Arq Neuropsiquiatr 2000; 58(2-A): 276-281

DOSE-DEPENDENT RELATIONSHIP BETWEEN CHRONIC TREATMENT WITH PHENYTOIN AND CEREBELLAR ATROPHY IN EPILEPSY PATIENTS

ANDRÉ DEL NEGRO*, CLARISSA DE ROSALMEIDA DANTAS*, VERÔNICA ZANARDI***, MARIA AUGUSTA MONTENEGRO**, FERNANDO CENDES***

Dose-related cerebellar atrophy in patients with epilepsy using phenytoin

ABSTRACT - The chronic treatment with phenytoin or the acute intoxication by this drug may cause permanent cerebellar injury with atrophy of cerebellum vermis and hemispheres, which can be detected by neuroimaging studies. The aim of the present study was to investigate the correlation between the dosage and duration of treatment with phenytoin and the occurrence of cerebellar atrophy. Sixty-six patients were studied and had their tomographies analyzed for cerebellar atrophy. Of the 66 patients studied, 18 had moderate/severe atrophy, 15 had mild atrophy and 33 were considered to be normal. The patients with moderate/severe atrophy were those with higher exposure to phenytoin (longer duration of treatment and higher total dosage) showing statistically significant difference when compared to patients with mild atrophy or without atrophy (p=0.02). Further, the patients with moderate/severe atrophy had serum levels of phenytoin statistically higher than those of patients with mild atrophy or without atrophy (p = 0.008). There was no association between other antiepileptic drugs dosage or duration of treatment and degree of cerebellar atrophy. We also found that older patients had cerebellar atrophy more frequently, indicating that age or duration of the seizure disorder may also be important in the determination of cerebellar degeneration in these patients. We conclude that although there is a possibility that repeated seizures contribute to cerebellar damage, long term exposure to phenytoin, particularly in high doses and toxic serum levels, cause cerebellar atrophy.

KEY WORDS : phenytoin, cerebellar atrophy, epilepsy, seizures.

Department of Neurology and Department of Radiology, Faculty of Medical Sciences, State University of Campinas (FCM/UNICAMP): *Medical student, **Medical Resident, ***Assistant Professor, PhD. Support: FAPESP, scientific initiation scholarship. Accepted: January 6, 2000.

Dr. Fernando Cendes - Department of Neurology - FCM/UNICAMP - P.O. Box 6111 - 13081-970 Campinas SP - Brazil. FAX 19 289 0880. Email: fcendes@unicamp.br

Diphenylhydantoin (DPH) is a first-line drug for treatment of many forms of epilepsy, because of both its effectiveness and affordability. Its mechanism of action consists in the effect of stabilizing the neuronal membrane by inhibiting voltage-sensitive sodium channels, thereby reducing the ionic current both at rest and during the action potential[1]. In this way, DPH prevents repetitive neuron spikes from being generated by the passage of intracellular current, without causing general depression of the central nervous system (CNS). Its use, however, is not devoid of adverse effects, the most common one being cerebellar dysfunction after acute intoxication, leading to symptoms such as ataxia and diplopia. Irreversible cerebellar atrophy can occur after acute intoxication[2] and also after chronic treatment with phenytoin[3-7]. Previous studies have indicated that cerebellar atrophy is due to the direct toxic effect of the drug on Purkinje cells or by hypoxia caused by generalized tonic-clonic seizures[3-7], or by these two factors acting in synergy[8-11].

The purpose of this study was to determine a correlation between cerebellar atrophy and chronic treatment with DPH.

METHOD

We conducted a retrospective study by examining the medical records of 127 patients followed in the Epilepsy Outpatient Service of the UNICAMP Clinical Hospital Neurology Department. From among the charts, we selected those that: had complete data about the sex and age of patients; type of anti-epileptic drug (AED) in current use and dose thereof; time for which the AED was used; early history of a clinical profile suggestive of medicine intoxication by the drug (ataxia, diplopia, dizziness and nystagmus, among others), checking the serum levels of the AED whenever possible. Finally, we checked whether the patient presented any underlying disease, such as neurocysticercosis, traumatic brain injury and brain calcifications, which could be associated with cerebellar atrophy.

After collecting the data, 59 of the patients whose medical records did not meet these requirements were excluded, and 2 patients were excluded for presenting with sequelae of ischemic lesions observed in computed tomography (CT), which would have made it difficult to determine the possible causative factors of atrophy. We evaluated the degree of cerebellar atrophy in 66 patients through cranial CT, ensuring it was performed "blindly" in relation to available clinical information. The evaluation was carried out separately by two different professionals with experience in CT, one being a radiologist and the other a clinical neurologist, both without information as to which AED the patient was being treated with, and how long the patients they were evaluating had been treated with the drug.

In order to ensure that the study would be as reliable as possible, we randomized the order of DPH users and users of other AEDs. In addition, we introduced into the radiological study 10 CTs that had previously been assessed as normal in patients who had no history of seizures or use of AED, and who had been given CT scans to evaluate the cause of their headaches.

Radiological evaluation of cerebellar atrophy in the cranial CTs of skull followed the parameters of Koller et al. 12 with minor changes:

1) - Cerebellar vermis - mild atrophy when two or three grooves can be observed on the midline (Fig. 1); moderate to severe atrophy when more than three grooves are visible in association with significant volume reduction of more than one of the vermis segments (Fig. 2 and 3).

2) - Cerebellar Hemispheres – slight atrophy of the cerebellum is visible, i.e., you can see prominent grooves between them, but without significant dilatation of tanks of the posterior fossa (Fig 1); moderate to severe atrophy when it is observed a significant volume reduction of the entire cerebellum with consequent increase in the cisterns of the posterior fossa (Figs. 2 and 3).

3) 66 cranial CTs of patients with epilepsy were examined, 37 of which were patients being treated with phenytoin and 29 of which were being treated with another AED that was not phenytoin, plus 10 patients who had come to the outpatient service with headaches as the control group, mentioned previously.

After evaluating the CTs, we classified the atrophy according to the criteria of Koller[12]: absent or mild, and moderate to severe, combining the assessment of the vermis and the cerebellar hemispheres. Initially, we also evaluated the size of the fourth ventricle; however, we ruled out that due to considerable variation in the results.

After this radiological assessment, we assigned a *Drug Score* as proposed by Kaneko et al. [13]. This *Drug Score* allows comparison between doses of different AEDs. Then we calculated the total amount of AED used by each patient throughout the treatment period up to the time the CT was taken.

After crunching the data, the Fisher test was applied to evaluate statistical differences between the groups of patients.

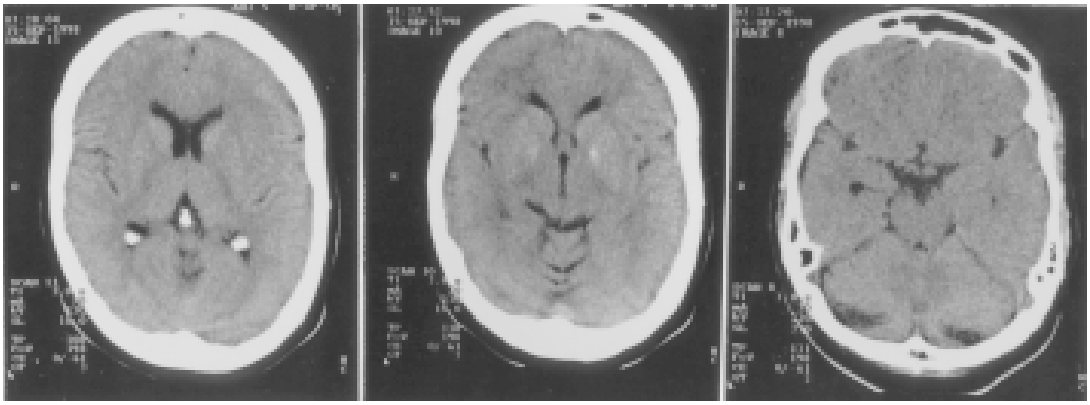

Fig. 1. Computed tomography scan showing what was considered slight cerebellar atrophy, predominantly in the vermis.

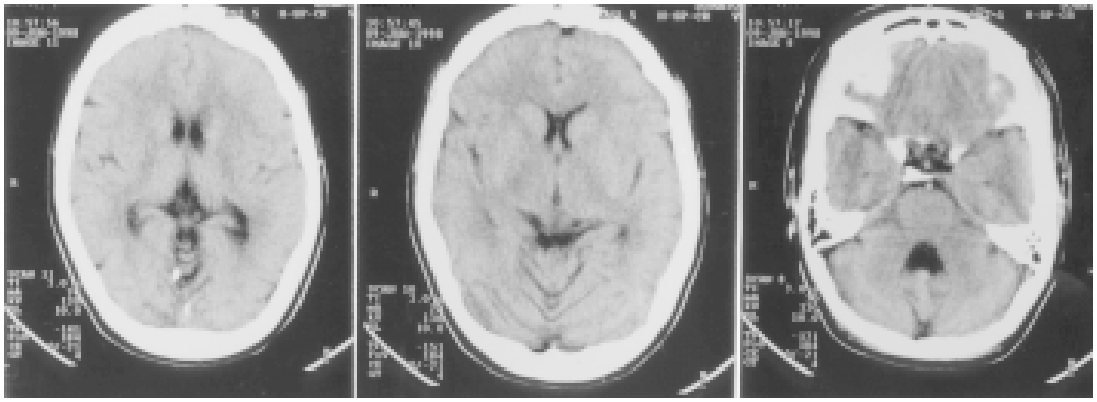

Fig. 1. Computed tomography scan showing what was considered slight cerebellar atrophy, predominantly in the vermis.
[TN: [sic] – author may have wanted this to be "moderate atrophy" and Fig. 2]

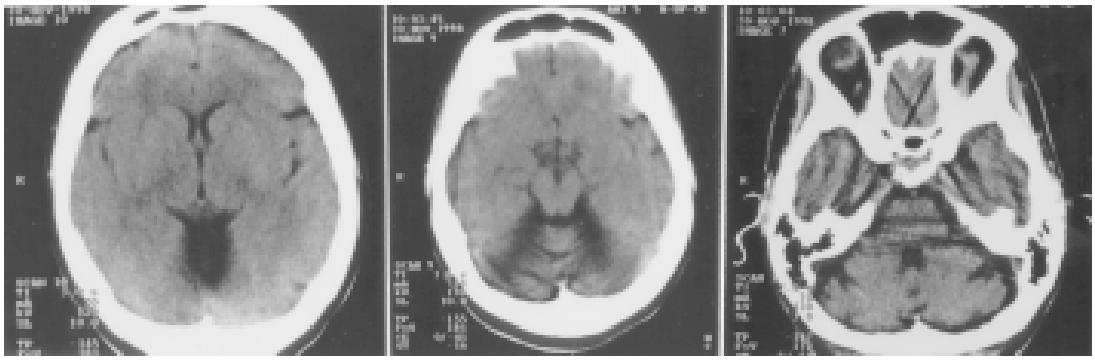

Fig. 3. Computed tomography scan showing what was considered severe cerebellar atrophy

RESULTS

Of the 66 patients with epilepsy evaluated, 37 were being treated with phenytoin and 29 with other AEDs. Comparing the group of patients treated with phenytoin with the group of patients using other anticonvulsants, we observed that the phenytoin group showed symptoms of vestibulocerebelar origin ($p = 0.04$) and more frequently had toxic serum levels ($p = 0.0004$) (Table 1). The duration and severity of the epilepsy was similar in both groups. There was no record of status epilepticus in the patients studied.

Table 1: Comparison of groups of patients treated with phenytoin and those treated with other drugs

	Phenytoin	Other drugs	P*
Gender (male/female)	17 M/21 F	9 M/22 F	Ns
Age (years)	38.5 ± 2.3	38.9 ± 2.8	Ns
Treatment duration (months)	79.6 ± 9.8	77.9 ± 9.04	Ns
Cerebellar syndrome (yes/no)	5 Yes / 33 No	31 No	0.04
Intoxication (yes/no)	8 Yes / 30 No	31 No	0.0004

Results expressed as mean ± standard deviation.
* Fisher test. Ns, statistical difference not significant

An individual analysis showed that only 4 patients were treated regularly with DPH for more than 10 years (average number of years: 13.63 ± 1.30), all of these showing significant cerebellar atrophy. Among users of other AEDS, 6 were treated regularly for more than 10 years (11.31 ± 0.87), and only 1 showed significant atrophy.

Among patients treated with phenytoin, 13 showed moderate to severe atrophy, 24 slight atrophy or absence of atrophy. Patients with moderate to severe cerebellar atrophy had more phenytoin exposure compared to patients with mild atrophy or without atrophy. Significant differences were observed in regard to the treatment time ($p = 0.03$) and total dose used ($p = 0.02$). In addition, patients with moderate to severe atrophy had serum levels of phenytoin significantly higher than patients with mild or no atrophy ($p = 0.008$) (Table 2).

Among users of other AEDs, 5 showed moderate to severe atrophy and 24 slight atrophy or absence of atrophy. There was no relationship between treatment duration and dosage of other anticonvulsants and degree of cerebellar atrophy (Table 3). However, we observed a significant difference between the average age of individuals with moderate to severe atrophy and those with mild or absence of atrophy ($p = 0.008$); indicating that the age factor and/or duration of epilepsy must also be important in a finding of cerebellar atrophy for these patients.

Table 2: Comparison among the 37 patients treated with phenytoin in respect to cerebellar atrophy

	Moderate to severe atrophy	Slight or absent atrophy	P*
Gender (male/female)	4 M/9 F	10 M/14 F	Ns
Age (years)	39.3 ± 4.0	37.9 ± 3.0	Ns
Serum level (mg/dl)	33.42 ± 5.2	16.62 ± 3.2	0.008
Treatment duration (months)	109.4 ± 23.2	63.2 ± 7.5	0.03
Dose (mg)	140.4 ± 368.7	53.5 ± 141.4	Ns
Total dose (g)	898.0 ± 178.6	535.1 ± 61.2	0.02
Cerebellar syndrome (yes/no)	2 Yes / 11 No	3 Yes / 21 No	Ns
Intoxication (yes/no)	8 Yes / 5 No	5 Yes / 19 No	0.004

Results expressed as mean ± standard deviation.
* Fisher test. Ns = statistical difference not significant.

Table 3: Comparison among the 29 patients treated with other AEDs in respect to cerebellar atrophy

	Moderate to severe atrophy	Slight or absent atrophy	P*
Gender (male/female)	3 M/2 F	6 M/18 F	Ns
Age (years)	55.2 ± 7.1	35.4 ± 2.8	0.008
Treatment duration (months)	64.8 ± 27.7	81.8 ± 10.2	Ns
Dose (mg)	22350.94 ±23884.66	20579.50 ± 23459.84	Ns
Total dose (g)	18738.0 ± 11274.5	22984.6 ± 4870.5	0.7187
Cerebellar syndrome (yes/no)	5 No	28 No	Ns
Intoxication (yes/no)	5 No	28 No	Ns

Results expressed as mean ± standard deviation.
* Fisher test. Ns = statistical difference not significant.

DISCUSSION

Although there are reports in the literature[1-10] of permanent ataxia associated with the use of phenytoin in high doses and for long periods, there are few studies with case-based material sufficient to identify the etiology of cerebellar atrophy. It is difficult to establish a clear correlation between the use of phenytoin and cerebellar atrophy because, in most cases, besides the use of anticonvulsant medication, patients also experience generalized tonic-clonic seizures and hypoxia resulting from their seizures. Cerebellar changes characterized by injury of Purkinje cells have been demonstrated experimentally in animals with high serum levels of phenytoin[14-15]. Rapport & Shaw[4] established the relationship between phenytoin and cerebellar atrophy with greater certainty when reporting this finding in a patient treated prophylactically with phenytoin and who had never presented with an epileptic seizure. However, these add to the controversy of studies[3,8] demonstrating that hypoxia, caused by frequent generalized seizures, is a likely cause of cerebellar injury.

The results of our study concord with the literature[3,7,9], and show that patients under chronic treatment with phenytoin, mainly those with high serum dosage and long treatment time, have more severe cerebellar atrophy compared to patients treated with phenytoin in smaller doses and patients using other AEDs, independent of dose and treatment time.

It is interesting to note that older patients showed a higher degree of cerebellar atrophy, indicating that the age factor and/or time of epilepsy may be important in determination of cerebellar degeneration.

We conclude that although the possibility exists that degeneration is secondary to hypoxia caused by repeated epileptic seizures, the contribution of phenytoin can be clearly established as one of the determining factors in cerebellar atrophy, especially in those patients taking high doses for long periods and having elevated serum levels.

REFERENCES