

The association between phenytoin (diphenylhydantoin) and permanent cerebellar damage

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Objective
To review reports of cerebellar damage after phenytoin poisoning

Methods
Systematic review of Ovid Medline & EMBASE up to March 2021, using the search terms*:
(phenytoin or diphenylhydantoin or Dilantin or DPH).mp.
AND
(cerebellum or cerebellar).mp.
Limited to: human AND adverse effects (.mp. = multi-purpose)

*Original search conducted in 2019. A repeated search to March 2021 yielded 28 further citations, only one of which reported a case.

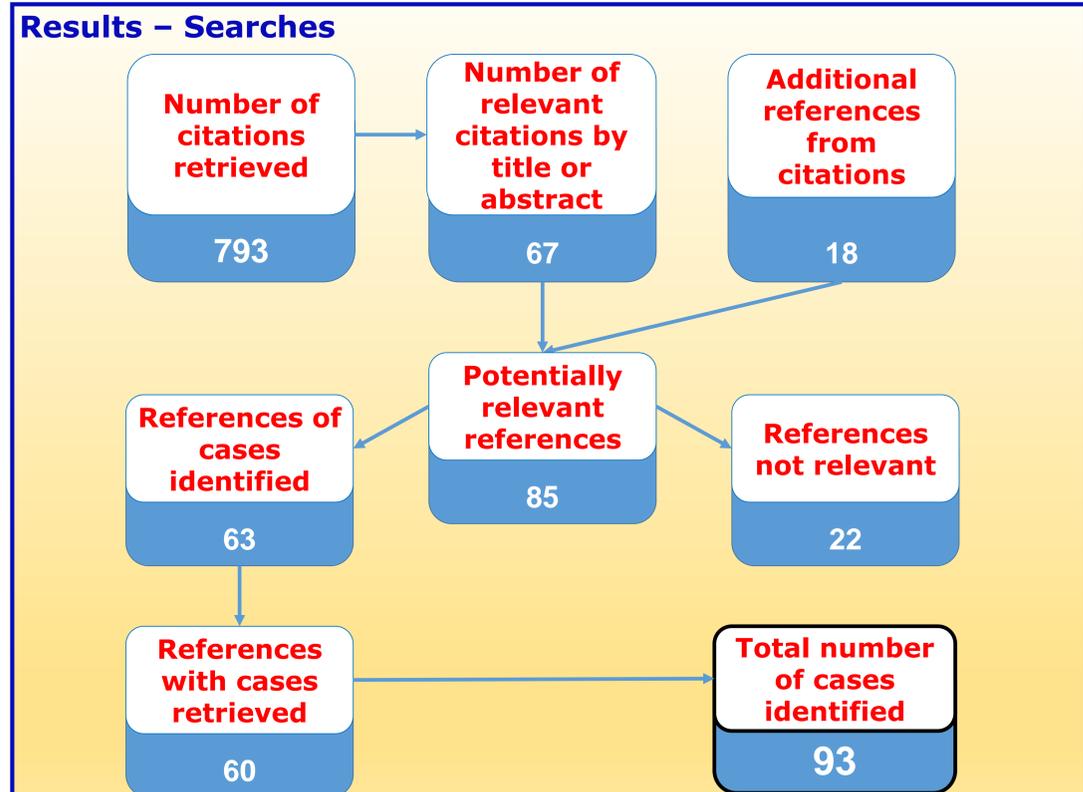


Figure 1. Search results and case identification.

Results – Data extraction

Parameter	Result	Number of cases with data
Median age (range) years	27 (2.7–78)	82
Exposure to phenytoin		
Acute or subacute exposure	13 patients	85
Chronic exposure only	73 patients	85
Cerebellar signs at presentation		
Ataxia	75 patients	79
Dysarthria	49 patients	79
Nystagmus	53 patients	79
Ataxia + dysarthria + nystagmus	39 patients	79
Phenytoin concentration		
Peak – median (range)	50 (8–128) mg/L	48
Outcome		
No residual cerebellar signs	12	72
Some improvement in signs	47	72
No improvement in signs	7	72
Progression of signs	1	72
Died	5	72

Table 1. Summary of case findings and outcome.

Results – Radiology
Scans were conducted at least once in 61 cases: 47 showed features of cerebellar atrophy, 12 had normal cerebellar scans, and 2 showed other or unreported signs. Of the 12 cases with normal cerebellar scans: 5 had residual physical signs, 5 recovered, and 2 died acutely.

Results - Histology
Histology of the cerebellum was reported in 10 cases. Purkinje cells were reduced or absent in all cases. (Figure 2). There was also an increase in the number of astrocytes (Bergmann's glial cells). The changes are characteristic, but not specific.

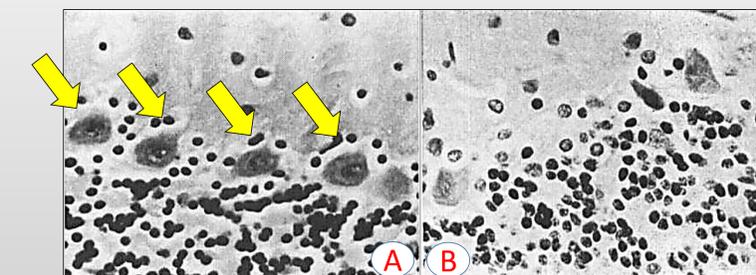


Figure 2. (A) Histology of the normal rat cerebellum; Purkinje cells (arrowed). (B) Loss of Purkinje cells after 18 days of high-dose phenytoin treatment in a rat.¹

Discussion
The association between cerebellar disorders, cerebellar atrophy, and phenytoin is not straight-forward. Cerebellar signs are common in patients receiving phenytoin, even when plasma concentrations are within the normal range (10–20 mg/L). For example, 19 of 47 patients (40%) treated with phenytoin for >1 year had ataxia.² In that study, cerebellar atrophy was present in MR scans of 6/13 patients with ataxia, and 7/17 patients without ataxia. These results accord with earlier findings in a Brazilian study, in which 2/13 patients with moderate or severe cerebellar atrophy and 3/24 patients with no or slight cerebellar atrophy showed cerebellar signs.³

Conclusions
Cerebellar ataxia is an important consequence of phenytoin overdose. It is irreversible in about one-third of reported patients. Radiological evidence of cerebellar atrophy may exist without physical signs, and ataxia may exist without radiological evidence of atrophy.

References:
¹From: Kogenge et al. Neurology 1965;15:823-9.
²Shanmugarajah et al. Seizure 2018;56:26–30.
³Del Negro et al. Arq Neuropsiquiatr 2000;58(2-A):276-281

