to-door neuroepidemiologic study had been carried out to determine the prevalence of epilepsy.[10] This prevalence survey served as the framework for the case-control study. A random cluster survey method was used, with each community constituting one cluster. Clusters were randomly selected communities to represent approximately 20% of the population in each area. Only communities with <2,000 inhabitants were selected in order to exclude urban areas. In total, 10,124 people were selected in 55 communities.

This was a two-phase study. In phase 1, the sample of the rural communities selected from the 10 areas of the Cordillera Province was screened door to door to identify persons who possibly had a disorder of neurologic interest. The interviewers who carried out the screening were local paramedical workers who had received prior training. In phase 2, all subjects found positive on screening underwent a complete neurologic examination performed by neurologists.[12]

We adopted the Sicilian Neuroepidemiologic Study screening instrument,[14] a slightly modified version of the World Health Organization Neuroscience Research Protocol.[15]

At least two control subjects per case were selected from subjects negative at the screening phase. These individuals were matched on sex, age (±5 years), and community. Both cases and control subjects had a blood sample taken for serology.

Informed consent was obtained from all adult participants and from parents or legal guardians of minors. The study design, including its ethical aspects, was reviewed and approved by the Bolivian Ministry of Social Welfare and Public Health and the local health authorities.

Diagnostic criteria of epilepsy. Epileptic cases were diagnosed on the basis of the definition proposed by the International League Against Epilepsy (ILAE) in 1993.[16] In an attempt to determine the accuracy of classification, patients with a clinical diagnosis of epilepsy underwent a standard EEG recording. We performed all EEG recordings in the field using a 20-channel (portable) machine.[10] Seizure types were identified on the basis of the classification proposed by ILAE in 1981.[17]

Serologic evaluation. All the serum samples were collected in the field and immediately centrifuged, aliquoted, and frozen at −20 °C. All samples were shipped on dry ice to the Centers for Disease Control and Prevention (Atlanta, GA) for the enzyme-linked immunoelectrotransfer blot (EITB) and to the Institute of Parasitology (Rome, Italy) for the *T. canis* ELISA. Laboratories were blind to the case-control status of sera.

EITB assay. The EITB assay for *T. solium* was performed using seven lentil/lectin-purified *T. solium* glycoprotein antigens in an immunoblot to detect specific antibodies. Each serum sample was diluted 1:100 with phosphate-buffered saline, 0.3% Tween-20, and 5% nonfat dry milk and mixed well before use. Antibody reaction against these glycoproteins was visualized with an H_2O_2/diaminobenzidine substrate system. A reaction to one or more glycoproteins was considered a positive result. The assay was repeated when results were ambiguous.[18,19]

ELISA. Specific *T. canis* IgG were detected with a commercial ELISA kit (*Toxocara* IgG specific; Lofarma Allergeni, Milan, Italy) using excretory/secretory antigens (*Toxocara* escretory-secretory antigen [TES-Ag]) from second-stage *T. canis* larvae.[20] Sera to be assayed (in duplicate) were diluted 1:1,000, and the results were determined photometrically at 492 nm by a microplate reader (Titertek Multiskan Plus, Flow Laboratories, McLean, VA). On the basis of the optical density of known positive and negative controls, a cut-off of 0.45 was selected. A Western blot analysis was performed to confirm any *T. canis*-positive ELISA results. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis analysis of TES-Ag showed that it is composed of several proteic components whose molecular mass ranged from 14 to >100 kd. All sera tested by immunoblot reacted with a component at 48 kd, while a different degree of reactivity was detected at 30, 40, and 95 to 100 kd. No reactivity was revealed against bands lower than 30 kd.[21]

Statistical analysis. Multivariable analysis using conditional logistic regression for a matched case control study was carried out using STATA (Stata Corp., College Station, TX).[22] The number of years of schooling and occupation of cases and control subjects were analyzed as potential confounding variables. Interactions were examined between all significant ($p < 0.05$) variables. Subgroup analysis was conducted in those with partial and with generalized epilepsy as well as among those with early (0 to 14 years of age) and adult (>14 years) onset.

Results. The prevalence survey detected 130 epileptic patients. A serum sample for the case-control study was available from 113 cases and 233 matched control subjects. None of the 233 control subjects was selected from the same household as the cases.

The clinical features of the 17 patients not included in the case-control study were similar to those of the other patients (9 males and 8 females; mean age 29.1 ± 26.2 years, mean age at onset 18.6 ± 19.9 years; 11 [58.8%] were classified as having partial seizures).

Table 1 *Baseline characteristics of cases and control subjects*

Characteristic	Cases, n = 113	Control subjects, n = 233
Mean ± SD age, y	23.7 ± 16.9	23.5 ± 16.2
Males, %	46.9	46.0
Females, %	53.1	54.1
Mean ± SD no. of people/household	7.3 ± 2.9	7.5 ± 2.8
Presence of latrines, %	54	45.7
Presence of pig, %	51.3	55.5
Pork consumption, %	98.2	97.4
Educational level		
None, %	27.3	22.2
Primary school, %	55.5	60.1
Occupation		
Homemaker, %	51.3	62.0
Farmer, %	32.1	25.3
Others	16.7	12.3

The baseline characteristics for matched cases and control subjects are shown in table 1. Of the 113 epileptic patients, 87 (75.5%) had a standard interictal EEG recording performed. On the basis of the ILAE classification, considering both EEG and clinical data, partial seizures were the most common type diagnosed (59; 52.2%); in particular, 10 patients had partial seizures without secondary generalization and 49 patients had partial seizures with secondary generalization. The mean ± SD age at onset was 17.3 ± 16.4 years for all patients, 20.5 ± 16.3 years for partial epilepsy, and 13.9 ± 15.9 years for generalized epilepsy. Seizure types, on the basis of the electroclinical classification, are shown in table 2.

Multivariable analysis showed that neither occupation nor years of schooling was significantly associated with risk for epilepsy in this population, and therefore they were not confounding variables. There were no significant interactions. Comparing univariate and adjusted results showed some evidence of confounding between *T. canis* and cysticercosis but no statistical interaction. Thus, all epileptic cases and control subjects on univariate analysis had an odds ratio (OR) of 1.85 (95% CI 0.99 to 3.4) for cysticercosis and 2.70 (1.41 to 5.19) for *T. canis*. When they are fitted simultaneously, the OR for cysticercosis was 1.67 (95% CI 0.88 to 3.16) and for *T. canis* 2.55 (1.31 to 4.94). All subsequent models included both EITB and ELISA results, and thus all results presented below are adjusted for the other infection.

Table 2 *Seizure type and EITB and ELISA positivity for epileptic categories*

Electroclinical classification	Cases, no. (%)	EITB, no. positive	ELISA, no. positive
Partial seizures without SG	10 (8.8)	2	2
Partial seizures with SG	49 (43.4)	13	14
Absence	9 (8.0)	1	2
Myoclonic	3 (2.7)	0	0
Tonic	2 (1.8)	1	2
Tonic-clonic	39 (34.5)	5	8
Not classifiable	1 (0.9)	0	0
Total no.	113	22 (19.5%)	28 (24.8%)

EITB positive = presence of antibodies against *T. solium* detected by enzyme-linked immunoelectrotransfer blot (EITB) assay; ELISA positive = presence of antibodies against *T. canis* antibody detected by ELISA; SG = secondary generalization.

Table 3 *Prevalence and OR of EITB and ELISA positivity*

	Cases		Control subjects		
Assay	No.	%	No.	%	OR (95% CI)
EITB positive	22/113	19.5	27/233	11.6	1.85 (0.99–3.4)
ELISA positive	28/113	24.8	28/233	12.0	2.70 (1.41–5.19)
Dual positive	7/113	6.0	5/233	1.9	0.96 (0.2–4.5)

OR = odds ratio; EITB positive = presence of antibodies against *T. solium* detected by enzyme-linked immunoelectrotransfer blot (EITB) assay; ELISA positive = presence of antibodies against *T. canis* antibody detected by ELISA; Dual positive = presence of antibodies against *T. solium* and *T. canis*.

T. solium. Of 113 epileptic patients, 22 tested positive with the EITB assay, giving a seroprevalence for *T. solium* antibodies of 19.5% among cases (25.4% for partial epilepsy and 13% for generalized epilepsy), whereas 27 control subjects tested positive with a seroprevalence of 11.6% (tables 2 and 3). The OR for EITB positivity was 1.85 (95% CI 0.99 to 3.4) (see table 3). When this model was restricted to the 54 subjects with generalized epilepsy, no association was found (OR 0.82; 95% CI 0.30 to 2.29), but for the 59 subjects with partial epilepsy, the OR for cysticercosis was 2.75 (1.44 to 6.61). When partial epilepsy was stratified by age at onset, the OR for those with onset of seizures between 0 and 14 years (26 patients) was 2.34 (95% CI 0.49 to 11.07). In those with adult-onset epilepsy, the OR was 3.66 (95% CI 1.10 to 12.10). When generalized epilepsy was stratified on this variable, there was only a minor change in the strength of the association (table 4).

T. canis. Twenty-eight of 113 patients tested positive by ELISA, giving a seroprevalence among cases of 24.8% (27.1% in those with partial epilepsy and 22.1% for generalized epilepsy), whereas 28 control subjects tested positive (12.0%) (see tables 2 and 3). The 28 positive cases and 28 positive control subjects were also positive on Western blot assay. In the model using all epileptic cases (113 cases; 59 partial and 54 generalized), *T. canis* antibody had an OR of 2.70 (95% CI 1.41 to 5.19) (see table 3). Among those with generalized epilepsy, the OR was 1.79 (95% CI 0.76 to 4.17) and with partial epilepsy 4.70 (95% CI 1.47 to 15.10). When partial epilepsy was stratified by age at onset, those who developed seizures in the first 14 years of life (26 patients) showed an OR of 1.18 (95% CI 0.21 to 6.47), whereas in those with adult onset, it was 18.22 (2.10 to 158.10). Stratification of those with generalized epilepsy by age at onset made little difference in the strength of the association (see table 4).

Of the 113 epileptic patients, 12 were mentally retarded, of whom only 2 (16.6%) were positive for *T. canis*

Table 4 *Stratified analysis for age at onset in subjects with partial and generalized epilepsy*

	Generalized epilepsy			Partial epilepsy		
Age at onset, y	No. of cases	*T. solium*	*T. canis*	No. of cases	*T. solium*	*T. canis*
0–14	34	1.50 (0.41–5.57)	1.60 (0.54–4.75)	26	2.34 (0.49–11.07)	1.18 (0.21–6.47)
≥15	20	0.33 (0.05–1.98)	2.20 (0.55–8.80)	33	3.66 (1.10–12.10)	18.22 (2.10–158.10)
All cases	54	0.82 (0.30–2.29)	1.79 (0.76–4.17)	59	2.75 (1.44–6.61)	4.70 (1.47–15.10)

Values are odds ratios (95% CI).

antibodies. No significant difference in seroprevalence was found between epileptic patients with or without (25.7%) mental retardation.

Of the 113 cases, 7 were seropositive for both *T. solium* and *T. canis*. Of these patients, four were classified as having partial epilepsy.

Discussion. Epilepsy is considered an important health problem in developing countries, where prevalence ranges from 2.47 to 57/1,000. The higher frequency of partial seizures in these countries compared with industrialized countries could be an indication of the high incidence of symptomatic epilepsy secondary to cortical damage (e.g., perinatal brain damage, head injury).[23]

NCC has been reported as the most frequent parasitic infection of the CNS and a major cause of epilepsy in several countries of Africa, Latin America, and Asia.[24-26] In particular, some studies have reported that NCC is the main cause of adult-onset partial epilepsy in *T. solium*-endemic areas.[23,26] Approximately 90% of patients with active parenchymal disease have epilepsy, and 70% of the cases exhibit partial and secondarily generalized seizures.[3] Diagnosis of NCC, especially in population-based surveys, is complex, considering that neuroimaging studies such as CT and MRI are rarely available or not practical in countries where NCC is endemic. EITB is considered the most practical screening tool for epidemiologic research. In clinical evaluations, the specificity of EITB was 100%, whereas the sensitivity for detection of cases with multiple intracranial cysticerci was 90 to 100%. However, the EITB demonstrated only 65% sensitivity in individuals with a single intracranial cyst (72% for an enhancing lesion and 40% for a calcified cyst).[27]

Epilepsy is a major health problem in the rural areas of the Cordillera Province of Bolivia, with a prevalence of 12.3/1,000 and with partial epilepsy as the most common type (53.2%).[10] The first objective of this study was to assess the relationship between epilepsy and NCC in this area. We found a significant positive association between EITB positivity and partial epilepsy. This association was stronger for late-onset partial epilepsy. No association was found with generalized epilepsy, suggesting a higher prevalence of idiopathic epilepsy in this group. Although NCC is often reported as a major cause of epilepsy in *T. solium*-endemic areas, the majority of data come from hospital settings. Few community-based case-control or cohort studies have been carried out to investigate this association, and those that have been report contradictory results.[28,29] Data reported in the literature are difficult to interpret owing to the variation in study design, diagnostic criteria, and classification of epilepsy as well as the different assays used. A similar study design (a population-based case-control study) was carried out in Ecuador. The authors did not find a significant association between cysticercosis and epilepsy, considering the serologic results on the basis of the EITB assay, but a significant association was found on the basis of CT scan results (OR 6.93). In this survey, the authors did not take into account the type of seizure or age at onset.[24] Our results are consistent with the data in literature where NCC is reported as an important cause of epilepsy[3,23] and not unexpected, considering that in the surveyed rural areas, domestic pigs are allowed to roam freely and basic sanitation is lacking.

The second objective of the study was to assess the relationship between epilepsy and toxocariasis. *T. canis* infection was diagnosed by ELISA and confirmed by Western blot to avoid problems of cross-reactivity with other helminthic infections. Studies carried out in Latin America have shown that the parasite is widespread and closely related to poor socioeconomic status.[9]

Studies in animal models have demonstrated that *T. canis* larvae can enter the CNS. In small rodents, larvae accumulate in the brain, producing a variety of CNS disorders. Given these observations, neurologic disorders in humans due to the presence of *T. canis* larvae in the CNS might not be an uncommon event.[30] In fact, involvement of the CNS in human toxocariasis has been described and invasion of the brain by nematode larvae demonstrated. Despite the higher seroprevalence of *T. canis* antibodies found in children with epilepsy vs control subjects in previous studies, there has been doubt about whether this implied causality.[6,31,32] Our results indicate a significant positive association between *T. canis* seropositivity and epilepsy (OR 2.70) when the analysis included all epileptic cases and control subjects. Progressively stronger associations were found when the analysis was restricted first to partial epilepsy (OR 4.70) and then to the late-onset part of this group (OR 18.22). As with NCC, no association was found with generalized epilepsy.

To our knowledge, only two other case-control studies have been carried out to assess a relationship between *T. canis* infection and epilepsy. In the first, a case-control study in children from the United States, a higher prevalence of *T. canis* antibodies was found in epileptic patients than in control subjects. But similar rates of *Toxocara* seropositivity were found in epileptic patients with a known or suspected etiology (other than toxocariasis) and in epileptic patients with unknown etiology.[31] In 1990, a case-control study was carried out in Italian children, showing an association between *T. canis* seropositivity and epilepsy.[6]

Other studies have reported some evidence of association between *T. canis* and mental retardation.[33,34] As mental retardation is frequent among epileptic patients, this can predispose them to *Toxocara* infection. We did not find significant differences in T. canis seropositivity between epileptic patients with or without mental retardation.

An important limitation of our study is the use of prevalent, rather than incident, cases. This does not allow us to be certain that exposure (*T. canis* or *T. solium* infection) occurred before the outcome (epilepsy). However, the strong and significant positive associations found between partial epilepsy and seropositivity for both *T. solium* and *T. canis* seem to be biologically plausible, given the higher prevalence of idiopathic epilepsy among the generalized forms and of symptomatic epilepsy in late-onset partial epilepsy. Thus, these data suggest that NCC and toxocariasis may explain in part the higher prevalence of epilepsy in developing countries. Our results concerning NCC are consistent with the data reported in the literature, whereas the strong epidemiologic association evidenced between *T. canis* infection and partial epilepsy is a new finding that deserves further study. We would underline that the presence of antibodies against *T. canis* or *T. solium* detected in serum does not provide evidence of a direct infection of the CNS; from a clinical point of view, other diagnostic procedures are necessary to achieve a defined diagnosis of epilepsy due to *T. canis* or *T. solium*.

On the basis of these data, correct classification of seizures is an important element to permit interpretation of the results from analytical studies. In several surveys carried out in rural areas of developing countries, seizure classification is based on clinical grounds, owing to the unavailability of EEG recordings. In the majority of these studies, a higher frequency of generalized seizure is reported. Considering only the clinical data, generalized seizures are the most common type; this is also true in our sample.[10] An overestimation of generalized seizures may be due to a misdiagnosis of partial seizures with rapid secondary generalization. This emphasizes the importance of the EEG recording to correctly classify the types of seizures in these populations.

We underscore that both toxocariasis and cysticercosis are preventable and treatable diseases, and our results confirm that they could play an important role in the incidence of epilepsy in endemic areas of developing countries. Efforts should be made to develop appropriate control programs in these areas.

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Field-specific visual-evoked potentials

Identifying field defects in vigabatrin-treated children

G.F.A. Harding, DSc; E.L. Spencer, BSc; J.M. Wild, PhD; M. Conway, BSc; and R.L. Bohn, PhD

Abstract—*Objective:* To derive a visual-evoked potential (VEP) technique for identifying visual field defects in children with epilepsy treated with vigabatrin and unable to perform perimetry. *Background:* Studies have linked vigabatrin to a specific pattern of visual field loss. Few studies have included the pediatric population because of difficulties in assessing the visual field by perimetry below a developmental age of 9 years. *Methods:* A field-specific VEP was developed with a central (0° to 5° radius) and peripheral stimulus (30° to 60° radius). Stimuli consisted of black and white checks that increased in size with eccentricity. Checks reversed at different rates, allowing separate central and peripheral responses to be recorded. Five vigabatrin-treated young adults with field defects were identified using this stimulus. Electroretinograms (ERG) were recorded to examine the effects of vigabatrin on retinal function. Thirty-nine children aged 3 to 15 years were included in the study. Twelve patients were examined by both the field-specific stimulus test and perimetry. The diagnostic performance of the field-specific stimulus test was compared with that of perimetry. *Results:* Thirty-five of 39 children complied with the field-specific stimulus, 26 of 39 complied with the ERG, and 12 of 39 complied with perimetry. Using the summed amplitude of the peripheral response from O_2 and O_1, responses below 10 μV were deemed abnormal. The field-specific stimulus identified 3 of 4 abnormal perimetry results and 7 of 8 normal perimetry results, giving a sensitivity of 75% and a specificity of 87.5%. When comparing perimetry results with the ERG parameters, only the 30-Hz flicker amplitude, with a cutoff below 70 μV, gave a useful indication of visual field loss. *Conclusion:* Field-specific VEP are well tolerated by children older than 2 years of age and are sensitive and specific in identifying vigabatrin-associated peripheral field defects.

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Previous studies[1-12] have shown a specific pattern of visual field loss attributable to vigabatrin. The visual field defect shows a bilateral concentric constriction that typically exhibits a binasal annular defect within the central 30° with relative temporal sparing.[8] The antiepileptic properties of vigabatrin are dependent on increasing the whole-brain concentration of gamma-aminobutyric acid (GABA) by irreversible binding to GABA-transaminase, thus preventing the metabolism of GABA. Vigabatrin is particularly effective in the treatment of infantile spasms (West's syndrome) and is also used in the

From the Neurosciences Research Institute (Dr. Harding, E.L. Spencer, and M. Conway), Aston University, Birmingham, UK; Department of Optometry and Vision Sciences (Dr. Wild), Cardiff University, Cardiff, UK; and Aventis Pharma (Dr. Bohn), Bridgewater, NJ.

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Address correspondence and reprint requests to Prof. Graham Harding, Neurosciences Research Institute, Aston University, Aston Triangle, Birmingham B4 7ET, UK; e-mail: g.f.a.harding@aston.ac.uk

