Seizure 56 (2018) 26–30

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

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

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ARTICLE INFO

Article history:
Received 20 December 2017
Received in revised form 22 January 2018
Accepted 29 January 2018

Keywords:
Ataxia
Cerebellum
Cerebellar degeneration
Epilepsy
Phenytoin

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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https://doi.org/10.1016/j.seizure.2018.01.019
1059-1311/

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

combination antiepileptic therapy was on one additional antiepileptic, 3/29 (10%) patients were on two additional antiepileptics and 2/29 (7%) patients were on 3 additional antiepileptics. Twenty-six of the 47 (55%) patients complained of poor balance.

Patients with clinical evidence of ataxia (PHTA)

Ataxia (PHTA) was present in 19/47 (40%) patients. Three patients were taking phenytoin monotherapy; 15 patients were taking one additional anti-epileptic therapy, and 1 patient was taking three additional anti-epileptic therapies.

Age at onset of balance problems in this group of patients was 61 ± 9 years. None of the patients had clinical signs of peripheral neuropathy (*i.e.* distal sensory loss or depressed deep tendon reflexes). Duration of ataxia ranged from one to 16 years (median of 2 years). Pure gait ataxia was seen in 5/19 (26%) patients with the majority having both gait and limb ataxia 14/19 (73%). Nystagmus was present in 9/19 (47%) patients.

Fourteen of the nineteen (74%) patients had mild ataxia (mobilising independently or with one walking aid) compared to 5/19 (26%) patients with moderate (mobilising with 2 walking aids or walking frame) ataxia. No patients had severe ataxia. The severity of ataxia using the SARA scale revealed a mean total SARA score of 8 ± 5 (range 4–17). There was a correlation seen between duration of ataxia and total SARA score (p 0.0122).

Table 1 demonstrates the frequency of involvement for each of the eight key SARA elements. The gait (100%), stance (95%) and heel-shin slide (79%) were the predominant SARA elements affected.

3.2. Brain imaging

MR Spectroscopy data analysis was based on 10 optimal scans done on patients with PHTA. The decision to exclude suboptimal MR spectroscopy data was based on previous published criteria [17]. Abnormal NAA/Cr area ratio (vermis NAA/Cr area ratio < 0.95 and/or hemisphere NAA/Cr < 1.00) [18] was recorded in 8/10 (80%) patients with PHTA. Predominantly vermian abnormalities were present in 5/10 (50%) patients with PHTA. The hemisphere was solely affected in 3/10 (30%) patients with PHTA. There was no significant difference between the prevalence of abnormal spectroscopy in the vermis *vs.* the cerebellar hemispheres.

3T MRI was available in 30 of the 47 patients. MRI was contraindicated in 5 patients and there were no available MRI data in 12 patients. The clinical reporting of cerebellar atrophy was undertaken by a neuroradiologist (NH) with expertise in cerebellar imaging. Cerebellar atrophy was reported in 13/30 (43%) patients with epilepsy taking phenytoin that comprised of 7/17 (41%) patients without ataxia and 6/13 (46%) patients with ataxia. Vermian atrophy was present in 12/13 (92%) patients and hemispheric atrophy in 5/13 (38%) patients.

MRI data that did not contain appropriate T1 volume sequences or follow the appropriate imaging protocol were excluded from volumetric analysis. Volumetric image analysis matched for age and gender with healthy controls was possible in 17 patients taking phenytoin. The analysis was thus based on 8 patients without ataxia (PHT) and 9 patients with ataxia (PHTA). Results are displayed as a whole group (PHT and PHTA) *vs.* age and gender matched healthy controls, subgroup PHT or PHTA *vs.* age and gender matched healthy controls and PHT *vs.* PHTA.

Cerebellar volume was significantly smaller (8.30 ± 1.05) in the whole study group (PHT and PHTA) when compared with healthy controls (9.36 ± 0.88); CI 95% 7.75–8.84, p 0.0015. There was correlation between duration of phenytoin and cerebellar volume (p 0.0247).

Cerebellar volume was significantly smaller in the subgroup PHT (8.88 ± 0.82) *vs.* healthy controls (9.71 ± 0.65); CI 95% 8.20–9.57, p 0.0188. Cerebellar volume was also significantly smaller in the subgroup PHTA (7.77 ± 0.99) compared to healthy controls (9.04 ± 0.97); CI 95% 7.02–8.53, p 0.0174.

Cerebellar volume was significantly smaller in the subgroup PHTA (7.77 ± 0.99) compared to the subgroup PHT (8.88 ± 0.82); CI 95% 7.02–8.53, p 0.0360.

Vermian volume was not significantly different when comparing the whole group and the subgroups with healthy controls. There was no correlation demonstrated between the severity of ataxia with cerebellar vermian or hemispheric NAA/Cr area ratio or with cerebellar volume.

3.3. Serological testing for gluten-related antibodies

Normal serum immunoglobulins were seen in 24/47 (51%) patients on phenytoin. Six of the 47 (13%) patients had low IgA levels including one patient with severe IgA deficiency.

Circulating anti-gliadin antibodies and/or TG2 were detected in 5/47 (11%) patients. None of the patients had circulating EMA. There was no difference in the prevalence of circulating anti-gliadin antibodies between the ataxic and non-ataxic patients taking phenytoin, and when compared to the healthy population.

Antibodies to TG6 were detected in 4/47 (9%) patients taking phenytoin. A similar proportion of healthy controls has been reported to have circulating anti-TG6 antibodies [19]. There was no significant difference between the subgroups of patients.

3.4. HLA genotyping for DQ2/DQ8

Nineteen of the 47 (40%) patients in the whole study group had HLA typing for DQ2 or DQ8. This was similar to the healthy population (30%, Dewar, 2004). There was no significant difference between the subgroups, using the χ^2 test.

3.5. Serum phenytoin levels

Phenytoin levels in the subgroup of patients with PHTA ranged from 2.0 g/L to 65.8 g/L (median 13.2 g/L). Only one of the nineteen patients with ataxia had phenytoin levels in the potentially intoxicating range (65.8 g/L) indicating that the ataxia in this group of patients was not a result of current phenytoin intoxication.

Table 1
Scale for the assessment and rating of ataxia (SARA) in patients with phenytoin-related ataxia.

SARA elements	Phenytoin-related ataxia
Gait	19/19 (100%)
Stance	18/19 (95%)
Sitting	2/19 (11%)
Speech disturbance	1/19 (5%)
Finger chase	7/19 (37%)
Nose-finger test	8/19 (42%)
Fast alternating hand movements	8/19 (42%)
Heel-shin slide	15/19 (79%)

4. Discussion

To our knowledge this is the first study detailing the clinical and radiological characteristics of cerebellar ataxia in patients with epilepsy and chronic exposure to phenytoin. Whilst 55% of patients complained of poor balance, clinical evidence of ataxia was present in 40%. Patients with phenytoin-related ataxia appear to predominantly have gait and limb ataxia of mild severity (mobilising independently or with one walking aid). Only 1 patient had phenytoin levels above the normal range indicating that the ataxia in this group of patients was not a result of acute phenytoin

intoxication. Previous studies have focused on patients with symptoms of phenytoin intoxication that manifest as nystagmus, tremor and ataxic syndrome, some of which are reversible on treatment adjustment and/or cessation.

The mean total SARA score in patients with phenytoin-related ataxia was 8 ± 5 implying mild ataxia. There was correlation between duration of ataxia and total SARA score (p 0.0122). The gait (100%), stance (95%) and heel-shin slide (79%) of the SARA elements were predominantly affected. No correlation was found between duration of epilepsy or duration of phenytoin treatment with the total SARA score. Clinically this study suggests that the type of ataxia seen in patients on long-term phenytoin is predominantly vermian.

None of the patients with phenytoin-related ataxia had clinical signs of peripheral neuropathy. This clinical exclusion in our study supports that the cerebellum is primarily involved in patients with epilepsy and chronic exposure to phenytoin. Although previous studies have shown that peripheral neuropathy can be associated with phenytoin, no link was found between phenytoin levels or the duration of phenytoin with the development of clinical neuropathy [20].

Structural evaluation with 3T MRI revealed variable degrees of cerebellar atrophy consistent with published literature [21]. The presence or not of cerebellar atrophy did not correlate with clinical evidence of ataxia, though there was a correlation between duration of treatment with cerebellar volume loss. Patients with phenytoin-related ataxia (as assessed clinically) had significantly smaller cerebellar volumes compared to patients on phenytoin without ataxia. This suggests that cerebellar atrophy is not always associated with clinical evidence of cerebellar dysfunction and that there may be a threshold beyond which atrophy will be accompanied by cerebellar signs.

Previous studies have not compared imaging with clinical findings in patients prescribed phenytoin but correlation between cerebellar atrophy and duration of epilepsy has been previously shown [22]. This may reflect a correlation between duration of epilepsy and exposure to antiepileptic drugs and therefore it is impossible to tease out any direct effect of the epilepsy alone. MR spectroscopy appears potentially more sensitive than volumetry in detecting underlying cerebellar dysfunction prior to demonstration of cerebellar structural abnormalities [23]. MR spectroscopy reflects underlying tissue biochemistry at the time of the scan as well as underlying structural changes such as reduction in the number of neurons; whereas volumetry represents accumulated cellular loss over the life of the patient.

Prevalence of gluten-related serology was no different to that in healthy controls. The above findings concur with a previous study on gluten-related antibodies in patients with epilepsy that included patients taking phenytoin and the healthy population [24]. Results for HLA DQ2/DQ8 (often associated with a tendency to autoimmunity) were not significant. We therefore, did not identify any potential additional factors likely to be contributing to the development of ataxia in this group of patients.

This study is limited by the relatively small sample size. Details of historical phenytoin levels or previous episodes of toxicity were not readily accessible. We did not have sufficient information about previous dosing to work out a life time total phenytoin dose or mean phenytoin blood level. We have also not accounted for effects of combinations of phenytoin with other antiepileptic drugs, whether seizure control had any influence on volumetric loss and whether either factor was associated with ataxia. A comparison with a group of patients with epilepsy on different anticonvulsant(s) may be a future direction.

5. Conclusions

This study shows that the prevalence of ataxia in patients with epilepsy and chronic exposure to phenytoin is 40% and that patients on long-term phenytoin have reduced cerebellar volume even if they have no clinical evidence of ataxia. The absence of additional contributory factors to the ataxia suggests that this is a direct toxic effect of phenytoin.

Ethics approval and consent to participate

The study was approved by the regional ethics committee (Yorkshire & The Humber, UK). Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article is included within the main article.

Conflicts of interest

Dr P. Shanmugarajah: none
Dr N. Hoggard: none
Professor D. Aeschlimann serves as a scientific advisor/collaborator to Zedira (without financial incentives) but receives royalties from Zedira for patents
Mrs Pascale Aeschlimann: none
Dr G. Dennis: none
Dr S. Howell: none
Professor M. Reuber: none
Dr R. Grünewald: none
Professor M. Hadjivassiliou: none

Funding

This work was supported by the Bardhan Research and Education Trust, Neurological Research Fund, Sheffield Hospitals Charity and Sheffield Teaching Hospital NHS Foundation Trust, UK.

Authors' contributions

PS and MH designed the study and produced the first draft of the manuscript. Patients with known epilepsy on long-term phenytoin were identified from GD, SH, MR and RG's epilepsy clinics. PS recruited all the patients and performed the clinical, brain imaging and laboratory assessments including analysis of the imaging data and ELISA experiments. NH provided radiology expertise on brain imaging. DA and PA provided laboratory expertise on TG6 antibody measurements. RG provided the statistical support and critical revision of the first draft. All authors read and approved the final manuscript.

Acknowledgements

National Blood Service Sheffield, UK; Department of Immunology, Northern General Hospital, Sheffield, UK and Academic Unit of Radiology, University of Sheffield, UK.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.seizure.2018.01.019.

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