Title page

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

Title character count: 93 (with spaces)

Manuscript word count: 2703

Abstract word count: 239

Number of references: 24

Number of tables: 1

Number of supplementary materials: 4

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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* remains 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 325mg. 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.

Keywords

ataxia; cerebellum; cerebellar degeneration; epilepsy; phenytoin

1. INTRODUCTION

1.1 Phenytoin ($C_{15}H_{12}N_20_2$) 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 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 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 600mg (median 325mg). 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 were 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 to 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.

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%)

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 to 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 to 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 to 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 to 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 have 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.

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.

DECLARATIONS

List of 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

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.

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.

Supplementary material

Scale for the Assessment and Rating of Ataxia (SARA).

Demographics of patients with epilepsy on long-term phenytoin.

Clinical characteristics and volumetric imaging data in patients with phenytoin-related ataxia.

MRI TI midline sagittal and axial T2-weighted images in a healthy patient and in a patient with cerebellar atrophy.

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Rater: _____date: _____patient:_____

Scale for the assessment and rating of ataxia (SARA)

1) Gait

Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.

0 Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)
1 Slight difficulties, only visible when walking 10 consecutive steps in tandem
2 Clearly abnormal, tandem walking >10 steps not possible
3 Considerable staggering, difficulties in half-turn, but without support
4 Marked staggering, intermittent support of the wall required
5 Severe staggering, permanent support of one stick or light support by one arm required
6 Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)
7 Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)
8 Unable to walk, even supported

Score _____

2) Stance

Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.

0 Normal, able to stand in tandem for > 10 s
1 Able to stand with feet together without sway, but not in tandem for > 10s
2 Able to stand with feet together for > 10 s, but only with sway
3 Able to stand for > 10 s without support in natural position, but not with feet together
4 Able to stand for >10 s in natural position only with intermittent support
5 Able to stand >10 s in natural position only with constant support of one arm
6 Unable to stand for >10 s even with constant support of one arm

Score _____

3) Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.

0 Normal, no difficulties sitting >10 sec
1 Slight difficulties, intermittent sway
2 Constant sway, but able to sit > 10 s without support
3 Able to sit for > 10 s only with intermittent support
4 Unable to sit for >10 s without continuous support

Score _____

4) Speech disturbance

Speech is assessed during normal conversation.

0 Normal
1 Suggestion of speech disturbance
2 Impaired speech, but easy to understand
3 Occasional words difficult to understand
4 Many words difficult to understand
5 Only single words understandable
6 Speech unintelligible / anarthria

Score _____

Rater: _____date: _____patient:_____

5) Finger chase

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

- **0 No dysmetria**
- **1 Dysmetria, under/ overshooting target <5 cm**
- **2 Dysmetria, under/ overshooting target < 15 cm**
- **3 Dysmetria, under/ overshooting target > 15 cm**
- **4 Unable to perform 5 pointing movements**

Score	**R**ight	**L**eft
mean of both sides (R+L)/2		

6) Nose-finger test

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

- **0 No tremor**
- **1 Tremor with an amplitude < 2 cm**
- **2 Tremor with an amplitude < 5 cm**
- **3 Tremor with an amplitude > 5 cm**
- **4 Unable to perform 5 pointing movements**

Score	**R**ight	**L**eft
mean of both sides (R+L)/2		

7) Fast alternating hand movements

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

- **0 Normal, no irregularities (performs <10s)**
- **1 Slightly irregular (performs <10s)**
- **2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s**
- **3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s**
- **4 Unable to complete 10 cycles**

Score	**R**ight	**L**eft
mean of both sides (R+L)/2		

8) Heel-shin slide

Rated separately for each side
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

- **0 Normal**
- **1 Slightly abnormal, contact to shin maintained**
- **2 Clearly abnormal, goes off shin up to 3 times during 3 cycles**
- **3 Severely abnormal, goes off shin 4 or more times during 3 cycles**
- **4 Unable to perform the task**

Score	**R**ight	**L**eft
mean of both sides (R+L) / 2		

Patient ID	Gender	Age at study, y	Subgroup	Epilepsy type	Treated on additional AED
6*	female	67	PHTA	unclassified	PMD
7	male	67	PHTA	generalised	LTC
10*	male	57	PHT	focal	ZNS
11	male	54	PHT	focal	CBZ
12	female	59	PHT	focal	LTC, PGL, PHB
13*	female	63	PHT	unclassified	-
14*	female	77	PHTA	general	PHB
15	male	49	PHT	focal	PGL
16	male	54	PHT	focal	PGL, OXC
17*	male	65	PHT	generalised	-
19	male	32	PHT	focal	LTG
22	male	74	PHTA	focal	LTC
26	female	42	PHT	unclassified	-
41	male	54	PHTA	unclassified	LTC
42*	male	77	PHT	unclassified	-
48*	male	53	PHTA	generalised	-
60*	female	72	PHTA	unclassified	VPA
65	male	73	PHTA	focal	-
66*	female	69	PHT	focal	CBZ, LTC
68*	female	74	PHTA	focal	LTG
71*	male	32	PHT	focal	VPA
73*	male	71	PHTA	generalised	VPA
74*	female	70	PHTA	focal	PGL
75*	female	63	PHTA	generalised	PHB
76*	female	57	PHTA	unclassified	VPA
79	male	39	PHT	focal	-
80*	male	65	PHTA	focal	PGL
81*	male	62	PHT	unclassified	-
82*	male	39	PHT	unclassified	-
83	male	46	PHT	focal	LTG
84	male	43	PHT	unclassified	LTC, VPA
87*	male	48	PHT	unclassified	-
88*	male	67	PHT	focal	PHB
93	male	40	PHT	focal	LTC
96*	female	66	PHT	focal	-
97*	male	63	PHTA	focal	-
98	female	61	PHTA	focal	CBZ
111*	male	88	PHT	focal	-
113	male	43	PHT	focal	-
115*	male	52	PHT	unclassified	-
124	male	57	PHT	focal	LTC
126*	female	60	PHTA	focal	CBZ
129*	male	49	PHT	focal	-
130*	male	55	PHTA	focal	CBZ, LTC, ZNS
131*	male	36	PHT	focal	-
141*	female	60	PHT	unclassified	-
144*	male	64	PHTA	focal	PHB

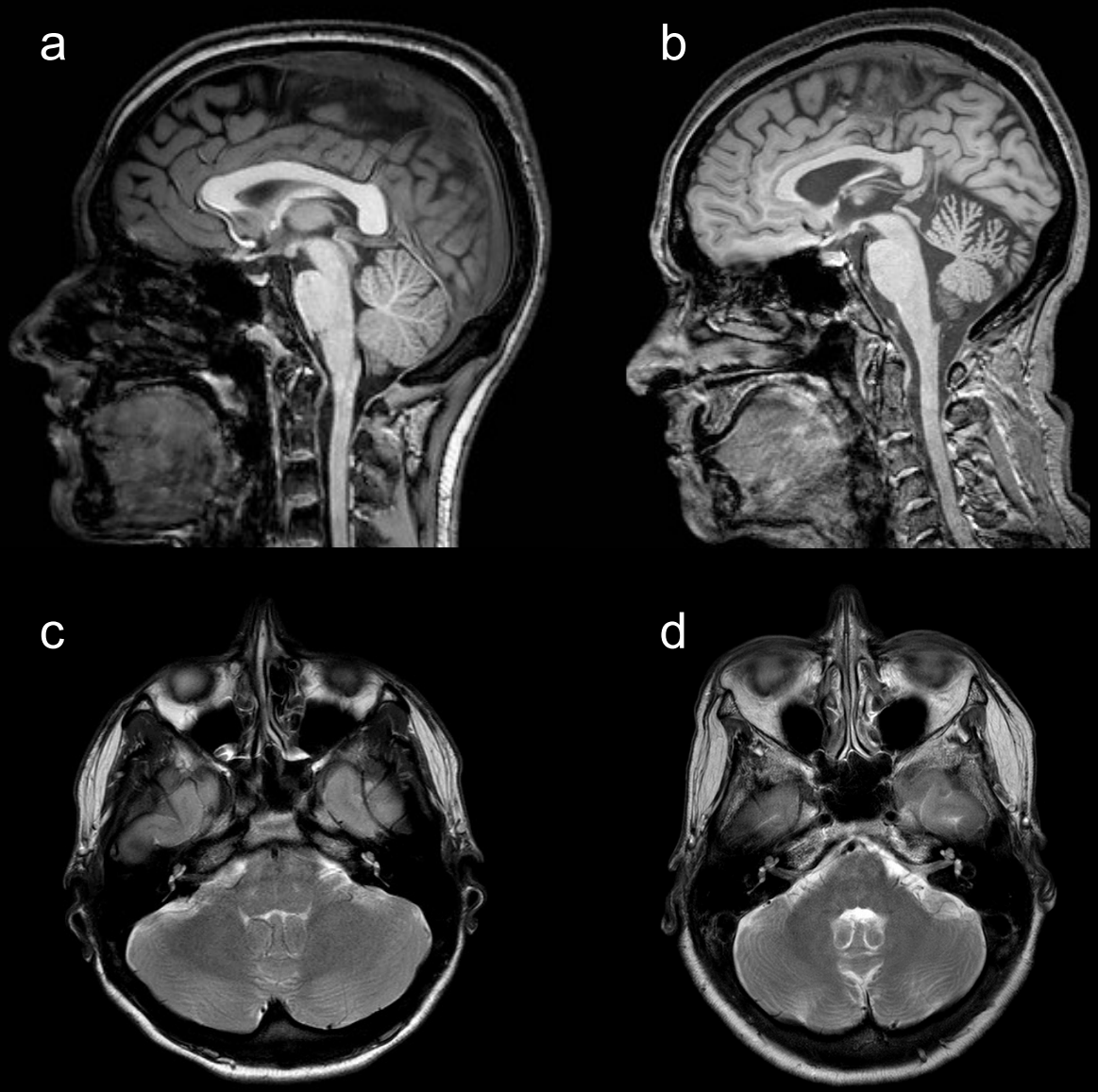
* = on phenytoin from time of initial diagnosis of epilepsy, y = years, PHT = no ataxia, PHTA = with ataxia,
CBZ = carbamazepine, LTC = levetiracetam, LTG = lamotrigine, PHB = phenobarbital, PGL = pregabalin, PMD = primidone,
OXC = oxcarbazepine, VPA = sodium valproate, ZNS = zonisamide

Demographics of patients with epilepsy on long-term phenytoin

Patient ID	Phenytoin level (g/L)	Severity of ataxia	Gait	Stance	Sitting	Speech disturbance	Finger chase	Nose-finger test	Fast alternating hand movements	Heel-shin slde	Total SARA score	Cerebellar volume (%CBV:TIV)
6	26.8	mild	2	0	0	0	0	0	1	1	**4**	9.38
7	2.0	mild	2	3	0	0	0	0	0	0	**5**	n/a
14	28.8	mild	3	3	0	0	0	0	0	0	**6**	n/a
22	65.8	moderate	5	4	1	0	1	1	1	2	**15**	n/a
41	9.0	moderate	5	4	0	1	0	0	0	1	**11**	8.61
48	21.3	mild	2	1	0	0	0.5	0.5	0	1	**5**	6.96
60	9.5	moderate	7	5	0	0	0	0	1	4	**17**	n/a
65	12.2	mild	2	3	0	0	0	0	0	1	**6**	7.77
68	14.6	mild	2	2	0	0	0	0	0	0	**4**	n/a
73	17.6	mild	3	3	0	0	1	1	1	2	**11**	8.12
74	14.6	mild	3	2	0	0	0	0	0	0	**5**	n/a
75	10.1	mild	1	2	0	0	0	1	0	1	**5**	6.19
76	1.8	mild	2	2	0	0	0.5	0.5	0.5	0.5	**6**	7.73
80	7.9	moderate	5	5	1	0	1	1	1	3	**17**	n/a
97	28.1	mild	2	2	0	0	2	2	1	1	**10**	8.36
98	n/a	mild	3	1	0	0	0	0	0	1	**5**	6.84
126	7.9	mild	2	2	0	0	0	0	0	0.5	**4.5**	n/a
130	14.2	mild	2	2	0	0	0	0	0	1	**5**	n/a
144	11.8	moderate	5	5	0	0	1.5	1.5	0.5	3	**16.5**	n/a

clinical characteristics (severity of ataxia, SARA elements subscores, total SARA score) of 19 patients with phenytoin-related ataxia (PHTA), SARA = Scale for the assessment and rating of ataxia,
only volumetric imaging data (cerebellar volume) of patients that were age- and gender- matched with healthy controls displayed, cerebellar volume is expressed as a percentage of total intracranial volume (%CBV:TIV)

Clinical characteristics and volumetric imaging data in patients with phenytoin-related ataxia



MRI TI midline sagittal and axial T2-weighted images in a healthy patient (a,c) and in a patient with cerebellar atrophy (b,d)