Ref: Ro J Neurol. 2017;XVI(3)
DOI: 10.37897/RJN.2017.3.8

Cerebellar atrophy with long-term phenytoin (PHT) use: Case report

Jamir P. Rissardo, Ana L.F. Caprara, Juliana O.F. Silveira
Departament of Neurology, Federal University of Santa Maria, RS, Brazil

ABSTRACT

Cerebellar atrophy can be found with long-term phenytoin (PHT) use or acute phenytoin intoxication. PHT may cause cerebellar symptoms, such as nystagmus, diplopia, dysarthria and ataxia. Clinical manifestations may be persistent. We report a case of a 41-year-old male who presented with cerebellar dysfunction and cerebellar atrophy after long-term phenytoin use. He had ataxic gait, preserved strength, commuting deep reflexes, dysmetria, dysdiadochocinesia, scanning speech and somnolence. Cranial computed tomography revealed enlargement of inter follicular cerebrospinal fluid spaces in cerebellum and also a slight enlargement of the fourth ventricle, suggesting signs of cerebellar volumetric reduction. PHT was withdrawn. Six months later, he presented improvement in his condition; he had atypical gait, mild dysmetria, diadochokinesia and normal speech. In conclusion, clinicians should be vigilant with patients on phenytoin. If the patient has cerebellar signs with a correspondent clinical history of phenytoin intoxication CT scan should be helpful as an initial cerebellar assessment.

Keywords: phenytoin, ataxia, cerebellum, atrophy

INTRODUCTION

Cerebellar atrophy can be found with long-term phenytoin (PHT) use (1), acute phenytoin intoxication (2,9), normal aging brain and alcohol abuse (3).

Nevertheless atrophy is often attributed to phenytoin use, its exact cause remains unknown (4).

PHT has a narrow therapeutic range with a wide pharmacokinetic variability (5). In this way, even a minor increase in the dose may lead to toxic concentrations, which may present by cerebellar symptoms, such as nystagmus, diplopia, dysarthria and ataxia. The clinical manifestations are usually reversible with reduction or withdrawal of the drug, but occasionally may be persistent (4).

Hereinafter, we report a case of a 41-year-old male who presented to our institution with clinical signs and symptoms of cerebellar dysfunction associated with progressive cerebellar atrophy after long-term phenytoin use.

CASE REPORT

A 41-year-old male admitted to our hospital presenting acute ataxia and scanning speech, for 20 days. He was diagnosed with epilepsy 29 years ago and had been in negligent use of phenytoin (frequent administration of high doses of phenytoin, he could not inform the amount) since then. He reported no episodes of seizures during this period. In his neurological examination, he had ataxic gait, preserved strength, commuting deep reflexes, dysmetria, dysdiadochokinesia, scanning speech and somnolence. The other systems were normal. His biochemical parameters (blood count (erythrocyte, leukocyte count) coagulation tests urea, creatinine, C reactive protein, lactic acid, sodium, potassium, calcium, chlorine, phosphorus, magnesium, albumin, oxaloacetate transaminase, pyruvic transaminase, venereal disease research laboratory, thyroid-stimulating hormone, tetra iodothyronine free, anti-thyroglobulin, anti thyroperoxidase, folic acid,

Corresponding author:
Jamir P. Rissardo
E-mail: jamirrissardo@gmail.com

Article History:
Received: 7 August 2017
Accepted: 14 September 2017

vitamin B12, alkaline phosphatase, gamma-glutamyl transferase, hepatitis B surface antigen, anti-hepatitis C virus, anti-human immunodeficiency virus types 1 and 2) were found to be within normal limits.

He also denied alcohol and tobacco use during this period. Considering these clinical features, we hypothesized cerebellar atrophy caused by phenytoin toxicity. Thus, we requested a cranial computed tomography, which revealed enlargement of inter follicular cerebrospinal fluid spaces in cerebellum and also a slight enlargement of the fourth ventricle, suggesting signs of cerebellar volumetric reduction (Fig. 1, 2 and 3).

Therefore, the patient was advised to discontinue phenytoin and was started on another antiepileptic drug. In his return, six months later, he presented significant improvement in cerebellar clinical signs and symptoms; he had atypical gait, mild dysmetria, diadochokinesia and normal speech.

DISCUSSION

Cerebellar syndrome accounts for approximately 13% of the patients in chronic use of phenytoin (6). The main cause of phenytoin intoxication, corresponding for approximately 39% of the cases, is self-medication while unsteady gait is the most

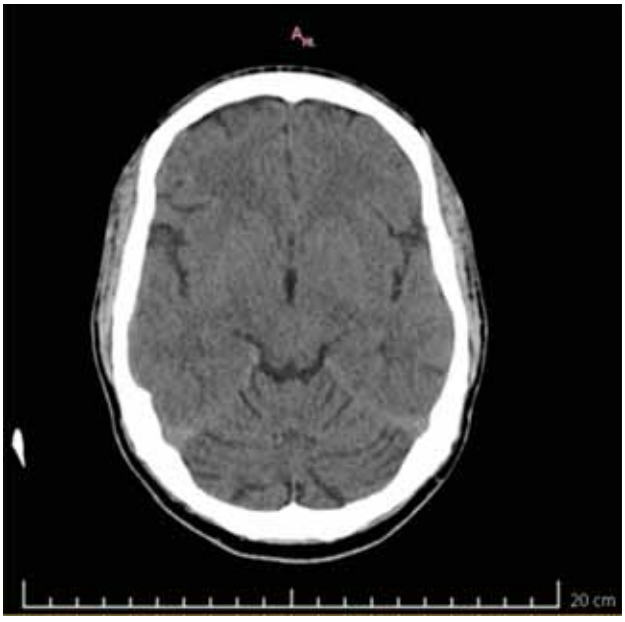

FIGURE 1. *CT axial*

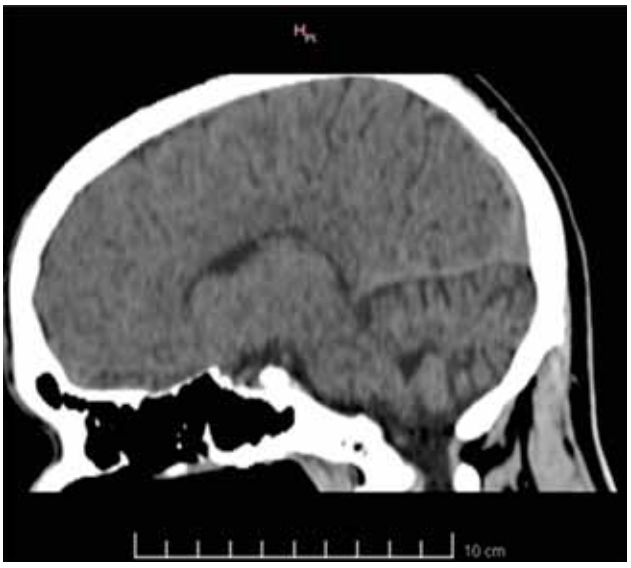

FIGURE 2. *CT sagittal*

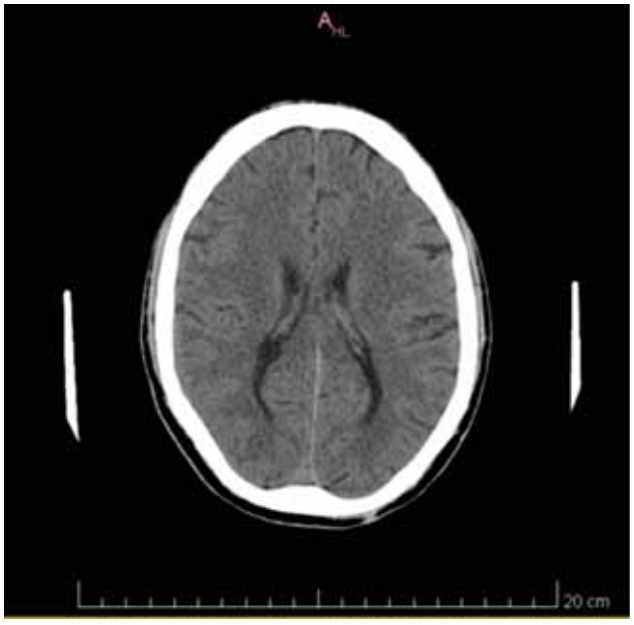

FIGURE 3. *CT axial*

FIGURE 1, 2, 3. *Non-contrast cranial computed tomography scan demonstrating enlargement of inter follicular cerebrospinal fluid spaces in cerebellum and a slight enlargement of the fourth ventricle, suggesting signs of cerebellar volumetric reduction*

common symptom, corresponding to 78% of all phenytoin intoxication cases (7).

The cause of cerebellar atrophy is still unknown, but it is often attributed to either seizure activity itself (10) or antiepileptic medication (1). In this context, for some authors hypoxia associated with frequent seizures is mainly responsible for cerebellar degeneration (8). On the other hand, there are reports of atrophy occurring in patients with well-controlled seizures or even without seizures (4).

There are several different imaging methods available for the diagnosis of cerebellar atrophy, like Computed Tomography (11), conventional magnetic resonance imaging (MRI) (12), MR Volumetry (13), MR spectroscopy and diffusion tensor MR imaging (14). However, cranial computed tomography is commonly the first exam to request and alone is sufficient for diagnosis (15).

In conclusion, a thorough patient's history should be obtained and clinicians should be vigilant with phenytoin use. In this way, it is essential to continuously check the use of this drug, especially in vulnerable patients. Moreover, if the patient has cerebellar signs with a correspondent clinical history of phenytoin treatment CT scan should be helpful as an initial cerebellar assessment.

ETHICAL STANDARDS

The study was performed in accordance with the ethical standards laid down in the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

HIGHLIGHTS

- Cerebellar atrophy can be found with long-term phenytoin (PHT) use.
- Clinical manifestations may be reversible or persistent with drug withdrawal.
- CT scan is helpful as an initial cerebellar assessment in such cases.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

REFERENCES

1. **Ghatak Nitya R., Rudy A.** Santoso, and William M. McKinney. "Cerebellar degeneration following long-term phenytoin therapy." *Neurology* 26.9 (1976): 818-818.
2. **Kuruvilla, Thomas, N.E. Bharucha.** "Cerebellar atrophy after acute phenytoin intoxication." *Epilepsia* 38.4 (1997): 500-502.
3. **Hayakawa K., et al.** "MR imaging of chronic alcoholism." *Acta Radiologica* 33.3 (1992): 201-206.
4. **Ney, Gershon C. et al.** "Cerebellar atrophy in patients with long-term phenytoin exposure and epilepsy." *Archives of neurology* 51.8 (1994): 767-771.
5. **Perucca Emilio.** "Is there a role for therapeutic drug monitoring of new anticonvulsants?." Clinical pharmacokinetics 38.3 (2000): 191-204.
6. **Del Negro A.D. et al.** "Relação dose–dependente do uso crônico de fenitoína e atrofia cerebelar em pacientes com epilepsia." *Arq. Neuropsiquiatr* 58.2-A (2000): 276-281.
7. **Hwang, Wen-Juh, Jing-Jane Tsai.** "Acute phenytoin intoxication: causes, symptoms, misdiagnoses, and outcomes." The Kaohsiung journal of medical sciences 20.12 (2004): 580-585.
8. **Dam M.** Phenytoin toxicity: neurological aspects of toxicity. In: Woodbury DM, Penry JK, Pippenger CD, eds. Antiepileptic drugs**.** New York: Raven Press, 1982:247-56.
9. **Baier W.K. et al.** "Cerebellar atrophy following diphenylhydantoin intoxication." *Neuropediatrics* 15.2 (1984): 76-81.
10. **Botez M.I., Attig E., Vezina J.L.** Cerebellar atrophy in epileptic patients. The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques 15.3 (1988): 299-303.
11. **Ramos A. et al.** CT findings in spinocerebellar degeneration. American journal of neuroradiology 8.4 (1987): 635-640.
12. **Xiong L. et al.** MR imaging of" spray heads: toluene abuse via aerosol paint inhalation. American journal of neuroradiology 14.5 (1993): 1195-1199.
13. **Luft, Andreas R. et al.** Patterns of age-related shrinkage in cerebellum and brainstem observed in vivo using three-dimensional MRI volumetry. *Cerebral Cortex* 9.7 (1999): 712-721.
14. **Lee Seung-Koo et al.** Diffusion tensor MRI and fiber tractography of cerebellar atrophy in phenytoin users. *Epilepsia* 44.12 (2003): 1536-1540.
15. **Koller William C. et al.** Cerebellar atrophy demonstrated by computed tomography. *Neurology* 31.4 Part 2 (1981): 405-412.