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Cerebellar Atrophy in Patients With Long-term Phenytoin Exposure and Epilepsy

Gershon C. Ney, MD; George Lantos, MD; William B. Barr, PhD; Neil Schaul, MD

Objective: Cerebellar atrophy has been noted in patients with phenytoin exposure. This finding has been attributed by some investigators to seizures, but by others to phenytoin. Previous studies included patients with mental retardation and convulsive seizures. We undertook a study in a group of nonretarded patients with partial epilepsy to better elucidate the cause of the cerebellar atrophy.

Design: Case control study.

Setting: Referral population from an epilepsy center.

Patients: Thirty-six patients with partial epilepsy and long-term phenytoin exposure were selected from a consecutive sample of admissions to an epilepsy center. Patients with histories of ethanol abuse, perinatal distress, anoxia, status epilepticus, or neurodegenerative disorders were excluded. Age- and sex-matched controls were selected from a pool of healthy volunteers and patients who had undergone magnetic resonance imaging for complaints of headache and dizziness.

Interventions: All patients and controls underwent magnetic resonance imaging.

Main Outcome Measure: Degree of cerebellar atrophy.

Results: The magnetic resonance imaging scans were reviewed in a blind fashion. A rating was assigned to each scan based on the degree of cerebellar atrophy. Cerebellar atrophy was significantly more pronounced in patients than in controls. No correlation was found between cerebellar atrophy and variables reflective of seizure severity or degree of phenytoin exposure.

Conclusions: Cerebellar atrophy may be seen in phenytoin-exposed patients with epilepsy in the absence of generalized tonic-clonic seizures or preexistent brain damage. Whether it is the phenytoin or the seizures that play the primary etiologic role remains unanswered. These factors may be synergistic.

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C EREBELLAR ATROPHY has been described in patients who have seizures and who are exposed to phenytoin.[1-6] The cause of this atrophy is controversial because it remains unclear as to whether the cerebellar atrophy results from phenytoin toxicity or from the effects of recurrent seizures. Animal studies designed to investigate the putative effects of cerebellar toxicity of phenytoin have yielded conflicting results.[2,7,8] Few human studies have been undertaken. Clinical studies, to date, have involved patients with tonic-clonic seizures and with diffuse central nervous system insults.[9,10] In addition, to our knowledge, none of the studies have used magnetic resonance imaging (MRI). We report on cerebellar size and morphological features in a group of phenytoin-exposed, nonretarded patients with partial epilepsy who were studied with MRI. The patient group was compared with an age- and sex-matched control group. Patients with potential sources of cerebellar atrophy other than seizures or phenytoin exposure were excluded.

RESULTS

Cerebellar ratings for patients and controls are presented in the **Table**. The pa-

See Patients and Methods on next page

From the Departments of Neurology (Drs Ney, Lantos, Barr, and Schaul), Radiology (Dr Lantos), and Psychiatry (Dr Barr), Long Island Jewish Medical Center and Hillside Hospital, Albert Einstein College of Medicine, New Hyde Park, NY.

PATIENTS AND METHODS

PATIENTS

The patients were selected from a group of 119 consecutive evaluations carried out from September 1987 through July 1991. All patients had undergone evaluations for intractable epilepsy in the Comprehensive Epilepsy Center of the Long Island Jewish Medical Center, New Hyde Park, NY. A total of 36 patients with a history of phenytoin exposure longer than 4 years were selected. Exclusionary criteria included a Wechsler Adult Intelligence Scale-Revised full-scale intelligence quotient of less than 70, a history of ethanol abuse, perinatal distress, anoxia, status epilepticus, and neurodegenerative disorders. A control group of 35 people was selected from a pool of healthy volunteers and individuals who had undergone MRI scans for complaints of headache and dizziness. The control group consisted of 15 women and 20 men ranging in age from 19 to 48 years (mean age, 32.8 years).

The study sample consisted of 16 women and 20 men ranging in age from 21 to 54 years (mean age, 34.1 years). Historical data, including seizure frequency, duration of epilepsy, history of febrile seizures, presence of secondary generalization, years of phenytoin exposure, maximum phenytoin dosage, and history of acute reversible cerebellar syndrome, were obtained through a chart review. Antiepileptic drugs (other than phenytoin) to which the patient had been exposed were also ascertained. Data were verified in most cases by a subsequent telephone interview with patients. All patients were administered the Wechsler Adult Intelligence Scale-Revised as part of their clinical workup. The sample's mean level of intellectual functioning was in the "average" range (Wechsler Adult Intelligence Scale-Revised full-scale intelligence quotient, 90.1; range, 70 to 132). The mean length of education was 13.2 years (range, 11 to 20 years). The mean duration of epilepsy (defined as chronic, recurrent seizures) was 19.4 years, with a range of 3 to 44 years (it should be noted that the patient with the duration of 3 years had been treated with phenytoin for 7 years before the epilepsy became chronic). Sixteen patients (44%) experienced partial complex seizures exclusively, while 20 patients experienced partial complex seizures with secondary generalization. The mean seizure frequency was 8.4 per month, with a range of two to 30 per month. The mean duration of phenytoin exposure was 13.7 years, with a range of 4 to 30 years. The mean maximum dosage of phenytoin therapy was 450 mg. The range of maximum daily dosage of phenytoin was 300 to 700 mg.

All of these patients with intractable seizures had received various antiepileptic medications, other than phenytoin, at some point during the course of their epilepsy. These drugs included carbamazepine (all of the patients), valproic acid (28 of 36 patients), benzodiazepines (26 of 36 patients), phenobarbital (25 of 36 patients), primidone (17 of 36 patients), acetazolamide (eight of 36 patients), methsuximide (five of 36 patients), and ethosuximide (three of 36 patients).

METHODS

All patients and controls underwent MRI scans on a 1.0-T whole-body MRI system (Magnetom, Siemens, Iselin, NJ). The imaging protocol included three-dimensional, gradient-echo, fast, low-angle-shot images acquired in the coronal plane. The methodology for this acquisition sequence has been described elsewhere.[11] This yielded 64 contiguous coronal slices of 3.1-mm slice thickness. Also obtained were spin-echo images in axial and coronal planes using proton density and T_2-weighted sequences (**Figure**). Scans from both groups were reviewed by a neuroradiologist (G.L.) who was blind to the clinical status of the subject (patient vs control). For the qualitative ratings of the MRI scans, emphasis was placed on the appearance of the cerebellar hemispheres as the cerebellar vermis is variable within normal control populations.[12] The degree of atrophy was judged by the size of the sulci and folia. Based on the degree of cerebellar atrophy seen on MRI, the patients and controls were divided into four groups as follows: group I, normal; group II, mild atrophy; group III, moderate atrophy; and group IV, severe atrophy. χ^2 Analysis was then used to analyze the ratings differences between the patient and control groups. The relationship between the patient group's atrophy ratings and the variables reflective of the degree of phenytoin exposure was analyzed using rank-order correlations (Spearman ρ). The phenytoin-related variables included maximum dosage and duration of phenytoin therapy. Atrophy ratings and variables reflective of seizure severity were also compared using rank-order correlations (Spearman ρ). The seizure-related variables included duration of epilepsy, seizure frequency, and presence of secondary generalization.

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tient group was found to have a greater frequency of cerebellar atrophy (χ^2=23.5; $P<.001$). One fourth of the patients (nine of 36) received cerebellar atrophy ratings in the moderate to severe range. None of the controls were in this range.

No statistically significant correlations were observed between atrophy ratings and years of duration of epilepsy (ρ=.05), seizure frequency (ρ=−.06), intellectual functioning (full-scale intelligence quotient, ρ=.01), maximum dosage of phenytoin therapy (ρ=.22), or duration of phenytoin treatment (ρ=−.12).

COMMENT

To our knowledge, this is the first study carried out to explore the etiologic role of phenytoin in cerebellar atrophy that employed a patient population with an average level of intelligence. This investigation was limited to patients with partial epilepsy. The cerebellar size of the patients was compared with that of age- and sex-matched controls. We found a group difference between the phenytoin-exposed epilepsy population and the controls, as the patients had significantly smaller cerebelli.

Cerebellar Atrophy Ratings for Patients and Controls		
Atrophy Rating	Patients (n=36)	Controls (n=35)
Normal	15	33
Mild	12	2
Moderate	7	0
Severe	2	0

The phenomenon of cerebellar insult in the setting of epilepsy was observed by Spielmeyer[13] in 1930. He described cerebellar atrophy in postmortem examinations of the brains of patients who had epilepsy with convulsive seizures. Zimmerman[14] made similar observations several years later. He provided detailed clinical descriptions of 16 patients in addition to his pathologic findings. All his patients had frequent convulsions, often in the setting of severe hypoxia resulting from terminal pneumonia, pertussis, and other causes of respiratory failure. These findings predated the introduction of phenytoin, and suggest that seizures alone can cause cerebellar atrophy. However, anoxia may have been a significant contributing factor. With the introduction of phenytoin and its continued use, case reports of acute and chronic cerebellar toxicity have appeared.[1-6,15-20] To confirm these observations, several formal investigations have been undertaken in humans. Dam[9] reported an autopsy series involving 32 brains from a group of institutionalized patients with tonic-clonic seizures that were compared with controls. The patient group included individuals with frequent convulsions and multiple episodes of status epilepticus. Data are not provided regarding the cognition of the patients. Fewer Purkinje's cells were found in the patients with seizures than in the nonepileptic controls. This finding was most striking in the subgroup of patients with the greatest frequency of convulsive seizures or multiple episodes of status epilepticus. The subgroup of patients with the most extensive phenytoin exposure also had fewer Purkinje's cells, but most of these patients had the most severe epilepsy. Patients with long-term phenytoin exposure and infrequent seizures had Purkinje cell densities that did not differ significantly from those of controls. It was concluded that Purkinje cell loss was related to frequent convulsions and not to phenytoin exposure. Cerebellar atrophy is seen as part of a histopathologic constellation in individuals with perinatal insults.[21] The possibility of preexistent global central nervous system damage, including cerebellar atrophy, cannot be excluded, as there are no details regarding cognition of this institutionalized population. The putative effects of phenytoin therapy may be inapparent in a group with preexistent cerebellar atrophy or atrophy caused by frequent convulsions.

Iivanainen et al[10] reported on 131 mentally retarded patients with epilepsy and phenytoin exposure. The majority of the patients were severely retarded, with 83% having an intelligence quotient of less than 35. No controls were employed. The authors thought that cerebellar atrophy as diagnosed with pneumoencephalography correlated with a history of phenytoin intoxication and serum phenytoin levels. As in the previously mentioned study, the issue of possible preexistent congenital cerebellar pathology is not addressed. At most, one could only conclude that phenytoin may play a role with respect to cerebellar atrophy in brain-damaged individuals.

In the only investigation that we know of in which modern neuroimaging techniques were used, Ballenger et al[22] compared the computed tomographic scans of 70 patients with seizures with those of a control group and failed to demonstrate cerebellar atrophy within the seizure group; 84% of the seizure group had had significant phenytoin exposure. Details of the epilepsy group are not available. Furthermore, mild cerebellar atrophy may have been missed on computed tomographic scans.

SALCMAN et al[23] reported the results of cerebellar biopsies in five patients with intractable epilepsy and phenytoin exposure. This series is unique in that it presents the cerebellar histopathologic findings from cases involving live patients with intractable epilepsy in whom clinical information is well documented. Several of the patients had frequent convulsions and episodes of status epilepticus. However, two of the patients had frequent complex partial seizures and never had a convulsion. Marked loss of Purkinje's cells was demonstrated in every case. This series suggests that partial seizures without convulsive movements may play a significant role in causing cerebellar atrophy.

Several studies in animals have been carried out over the last three decades to confirm or refute the possibility that phenytoin is toxic to the cerebellum.[7-10] Kokenge and Kutt[2] reported a selective loss of Purkinje's cells in rats and cats intoxicated with phenytoin. Dam[7,8] subsequently carried out similar experiments in pigs and monkeys, and failed to replicate the previous findings of Purkinje cell loss.

The neuropathology literature, predating the introduction of phenytoin, documents that convulsions are associated with cerebellar atrophy. Subsequent literature concerning phenytoin-induced cerebellar atrophy often involved patients with preexistent global central nervous system damage or frequent convulsions. The one study that reported seizure types included patients with status epilepticus and frequent convulsions. It is unclear whether sei-
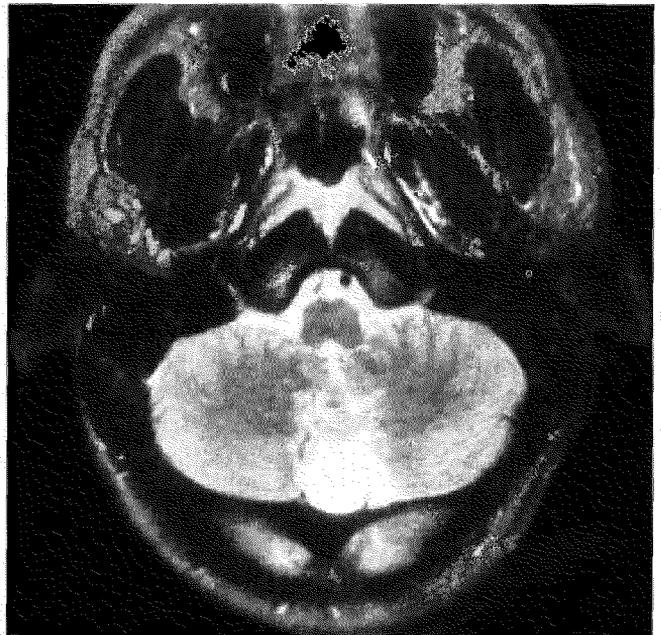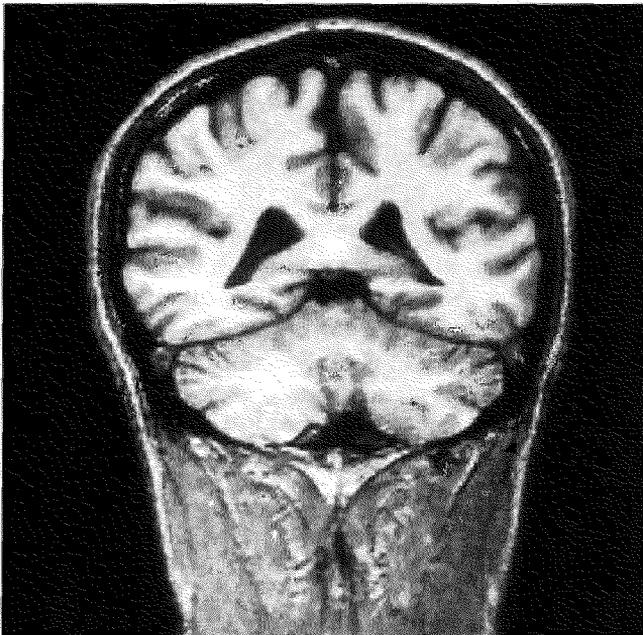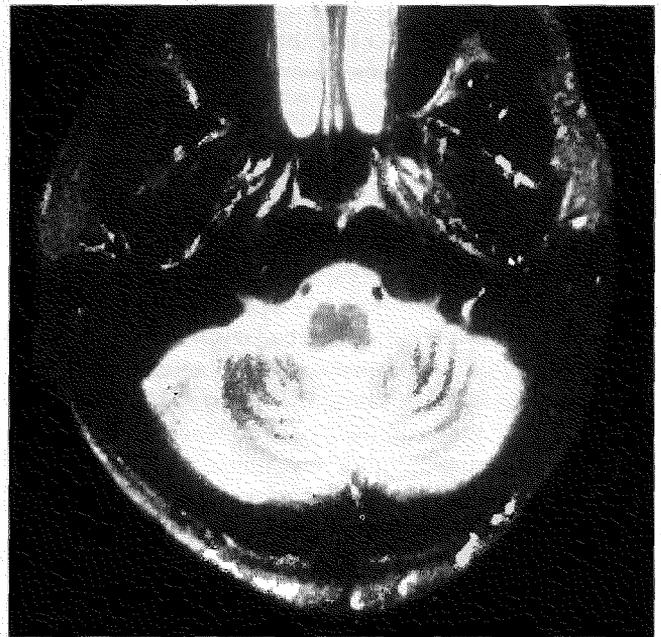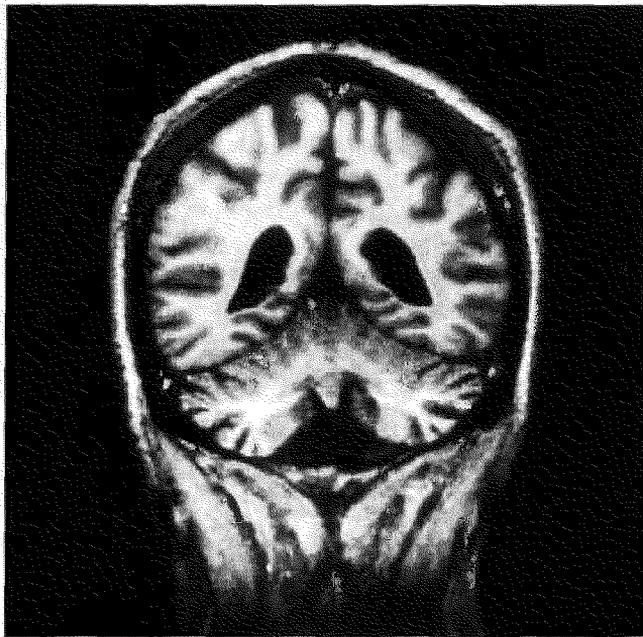
Top left and top right, Magnetic resonance images of a 31-year-old patient with frequent partial complex seizures, no convulsions, and a 5-year exposure to phenytoin (400 mg/d); this patient's degree of cerebellar atrophy was severe. Bottom left and bottom right, Magnetic resonance images of a matched control.

zures, phenytoin, preexistent brain damage, or a combination of these factors results in the finding of cerebellar atrophy in these patients.

Our findings in a population with an average level of intelligence indicate that a certain proportion of patients with long-term phenytoin exposure and epilepsy but without preexisting diffuse brain damage develop cerebellar atrophy. We also noted that cerebellar atrophy was not uniquely related to tonic-clonic seizures, as 44% of our patients had only zero to five convulsions per lifetime. Furthermore, there was no correlation between the degree of cerebellar atrophy and the presence of tonic-clonic seizures. Our study supports the observations of

Salcman et al[23] that phenytoin-exposed patients with partial complex seizures without generalization in the absence of diffuse brain insult may also develop cerebellar atrophy.

Our study was unable to clearly elucidate whether the cerebellar atrophy resulted from seizures or from exposure to phenytoin. The extent of cerebellar atrophy did not correlate with any of the studied clinical variables reflective of seizure severity or extent of phenytoin exposure. The inability to resolve this issue may have been from inadequate sample size or from the lack of sensitivity in quantifying phenytoin exposure and seizure severity. Alternatively, phen-

ytoin and seizures may act synergistically to cause cerebellar atrophy.

Whether the cerebellar atrophy results from seizures, phenytoin, or both remains unclear. However, either explanation remains tenable. Focal seizures have been demonstrated to cause brain damage at sites remote from the seizure focus.[24] This is thought to occur because the ictal discharge causes neuronal excitation via connecting pathways, with the resultant release of excitatory neurotransmitters.[25] It has also been shown that experimentally induced epileptiform activity in the cerebral cortex causes increased neuronal firing in Purkinje's cells as well as in the dentate nucleus.[26] The discharges are thought to be propagated along the corticopontocerebellar tracts. Current thinking implies that these projections are very active physiologically and mediate significant information transfer from cerebrum to cerebellum.[27,28] Thus, it is feasible that focal seizures in humans mediate cell injury in the cerebellum by inducing concomitant aberrant discharges with resultant neuroexcitatory-mediated damage. Phenytoin has a propensity for the cerebellum, as the primary manifestation of acute toxicity is a cerebellar syndrome. More recently, investigators have implicated a specific binding site for phenytoin "in the vicinity of Purkinje cells and granule cells."[29] Phenytoin has been demonstrated to induce increased firing rates in cerebellar neurons.[30] While some believe that this increased neuronal activity is protective against cortical seizures, it may in fact be harmful to the cerebellar neurons. Seizure-induced neuronal excitability and phenytoin-induced neuronal excitability may act in combination to cause cerebellar atrophy.

The mechanism for the observed cerebellar atrophy remains unclear. To resolve this issue, larger prospective studies will be required. As we are now in an era in which there is a growing number of commonly used antiepileptic drugs, more patients who have seizures but have not been exposed to phenytoin will be available to enroll in these studies. Future studies will be able to compare phenytoin-exposed patients with phenytoin-naive patients. Emerging radiographic techniques that accurately quantify volumes of specific neuroanatomic structures may prove helpful.

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