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Case Report

Imaging in phenytoin induced neurotoxicity: a case series

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ABSTRACT

Phenytoin is a commonly used anti-epileptic drug for various types of seizure disorders except for absent seizures. Long term dose dependant neurological side effects of phenytoin therapy include cerebellar atrophy, cerebral atrophy and brain stem atrophy. Skull hyperostosis, gum hypertrophy and megaloblastic anemia are other known effects of Long term therapy. We present four cases depicting clinical and neuroimaging findings of Phenytoin induced Toxicity.

Keywords: Anti-epileptic drugs, Cerebellar Degeneration, Epilepsy

INTRODUCTION

Epilepsy is a common neurological disease with a prevalence of more than 10 million in the Indian population.[1] Phenytoin is a commonly and widely prescribed antiepileptic drug used in all age groups of patients and in the management of various types of epilepsy and status epilepticus, with the exception of absence seizures. It has well known neurological, metabolic, musculoskeletal, hematological and endocrine side effects. High dose intake is known to cause encephalopathy and acute cerebellar atrophy in rare cases. Chronic intake of phenytoin is a known cause of cerebello-vermian atrophy. We present four cases on Long term phenytoin therapy presenting with spectrum of findings suggestive of phenytoin toxicity.

CASE REPORT

Case 1

A 30 year old non-alcoholic male patient presented with long standing history of seizures for 17 years. He had difficulty in chewing and speech since last seven years. He had recent onset headache and difficulty in Walking.

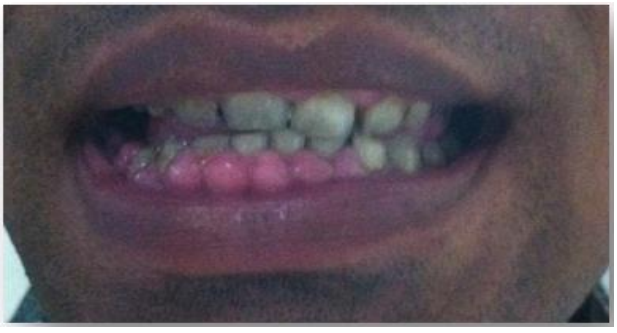

Figure 1: Localised gum hypertrophy in lower jaw.

Patient was diagnosed with neurocysticercosis 16 years back and was on oral Phenytoin 100mg -200 mg/day since 16 years. His complete blood count (CBC) revealed macro-ovalocytosis with raised Mean Corpuscular Volume (MCV) of 114 fL. On general examination, localized gum hypertrophy was seen in the mandibular

alveolus. Neurological examination revealed positive cerebellar signs like ataxia and dysarthria. Non Contrast Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) of brain revealed an old healed calcified granuloma in the right frontal lobe along with diffuse cerebellar hemispheric and vermian atrophy. Bone window images on CT showed diffuse diploic space widening, predominantly involving the frontal bones. (Figure 1, 2, 3).

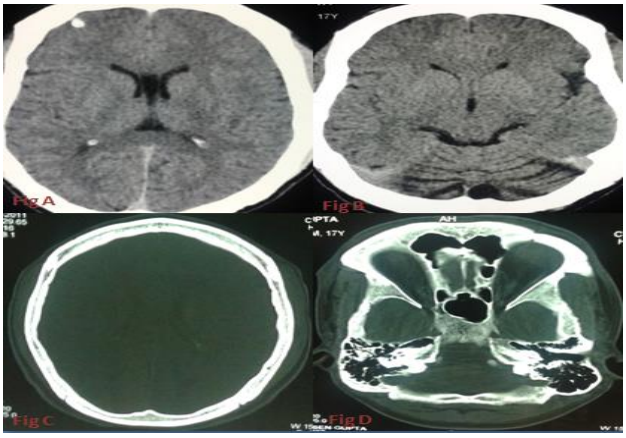

Figure 2: Axial NCCT (A and B) showed an old healed granuloma in right frontal lobe. Bilateral cerebellar hemispheric and vermian atrophy seen with prominent foliae. Bone algorithm (C and D) showed diffuse calvarial thickening with widened diploic spaces, predominantly involving the frontal bones.

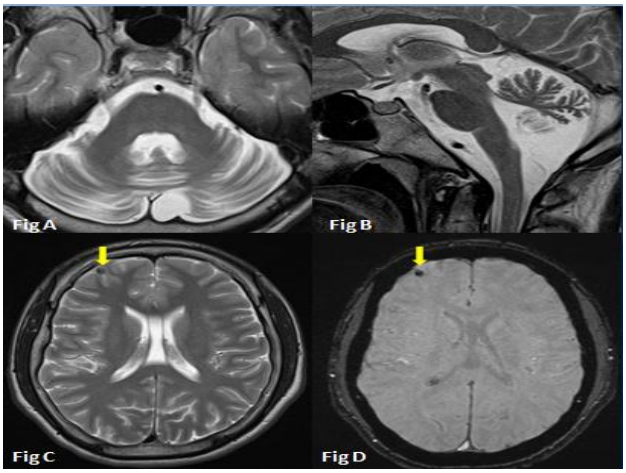

Figure 3: Axial and Sagittal T2WI showed Gross cerebellar hemispheric and vermian atrophy with prominent cerebellar foliae. Axial T2 and GRE images showed an Old healed calcified granulomatous lesion in right frontal lobe. Diffuse diploic widening is seen.

Case 2

A 35 year old female patient of seizure disorder since last 15 years, complained of dizziness and difficulty in walking along with difficulty in chewing for the last two months. Patient was on phenytoin therapy (100-200 mg/day) since last 12 years. Oral examination revealed diffuse gum hypertrophy. Neurological examination revealed positive cerebellar signs of gait ataxia and bilateral nystagmus.MR imaging revealed diffuse cerebellar hemispheric and vermian atrophy with prominent cerebellar foliae and fourth ventricle. (Figure 4, 5).

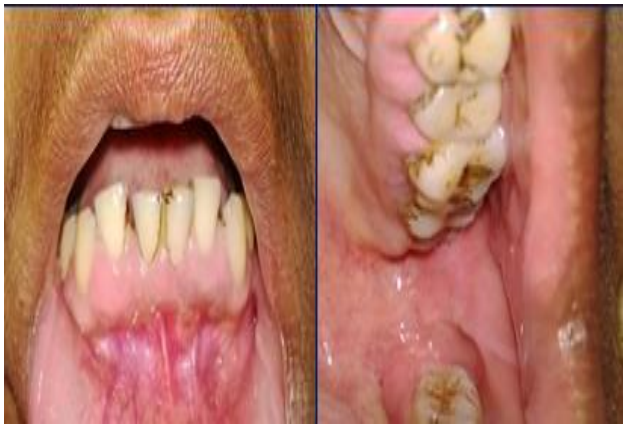

Figure 4: Diffuse hypertrophy of gums in both upper and lower jaw.

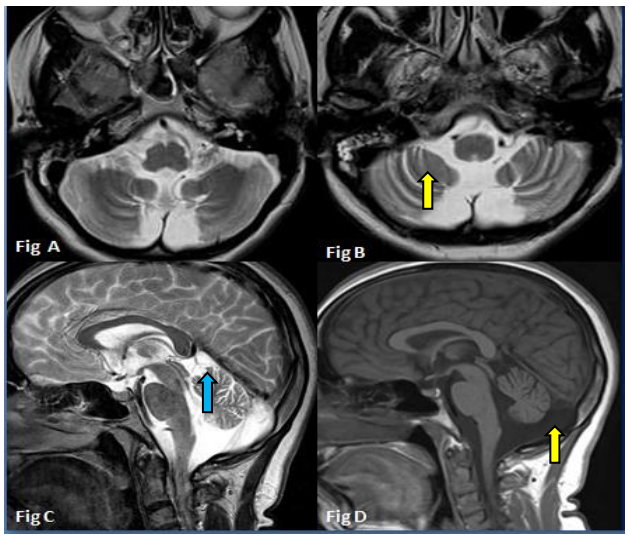

Figure 5: Axial T2WI (Fig A and B), Sagittal T2WI (Fig C) and T1WI (Fig D) images showed cerebellar hemispheric and vermian atrophy with prominent foliae (Yellow Arrow) and fourth ventricle (Blue Arrow).

Case 3

A 40 year old non-alcoholic male patient presented with history of seizures since 22 years. Patient presently had difficulty in walking, forgetfulness and reduced vision. He had history of 'on and off' uptake of oral phenytoin in the dose of 150 mg/day since, 15 years. Neurological examination revealed gait ataxia.MRI Brain revealed

Prominent cerebellar foliae with cerebellar hemispheric atrophy (Figure 6).

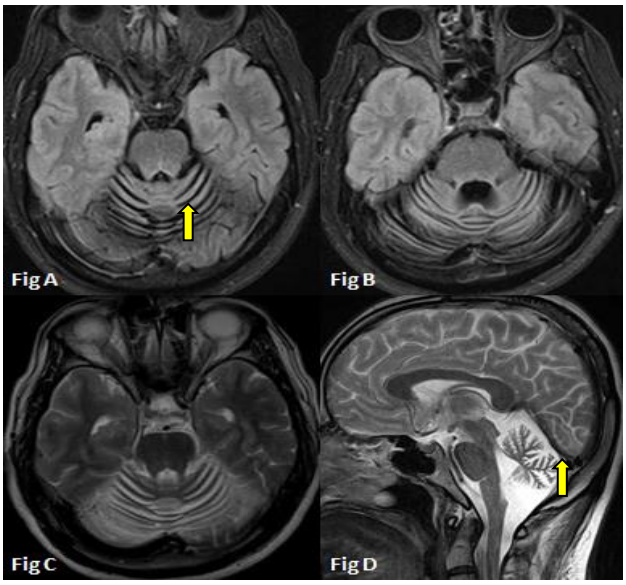

Figure 6: Axial FLAIR and T2WI (Fig A& B) with Sagittal T2WI (Fig D) showed Cerebellar hemispheric atrophy with prominent foliae(Yellow Arrow) and prominent fourth ventricle.

Case 4

A Seven year old male child, with history of birth asphyxia and seizures since one year of age presented with nystagmus. The child was on Syrup Phenytoin 50-100 mg/day since last six years. Plain CT brain showed cerebellar atrophy with cerebellar folial prominence and diploic widening in the skull (Figure 7).

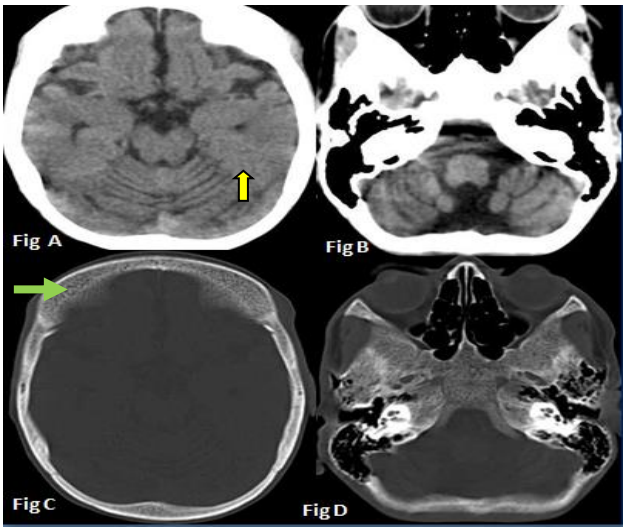

Figure 7: Cerebellar hemispheric and vermian atrophy with prominent foliae (Yellow Arrow) shown in Axial NECT images (A & B).Bony algorithm shows hyperostosis with diploic widening(Green Arrow) (C & D).

DISCUSSION

Both short and long term therapy with phenytoin has known neurotoxic effects. Amongst the many known neurotoxic side effects of Phenytoin, the dose dependant and reversible ones includedrowsiness, nystagmus, diplopia and cerebellar symptoms like ataxia, in-coordination and dysarthria. Both cerebellar atrophy and hyperostosis of skull can be seen after long term phenytoin use.[1,2]

Phenytoin is known to cause diffuse atrophy of purkinje cells of the cerebellum both clinically and experimentally. Along with the drug's action, cerebellar atrophy post phenytoin therapy in epileptic patients is also attributed to seizure mediated cell loss secondary to ischemic injury.[3]

A higher dosage intake for a longer period of use is associated with more pronounced atrophic changes. Serum phenytoin levels have been observed to be higher in patients with moderate to severe cerebellar changes than those with mild or no cerebellar changes. Also, the neurotoxicity has been found to be more profound with older patients.[2,4]

MRI brain is the best available imaging modality to assess the cerebellar damage. The size of sulci and foliae are used to assess the degree of cerebellar atrophy.[2] The common differential diagnoses of cerebellar atrophy include Alcoholic atrophy, Multi system atrophy (MSA) and Ataxia telangiectasia.

While alcoholic changes include both cerebral and cerebellar atrophy, which have a predilection for superior cerebellar vermis. Involvement of cerebellar hemispheres is less extensive which helps in differentiating from MSA. In patients of MSA-Cerebellar type, atrophy of cerebellum is associated with T2/FLAIR hyperintensity suggesting gliosis and the cerebellar white matter is affected more than the cerebellar cortices. This is in contrast to the diffuse cerebellar atrophy caused by long term phenytoin intake.[5] Hereditary ataxias present as cerebellar hemispheric and vermian atrophy along with changes in extracerebellar structures such as brainstem and basal ganglia.[6]

Diffuse diploic widening has been associated with long term pheytoin use. Osteoblast proliferation by upregulation of growth factor B1 is thought to be the mechanism of skull hyperostosis by phenytoin.[7]

Other side effects of phenytoin include hematological side effects like megaloblastic anemia, osteomalacia, hirsutism and gingival hyperplasia.[8]

Phenytoin is known to cause a decrease in folate levels resulting in megaloblastic anemia. The mechanism of gum hypertrophy, though is more complex and is a

resultant of a manipulation of extracellular matrix metabolism.[9]

Phenytoin has a long half-life and thus has an advantage of lesser daily dosage however; it follows non-linear pharmacokinetics which means a small increment in dose above the required maintenance dose may cause marked side effects. These properties have now led to other newer drugs such as Lamotrigine and Topiramate to take over Phenytoin in the long term treatment of epilepsy, especially in young patients where longer treatment duration is expected.[10]

Hence, a matrix of toxic features are associated with long term phenytoin therapy. It is thus the physician's prerogative to be alert and quick in picking up any of the numerous side effects of phenytoin and take apt radiological and hematological aid for accurate diagnosis. It is prudent to keep a check on the dosage and duration of Phenytoin and if need be, switch to newer therapeutic lines in order to prevent and reverse any known toxic effects of Phenytoin.

CONCLUSION

Neuroimaging and haematological findings along with clinical history are hence pivotal in reaching an etiological diagnosis. MRI is the most sensitive imaging modality to depict neurotoxic changes.

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REFERENCES

1. 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. Neurol Asia. 2013;18(1):107-1.
2. De Marco FA, Ghizoni E, Kobayashi E, Li LM, Cendes F. Cerebellar volume and long-term use of phenytoin. Seizure. 2003;12(5):312-5.
3. Tamrazi B, Almast J. Your brain on drugs: imaging of drug-related changes in the central nervous system. Radiographics. 2012;32(3):701-19.
4. Del Negro AN, Dantas CD, Zanardi VE, Montenegro MA, Cendes FE. Dose-dependent relationship of chronic use of phenytoin and cerebellar atrophy in patients with epilepsy. Arquivos de neuro-psiquiatria. 2000.
5. Matsusue E, Fujii S, Kanasaki Y, Kaminou T, Ohama E, Ogawa T. Cerebellar Lesions in Multiple System Atrophy: Postmortem MR Imaging-Pathologic Correlations. Americ J Neuroradiol. 2009;30(9):1725-30.
6. Poretti A, Wolf NI, Boltshauser E. Differential diagnosis of cerebellar atrophy in childhood. Eur J Paediatr Neurol. 2008;12(3):155-67.
7. Chow KM, Szeto CC. Cerebral atrophy and skull thickening due to chronic phenytoin therapy. Canadian Medical Association J. 2007;176(3):321-3.
8. Menon VB, Kurian J, Undela K, Ramesh M, Gowdappa HB. Phenytoin toxicity: A case report. J Young Pharmac. 2015;7(3):272.
9. Corrêa JD, Queiroz-Junior CM, Costa JE, Teixeira AL, Silva TA. Phenytoin-induced gingival overgrowth: a review of the molecular, immune, and inflammatory features. ISRN dentistry. 2011:25;2011.
10. Lowenstein DH. Seizures and epilepsy. Harrison's principles of internal medicine. 2016;19(2):2254.

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