Cerebellar volume and long-term use of phenytoin

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Objectives: To perform MRI cerebellum volumetry in patients exposed to phenytoin and to identify factors associated with cerebellar atrophy (CA).

Methods: From 100 consecutive epilepsy patients we selected those with phenytoin use for more than 2 months and with MRI scan available for volumetric studies. We obtained cerebellar volumes corrected for total intracranial volume. Volumes below 2 standard deviations from the mean of control group were considered abnormal.

Results: We studied 56 patients (33 women). Mean age was 33.6 years and mean duration of epilepsy was 17.6 years. Mean daily dose of phenytoin was 301 mg. CA was detected in 20 (35.7%) patients. CA was not associated with frequent generalised seizures. CA correlated with duration of epilepsy ($r = -0.34$; $P = 0.01$) and years of treatment with phenytoin ($r = -0.48$; $P = 0.001$), but not with age and mean daily dosage of phenytoin ($P > 0.05$). However, a multiple correlation analysis as well as a backward stepwise multiple regression analysis including all variables showed that only duration of treatment was significantly associated with CA ($P = 0.001$).

Conclusions: CA is frequently associated with long-term use of phenytoin. Although duration of epilepsy may have an influence in the CA, this is clearly less important than the time of exposure to phenytoin.

Key words: cerebellar atrophy; epilepsy; volumetry; MRI.

INTRODUCTION

Phenytoin is one of the first line antiepileptic drugs (AEDs) for many epilepsy syndromes. High efficacy for partial as well as generalised seizures and low cost contributes to its widespread use. As with other commonly used AEDs, adverse effects can be frequently identified and sometimes lead to drug discontinuation[1]. One of most important adverse effect observed in phenytoin use is the cerebellar toxicity, associated with ataxia, tremor, nystagmus and diplopia[1]. Cerebellar atrophy (CA) may be observed in phenytoin-exposed patients with epilepsy in the absence of generalised tonic–clonic seizures (GTCS) or pre-existent brain damage[2, 3]. Whether it is the phenytoin[2, 4–8], the seizures[2, 9] or the initial brain insult[10] that play the primary aetiologic role in CA, it remains unclear[3, 11, 12].

The aim of this study was to investigate whether cerebellar volumes of patients exposed to long-term use of phenytoin or other variables are associated to CA.

PATIENTS AND METHODS

Ascertainment of subjects

We selected 100 consecutive epilepsy patients followed in our epilepsy clinic who had MRI scan available for cerebellar volumetric studies. We then excluded patients who used phenytoin for less than 2 months, patients who had status epilepticus, severe head trauma or meningitis, and those with insufficient available clinical data.

All patients included in this study signed a written informed consent for research protocol, approved by the Ethics Committee of our medical school.

We collected clinical data, including age at seizure onset, duration of epilepsy (defined here as duration

of recurrent seizures), epilepsy syndrome, risk factors, dosage and duration of phenytoin treatment, and frequency of GTCS. Although we ascertained frequency of GTCS by seizure calendars, it is well known that seizure frequency is not a highly reliable measure. None of the patients evaluated here were completely seizure-free and the majority were candidates for surgical treatment.

MRI studies

MRI scans were obtained in a 2 T scanner (Elscint Prestige®), with acquisitions in three orthogonal planes (axial, sagital and coronal). We used 6 mm slices sagital T1 acquisition for cerebellar measurements (T1 spin echo, 6 mm thick, flip angle = 180°; repetition time (TR) = 430, echo time (TE) = 12, matrix 200 × 350, field of view (FOV) = 25 cm × 25 cm, interslice gap of 0.6 mm).

Images were transferred to a PC and saved as stacks in TIFF format. We used Scion Image program® for manual delineation of cerebellar areas and total intracranial volumes (TIV), for each subject (all the segmentations were performed by one examiner). TIV were obtained by outlining the external boundaries of the brain in sagital slices (excluding cerebellum and brain stem) and calculating the sum of all cross-section areas. We calculated the total cerebellar volume by multiplying the total area from all cerebellar slices by the width (6 mm) and then normalised it by the TIV as follows: normalised cerebellar volume = patient's cerebellar volume/patient's TIV.

Twenty healthy adult volunteers, from laboratory personnel, were used as the control group in this study (mean age = 30.1 years, ranging from 22 to 62 years). None of them had any medical problem.

Cerebellar volumes were transformed into Z-scores (standardised scores that express the number of standard deviations away from the mean of the control group) to facilitate interpretation of severity of atrophy in individual patients. Volumes below −2 standard deviation (SD) from the mean of control group were considered abnormal. CA was classified in mild (−2 to −3 SD), moderate (−3 to −4 SD) and severe (below −4 SD) according to the Z-scores obtained from each patient.

Statistical analyses

We performed Pearson's correlation analysis and a backward stepwise multiple regression analysis to determine the most significant correlation. Chi-square test and ANOVA were performed whenever appropriate.

RESULTS

A total of 56 patients were studied (33 women). Mean present age was 33.6 years (ranging from 4 to 65 years) and age at seizure onset varied from 1 to 64 years (mean = 16 years). Duration of epilepsy ranged from 1 to 41 years (mean = 17.6 years). One patient had primary generalised epilepsy, 43 had temporal lobe epilepsy and 12 had partial extra-temporal epilepsy.

History of alcohol consumption was positive in 12 (21.5%) patients, earlier febrile seizures in 10 (18%) and signs of phenytoin intoxication were previously observed in 16 (28.5%) patients.

Mean daily dose of phenytoin was 301 mg (ranging from 100 to 650 mg). Blood serum levels of phenytoin were available in 18 patients, with toxic levels in 9 patients. Frequency of GTCS, obtained by seizure calendars, was available in 55 patients: 25 never had GTCS or were seizure-free for at least 2 years, 2 had daily GTCS, 22 had 1–3 GTCS per month, 2 patients had 5–15 GTCS per month and 5 patients had sporadic GTCS, once or twice per year.

CA was observed in 20 (35.7%) patients: 9/20 (45%) had mild atrophy (Z-scores from −2 to −3), 9/20 (45%) had moderate atrophy (Z-scores from −3 to −4) and 2/20 (10%) had severe atrophy (Z-scores below −4). Destructive pre-existing brain damage, related to perinatal insults, were observed in 5 patients, but none of them had CA.

CA was not significantly associated with history of alcohol intake or febrile seizures in this group of patients, as it occurred in only 2/12 (16.6%) of those with alcoholism and 2/10 (20%) patients with earlier febrile seizures. However, it was identified in 9/16 (56%) patients who had had clinical evidences of phenytoin intoxication.

GTCS did not occur more frequently in patients with CA as compared to those without atrophy: 12/20 (60%) had never had GTCS or were seizure-free for at least 2 years, whereas 8/20 (40%) had at least 1 GTCS per month (2 patients had frequent GTCS, up to 6 per month in 1 and up to 15 per month in the remaining patient).

Cerebellar volumes were similar in patients with frequent GTCS and with rare GTCS (ANOVA, $F[1] = 0.164$, $P = 0.68$). In addition, there was no difference regarding frequency of GTCS between patients with and without CA (Pearson's Chi-square, $P = 0.74$).

CA correlated with duration of epilepsy ($r = −0.34$; $P = 0.01$) and duration of treatment with phenytoin ($r = −0.48$; $P = 0.001$), but not with age, age at seizure onset, maximum dosage used and mean daily dosage of phenytoin ($P > 0.05$). However, when including all variables in a multiple correlation analysis (excluding age at seizure onset, as this is a variable that confounds with duration of epilepsy), only duration

of treatment with phenytoin variable was significantly correlated with CA ($r = -0.46$; $P = 0.01$). A backward stepwise multiple regression analysis confirmed that duration of treatment with phenytoin was the variable most correlated with CA ($P = 0.001$).

DISCUSSION

There are several reports of cerebellar toxicity related to phenytoin and neuroimaging studies have focused on visual assessment of CA[2, 3, 12, 13].

In a previous study[5], we evaluated CA by CT scan in 66 consecutive patients with epilepsy followed in a tertiary epilepsy centre. Patients were divided into two groups, those who used phenytoin and those who did not. Of the 66 patients studied, 18 (27%) had moderate/severe atrophy, 15 (23%) had mild atrophy and 33 (50%) were considered normal. Patients with moderate/severe atrophy were those with longer 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. In addition, patients with moderate/severe CA had serum levels of phenytoin statistically higher than those of patients with mild atrophy or without atrophy. There was no association between other AED dosage or duration of treatment and degree of CA.

We also found that older patients had CA more frequently, indicating that age or duration of the seizure disorder could also be important in the determination of cerebellar degeneration in these patients[5]. Similar findings have been reported by other studies[2, 3, 12], however, data derived from qualitative analyses of CA do not allow more robust statistical correlations and make interpretation of results difficult.

MRI-based cerebellar volumetric measurements allow objective evaluation of less severe, usually asymptomatic CA, and provide numerical data that can be correlated with several other variables and may be used for monitoring progression of atrophy. Two previous studies reported CA by volumetric measurements after phenytoin intoxication[11, 14]. Luef *et al.*[11] concluded that phenytoin overdosage does not necessarily result in CA. However, they included only 11 patients who had experienced clinical intoxication with phenytoin.

In the present study we confirmed that CA is frequently associated with long-term use of phenytoin. This is corroborated by the finding of more severe atrophy in those patients who have had phenytoin intoxication. In this series, frequency of GTCS did not influence the occurrence or severity of CA. Although duration of epilepsy may have an influence in the CA, this is clearly less important than the length of

exposure to phenytoin. It is also possible that duration of epilepsy in this series confounded with duration of treatment; i.e. patients with longer treatment with phenytoin had longer duration of epilepsy and *vice versa*. Otherwise, one would expect a correlation between CA and age of onset as well as with duration of epilepsy. Multiple correlation analysis and a backward stepwise multiple regression analysis confirmed that duration of treatment with phenytoin was the variable most correlated with CA.

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