Original Research Paper

Volume - 11 | Issue - 06 | June - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Neurology

PHENYTION INDUCED CEREBELLAR DEGENERATION – A CASE REPORT

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ABSTRACT Epilepsy is an important health problem due to its high prevalence and potential for causing long-term morbidity. It is commonly treated with Phenytoin(PHT). It has wide pharmacokinetic variability and a narrow therapeutic range that leads to toxicity.As with other Anti Epileptic Drugs, adverse effects of PHT have been identified and some may lead to drug discontinuation. Well-known dose-related reversible adverse effects of PHT include nystagmus, ataxia, diplopia, and drowsiness. Ataxia related to PHT therapy usually involves gait rather than fine motor movements.There is a relationship between Phenytoin intoxication symptoms and drug concentration and in the majority of patients, ataxia appears at a Phenytoin plasma concentration of approximately 30 ug/mL.However,there are few reports of cerebellar ataxia being a chronic adverse effect of therapeutic-range PHT treatment.Here, we report a case of Phenytoin induced cerebellar degeneration in a 42-year-old female to emphasize the importance of periodic anticonvulsant drug level monitoring .

KEYWORDS : Phenytoin(PHT), Cerebellar Degeneration, Epilepsy, Seizures

INTRODUCTION

Phenytoin is commonly prescribed drug for seizures,However the drug is usually prescribed for brief period as the seizures are mostly secondary to metabolic or electrolyte imbalance associated with acute infections. Epilepsy is one of the conditions which warrant the use of this drug for years together.

Phenytoin acts by prolonging the inactivated state of voltage activated sodium channels and governs the refractory period of neurons, thus limiting the repetitive firing of action potentials. Three factors govern the pharmacokinetic features of PHT 1)the extent of protein binding 2) non-linear elimination kinetics 3)its ultimate metabolism by the liver. Up to 90% of the administered phenytoin is protein bound, and there exists a distinction between the total and free plasma levels of phenytoin. Even small variations in protein binding can drastically alter the amount of free drug in the serum. Phenytoin is metabolized mostly in the liver by cytochrome P450 isoforms CYP2C9/10 and CYP2C19.1.

The long term use of PHT at therapeutic and toxic levels can cause cerebellar changes including atrophy. However, the phenytoin induced cerebellar syndrome can be reversed by timely cessation of Phenytoin therapy.

Case History

A 42 year-old female was admitted in our hospital(SSSMCRI) in September 2019 under the department of General Medicine with ataxia,scanning speech,horizontal nystagmus,hypotonia,dysmetria and dysdiadochokinesia. Her past history included history of left tuberculoma for which she was operated in 1997 elsewhere and was commenced on Tab.Phenytoin 300mg HS.She was seizure free there after but hasn't stopped Phenytoin because of poor follow up.

Central nervous system examination now revealed normal mentation with cerebellar signs.She had no other neurological and other systemic problems .The routine laboratory examinations could not reveal any explanatory reasons for the present condition of the patient.MRI Brain (**Figure1**) showed prominent sulcal spaces in bilateral cerebellum suggestive of volume loss .

Serum phenytoin level was checked and it was found to be 52.4 mcg/ml which lies outside the therapeutic range of phenytoin (10-20 µg/ml) and Phenytoin was discontinued. In the absence of other demonstrable cause, the selective morphologic changes in the cerebellum are attributed to long-term administration of phenytoin.

After a 4 month follow up patient showed significant improvement and is symptomatically lot better

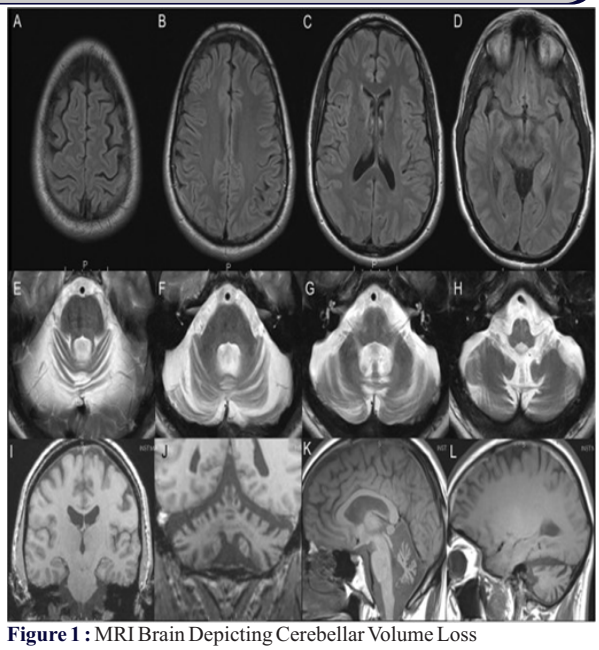

Figure 1 : MRI Brain Depicting Cerebellar Volume Loss

DISCUSSION

Phenytoin is one of the commonest and the first line antiepileptic drugs.The pharmacokinetics of PHT follow a non-linear path i.e. the rate of elimination varies as a function of concentration. At very low plasma levels, the elimination follows first order kinetics. However, in the therapeutic range, only a small proportion of the drug is metabolized because of saturation of enzymatic pathways..These adverse effects are usually reported if the drug serum levels are above the therapeutic range.Above the therapeutic range, even a small increase in the dose can markedly elevate the plasma concentration as well as the half-life of phenytoin.

This shift from first order to zero order kinetics occurs unpredictably.At plasma concentrations of 10 µg/ml, the plasma half-life of phenytoin ranges between 6 to 24 h, which however may vary with higher concentrations.Normally, approximately 90% of the circulating phenytoin is bound to albumin, whereas the therapeutic free phenytoin levels are 1-2 µg/ml. The inappropriate absorption of phenytoin into cells which leads to undesirable side effects, is largely from the free plasma pool. Individuals with decreased protein binding

may show clinical toxicity even at normal level total phenytoin in blood plasma. However, such individuals have an elevated free phenytoin level. Thus, the measurement of free drug concentration in the serum can be a useful aid in the assessment of phenytoin toxicity.

These effects are, however reversible in few months on reducing the dose of PHT unlike gingival hypertrophy and hyper-trichosis for which reversal might be very gradual.Our patient presented with severe cerebellar disorder and she was on the drug for 22 years. But she started recovering steadily after withdrawing the drug. Hence, a regular monitoring for adverse drug reaction should be considered in patients who are on PHT on long term basis.

CONCLUSION

This case report underlines the importance of periodic anticonvulsant drug level monitoring and the importance of workup for the cause of seizures before starting anti convulsants and also accurate dosing of drugs having a narrow therapeutic index with identification of noncompliance in patients being treated with drugs like Phenytoin.

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