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Phenytoin-related ataxia in patients with epilepsy: clinical and radiological characteristics

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ABSTRACT

Purpose: Phenytoin is an effective anticonvulsant for focal epilepsy. Its use can be associated with long-term adverse effects including cerebellar ataxia. Whilst phenytoin is toxic to Purkinje cells *in vitro*; the clinical and radiological phenotype and mechanism of cerebellar degeneration *in vivo* remain unclear. We describe the prevalence, clinical and radiological characteristics of phenytoin-related ataxia.
Methods: Patients with epilepsy receiving treatment with phenytoin were recruited from the Epilepsy clinics at Royal Hallamshire Hospital, Sheffield, UK. Neurological examination was performed on all patients after recruitment. Patients were categorised into those with and without ataxia. We determined the severity of ataxia clinically (SARA score) and the pattern of cerebellar involvement by neuroimaging (MRI volumetry and MR spectroscopy).
Results: Forty-seven patients were recruited. Median duration of epilepsy was 24 years, median duration of phenytoin treatment was 15 years and current median phenytoin daily dose was 325 mg. Fifty-five percent of patients complained of poor balance. Clinical evidence of ataxia was seen in 40% patients. Gait, stance and heel-shin slide were the predominant features of cerebellar dysfunction. MRI demonstrated structural, volumetric and functional deficits of the cerebellum. Only one patient with ataxia had phenytoin levels above the normal range.
Conclusions: Cerebellar ataxia is present in 40% of patients with epilepsy and chronic exposure to phenytoin. Patients on long-term phenytoin have reduced cerebellar volume even if they have no clinical evidence of ataxia. Evidence of structural deficits on imaging suggests a predilection for vermian involvement.

1. Introduction

1.1. Phenytoin ($C_{15}H_{12}N_2O_2$)

Phenytoin ($C_{15}H_{12}N_2O_2$) is a hydantoin aromatic anticonvulsant. Its primary mode of action is the blockage of voltage-dependent neuronal sodium (Na^+) channels [1]. The sodium channel blockade increases the membrane threshold for depolarisation, ultimately lowering the neuronal cell susceptibility to epileptogenic stimuli.

Phenytoin was first used as an anticonvulsant in 1938 [2]. This breakthrough discovery later established phenytoin as one of the most effective antiepileptic drugs (AEDs) available [3]. Its use, however, is now in decline partly due to competition from new antiepileptic drugs, complex kinetic profile, multiple drug-interactions and long-term adverse effects that include abnormal

Abbreviations: AED, antiepileptic drug; AGA, anti-gliadin antibody; EMA, endomysial antibody; HLA, human leukocyte antigen; MRI, magnetic resonance imaging; NAA/Cr, *N*-acetyl aspartate:creatine ratio; PHT, patients without clinical evidence of ataxia; PHTA, patients with clinical evidence of ataxia; SARA, Scale for the Assessment and Rating of Ataxia; TG2, transglutaminase 2; TG6, transglutaminase 6.

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bone mineral metabolism and potentially irreversible cerebellar ataxia.

Patients with acute phenytoin intoxication may have drowsiness, nystagmus, dysarthria, tremor, ataxia and cognitive difficulties. Chronic phenytoin use is associated with cerebellar degeneration [4]. Evidence for cause and effect is not always clear-cut; some reports suggest that cerebellar degeneration is secondary to seizure-mediated cell loss rather than a direct effect of phenytoin. However, phenytoin has been shown to be toxic to Purkinje cells *in vitro* [5–9]. The prevalence of cerebellar damage in chronic phenytoin use and the clinical and radiological phenotype remain unclear.

1.2. Aim

The aim of this study was to investigate the prevalence of ataxia in patients with epilepsy on long-term phenytoin and to determine the clinical and radiological characteristics of phenytoin-related ataxia. The study also aimed to determine any additional contributory factors to cerebellar degeneration.

2. Material and methods

2.1. Patient selection and clinical assessments

The study was approved by the regional ethics committee (Yorkshire & The Humber, UK). Patients with a clinical diagnosis of epilepsy taking long-term phenytoin treatment were identified from the Epilepsy outpatient clinics at the Royal Hallamshire Hospital, Sheffield, UK. Of 52 consecutive patients approached, (47/52) 90% agreed to take part. Written informed consent was obtained from all patients.

'Long-term phenytoin' was defined as having been treated with phenytoin for more than 1 year. After recruitment, all patients underwent a full neurological examination focusing on clinical evidence of cerebellar ataxia and to exclude a peripheral neuropathy. Patients were categorised into 2 subgroups (PHT – patients with no clinical evidence of ataxia, and PHTA – patients with clinical evidence of ataxia). Only patients who were on phenytoin treatment at the time of study were included in the project.

Detailed neurological history was obtained from the patients recruited and from their clinical records. This included type of epilepsy (focal, general or unclassified), duration of epilepsy, duration of phenytoin treatment and whether the patients had been on phenytoin from the time of the initial epilepsy diagnosis, current dose of phenytoin and any additional therapy with other antiepileptic agents. Age of onset, duration of symptoms of poor balance (ataxia) and requirement for mobility aids was documented in the subgroup of patients with PHTA.

Cerebellar ataxia when present was classified as affecting gait, limb (lower ± upper limb) or both and severity was assessed as mild (mobilising independently or with one walking aid), moderate (mobilising with 2 walking aids or walking frame) or severe (wheelchair-dependent). The severity assessment was adapted from previously published data [10]. Objective measurement of the severity of ataxia was rated using the Scale for the Assessment and Rating of Ataxia (SARA) [11,12] (see Supplementary material).

2.2. Brain imaging

Volumetric 3T MR imaging and single-voxel H^1 MR spectroscopy of the cerebellum were undertaken in patients with clinical evidence of ataxia. The brain imaging protocols for structural, volumetric and spectroscopy studies have been previously reported [13,14]. In the group of patients without ataxia, any existing volumetric 3T MR imaging that was done on participants, using the same imaging protocol, were included in the volumetric analysis.

MR spectroscopy imaging outcome measures comprised of N-acetyl aspartate to creatine (NAA/Cr) area ratios of both the cerebellar vermis and hemisphere. MR volumetric imaging outcome measures comprised of cerebellar volume (expressed as a percentage of total intracranial volume, %CBV:TIV) and vermian volume (expressed as a percentage of total intracranial volume, %V:TIV).

Patients included in the volumetric analysis were age- and gender- matched with healthy controls who had undertaken the same MR imaging protocol. The demographic details of the healthy controls who had undergone a thorough screening health questionnaire before inclusion have been reported previously [15].

2.3. Blood collection and serological tests

Blood samples were collected at recruitment. Tests included serum B12, folate and thyroid function. Immunological tests included total immunoglobulin levels, IgA and IgG anti-gliadin antibodies (AGA), anti-endomysial antibodies (EMA) and IgA anti-transglutaminase 2 (TG2) antibodies assayed at the Immunology Department, Northern General Hospital, Sheffield [14]. Patient sera were also used for the detection of IgA and IgG to transglutaminase 6 (TG6) by ELISA as previously described [16]. Human Leukocyte Antigen (HLA) typing was performed at the National Blood Service, Sheffield, UK. Serum phenytoin levels were measured if there was clinical evidence of ataxia on examination. All patients were investigated for other causes of ataxia and no alternative aetiology was found.

2.4. Statistical analysis

Statistical analysis was performed using PRISM 6 software package (GraphPad Software Inc.). Demographic, clinical and imaging characteristics are presented as means with standard deviations (mean ± SD). The Independent-Samples Mann-Whitney *U* Test was used to determine any difference between mean cerebellar volume, expressed as a percentage of total intracranial volume (%CBV:TIV) and mean vermian volume, expressed as a percentage of total intracranial volume (%V:TIV) between patients and controls. The χ^2 test was used for comparing the prevalence of anti-gliadin antibodies and anti-transglutaminase 6 antibodies in the study group with that of the healthy population; and between the subgroups. Results were considered statistically significant if $p < 0.05$.

3. Results

3.1. Clinical presentation

Forty-seven consecutive patients with known epilepsy and taking phenytoin long-term were recruited with mean age of 58 ± 13 years. There were 32 male and 15 female patients. Twenty-eight (60%) patients had focal epilepsy, 6/47 (13%) had generalised epilepsy and in 13/47 (28%) patients the type of epilepsy was unclassified. Duration of epilepsy ranged from 2 to 67 years (median 24 years) and duration of phenytoin treatment ranged from one to 67 years (median 15 years). Thirty (64%) patients had been taking phenytoin from the time of epilepsy diagnosis. The phenytoin total daily dose ranged from 100 to 600 mg (median 325 mg). Eighteen (38%) patients were taking phenytoin as monotherapy compared to 29/47 (62%) patients on combination antiepileptic therapy. Twenty four of the 29 (83%) patients on