Phenytoin and damage to the cerebellum - a systematic review of published cases

Ferner, Robin; Day, Rachael; Bradberry, Sally

DOI:
10.1080/14740338.2022.2058487

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Ferner, R, Day, R & Bradberry, S 2022, 'Phenytoin and damage to the cerebellum - a systematic review of published cases', *Expert Opinion on Drug Safety*, vol. 21, no. 7, pp. 957-977. https://doi.org/10.1080/14740338.2022.2058487

Taylor & Francis
Taylor & Francis Group

Expert Opinion on Drug Safety

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieds20

Phenytoin and damage to the cerebellum – a systematic review of published cases

Robin Ferner, Rachael Day & Sally M Bradberry

To cite this article: Robin Ferner, Rachael Day & Sally M Bradberry (2022) Phenytoin and damage to the cerebellum – a systematic review of published cases, Expert Opinion on Drug Safety, 21:7, 957-977, DOI: 10.1080/14740338.2022.2058487

To link to this article: https://doi.org/10.1080/14740338.2022.2058487

Published online: 20 Apr 2022.

EXPERT OPINION ON DRUG SAFETY
2022, VOL. 21, NO. 7, 957–977
https://doi.org/10.1080/14740338.2022.2058487

Taylor & Francis
Taylor & Francis Group

SYSTEMATIC REVIEW

Phenytoin and damage to the cerebellum – a systematic review of published cases

Robin Ferner [a,b], Rachael Day[a] and Sally M Bradberry[a,b,c]

[a]National Poisons Information Service (Birmingham Unit), City Hospital Birmingham, Birmingham, UK; [b]School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK; [c]School of Biosciences, University of Birmingham, Birmingham, UK

ABSTRACT

Introduction: The antiseizure medication phenytoin has been associated with changes in the cerebellum, cerebellar signs, and permanent cerebellar damage. We have systematically reviewed the clinical and radiological features, and their correlation.

Areas covered: We identified sixty case reports and case series of the effects of phenytoin on the cerebellum by searching Medline and Embase and relevant reference lists. The reports described 92 [median 1, range 1–5] cases, documented median age 28 [2.7–78] years. Eighty-one cases described one or more clinical sign of ataxia (present in 96%), dysarthria (63%), and nystagmus (70%). The neurological outcome (in 76 cases): 10 (13%) recovered by 12 months; 55 (72%) suffered residual disability; and 11 (14%) died. Median serum phenytoin concentration (48 cases) was 50 (interquartile range 31–66) mg/L; only three values were below 20 mg/L. The radiological findings included cerebellar atrophy in 41 of 61 patients (67%) with at least one scan.

Expert opinion: Evidence mainly comes from case reports, and is inevitably biased. Most patients with cerebellar dysfunction have phenytoin concentrations above the reference range. Clinical signs of ataxia can persist without radiological evidence of cerebellar atrophy, and cerebellar atrophy is seen without any clinical evidence of cerebellar dysfunction.

ARTICLE HISTORY
Received 19 October 2021
Accepted 23 March 2022

KEYWORDS
Phenytoin; drug-related side effects and adverse reactions; poisoning; cerebellar diseases; ataxia; dysarthria

1. Introduction

Phenytoin (diphenylhydantoin, Dilantin®) was introduced into clinical practice as an antiseizure medication (anti-epileptic drug, anticonvulsant) by Merritt and Putnam in 1938 [1]. A review of 329 patients in 1939 supported 'the strong anticonvulsant properties and marked toxic effects of this drug,' for by that time, the adverse effects of ataxia, nystagmus, tremor, dizziness, and visual and psychological disturbance had been observed in treated patients [2]. By the 1960s, the adverse effects had been correlated with serum concentrations of phenytoin: 'nystagmus appearing at approximately 20 [mg/L], ataxia at about 25–30 [mg/L], and disorientation and somnolence at greater than 35 [mg/L].' [3] The ataxia, nystagmus, and tremor are characteristic of cerebellar dysfunction. Phenytoin has non-linear pharmacokinetics, and this makes dosage adjustment difficult. A small increase in dose can result in an unexpectedly large increase in plasma concentration, and consequent phenytoin toxicity. In most cases, cerebellar signs disappear when phenytoin treatment is stopped, or the dosage is reduced.

However, in 1958, Utterbach *et al* presented an abstract to the American Neurological Association of 'Parenchymatous cerebellar degeneration with Dilantin® intoxication' that reported histological findings in cats given phenytoin. They also described two patients who were treated with phenytoin, developed cerebellar signs, and recovered after their phenytoin treatment ceased [4]. Haberland later described three patients treated with phenytoin who developed progressive cerebellar signs and ultimately died (although not necessarily from phenytoin poisoning), and who at post mortem showed histological evidence of cerebellar degeneration [5]. Since then, cases have been published of a persistent cerebellar syndrome after intoxication with phenytoin, both after long-term treatment and after acute intoxication.

We reviewed the medical literature to identify case series and case reports of cerebellar changes associated with phenytoin treatment.

2. Methods

We searched Medline and Embase in the Ovid® database, without language restriction, using the following search terms: (phenytoin or diphenylhydantoin or Dilantin or DPH).mp. AND (cerebellum or cerebellar).mp. The search was limited to humans and to adverse effects. We ran the search on 13 April 2021.

From the retrieved references, we used titles and abstracts to select case reports or case series that included cerebellar changes with phenytoin. We considered any finding of ataxia, dysarthria, or nystagmus to indicate that clinical features of cerebellar disorder were present. We additionally sought references listed in the retrieved articles but not found by the search strategy.

We tabulated the results for each case report or case series according to author, year of publication, patient age and sex,

CONTACT Robin Ferner r.e.ferner@bham.ac.uk National Poisons Information Service (Birmingham Unit), City Hospital Birmingham; University of Birmingham, Birmingham, UK

Article highlights

- Phenytoin is still widely used as an antiseizure medication.
- Cerebellar signs are common.
- Most phenytoin-treated patients with cerebellar dysfunction have phenytoin concentrations above the reference range.
- In most cases, signs regress when phenytoin concentration is reduced.
- Phenytoin can damage cerebellar Purkinje cells.
- Clinical signs of ataxia can persist without radiological evidence of cerebellar atrophy, and cerebellar atrophy can be seen without clinical evidence of cerebellar dysfunction.

This box summarizes key points contained in the article.

clinical history, exposure to phenytoin, concentration measurements, radiological findings, and neuropathology. Each reference was screened by one reviewer (REF) and cross-checked by a second reviewer (RD); any disagreements were resolved by consensus.

Results were presented as absolute numbers and percentages.

3. Results

3.1. Search results

The search results were as follows:
1. (phenytoin or diphenylhydantoin or Dilantin or DPH).mp. 87,524
2. (cerebellum or cerebellar).mp.273,862
3. 1 and 2 1484
4. Remove duplicates from 3 1199
5. Limit to humans and adverse effects 793
Of the 793 references, 66 appeared relevant. An additional 18 references were retrieved from citations within them, providing in total 84 references.

3.2. Retrieved references

Sixty-two of the references contained information on one or more human cases. Two reports in Finnish [6,7], one of which was also reported in English [8], and one of which formed part of a large review [9], were not retrieved, leaving 60 references in total. Four references were available to us only in abstract: one because it was presented to a meeting, and three because there was an English abstract, but the original paper was in Korean [10] or Japanese [11]. One case of encephalitis, with no evidence of phenytoin intoxication, was excluded [12], so that our analysis was based on 92 reported cases.

3.3. Case reports

Details of cases are given in Table 1 and Table 2.

3.3.1. Clinical features

(Figure 1) Age was documented in 87 cases, with a median of 28 [range 2.7–78] years. At least one feature of a cerebellar disorder was mentioned explicitly in 81 of the 92 cases; one case showed no signs. Of the 81 clinical case reports, 78 (96%) described ataxia, 51 (63%) recorded dysarthria or speech difficulties, and 57 (70%) noted nystagmus. Fifteen patients were recorded to have ataxia alone, and two to have nystagmus alone. Twenty-three cases (28%) exhibited two of the three features, and 41 cases (51%) exhibited all three.

In addition, reports mentioned features such as lethargy, drowsiness, and stupor; diplopia; and hypotonia. Several patients had an underlying brain disorder. In some reports, neurological signs such as extensor plantar responses (five cases) were recorded.

3.3.2. Clinical course

(Figure 2) Eleven patients (14%) died out of the 76 whose neurological outcome was stated, although deaths were not necessarily caused by phenytoin poisoning. Ten patients (13%) recovered after a time, and were normal at re-assessment, which was up to 12 months after the original presentation. Cerebellar signs improved to some degree in 41 patients (66%) assessed at different intervals from 14 days to 4 years after presentation, although the patient often remained disabled. There was no remission of neurological signs in 14 patients (18%), assessed in one case up to 6 years after initial presentation.

3.3.3. Phenytoin concentration measurements

The maximum phenytoin concentration at or soon after presentation was provided in 47 case reports. The median value was 50 (range 3–128; interquartile range 31–67) mg/L, and only four values were below 20 mg/L.

3.3.4. Radiological findings in the cerebellum and posterior fossa

(Figure 3) We took radiological investigations to support a finding of cerebellar atrophy if they reported cerebellar atrophy; or there was prominence of the cerebellar folia or widening of the cerebellar sulci or both; or an increase in size of the fourth ventricle. Some patients underwent radiological investigations at the time of admission and at follow-up. The most abnormal result was invariably the last result obtained.

Two patients underwent carotid angiography, with normal results.

In 14 cases, patients had pneumoencephalograms after developing symptoms attributed to phenytoin. Five studies were normal or only slightly abnormal, four were reported to show enlargement of the fourth ventricle, and five were reported to show cerebellar atrophy.

There were 35 cases with recorded CT scan results, six of which showed no cerebellar abnormality. In the 29 (85%) patients with abnormal scans, cerebellar atrophy, cerebellar degeneration, clearly outlined cerebellar sulci or folia, or enlargement of the fourth ventricle, or a combination of these findings, was observed. One scan was interpreted to demonstrate cerebellar infarction.

Fifteen patients had MRI scans reported: one scan as normal, one as showing 'prominent cerebellar folia,' and one both prominent folia and cerebellar atrophy. Twelve MRI scans (80%) in total were reported to show cerebellar atrophy or 'shrinkage of cerebellum.' A further patient underwent MRI scanning, but the scan was not described.

Table 1 Phenytoin & the cerebellum. Clinical signs, outcome, and exposure to phenytoin Abbreviations and references are given at the end of Supplementary Table 2, below.

Author	Ref	Clinical	Cerebellar signs	Outcome	Exposure to phenytoin	Concentration
Abe 1991	*1*	Unknown; Δ treatment resistant epilepsy with severe mental and physical disorders			Chronic treatment	Always within non-toxic range
Afifi 1968	*2*	10 F, seizures since age 5 y. Phenytoin for 15 m before presenting with ataxia, nystagmus, diplopia. Phenytoin re-introduced for 2 to 3 m, then stopped. After 4 m, recurrent ataxia, later mild dysarthria and other signs. At surgery, a small atrophic cerebellum was biopsied	ADN	Residual ataxia at 4 m; gone at 6 m after the acute episode	200 mg/d for 15 m	
Alioğlu 2000 [c]	*3*	25 F, seizures for 20 y. Confusion, urinary incontinence, severe truncal ataxia, nystagmus, diplopia, dysarthria, dysmetria, dysdiadochokinesis, intention tremor	ADN	8 m later: cerebellar signs improved; 28 m clinical state stable	Acute phenytoin intoxication; 300 mg/d for 10 y; ↑ 600 mg/d 25 d before admission for ↑ fits;	50 mg/L
Arora 2018	*4*	30 M, neurocysticercosis; Recent onset of difficulty walking; Ataxia and dysarthria	AD		16 y 100–200 mg/d	
Arora 2018	*4*	35 M, seizures for 15 y; 2 m difficulty in walking; Nystagmus, gait ataxia	AN		12 y 100–200 mg/d	
Arora 2018	*4*	40 M, seizures for 22 y. Gait ataxia	A		15 y 150 mg/d 'on and off'	
Arora 2018	*4*	7 M, birth asphyxia and seizures for 6 y; nystagmus	N		6 y 50–100 mg/d	
Awada 1999	*5*	30 M, admitted with first seizure, and cerebral mass; after 6 d, given anti-TB quadruple therapy. After a few days, ataxia, dysarthria, confusion and stupor. Transferred: nystagmus, ataxia, dysarthria, combativeness	ADN	Nystagmus gone by day 12, but ataxia persisted, with dysmetria	750 mg/d for 3 d, then 600 mg/d for 2 d, then 300 mg/d, all IV; increased again to 600 mg	298 μmol/L (therapeutic 40–79), then 238, 141, 100, 36, 0 μmol/L on d 0, 2, 8, 13, 23, and 34.
Baier 1984	*6*	18 F, focal seizures from 4 y. Worse at 14 y. Ataxia	A	Recurrent ataxia, incomplete resolution	10 y 150 mg/d from 4 y; then 4 y 200–400 mg/d	maximal blood level 39.7 mg/L
Baier 1984	*6*	18 F, generalized seizures from 2 y. Complex partial seizures from 8 y. ℞ including phenytoin. Developed moderate gait ataxia, nystagmus, diplopia, dysarthria	ADN	Improved after phenytoin was stopped	Initially 150 mg/d; Symptoms on 200 mg/d	30.6 mg/L when ataxic
Baier 1984	*6*	33 F, epilepsy from 6 y. ℞ included phenytoin; 18 y when treated with high dose, suddenly became unable to walk. Coarse ataxia	A	Since then, coarse ataxia, wheelchair-dependent	15 y 100 mg/d	
Baier 1984	*6*	40 M, seizure from age 9 y. ℞ phenytoin etc.; Repeatedly hospitalized for DPH intoxications; with ataxia, nystagmus, diplopia, vomiting, intention; tremor, while on 300–500 mg/d; 24 y: incomplete recovery; stopped; 29 y: restarted; 300 mg/d; dramatic deterioration	ADN	Irreversible disabling ataxia	300–500 mg/d	29 y: Blood concentration 24 mg/L
Baier 1984, 1985	*6*	7 F, complex partial seizures from 2 y; 7 y, ataxia	A	Not fully reversed by change to primidone	150–225 mg/d from 5 y	10–51.4 mg/L
Baier 1984, 1985	*7*	12 F, clonic seizures from 3 m with recurrent ataxia; 12 y ↓motor function, coarse ataxia of trunk and extremities; Phenytoin discontinued, but only slight improvement	A	Phenytoin discontinued, but only slight improvement	4 y 125–150 mg/d; 3 y none; 6 y 250 mg/d	One value 31.2 mg/L; 24.9 mg/L at 12 y
Baier 1984, 1985	*7*	41 F, epilepsy from menarche. Phenytoin 300 mg/d, ; 19 y first report of ataxia, nystagmus, dysarthria, diplopia, vomiting; Four further episodes	ADN	Disabling ataxia, confined to a wheelchair	150-400 mg/d	
Basker	*8*	30 M, hours of dizziness and slurred speech	AD	Some improvement over 5 d	100 mg twice daily for 4 y	

(*Continued*)

Table 1 (Continued).

Author	Ref	Clinical	Cerebellar signs	Outcome	Exposure to phenytoin	Concentration
Botez 1985	*9*	17 F, seizures at 3 y, phenytoin from 4–6 y; further seizures at 16 y. ℞ phenytoin. After 13 m, admitted with ataxia, nystagmus, moderate dysarthria; phenytoin stopped, but initially no improvement	ADN	Initially no improvement; 6 m post admission: dysarthria and ataxia improved	300 mg/d for 16 y	On admission 48 mg/L
Botez 1985	*9*	50 F, hypertension; intracerebral bleed. ℞ phenytoin; After 3 y, limb ataxia for 1 m, nystagmus, slurred speech, choreoathetosis, facial dyskinesia	ADN	Choreoathetosis, facial dyskinesia resolved within 7 d of stopping phenytoin; 3 y post admission she had only mild dysarthria, dysmetria, and dysdiadochokinesia; + moderate ataxia	300 mg/d	127.8 mg/L
Brostoff 2008	*10*	58 M, found semiconscious; brought by ambulance; dysarthric + gait ataxia + nystagmus; known epilepsy ℞ phenytoin; initial diagnosis ethanol intoxication	ADN	After phenytoin withdrawn, 'gradual and full recovery'	300 mg/d	49 mg/L on admission 59 mg/L on fourth day of admission
Brostoff 2008	*10*	72 M, fell at home; 1 w worsening balance + coordination. Previous CVA. O/E left hemiplegia, right-sided dysdiadochokinesia, nystagmus, gait ataxia	AN	Recovery after phenytoin withdrawn	400 mg/d	38.9 mg/L on day after admission
Brostoff 2008	*10*	50 M seizure; Type II DM, alcoholic, hypertensive. O/E slurred speech, dysmetria, nystagmus	DN	Slowly improved after phenytoin stopped	300 mg/d	36.2 mg/L
Cochat 1987	*11*	32 m F, febrile convulsion at 29 m, presented with two generalized seizures treated with diazepam, then a third. Given phenytoin then nystagmus and cardiovascular collapse corrected with fluids and beta-agonists	N	Phenytoin in the normal range after 3 d. At 6 m, no cerebellar signs	3 × 20 mg/kg	72 mg/L
Craig 2004	*12*	38 M, deliberately took at least 10 g phenytoin + ethanol 12–16 h earlier. Previous bleed ?Moyamoya disease. IDDM. Dysarthria, nystagmus, ataxia. Biphasic course. In hospital for 100 d	ADN	Persistent cerebellar toxicity	300 mg/d for 2 y + 10 g at once	181 µmol/L (normal therapeutic range 40–80 µmol/L) on admission; peak value (day 15) 356 µmol/L .
Dasari 2016	*13*	40 F, phenytoin for 8 y for seizures. 2 d of ataxia, dysarthria, nystagmus, and 'bilateral cerebella signs'	ADN	Improved within 5 d	300 mg/d	31.4 mg/L
Dreyer 1966	*14*	20 F, epilepsy from 12 y. No cerebellar signs at 17 y 8 m. Possible overdose. Difficulty in walking. O/E: truncal ataxia, dysarthria, nystagmus, dysdiadochokinesia, tremor	ADN	After 17 m, slow regression of cerebellar symptoms with stationary defect	Took 80–100 tablets of Zentropil® in a few days	
Dreyer 1966	*14*	16 M, Epilepsy from age 12 y. Presented after an influenzal illness with somnolence, gross nystagmus, dysarthra, astasia, abasia, dysmetria, intention tremor, atonia	ADN	Phenytoin stopped, and nystagmus, tremors, and dysmetria improved. Gait and truncal ataxia, and dysarthria persisted at 18 m	Zentronal® 5 tablets/d for 2 y	
Dreyer 1966	*14*	29 sex unstated, Trisomy 21, epilepsy from age 18 y. admitted unable to stand or walk. Nystagmus. Dysmetria, dysdiadochokinesia, gingival hyperplasia	ADN	Improved after phenytoin treatment stopped, but ataxia of the trunk and extremities persisted at 5½ m	Zentropil® 3 tablets/d	

(*Continued*)

Table 1 (Continued).

Author	Ref	Clinical	Cerebellar signs	Outcome	Exposure to phenytoin	Concentration
Dreyer 1966	*14*	8 M, known porencephaly after encephalitis. Truncal ataxia, nystagmus. Unable to stand or walk, hypotonia, hypertrichosis, gingival hypertrophy. Also pyramidal signs	AN	Improved after phenytoin treatment stopped	Zentropil® 5 tablets/d	
Dreyer 1966	*14*	29 sex unstated, titubation at 2 y, generalized seizures from 6 y. Ataxia of gait, nystagmus. Suffered a fatal head injury after falling down stairs	AN		Citrullamon® phenytoin, 6 tablets/d then Zentropil® 3 tablets/d; reduced to 2 tablets/d	
Feuerstein 1983	*15*	42 F previous cerebral haematoma, taking phenytoin. Presented with truncal, standing, and gait ataxia; tremor; nystagmus; variable diplopia	AN	At 5½ m, cerebellar disorder only slightly improved in addition to the ongoing bilateral reduction in vision		53 mg/L
Ghatak 1976	*16*	78 F, phenytoin for 20 y; died of bronchopneumonia; ataxia, nystagmus, intention tremor, dysarthria, hypotonia	ADN	Progressive over several years	200-400 mg/d for 20 y; unknown dose previously	14–21 mg/L
Gill 1978	*17*	54 M, admitted for detoxification. Treated with phenytoin and phenobarbitone for 7 y after cerebral trauma 18 y prior to admission. Confusion; next day slurred speech, gross nystagmus and ataxia, emotional lability, disorientation	ADN	Day 9, nystagmus gone, ataxia persisted. Day 14, still slightly unstable while walking	3 × 100 mg/d	69 mg/L on admission; 53 mg/L on day five; 48 mg/L on day 6; 4 mg/L on day 14.
Guerrero 1997	*18*	15 M, presented with dysarthria; 2 m later, phenytoin after craniotomy for a meningioma at 12 y. No clinical signs of cerebellar disease After 12 m, and more after 18 m, CT signs of cerebellar atrophy. Stable after substitution of valproate for phenytoin	0	Never had signs	3 × 100 mg/d	8 and 9 mg/L
Guirao-Bringas 2012	*19*	37 F, taking phenytoin for 25 y; on examination, disequilibrium, dysmetria, nystagmus, ataxia. Treatment changed	AN	3 y later, scanning speech, slight ataxia, and horizontal nystagmus persisted	400 mg/d	'within the therapeutic range'
Gupta 2013	*20*	20 F, left basal ganglia bleed 2 m before; O/E sleepy, tremor, dysarthria, nystagmus, blurred vision, truncal + gait ataxia; right hemiparesis. Also orofacial dyskinesia, choreiform movements. Weight less than 40 kg	ADN	Over 1 m, near complete improvement in her right sided weakness and dyskinesia but her ataxia and cognitive dysfunction persisted	300 mg/d for 8 w	55 mg/L
Haberland 1962	*21*	28 F, seizures from 6–12 months old. Phenytoin + phenobarbital. Weak, anorexic, in pain. Staggered, fell frequently, dysarthria, incoordination. Cerebellar signs progressed to helplessness after 1 y. Died of pneumonia	AD	Cerebellar signs progressed to helplessness after 1 y. Died of pneumonia		
Haberland 1962	*21*	27 F, 'feeble-minded,' epilepsy from 13 y. Phenytoin + phenobarbital from 20 y. Gait ataxia and incoordination after 7 y. Phenytoin stopped after 9 y	A	Cerebellar signs progressed to helplessness after 3 y. Died of broncho-pneumonia	3 × 1½ grains = 3 × 97.5 mg/d	
Haberland 1962	*21*	55 F, partial seizures from 2 y; generalized from 12 y. Average doses of phenytoin + phenobarbital. Developed progressive gait ataxia, then incoordination of upper limbs. Phenytoin reduced, then replaced by primidone	A	Cerebellar signs progressed to helplessness after 3 y. Became severely anaemic and died		

(*Continued*)

Table 1 (Continued).

Author	Ref	Clinical	Cerebellar signs	Outcome	Exposure to phenytoin	Concentration
Herberg 1975	*22*	26 F, seizures from 16 y. ℞ phenytoin 500 mg/d 'irregularly' for 9 y. Chlorpromazine added; and dose then increased. Falls, gait ataxia progressing over 4 m to severe truncal and appendicular ataxia, slurred speech and nystagmus. Phenytoin withdrawn. Improvement over some months, but truncal ataxia persisted	ADN	Phenytoin withdrawn. Improvement over some months, but truncal ataxia persisted	500 mg/d	69.3 mg/L
Herberg 1975	*22*	16 F, generalized seizure at 2 y. Δ epilepsy at 10 y, ℞ phenytoin 150 mg/d; slowly increased to 400 mg/d + phenobarbital; then 500 mg/d. Then reduced to 300 mg/d Seen 9 m after developing ataxia, and 6 m after being confined to a wheelchair. O/E dysarthria, truncal ataxia, limb ataxia, nystagmus, gum hypertrophy	ADN	Some improvement in 20 m after ceasing phenytoin, but still had dysarthria and needed crutches	500 mg/d at maximum	
Herberg 1975	*22*	25 F, physical education teacher with seizure disorder; phenytoin, then loss of balance. Stopped work. Developed dysarthria, truncal ataxia, muscular hypotonia	AD	After 10 m, improved, but still had wide-based gait	300 mg/d	
Herberg 1975	*22*	45 F, history of alcohol misuse. After treatment for 9 y, developed slurred speech, ataxia, confusion. Dose reduced for 4 y but seizures returned. Dose increased again, developed abnormal gait, ataxia, nystagmus, dysarthria	ADN	Improved following reduction in dose to 300 mg/d but symptoms recurred on increase to 400 mg/d. On reduction to 200 mg/d, ataxia improved and nystagmus and dysarthria disappeared within 6 w. Ataxia absent 10 m later	400 mg/d	
Hiroshini 2000	*23*					69.2 mg/L [?]
Hirzel 1978	*24*	25 F, seizures from 12 y. Phenytoin from 14 y. Marked gum hypertrophy, brisk reflexes, dysmetria, intention tremor, unsteadiness, Romberg positive	A		400 mg/d for 3 y then 600 mg/d for 3 y then 500 mg/d for 2 y	
Hirzel 1978	*24*	25 F, premature; absence seizures from 5 y; generalized seizures from 19 y. Ethosuximide, phenobarbitone and phenytoin for several years. Massive gum hypertrophy, abasia, truncal ataxia, dysmetria, dysarthria	AD		500 mg/d	
Hofmann 1958	*25*	28 F, 'dizzy spells' from 13 y. Partial then four generalized seizures in 24 hours, then admitted. Fever, neck stiffness, bilateral extensor plantars, clear CSF. Recurrent partial seizures. IV phenytoin, then IM every four hours. Her condition worsened, she became decorticate, and then died		Died during acute episode	250 mg IV, then 250 mg IM every 4 h for 8 d, then 100–250 mg every 6 to 8 h ≡ 20–30 mg/kg/d for almost 2 w	
Höglmeier 1969	*26*	20 F, commotio cerebri aged 13 y, then one or two fits daily. Seen at 14 y, height 151 cm, weight 70 kg. Treatment increased. Reviewed after 6 m with 3 w of unsteadiness. and ataxia. Resolved after 17 d. At 19 y, admitted with nystagmus, gingival hypertrophy, intention tremor, truncal ataxia, reduced muscle tone, increased reflexes, dysarthria, unable to stand unaided	ADN	After 1 y, able to eat by herself; only able to walk with a walker or with strong support from helpers	5-methyl-5-(1′2′ dibromo-2′-phenyl-ethyl) hydantoin with phenobarbital, then methylphenytoin, then methylphenytoin + phenytoin	

(*Continued*)

Table 1 (Continued).

Author	Ref	Clinical	Cerebellar signs	Outcome	Exposure to phenytoin	Concentration
Horne 1973	*27*	30 F, epilepsy for 2 y, treated with phenytoin, primidone, and phenobarbitone. On admission, ataxia, dysarthria, nystagmus, dysdiadochokinesis, hyporeflexia. Became increasingly demented. Vitamin treatment was started and phenytoin continued, and dementia receded, but ataxia and nystagmus remained	ADN	Phenytoin treatment ceased. Ataxia and nystagmus persisted on review after 5 y. Confined to a wheelchair	Started on 150 mg/d, then increased to 300 mg/d for 4 y or more	
Horne 1973	*27*	36 F, seizures since age 11 y. When she was treated with phenytoin, she became mute and unable to walk. Phenytoin was continued. When admitted, she had ataxia, dysarthria, and nystagmus	ADN	'Cerebellar syndrome' 4 y later	Started on 200 mg/d, then increased to 400 mg/d	
Imamura 1992	*28*	39 M, admitted with 7 w history of gradually developing ataxia, dysarthria, nystagmus, and confusion	ADN	2 w after phenytoin ceased, nystagmus disappeared but slurred speech and ataxia remained. Minimal improvement in cerebellar signs 10 m	9 y, up to 600 mg/d	86 mg/L; therapeutic range 2 w later
Isago 1982	*29*	29 M, generalized epilepsy for 12 y, 'vague cerebellar signs,' of ataxic gait and truncal ataxia, but neuro-otology disclosed upbeat nystagmus	AN	Tablets reduced to 3 per day (Phenytoin 150 mg, phenobarbital 150 mg and mephobarbital 150 mg) and on day 8, no nystagmus or ataxia	Phenytoin 450 mg, phenobarbital 450 mg and mephobarbital 450 mg for 12 y	On day 8 of reduced dose: phenytoin 3 mg/mL [*sic - probably 3 mg/L*]
Janzik 1975	*30*	unstated age M, taking phenytoin for epilepsy. Presented with nystagmus, severe gait ataxia, and psychological symptoms	AN	Nystagmus still present and Romberg's positive at 1 m; at 8.5 m the neurological findings and the EEG were unremarkable. ENG showed no more evidence of a central vestibular disorder	3 × 1 Tablette Zentropil®	51 mg/L
Kim 1991	*31*	23 M		slowly resolving cerebellar signs	Phenytoin 300 mg, increased to 400–500 mg for 4 y, also phenobarbital and sodium valproate	
Kim 1991	*31*	30 M		slowly resolving cerebellar signs		22.8 mg/L
Kim 1991	*31*	23 M		slowly resolving cerebellar signs		
Kokenge 1965	*32*	18 F, seizures from age 8 y. Presented unable to walk after several y of phenytoin + phenobarbital, and more recent chlordiazepoxide and primidone. On admission, stupor, dysarthria, nystagmus, truncal ataxia, normal reflexes, flexor plantars. All ℞ stopped. Phenytoin restarted 2 m after admission	ADN	Stupor resolved, ataxia and nystagmus diminished; they were still present at 8 m post admission and 12 m post discharge	Was prescribed 300 mg/d, sometimes up to 500 mg/d; took up to 900–1000 mg phenytoin/d	59 mg/L on fifth day of admission; 15 mg/L on day 9; zero on day 22.
Krüger 1978	*33*	13 F, generalized seizures from 5 y. Admitted with gross ataxia, dysarthria, nystagmus, upgoing right plantar reflex. Dose reduced to 2 tablets/d	ADN	Some improvement after 2 m	5 tablets/d reduced to 4 tablets/d phenytoin	
Krüger 1978	*33*	16 F, generalized seizures from 12 y. Phenytoin and Finlepsin® (carbamazepine). Deteriorated in the 8 w before admission, unable to stand. On admission, ataxia, dysarthria, nystagmus, hypotonia, dysdiadochokinesis, past-pointing	ADN	Speech and walking had improved 7 m after discharge. Persistent ataxia, dysarthria, and nystagmus 2 y later	3 tablets/d	Plasma phenytoin 8.3 mg/L (normal 2-4 mg/L)
Kumar 2013	*34*	16 M, birth asphyxia; seizures for 10 y, phenytoin for 10 y. Admitted with fever and weakness, thought to be viral. On recovery, truncal and limb ataxia, nystagmus	AN		5 mg/kg/d	30 mg/L
Kuruvilla	*35*	30 F, acute encephalitis aged 10 m, followed by seizures. Died from acute respiratory failure			Phenytoin, phenobarbital, carbamazepine, and sodium valproate for 19 y	'Never rose to a toxic level'

(*Continued*)

Table 1 (Continued).

Author	Ref	Clinical	Cerebellar signs	Outcome	Exposure to phenytoin	Concentration
Kuruvilla 1997	*35*	38 M, tonic-clonic seizures for 10 y, admitted with delirium and ataxia 1 m after taking a double dose for 1 d, when he developed diplopia and ataxia, but CT was normal. He then inadvertently received doubled doses for 2–3 w. On admission, encephalopathic, with urinary incontinence, severe ataxia, and extensor plantars. Afterwards it was stopped. Dysarthric and ataxic	AD	By 1 m, cognition was markedly improved but dysarthria and severe ataxia persisted at 9 m	300 mg/d (up to 600 mg/d for 2–3 w)	83.5 mg/L
Lindvall 1984	*36*	32 M, acute subarachnoid haemorrhage at age 25 y, then post-op aneurysm surgery ℞ phenytoin 400 mg/d. After 1 m, dysarthria and disequilibrium. O/E slightly drowsy, severe limb ataxia and nystagmus and dysarthria. Dose of phenytoin ↓100 mg for 2 w with carbamazepine + phenobarbitone, then phenytoin stopped	ADN	After 1 m, slight dysarthria + gait ataxia; no nystagmus. After 3 y, able to work. After 6 y, slight unsteadiness on running or turning rapidly. O/E slight ataxia	400 mg/d	85 mg/L
Logan 1969	*37*	[Case 3] 8 M, progressive mental and neurological impairment since age 6 y; for 9 m had progressive dysarthria and gait disturbance. ℞ then phenytoin, primidone. Mild limb ataxia, hyperreflexia, extensor plantars but no nystagmus. Phenytoin dose increased. Signs worse over the next 4 m; poorly responsive, unable to speak, unable to sit or walk, ankle clonus. Phenytoin stopped	AD	After 3 w, more alert, speech intelligible, able to walk	125 mg/d (4.6 mg/kg) at 7.25 y200 mg/d (7.3 mg/kg/d) at 8 y	68.5 mg/L at 8.3 y
Lusins 1972	*38*	21 M, RTA and coma for 30 h. After 3 w, generalized seizures. After 1 y, ℞ phenytoin. After 3 m, gait ataxia and dysarthria. After 13 m of phenytoin, O/E nystagmus, dysarthria, truncal ataxia, limb ataxia. Diminished vibration sense, absent ankle jerks. Phenytoin dose decreased, then stopped after 3 y	ADN	21 m later, he still had nystagmus, dysarthria, gross truncal and limb ataxia	300 mg/d	Most values 30–45 mg/L; peak c. 60 mg/L
Masur 1989	*39*	21 M, complex partial seizures since age 15 y. For 5 y, treated with carbamazepine and phenytoin. O/E normal, no cerebellar signs. Took 7000 mg phenytoin overdose. Then coma, and later nystagmus, intention tremor, ataxia, dysarthria	ADN	After 2 w, nystagmus gone, intention tremor better. After 18 m, moderate dysarthria and dysmetria	300 mg/d + single dose of 7000 mg	Over 50 mg/L for 14 days after overdose; 18 mg/L at 20 d; 0 mg/L at 6 w
Matsuyama 1972	*40*	49 M, 'mental retardation' and generalized seizures from age 5 y. Increasing ataxia, weakness, bronchopneumonia, death	A	'These cerebellar [symptoms] were brought to incomplete remission by reduction of the phenytoin dose'	200–300 mg/d (Aleviatin®)	
Mavroudis 2012	*41*	7 M, generalized seizures from age 2 y. For last 3.5 y, phenytoin only. Developed ataxia, incoordination and nystagmus and treatment was then discontinued. Died in an accident	AN		8 mg/kg/d	
McLain 1980	*42*	50 M, seizures from age 6 y; astrocytoma removed age 7 y. Seizures again at 10 y; ℞ phenytoin at 12 y sometimes with phenobarbital or mephobarbital. Phenytoin stopped from 22–30 y, then restarted. At 48 y, showed progressive gait ataxia + irascibility. Aged 49 y, dyscalculia, dysarthria, gait ataxia, intention tremor, nystagmus	ADN	Following dose reduction, some improvement in gait, dysarthria and nystagmus but the patient remained ataxic	300 mg/d (up to 400 mg/d)	31 mg/L; fell to 15 mg/L when dose reduced to 250 mg/L.

(*Continued*)

Table 1 (Continued).

Author	Ref	Clinical	Cerebellar signs	Outcome	Exposure to phenytoin	Concentration
McLain 1980	*42*	29 F, generalized seizures aged 20 y. ℞ phenytoin from age 24 y. Soon developed gait ataxia. Over 6 m became chair-bound. Phenytoin withheld for 6 m; no change. Then phenytoin restarted. O/E at 27 y, wasting, contractures, truncal ataxia, dysarthria, nystagmus, diffuse weakness, hypotonia absent lower limb reflexes, intention tremor, diffuse weakness, dysmetria	ADN	2 y later, nystagmus had resolved, but neurology otherwise unchanged	300 mg/d	63 mg/L
McLain 1980	*42*	27 M, generalized seizures from age 5 y. ℞ mephenytoin and phensuzimide from age 12 y. ℞ phenytoin from age 14 y. Fluctuating ataxia, with or without nystagmus, as dose varied. At 24 y, dose was increased. In the next 3 y he had truncal ataxia, with marked incoordination of the limbs	AN	Some improvements in ataxia but still unable to walk without assistance	Phenytoin 400 mg/d, then 300 mg/d then 200 mg/d then 100 mg/d then 200 mg/d; after 7 m 100 mg/d again. Subsequently 300 mg/L, then varying between 100–200 mg/d and eventually 50 mg/d	45 mg/L on 200 mg/d; 37 mg/L on 100 mg/d; 12 mg/L on 50 mg/d.
McLain 1980	*42*	34 F, seizures from age 8 y. ℞ phenytoin and phenobarbital. O/E at 34 y: dysarthria, lethargy, mild truncal ataxia, ataxic gait, incoordination, nystagmus	ADN		Initially 120 mg/d; then 160–200 mg/d	19 mg/L.
McLain 1980	*42*	58 F, seizures from age 20 y; generalized from age 30, when ℞ phenytoin; phenobarbital added after 14 m. At 53 y, mild nystagmus and at 54 y, mild gait ataxia, worse by 58 y. O/E then slight gait ataxia, upper limb intention tremor and loss of reflexes, nystagmus	AN		300 mg/d, then 250 mg/d	23 mg/L at 300 mg/d, then 15 mg/L at 250 mg/d
Mukherjee 1996	*43*	19 M, generalized seizure treated with phenytoin for 5 y, presented with gait and limb ataxia, dysarthria, nystagmus, incoordination, encephalopathy	ADN	After withdrawal, signs partly improved, but ataxia and dysarthria were still present after 10 m	300 mg/d, then 400 mg/d for 15 d	29.5 mg/L [previously 16.2 mg/L]
Nauth-Misir 1948	*44*	18 F, epilepsy since aged 14 y. overdose of 250 × 100 mg tablets phenytoin. C/O headache and nausea. O/E truncal ataxia, nystagmus, dysarthria, intention tremor, limb ataxia. Reflexes absent, extensor plantars	ADN	After 2 d, ataxia gone, speech better, but nystagmus still. Gone after 3 d	300 mg/d, then an overdose	
Pla 1980	*45*	24 M, alcohol excess and seizures from the age of 18 y, presented unwell with ataxia, ataxic dysarthria, nystagmus, somewhat increased tone in the lower limbs, dysdiadochokinesia	ADN	After 2 y, the ataxia was unchanged, the dysarthria had somewhat improved, and the nystagmus had gone	300 mg/d	65 mg/L
Procházková 1984	*46*	22 F, seizures from 13 y. Phenytoin, phenobarbitone, Lepsiral® (primidone). Ataxia, hirsutism, gingivitis, somnolence	A	Remained unable to walk because of ataxia	Sodanton® 2/d	
Procházková 1984	*46*	25 F, seizures from 10 y. Admitted with possible hepatitis. On neurological examination 'marked neo- and paleo-cerebellar symptomatology and mental restlessness'		After phenytoin was stopped, the condition improved, but remained unable to walk	Sodanton® 3/d	227.9 µmol/L (normal therapeutic range 40–80 µmol/L)
Procházková 1984	*46*	18 F, febrile convulsions then generalized seizures. Admitted with vomiting, dizziness, and fever	A	After phenytoin withdrawn 'gingivitis and dermatitis resolved, but severe ataxia persisted'		197.6 µmol/L

(*Continued*)

Table 1 (Continued).

Author	Ref	Clinical	Cerebellar signs	Outcome	Exposure to phenytoin	Concentration
Pulliainen 1998	*47*	17 F, first seizure aged 4 y; ℞ phenytoin after sixth seizure. Stable on 350 mg/d for 7 m, then balance difficulties. Dose reduced. O/E no obvious ataxia, no nystagmus, negative Romberg, slight change in speech. After 3 m without phenytoin, ataxia, dysdiadochokinesis, Romberg positive, but no nystagmus	A	After 10 m, some improvement; after 20 m, unable to concentrate; after 2 y, mild ataxic symptoms persisted	Phenytoin 200 mg/d for 1 m, then 300 mg/d for 1 m, then 400 mg/d for 1 m, then 200 mg/d for 3 w, then 300 mg/d for 1 m, then 350 mg/d for 1 m	Dose mg/d / Conc mg/L 200 / 4 300 / 7.6 400 / 34.1 200 / 4 300 / 4.1 350 / 15.7 Later / 40
Pumar 1995	*48*	41 M, post-traumatic epilepsy, phenytoin for 15 y, presented with gait ataxia and cerebellar signs	A			
Rapport 1977	*49*	47 F, tuberculous meningitis; ℞ phenytoin as prophylaxis. Died 6 w after admission		Died during acute episode	300 mg/d for just 6 w	
Riley 1972	*50*	22 F, seizures since age 10 y. Admitted to a mental hospital. Discharged on phenytoin and primidone. Deterioration over 9 m, and admitted drowsy, unable to sit, dysarthric, limb ataxia, nystagmus, diplopia, absent knee and ankle jerks, gum hypertrophy	ADN	Phenytoin stopped, and some improvement. Difficulties in standing and walking persisted. At 1 y, still gross limb ataxia, dysarthria, hypotonia; but no nystagmus; confined to a wheelchair	500 mg/d	
Selhorst 1972	*51*	16 F, seizure, ℞ phenytoin + mephobarbital; dose reduced because seizures 'hysterical.' Then for 28 m variable phenytoin dosage. O/E gingival hyperplasia; dysarthria, nystagmus, truncal ataxia, extensor plantars, 'asynergy of limbs'	ADN	Phenytoin stopped. After 2 y and 6 y, severe truncal and limb ataxia, nystagmus on lateral gaze, absent ankle jerks, mild dysarthria	400 mg/dThen 300 mg/dThen 300 – 1000 mg/d depending on seizure frequency for 28 m	
Selhorst 1972	*51*	22 M, presented with limb and gait ataxia, dysdiadochokinesis. Aged 11 y, seizure then phenobarbital; age 14 y, further seizure then ℞ phenytoin; over following 7 y, primidone added. Aged 21 y, phenytoin dosage increased, ataxia, dysarthria	AD	Phenytoin withdrawn without improvement	300 mg/d for 10 yThen 400 mg/dThen 600 mg/d	
Shimizu 1990	*52*	30 M, seizures from age 11 y. Probably had phenytoin, trimethadione, primidone, valproate and clonazepam for 20 y. When 27 y, had transient drowsiness, ataxia, dysarthria. O/E at 30, severe truncal ataxia intention tremor, nystagmus, dysarthria, dysdiadochokinesis. Unable to walk or sit. Gum hypertrophy, coarse facies, hirsutes	ADN	Symptoms improved when phenytoin dose was tapered		21 mg/L
Tan 2001	*53*	54 F, non-epileptic 'fits;'℞ phenytoin for 30 y. For 1 y, gradually increasing unsteadiness and dysarthria. O/E dysarthria, dysmetria, dysdiadochokinesis, gait ataxia	AD		300 mg/d for > 30 y	
Teta 1990	*54*	20 M, admitted with diplopia, vertigo, and ataxia. O/E fluctuating clinical state; oculomotor palsies, nystagmus, dysarthria, truncal ataxia, dysmetria, difficulties of co-ordination	ADN	Oculomotor signs regressed after 60 h, but nystagmus, dysarthria and ataxia persisted. O/E normal neurologically after 1 m		On admission 31.2 mg/L; day 2, 73.6 mg/L; day 4, 71.7 mg/L; day 7, 30.5 mg/L ; day 9, 4.3 mg/L.

(*Continued*)

Table 1 (Continued).

Author	Ref	Clinical	Cerebellar signs	Outcome	Exposure to phenytoin	Concentration
Utterback 1958	*55*	[Abstract] '…Histories are presented of two patients who developed cerebellar ataxia on large doses of Dilantin and made incomplete recovery after Dilantin was discontinued. Histologic changes strikingly similar to those seen in cats were demonstrated in the cerebellum of an epileptic patient who had received large doses of Dilantin and died in status epilepticus'	A			
Utterback 1958	*55*	As above	A			
Villa 1994	*56*	48 M, with a history of convulsions, admitted with a severe pancerebellar syndrome. Had been treated with phenobarbital, carbamazepine. Phenytoin for the last 2 y. On admission, truncal and limb ataxia, nystagmus	AN	Phenytoin stopped, and cerebellar symtpoms greatly improved within 48 h, but ataxia and nystagmus persisted. Then surgery for a benign tumour, with regression of convulsions. However, afterwards he had truncal and limb ataxia which persisted at 1 y	Irregular and variable dose around 100 mg/d. Increased abruptly shortly before admission to 400 mg/d	44 mg/L
Zuin 2003	*57*	35 F, cerebral palsy, established on phenytoin for generalized seizures. Admitted for pulmonary tuberculosis. Five days after the introduction of anti-tuberculous therapy she developed ataxia, dysarthria, and nystagmus, and mild obtundation	ADN	After 20 d, substantial improvement: able to walk unassisted; dysarthria gone; some persistent nystagmus	300 mg/d	40 mg/L
Ogawa 1976	*58*	No evidence of phenytoin use		M		

Table 2. Radiological and pathohistological findings; comments

Author	Ref	Radiological	Patho-histological	Comments
Abe 1991	*1*		Cerebellar degeneration with 'discontinuous and focal changes, with disparity between Purkinje cell and granular layer'	Abstract only. Original in Japanese
Afifi 1968	*2*	Pneumoencephalogram 6 m after acute ataxia: normal; 2.5 y later: gross cerebellar atrophy	Almost complete loss of Purkinje cells, some rarefaction of granular cells, no gliosis	
Alioğlu 2000 [c]	*3*	MRI: normal on admission; at 8 m: 4th ventricle, cisterna magna enlarged; at 15 m: cerebellar atrophy more severe; at 28 m: atrophy more pronounced still		'After phenytoin was discontinued, clinical findings of cerebellar dysfunction regressed, but MR cerebellar atrophy progressed'
Arora 2018 [d]	*4*	MRI: diffuse cerebellar hemispheric and vermal atrophy		
Arora 2018	*4*	MRI: diffuse cerebellar hemispheric and vermal atrophy with prominent cerebellar folia and 4th ventricle		
Arora 2018	*4*	MRI: Prominent cerebellar folia with cerebellar hemispheric atrophy		
Arora 2018	*4*	CT: cerebellar atrophy		
Awada 1999	*5*	CT: tuberculoma; 6 w: slight cerebellar atrophy on CT and MRI.		
Baier 1984	*6*	CT at 14 y: normal; at 18 y: cerebellar vermal and hemispheric sulci clearly seen		Incomplete data on phenytoin exposure
Baier 1984	*6*	CT: infratentorially, pronounced dilatation of the cerebello-medullary cistern and 4th ventricle		Improved after phenytoin was stopped
Baier 1984	*6*	CT at 33 y: 'early cerebellar atrophy'		
Baier 1984	*6*	CT at 31 y: infratentorially, 4th ventricle and basal cisterns clearly dilated		
Baier 1984, 1985	*6*	CT: cerebellar atrophy, markedly affecting the vermal region		Incomplete data on phenytoin exposure
Baier 1984, 1985	*7*	CT aged 8 y: no cerebellar atrophy; aged 12 y: pronounced; dilation of cisterna magna and 4th ventricle, cerebellar; hemispheric sulci clearly visible		Incomplete data on phenytoin exposure
Baier 1984, 1985	*7*	CT at 41 y: 'basal cisterns and subarachnoid space dilated; clearly visible cerebellar sulci'		at least five recurrent episodes of 'acute' toxicity. improving after DPH dose reduction, but no full recoveries
Basker	*8*	MRI: 'shrinkage of cerebellum'		
Botez 1985	*9*	CT on admission: marked cerebellar atrophy but no cerebral atrophy; 3 y later: unchanged		Authors suggest that thiamine + folate contributed to improvement
Botez 1985	*9*	CT: encephalomalacia (related to old stroke) and ponto-cerebellar atrophy		Authors suggest that thiamine + folate contributed to improvement
Brostoff 2008	*10*	CT: 'no evidence of a cerebellar bleed or other pathology'		
Brostoff 2008	*10*	CT: showed extensive old right MCA territory ischaemic damage but no posterior fossa pathology		
Brostoff 2008	*10*	CT: involutional change and small vessel disease		
Cochat 1987	*11*	CT after overdose: normal; at 6 m: hypodense round area crossing the left border of the 4th ventricle, suggestive of cerebellar necrosis; 4.5 y later: some residual 4th ventricle changes		
Craig 2004	*12*			
Dasari 2016	*13*	No comment on MRI findings for cerebellum		?Part of case series
Dreyer 1966	*14*	Pneumoencephalogram: normal at presentation		
Dreyer 1966	*14*			
Dreyer 1966	*14*			
Dreyer 1966	*14*			
Dreyer 1966	*14*		Cerebellar atrophy. Shrunken Purkinje cells, with reduced numbers; increase in Bergmann glial cells. Cyst of the cisterna magna.	
Feuerstein 1983	*15*	CT: atrophy of the cerebellar vermis & frontal atrophy		

(*Continued*)

Table 2. (Continued).

Author	Ref	Radiological	Patho-histological	Comments
Ghatak 1976	*16*		Disproportionately small cerebellum; virtually total loss of Purkinje cells throughout the cerebellum; mild degree of diffuse rarefaction of the granular layer.	
Gill 1978	*17*			
Guerrero 1997	*18*	CT at 12 m: no atrophy; CT at 24 m: cerebellar atrophy, both hemisphere and vermis		
Guirao-Bringas 2012	*19*	CT 5 y after presentation: 'Atrofia cerebelosa'		
Gupta 2013	*20*	Repeat MRI: at 6 m follow-up revealed resolved bleeding left lentiform nucleus with bilateral cerebellar atrophy.		
Haberland 1962	*21*		Generalized cerebral atrophy. Moderate atrophy of folia of cerebellar hemispheres. Almost complete disappearance of Purkinje cells in hemispheres and vermis, with corresponding increase in number and size of Bergmann astrocytes	
Haberland 1962	*21*		Severe generalized cerebellar cortical atrophy. Almost complete loss of Purkinje cells, with marked proliferation of Bergmann astrocytes	
Haberland 1962	*21*		Cerebral sclerosis. Definite atrophy of ventral part of cerebellum. Loss of Purkinje cells in atrophic areas, with marked proliferation of Bergmann astrocytes	
Herberg 1975	*22*			
Herberg 1975	*22*			
Herberg 1975	*22*			Author questioned 'a genetic low ceiling for phenytoin parahydroxylation'
Herberg 1975	*22*			
Hiroshini 2000	*23*	MRI: prominent cerebellar folia		In Japanese - no direct translation
Hirzel 1978	*24*	Pneumoencephalogram: dilated 4th ventricle		'The authors report two cases with roentgeno-mophologically [sic] established cerebellar atrophy caused by chronic diphenylhydantoin overdosing'
Hirzel 1978	*24*	Pneumoencephalogram: widening of cerebellar folia [*sic*]		
Hofmann 1958	*25*	Carotid angiograms: normal	Virtual disappearance of Purkinje cells	Similar to changes noted in animals (quoting Utterback)
Höglmeier 1969	*26*	Two pneumoencephalograms: normal		
Horne 1973	*27*	Pneumoencephalogram after 1 y phenytoin treatment 150 mg/d: normal; after 10 y: almost complete cerebellar atrophy		
Horne 1973	*27*	Pneumoencephalogram: cerebellar atrophy		
Imamura 1992	*28*	CT at 3 and 5 m post-onset of cerebellar dysfunction: cerebellar atrophy		
Isago 1982	*29*			Abstract only
Janzik 1975	*30*	Pneumoencephalogram: normal		Extremely long phenytoin half-life
Kim 1991	*31*	CT: atrophy, with enlargement of 4th ventricle, cisterna magna, and other spaces		In Korean
Kim 1991	*31*	CT: cerebellar atrophy and expansion of 4th ventricle		In Korean
Kim 1991	*31*	CT: enlargement of 4th ventricle and cisterna magna and atrophy of the vermis		

(*Continued*)

Table 2. (Continued).

Author	Ref	Radiological	Patho-histological	Comments
Kokenge 1965	32			Studies in rats and cats showed loss of Purkinje cells induced by phenytoin if the concentration remained high for 14 d. Author hypothesized that a combination of drugs may be more damaging than one alone
Krüger 1978	33			
Krüger 1978	33	Pneumoencephalogram: minor abnormalities		
Kumar 2013	34	MRI: cerebellar atrophy		
Kuruvilla	35		The autopsy showed marked cerebellar atrophy, in addition to moderate internal hydrocephalus. The nature and distribution of the cerebellar lesions were virtually identical to those of chronic phenytoin intoxication	'There may be a side effect on the cerebellum under certain circumstances even with a non-toxic level of [phenytoin]'
Kuruvilla 1997	35	MRI on admission: mild generalized atrophy; at 6 m: severe cerebellar atrophy		'This case provides evidence that prolonged acute PHT intoxication may rarely result in irreversible cerebellar atrophy'
Lindvall 1984	36	CT on admission: slight widening of one lateral ventricular horn; at 6 y: CT scan shows marked cortical cerebellar atrophy and enlargement of the 4th ventricle and basal cisterns		'Was it the drug or was it other mechanisms? 'In our opinion the protracted cerebellar dysfunction and the cerebellar atrophy demonstrated by CT scans were closely related to short-term phenytoin intoxication in the present patient.'
Logan 1969	37	Pneumoencephalogram at 8 y: mild cerebral and cerebellar atrophy; at 8.5 y: more prominent		Progressive neurological disease; a rather doubtful case in a series of four cases designed to demonstrate something else
Lusins 1972	38	Pneumoencephalogram before ℞ phenytoin: normal; angiogram after phenytoin therapy; normal		'Our patient's blood levels were frequently at the 50 µg/ml level for prolongedperiods of time'
Masur 1989	39	CT 8 m prior to overdose: normal; 4 w after overdose: cerebellar atrophy; 1 y after overdose: slightly more pronounced cerebellar atrophy		
Matsuyama 1972	40		Cerebellar folia mildly atrophic. On histology, almost complete disappearance of Purkinje cells from bilateral ventral surfaces in the cerebellar hemisphere; preserved on the dorsal surface. Where Purkinje cells had disappeared, Bergmann's glia were markedly increased in number and size	
Mavroudis 2012	41		Cerebellum macroscopically normal. Compared with 2 controls, 'The density of the Purkinje cells was remarkably decreased in the phenytoin-treated patient'	
McLain 1980	42	CT: cerebellar atrophy		
McLain 1980	42	CT: cerebellar atrophy		
McLain 1980	42	CT: cerebellar atrophy		
McLain 1980	42	Pneumoencephalogram initially: normal; CT at 34 y: cerebellar atrophy		
McLain 1980	42	CT: mild cerebellar atrophy		
Mukherjee 1996	43	CT: symmetrical cerebellar atrophy		
Nauth-Misir 1948	44			
Pla 1980	45			Some time later, given 1000 mg phenytoin IV. Slow elimination. Authors suggest an enzyme defect
Procházková 1984	46			

(*Continued*)

Table 2. (Continued).

Author	Ref	Radiological	Patho-histological	Comments
Procházková 1984	*46*			
Procházková 1984	*46*			
Pulliainen 1998	*47*	CT before phenytoin:- no sign of cerebellar atrophy; CT & MRI: severe cerebellar cortical atrophy.		
Pumar 1995	*48*	CT & MRI: severe cerebellar atrophy with dilation of the 4th ventricle		
Rapport 1977	*49*	Pneumoencephalogram: only mild, symmetrical ventricular dilatation	Two small tubercles, leptomeningeal thickening. In the cerebellum there was a mild chronic inflammatory exudate in the lepto-meninges and in the perivascular spaces of the cerebellar white matter. There was marked diffuse loss of Purkinje cells with Bergmann's gliosis and oedema in a similar distribution	'Isoniazid is known to increase serum levels of phenytoin as much as four times, and 10% of the patients on both drugs have evidence of DPH intoxication.' BNF: Isoniazid increases the concentration of phenytoin. Manufacturer advises monitor concentration.Severity of interaction:ModerateEvidence for interaction:Study
Riley 1972	*50*			
Selhorst 1972	*51*	Pneumoencephalogram: enlarged 4th ventricle		EMG consistent with peripheral neuropathy
Selhorst 1972	*51*	Pneumoencephalogram: enlarged 4th ventricle		
Shimizu 1990	*52*	CT & MRI: mild cerebral and cerebellar atrophy		'It was concluded that the cerebellar dysfunction observed in this case might be dependent on both the high serum level of PHT with characteristic pharmacokinetic properties and the organic damage to the brain, especially the cerebellum'
Tan 2001	*53*	MRI: severe, pan-cerebellar atrophy		'This case illustrates severe cerebellar neurotoxicity due to phenytoin in the absence of epilepsy'
Teta 1990	*54*	MRI: normal		
Utterback 1958	*55*			Study in cats: cerebellar changes only. Widespread destruction of Purkinje cells, cystic gliosis
Utterback 1958	*55*			
Villa 1994	*56*	On admission: cystic lesion in Left temporal lobe. Cerebellum normal. Also normal at 1 y		
Zuin 2003	*57*	CT 4 y before: normal; MRI 20 d after onset: intense cerebellar atrophy		
Ogawa 1976	*58*			

Nomenclature

The nomenclature of epilepsies has change over time. Terms such as 'grand mal' and 'petit mal' are no longer used. We have retained the terms focal, partial, and generalized seizures. The nomenclature of the International League Against Epilepsy would differentiate seizures of focal onset with impaired awareness from those maintained awareness, and motor from non-motor seizures of generalized onset, but the papers we have reviewed almost all predated this change.[59].

Abbreviations

↑ = increased, ↓ = decreased, A = ataxia, BNF = British National Formulary, Conc = concentration, CT = computed tomography, CVA = cerebrovascular accident, d = day(s), D = dysarthria, DM = diabetes mellitus, DPH = diphenylhydantoin (phenytoin), F = female, M = male, m = month(s), MRI = magnetic resonance imaging, N = nystagmus, NK = not known, O/E = on examination, PHT = phenytoin, Ref = reference, ℞ = prescribed, w = week (s), y = year(s), Δ = diagnosis.

References

1. Abe H, Yagishita S. [Chronic phenytoin intoxication occurred below the toxic concentration in serum and its pathological findings]. No To Shinkei. 1991;43(1):89-94.
2. Afifi AK, Van Allen MW. Cerebellar atrophy in epilepsy. Pneumographic and histological documentation of a case with psychosis. J Neurol Neurosurg Psychiatry. 1968 Apr;31(2):169-74.
3. Alioğlu Z, Sari A, Velioğlu SK, Ouml;zmenoğlu M. Cerebellar atrophy following acute phenytoin intoxication. J Neuroradiol. 2000 Mar;27(1):52-5.
4. Arora M, Boruah DK, Thatter V, Bharwara S. Imaging in phenytoin induced neurotoxicity: a case series. Int J Res Med Sci. 2018 Jan;6(1):355-358
5. Awada A, Amene P, al Jumah M, al Beladi K. Ataxie cérébelleuse résiduelle après intoxication aiguë par la diphénylhydantoïne. Rev Neurol (Paris). 1999 Apr;155(4):306-8.
6. Baier WK, Beck U, Doose H, Klinge H, Hirsch W. Cerebellar atrophy following diphenylhydantoin intoxication. Neuropediatrics. 1984 May;15(2):76-81.
7. Baier WK, Beck U, Hirsch W. CT findings following diphenylhydantoin intoxication. Pediatr Radiol. 1985;15(4):220-1.

8. Basker V, Moudgil K. Idiopathic Late-Onset Cerebellar Ataxia with Phenytoin: A Case Report. J Young Pharm. 2020;12(1):102-103.
9. Botez MI, Gravel J, Attig E, Vézina JL. Reversible chronic cerebellar ataxia after phenytoin intoxication: possible role of cerebellum in cognitive thought. Neurology. 1985 Aug;35(8):1152-7
10. Brostoff JM, Birns J, McCrea D. Phenytoin toxicity: an easily missed cause of cerebellar syndrome. J Clin Pharm Ther. 2008 Apr;33(2):211-4.
11. Cochat P, Hartemann E, Duc H, Berthier JC, Rousson A. Nécrose cérébelleuse localisée après surdosage en diphényl-hydantoïne. Arch Fr Pediatr. 1987 Nov;44(9):824-5.
12. Craig S. Phenytoin overdose complicated by prolonged intoxication and residual neurological deficits. Emerg Med Australas. 2004;16(4):361-5.
13. Dasari JR, Vurumadla S, Prasad OP. A case Report on henytoin induced ataxia. Asian J Pharm Clin Res. 2016;9(4):5-6.
14. Dreyer R. Diphenylhydantoinintoxikation. Fortschritte Der Neurologie, Psychiatrie und ihrer Grenzgebiete. 1966;34:224-235.
15. Feuerstein T, von Reutern GM, Cramer H. Phenytoinintoxikation bei Abbaustörung, Kasuistik eines Falls mit Kleinhirnatrophie. Nervenarzt. 1983 Feb;54(2):106-9.
16. Ghatak NR, Santoso RA, McKinney WM. Cerebellar degeneration following long-term phenytoin therapy. Neurology. 1976 Sep;26(9):818-20.
17. Gill MA, Kern JW, Kaneko J, McKeon J, Davis C. Phenytoin overdose. Kinetics. West J Med. 1978 Mar;128(3):246-8.
18. Guerrero AL, Paniagua JA, Díaz Cascajo P, Cacho J, Arias P, Martín JA. Atrofia cerebelosa en relación temporal con la introducción de fenitoína [Temporal cerebellar atrophy following phenytoin therapy]. Neurologia. 1997 Jun-Jul;12(6):259-61.
19. Guirao-Bringas P, Díaz-Pérez G. Atrofia cerebelosa y uso crónico de fenitoína. Revisión de la literatura y presentación de un caso clínico. Rev chil neuro-psiquiatr. 2012;50(1):42-50.
20. Gupta M, Patidar Y, Khwaja GA, Chowdhury D, Batra A, Dasgupta A. Persistent cerebellar ataxia with cerebellar cognitive affective syndrome due to acute phenytoin intoxication: A case report. Neurology Asia. 2013;18 (1):107-111.
21. Haberland C. Cerebellar degeneration with clinical manifestation in chronic epileptic patients. Psychiatr Neurol (Basel). 1962;143:29-33.
22. Herberg KP. Delayed and insidious onset of diphenylhydantoin toxicity. South Med J. 1975 Jan;68(1):70-5.
23. Hiroshini M. Cerebellar atrophy associated with phenytoin intoxication. No to shinkei 2000;52:264-268.
24. Hirzel S. Toxicshce "atrophie cerebelleuse." Psychiatrie Neurol Med Psychol. 1978; 30(3):185-190.
25. Hofmann WW. Cerebellar lesions after parenteral dilantin administration. Neurology. 1958 Mar;8(3):210-4.
26. Höglmeier H, Wenzel U. Zerebellarer Dauerschaden durch vorübergehende Hydantoinüberdosierung. Dtsch Med Wochenschr. 1969 Jun 20;94(25):1330-2.
27. Horne PD. Long term anticonvulsant therapy and cerebellar atrophy. J Ir Med Assoc. 1973 Mar 24;66(6):147-52.
28. Imamura T, Ejima A, Sahara M, Saito H, Tsuburaya K. [Cerebellar atrophy and persistent cerebellar ataxia after acute intoxication of phenytoin]. No To Shinkei. 1992 Feb;44(2):149-53.
29. Isago H,Asano K,Himi T,Kataura A. Upbeating Nystagmus Resulting from Anticonvulsant Intoxication: Report of a Case. Auris Nasus Larynx 1982;9(1):15-24.
30. Janzik HH, Mayer B, Petruch F. DPH-Intoxikation–Klinische und neuropsychologische Befunde bei einer extrem langsamen Diphenylhydantoin-Elimination. Med Welt. 1975 Jan 10;26(2):79-81.
31. Kim JH, Kwon SH, Lee MS, Choi IS. [Cerebellar atrophy following long-term anticonvulsant therapy—three cases.] J Korean Med Assoc. 1991;34(11):1251-1256.
32. Kokenge R, Kutt H, Mcdowell F. Neurological sequelae following Dilantin overdose in a patient and in experimental animals. Neurology. 1965;15:823-9.
33. Krüger H. Schwere Kleinhirnschäden durch Diphenylhydantoin–ein Beitrag zur Problematik der Hydantoinintoxikation. Z Arztl Fortbild (Jena). 1978 Oct 1;72(19):944-7.
34. Kumar N, Chakraborty A, Suresh SH, Basappaji S, Betdur AL. Phenytoin-induced cerebellar atrophy in an epileptic boy. Indian J Pharmacol. 2013 Nov-Dec;45(6):636-7.
35.Kuruvilla T, Bharucha NE. Cerebellar atrophy after acute phenytoin intoxication. Epilepsia. 1997 Apr;38(4):500-2.
36. Lindvall O, Nilsson B. Cerebellar atrophy following phenytoin intoxication. Ann Neurol. 1984 Aug;16(2):258-60.
37. Logan WJ, Freeman JM. Pseudodegenerative disease due to diphenylhydantoin intoxication. Arch Neurol. 1969 Dec;21(6):631-7.
38. Lusins JO, Jutkowitz R. Residual cerebellar systems dysfunction and peripheral neuropathy after diphenylhydantoin therapy. Mt Sinai J Med. 1972 Nov-Dec;39(6):617-21.
39. Masur H, Elger CE, Ludolph AC, Galanski M. Cerebellar atrophy following acute intoxication with phenytoin. Neurology. 1989 Mar;39(3):432-3.
40. Matsuyama Y, Nakagawa M. [Autopsy case of chronic diphenylhydantoin poisoning]. No To Shinkei. 1972 Feb;24(2):203-11.
41. Mavroudis IA, Manani MG, Petrides F, Kiourexidou M, Njau SN, Costa VG, Baloyannis SJ. Dendritic, axonal, and spinal pathology of the Purkinje cells and the neurons of the dentate nucleus after long-term phenytoin administration: a case report. J Child Neurol. 2013;28(10):1299-304.
42. McLain LW Jr, Martin JT, Allen JH. Cerebellar degeneration due to chronic phenytoin therapy. Ann Neurol. 1980 Jan;7(1):18-23.
43. Mukherjee SC. Permanent cerebellar syndrome following acute phenytoin intoxication. Neurol India. 1996 Oct-Dec;44(4):234-235.
44. NAUTH-MISIR TN. A case of gross overdosage of soluble phenytoin. Br Med J. 1948;2(4578):646.
45. Pla AR. Degeneración cerebelosa permanente secundaria a la difenilhidantoína. Medicina Clinica. 1980;75(9):387-90.
46. Procházková V, Urban P. Hydantoinátová atrofie (degenerace) mozecku [Hydantoin atrophy (degeneration) of the cerebellum]. Cesk Neurol Neurochir. 1984 Aug;47(4):261-4.
47. Pulliainen V., Jokelainen M., Hedman C., Pammo O. A case of cerebellar atrophy after phenytoin intoxication: Neurologic, neuroradiologic, and neuropsychological findings. Journal of Epilepsy. 1998;11(5):241-247.
48. Pumar J, Villalon JM, Martinez de Alegri J. Atrofia cerebelosa tras tratamiento prolongado con fenitoína. Rev Esp Neurol. 1995;10(4):201-2.
49. Rapport RL 2nd, Shaw CM. Phenytoin-related cerebellar degeneration without seizures. Ann Neurol. 1977;2(5):437-9.
50. Riley CG. Chronic hydantoin intoxication: case report. N Z Med J. 1972 Dec;76(487):425-8.
51. Selhorst JB, Kaufman B, Horwitz SJ. Diphenylhydantoin-induced cerebellar degeneration. Arch Neurol. 1972 Nov;27(5):453-5.
52. Shimizu K, Izumi T, Nakano K, Mitsuishi Y, Fukuyama Y. Acute Exacerbation of Cerebellar Symptoms Observed in a Case of Chronic Phenytoin Intoxication. Brain & Development 1990;12(2):271.
53. Tan EK, Chan LL, Auchus AP. Phenytoin cerebellopathy without epilepsy. Acta Neurol Scand. 2001 Jul;104(1):61-2.
54. Teta D, Uldry PA, Regli F. Ophtalmoplégie, syndrome cérébelleux et troubles de la vigilance réversibles après intoxication à la phénytoïne. Schweiz Med Wochenschr. 1990 Oct 13;120(41):1504-7.
55. Utterback RA. Parenchymatous cerebellar degeneration complicating diphenylhydantoin (Dilantin) therapy. Arch Neurol Psych. 1958;80:180-181.
56. Villa AM, Sica RE. Ataxia cerebelosa persistente después de la administración tóxica de difenilhidantoina. Arq Neuropsiquiatr. 1994;52(4):572-4.
57. Zuin DR, Neme R, Porta L, Vera J, Lopez OL. Atrofia cerebelosa aguda por intoxicación con difenilhidantoína producto de interacción medicamentosa. Rev Neurol. 2003 Jan 16-31;36(2):195-6.
58. Ogawa M, Maeda F, Okubo H. [Acute cerebellar ataxia in adults: A clinical case.] J Kansai Med Univ. 1976;28(3):507-512.
59. International League Against Epilepsy. 2017 Revised Classification of Seizures. https://www.epilepsy.com/article/2016/12/2017-revised-classification-seizures Accessed 2022-02-19.

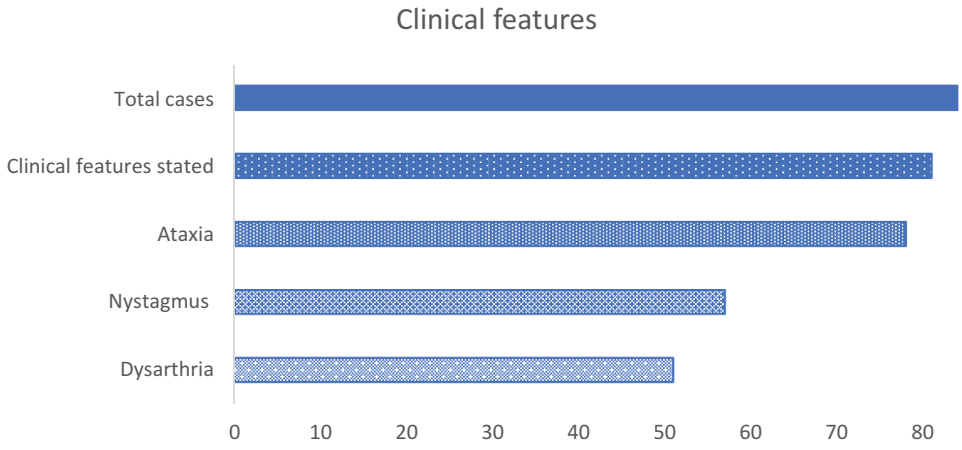

Figure 1. The clinical features, which was recorded in 81 of the 84 cases.

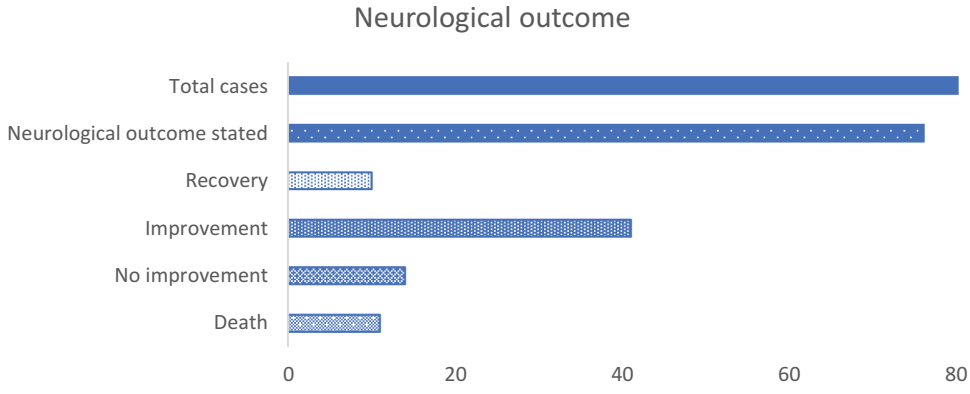

Figure 2. The neurological outcome, which was recorded in 62 of the 84 cases.

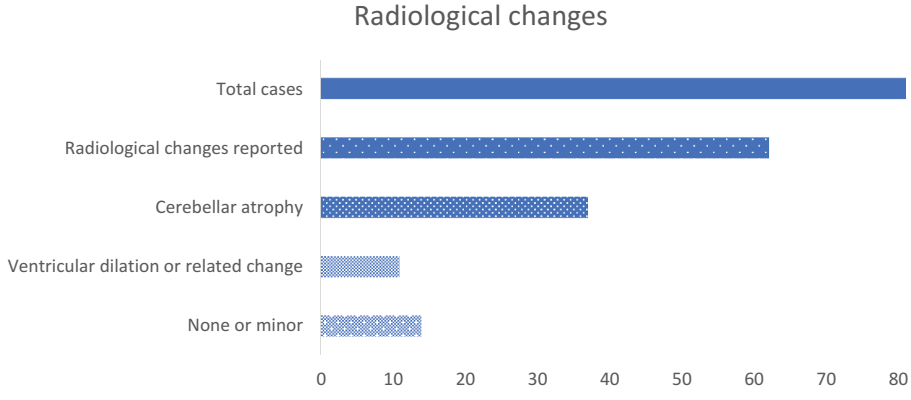

Figure 3. The radiological findings, which were recorded in 62 of the 84 cases.

Altogether, radiology by one or more modality was reported to show cerebellar atrophy in 37/62 patients (60%) and ventricular dilation or other changes without explicit mention of cerebellar atrophy in 11/62 (18%); examinations in 14 patients showed no or 'minor' abnormalities. Where scans were repeated after an interval of weeks or months, the later scan was almost always reported to be more abnormal than the earlier scan.

3.3.5. Correlation of clinical and radiological findings

Two patients with normal scans died, five recovered, and five were left with neurological deficits. Of the 10 patients who made a clinical recovery, three had no scan reported, one had clearly seen cerebellar sulci on CT scan, and one a possible cerebellar infarct. Two patients had normal pneumoencephalograms, two had normal CT scans, and one a normal MRI scan.

3.3.6. Histopathological findings

Twelve cases underwent postmortem examination, including one boy who was killed in a road traffic collision [13]. Ten reports stated explicitly that there was disproportionate or almost total loss of Purkinje cells in the cerebellum, and six also commented on an increase in Bergmann glial cells or Bergmann gliosis. The remaining reports described 'Cerebellar degeneration' with 'discontinuous and focal changes, with disparity between Purkinje cells and granular layer,' [11] and cerebellar lesions 'virtually identical to those of chronic [phenytoin] intoxication' [14].

4. Previous studies of the effects of phenytoin on the cerebellum

4.1. Histopathology

4.1.1. Salcman et al 1978, Spielmeyer 1930

Salcman and colleagues described a series of five men with intractable epilepsy who underwent surgery to implant cerebral electrodes. The authors took the opportunity to biopsy the cerebellum [15]. All five patients had been treated with phenytoin, although only one had evidence of ataxia at the time of biopsy. Biopsies showed severe loss of Purkinje cells in four patients, and moderately severe loss in the remaining case.

Bergmann glial cells were increased. They compared these findings with those in ten control biopsies – five postmortem biopsies from children who had died in status and five from adults undergoing surgery for oligodendroglioma – in which changes were largely absent. However, there were no details of drug treatment in the control patients.

Salcman *et al* drew attention to the findings of Spielmeyer, who had described loss of Purkinje cells in patients with epilepsy in postmortem specimens obtained prior to the use of phenytoin [16]. Hypoxic or hypoglycemic damage was said to preferentially affect hippocampal cells, and then Purkinje cells; so that histological examination of the cerebellum alone might not distinguish between hypoxia (or hypoglycemia) and toxicity from phenytoin.

Several animal studies in different species, but not all, have demonstrated similar histopathological changes in the cerebellum after exposure to toxic doses of phenytoin.

4.1.2. Kokenge et al 1965

Kokenge *et al* studied 36 rats given phenytoin 100–200 mg/kg/day and 12 cats given up to 30 mg/kg/day [17]. There was loss of Purkinje cells and edema of Bergmann's glial layer in all animals examined at 18 days. The cats proved much more susceptible to phenytoin than the rats.

4.1.3. Kiefer et al 1989

The study by Kiefer *et al* compared 30 mice treated with phenytoin and 30 control mice, sacrificed in groups of six treated and six control animals at 3, 6, 10, 14, and 48 days after the start of (high-dose) phenytoin treatment [18]. These workers demonstrated progressive changes in morphology and reduction of number of Purkinje cells in the cerebellum from day 6, although clinical effects of ataxia, drowsiness, and weight loss were seen only from day 35.

4.2. Radiology

4.2.1. Pneumoencephalograms

4.2.1.1. Iivanainen *et al* 1977. Iivanainen *et al* subjected 338 patients with epilepsy and 'mental retardation' to pneumoencephalography [19]. One hundred and thirty-one patients had been treated with phenytoin, of whom 19 had definite cerebellar signs on clinical examination. Abnormal pneumoencephalograms were found in 93% of the patients, of whom 36 were recorded to have cerebellar atrophy. Atrophy was present in significantly more patients who had suffered a clinical episode of phenytoin intoxication (8/36) than in those who had not (1/51; $\chi^2 = 4.5$, $P < 0.05$).

4.2.2. CT scans

4.2.2.1. Koller *et al* 1980. In 1980, Koller and colleagues published a letter with preliminary data on eight patients 'on long-term phenytoin therapy' whose CT scans showed cerebellar atrophy, but who had no clinical signs of a cerebellar disorder [20].

4.2.2.2. Kessler *et al* 1985. Kessler *et al* studied 310 patients with epilepsy treated with a variety of antiseizure medication: 54 took phenytoin alone; 32 took phenytoin with carbamazepine; and 13 took phenytoin with primidone [21]. Cerebellar atrophy was present in 25% of patients treated with phenytoin alone, 70% of those treated with phenytoin and carbamazepine, and 9% of those treated with carbamazepine alone. (The findings were presented graphically, and so data are approximate.)

4.2.2.3. Bechinger *et al* 1986. Bechinger *et al* studied neurological findings, CT results, and treatment details in 242 stable patients with epilepsy [22]. Alcohol, a recognized cause of cerebellar atrophy, may have played a role in 31 cases. The CT reports were masked, without knowledge of the treatments. In those 211 patients in whom alcohol played no part, 89 were treated with phenytoin, 45 with other antiseizure medication, and 77 without medication. Cerebellar atrophy was present in 30/89 (33%), 5/45 (11%), and 8/77 (10%) respectively. In the subset of 18/31 patients with alcoholism who did not take medication, 6/18 (33%) had cerebellar atrophy. While cerebellar atrophy was present in only 10% of patients treated with phenytoin for less than one year, it was present in 52% of those treated for over 10 years.

4.2.2.4. Del Negro *et al* 2000. Del Negro *et al* examined 37 or 38 patients who had been treated with phenytoin and 29 who had been treated with other antiseizure medication (the abstract and the text give different numbers) [23]. Cerebellar atrophy was present in CT scans of 5/38 patients treated with phenytoin, including all four patients who had taken it for more than 10 years. Clinical cerebellar signs were present in 2/13 patients with moderate or severe CT changes, and 3/21 with no or mild CT changes. None of the control patients had either clinical or radiological evidence of cerebellar damage.

4.2.3. Magnetic resonance imaging (MRI)

4.2.3.1. Shanmugarajah *et al* 2018. Shanmugarajah *et al* studied 47 patients treated for at least one year with phenytoin for epilepsy [24]; the median duration of phenytoin treatment was 15 (range 1–67) years. On examination, 19/47 patients (40%) had gait ataxia, and 9/47 (19%) also had nystagmus. Only one had dysarthria.

Thirty of the patients underwent 3 Tesla MRI scanning [24]. The scans were reported to show cerebellar atrophy in 13 patients, six of whom had ataxia and seven of whom did not. Cerebellar volume was significantly smaller in the subgroup with ataxia, 7.77 ± 0.99 units compared to the subgroup who did not, 8.88 ± 0.82 units, P = 0.036.

4.2.3.2. Ney *et al* 1994. Thirty-six patients exposed for a median of nearly 14 years to phenytoin, and 35 normal control subjects were examined by MRI in a study by Ney *et al* [25]. There was no evidence of cerebellar atrophy in 15/36 patients or 33/35 controls; mild cerebellar atrophy was seen in 12/36 patients and 2/35 controls. In 7/36 patients, cerebellar atrophy was moderate, and in 2/36 it was severe. There was no obvious correlation between the presence or degree of atrophy and seizure frequency or phenytoin exposure. The authors stated that 'Our study was unable to clearly elucidate whether the cerebellar atrophy resulted from seizures or from exposure to phenytoin.'

4.2.3.3. Luef *et al* 1996a. Luef *et al* examined MRI scans in 11 patients with epilepsy, all of whom had been treated with phenytoin and had at least one episode during which the serum phenytoin concentration (21.4–95.6 mg/L) exceeded the reference range [26]. At the time of the increased serum phenytoin concentration, clinical signs of cerebellar disorder were absent in three patients; and eight had nystagmus, which was associated with ataxia in two patients. Only one patient had persistent signs at the time of MRI. Six of the 11 patients had MRI evidence of cerebellar atrophy, involving the vermis (one patient), the cerebellar hemispheres (one patient) or both (four patients). The radiological findings did not relate to the clinical findings or phenytoin concentration.

4.2.3.4. Luef *et al* 1996b. A linked study [27] compared cerebellar volume, measured on MRI scans, in 11 phenytoin-treated patients and 11 control subjects. Cerebellar volume was inversely related to phenytoin exposure (measured by dose and duration of treatment) but not to clinical signs.

4.2.3.5. De Marcos *et al* 2003. De Marcos and colleagues [28] also examined cerebellar volumes by MRI scanning in 56 patients who had been treated with phenytoin for at least 2 months, and 20 healthy adults. They used z-scores (based on the number of standard deviations from the control mean volume) to grade cerebellar atrophy. It was present in 20/56 patients, being mild in nine, moderate in nine, and severe in two. Cerebellar atrophy was present in 9/16 patients who had suffered a clinical episode of phenytoin intoxication, and correlated with duration of phenytoin treatment (calculated $r^2 = 0.21$, P = 0.01).

5. Expert opinion

Phenytoin has been the mainstay of antiseizure medication therapy since the 1930s, and is still widely prescribed, although it is gradually being replaced by other drugs. In England in January 2017, more than 67,000 prescriptions were written in general practice for phenytoin sodium, although by November 2021, the number had fallen to under 48,000 [29]. We predict that *de novo* usage will continue to decline, so that most patients remaining on phenytoin treatment will have been treated for many years.

Cerebellar signs are the cardinal clinical feature of phenytoin intoxication. It is standard clinical practice to examine phenytoin-treated patients for ataxia, dysmetria, and nystagmus, and to reduce phenytoin dosage if such signs are present, guided by serum phenytoin concentrations. Usually, such signs are transient. However, from the 1950s it became clear that cerebellar disorder persisted in some patients even after phenytoin was withdrawn.

We have been unable to identify any formal epidemiological study of the association between phenytoin treatment and cerebellar disorders. We have therefore systematically searched the literature for case reports and case series. In the cases collected here, ataxia was recorded to be present in almost all of the patients in whom clinical details were provided. Most cases arose during therapeutic dosing. Only one case was of deliberate overdosage [30]; one patient who did not have seizures was prescribed phenytoin for prophylaxis [31]; and one report described iatrogenic intoxication with parenteral phenytoin [32].

Eleven (14%) patients died of the 76 whose outcomes were reported, and only 10 (13%) recovered completely. Many patients remained disabled by ataxia and were unable to walk, or required assistance to do so.

There were insufficient data to show whether the probability of recovery correlated with peak serum phenytoin concentration. For many of the early cases, no phenytoin concentration was reported.

Cerebellar atrophy, demonstrated radiologically or histologically, was common in patients who had been treated with phenytoin for a year or more, whether or not they had symptoms or clinical signs of cerebellar disturbance.

Our review shows clearly that clinical signs of ataxia can persist without radiological evidence of cerebellar atrophy, and cerebellar atrophy can be seen without any clinical evidence of cerebellar dysfunction. This disjunction between clinical and radiological signs has not been explained. It is not simply a postmortem artifact, since *in vivo* cerebellar biopsies showed histological changes. Although the early literature demonstrated that loss of Purkinje cells could be found in patients who had died from status epilepticus, and so was not specific to phenytoin intoxication, animal studies strongly support the view that phenytoin toxicity can damage Purkinje cells, and cause related changes in Bergmann astroglia.

However, the evidence on the clinical course and the relation to radiological change comes mainly from case reports. All deductions from published series of cases are limited by the selective nature of case reports: their publication depends on several nonrandom factors, such as the enthusiasm of the

reporter, the nature of the case, and the vagaries of peer-reviewed publication, which may favor unusual cases. These limitations apply to the current work. The literature spans a period of over sixty years, during which medical practice has changed substantially, and so the cases may not reflect either current therapeutic practices or their outcomes.

Better information on the clinical significance of phenytoin intoxication sufficient to cause cerebellar signs would be helpful clinically and for medico-legal reasons. It will require carefully conducted prospective follow-up studies of patients who are acutely intoxicated, or who develop cerebellar signs while taking phenytoin chronically, but such studies are unlikely to be performed.

Rare cases of cerebellar damage have been reported in patients whose measured phenytoin concentration has been within the accepted reference range. However, most patients with cerebellar dysfunction have phenytoin concentrations above the reference range.

Prescribers should be mindful of the non-linear pharmacokinetics of phenytoin, and be guided by patient reports of possible cerebellar dysfunction and by clinical signs, as well as concentration measurements, to reduce the dose when necessary. Since high concentrations, especially if maintained for some time, can cause permanent cerebellar damage, prescribers should advise patients to attend promptly if cerebellar symptoms appear, and adjust dosage appropriately. For patients with newly-diagnosed epilepsy, phenytoin is no longer the drug of first choice.

Declaration of interest

REF has written widely about adverse drug reactions and interactions and has from time to time received fees for legal reports, payments for articles, and royalties on books that they have written on the subject. SMB is Director of the Birmingham Unit of the National Poisons Information Service, which is commissioned by Public Health England.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

The views expressed in this work are those of the authors, and do not represent those of the National Poisons Information Service or of Public Health England.

Availability of data and material

Only published data were used in this research.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Robin Ferner http://orcid.org/0000-0003-3769-1346

References

1. Merritt HH, Putnam TJ. Sodium diphenyl hydantoinate in the treatment of convulsive disorders. JAMA. 1938;111(12):1068–1073.
• ***The introduction of phenytoin to clinical practice.***
2. Blair D. The treatment of epilepsy by sodium di-phenyl hydantionate (Epanutin). Postgrad Med J. 1939;15:344–350.
3. Kutt H, Haynes J, McDowell F. Some causes of ineffectiveness of diphenylhydantoin. Arch Neurol. 1966;14(5):489–492.
4. Utterback RA. Parenchymatous cerebellar degeneration complicating diphenylhydantoin (Dilantin) therapy. Arch Neurol Psych. 1958;80:180–181. • *A description of cerebellar degeneration in cats treated with phenytoin*.
5. Haberland C. Cerebellar degeneration with clinical manifestation in chronic epileptic patients. European Neurology. 1962;143:29–33.
•• ***The first description of cerebellar degeneration in patients treated with phenytoin.***
6. Pulliainen V, Jokelainen M, Hedman C, et al. Fenytoiini-intoksikaation aiheuttama pikkuaivovaurio. Duodecim. 1997;113(22):2309–2313.
7. Iivanainen M, Viukari M. Fenytoiinimyrkytys–epilepsialääkityksen salakavala komplikaatio. Duodecim. 1970;86(17):955–962.
8. Pulliainen V, Jokelainen M, Hedman C, et al. A case of cerebellar atrophy after phenytoin intoxication: neurologic, neuroradiologic, and neuropsychological findings. J Epilepsy. 1998;11(5):241–247.
9. Iivanainen M, Viukari M, Seppäläinen AM, et al. Electroencephalography and phenytoin toxicity in mentally retarded epileptic patients. J Neurol Neurosurg Psychiatry. 1978;41(3):272–277.
10. Kim JH, Kwon SH, Lee MS, et al. Cerebellar atrophy following long-term anticonvulsant therapy—three cases. J Korean Med Assoc. 1991;34(11):1251–1256.
11. Abe H, Yagishita S. Chronic phenytoin intoxication occurred below the toxic concentration in serum and its pathological findings. No to Shinkei = Brain and Nerve. 1991;43(1):89–94.
12. Ogawa M, Maeda F, Okubo H. Acute cerebellar ataxia in adults: a clinical case. J Kansai Med Univ. 1976;28(3):507–512.
13. Mavroudis IA, Manani MG, Petrides F, et al. Dendritic, axonal, and spinal pathology of the purkinje cells and the neurons of the dentate nucleus after long-term phenytoin administration: a case report. J Child Neurol. 2013;28(10):1299–1304.
14. Kurihara M, Imai M, Kumagai K, et al. An autopsy Case of a severely handicapped woman with cerebellar atrophy possibly due to phenytoin. Abstracts from the 18th annual meeting of child neurology association in Kanto district Kanagawa. Brain Dev. 1991 Mar 23;13(5):379.
15. Salcman M, Defendini R, Correll J, et al. Neuropathological changes in cerebellar biopsies of epileptic patients. Ann Neurol. 1978;3(1):10–19.
16. Spielmeyer W. The anatomic substratum of the convulsive state. Arch Neurol Psych. 1930;23:869–875.
17. Kokenge R, Kutt H, Mcdowell F. Neurological sequelae following dilantin overdose in a patient and in experimental animals. Neurology. 1965;15:823.
18. Kiefer R, Knoth R, Anagnostopoulos J, et al. Cerebellar injury due to phenytoin. Identification and evolution of purkinje cell axonal swellings in deep cerebellar nuclei of mice. Acta Neuropathol. 1989;77(3):289–298.
19. Iivanainen M, Viukari M, Helle EP. Cerebellar atrophy in phenytoin-treated mentally retarded epileptics. Epilepsia. 1977;18(3):375–386.
20. Koller WC, Glatt SL, Fox JH. Phenytoin-induced cerebellar degeneration. Ann Neurol. 1980 Aug;8(2):203–204.
21. Kessler C, Henningsen H, Reuther R, et al. Zur Kleinhirnatrophie bei Epilepsiekranken: eine computertomographische Untersuchung. Fortschr Neurol Psychiatr. 1985 Dec;53(12):437–441.
22. Bechinger D, Klotz R, Kornhuber HH. Kleinhirnschäden durch phenytoin [cerebellar injury caused by phenytoin]. Dtsch Med Wochenschr. 1986 Feb 7;111(6):237–238.

23. Del Negro A, Dantas CD, Zanardi V, et al. Relação dose-dependente do uso crônico de fenitoína e atrofia cerebelar em pacientes com epilepsia. Arq Neuropsiquiatr. 2000 Jun;58 (2A):276–281.
24. Shanmugarajah PD, Hoggard N, Aeschlimann DP, et al. Phenytoin-related ataxia in patients with epilepsy: clinical and radiological characteristics. Seizure. 2018;56:26–30.
•• ***The correlation of clinical and radiological features in a recent study.***
25. Ney GC, Lantos G, Barr WB, et al. Cerebellar atrophy in patients with long-term phenytoin exposure and epilepsy. Arch Neurol. 1994;51 (8):767–771.
26. Luef G, Marosi M, Felber S, et al. Kleinhirnatrophie und Phenytoinintoxikation. Eine MR-Studie. Nervenarzt. 1993Aug;64 (8):548–551.
27. Luef G, Burtscher J, Kremser C, et al. Magnetic resonance volumetry of the cerebellum in epileptic patients after phenytoin overdosages. Eur Neurol. 1996;36(5):273–277.
•• ***MRI scans of cerebellar damage after phenytoin overdosage.***
28. De Marcos FA, Ghizoni E, Kobayashi E, et al. Cerebellar volume and long-term use of phenytoin. Seizure. 2003;12(5):312–315.
29. Sodium P. EBM datalab, department of primary care health sciences, University of Oxford. https://openprescribing.net/chemical/0408010Q0/.
30. Craig S. Phenytoin overdose complicated by prolonged intoxication and residual neurological deficits. Emerg Med Australas. 2004;16(4):361–365.
31. Rapport RL 2nd, Shaw CM. Phenytoin-related cerebellar degeneration without seizures. Ann Neurol. 1977;2(5):437–439.
32. Hofmann WW. Cerebellar lesions after parenteral dilantin administration. Neurology. 1958 Mar;8(3):210.