Phenytoin induced cerebellar atrophy: A case report

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Abstract
The significant dose-related as well as idiosyncratic drug toxicity are encountered in pediatric practice occasionally due to the zero order pharmacokinetics and narrow therapeutic margin of phenytoin. Among uncommon side effects reported in patients with phenytoin exposure are cerebellar atrophy and at times its clinical presentation is masquerading as acute encephalitis. An unusual presentation of phenytoin toxicity in a 15-year-old girl suffering from multiple tubercular with seizure who developed bilateral cerebellar atrophy besides other features of Phenyltoin toxicity over 3 years of drug use has been reported here along with possible approaches to minimize the possibility of dosing error in its prescription.

Keywords: Phenyltoin, Cerebellar atrophy, Multiple tuberculoma.

Introduction
Seizures are one of the commonest pediatrics emergencies and phenytoin is a commonly prescribed drug in such situation in India. 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. Children constitute approximately 40% of India's population but information on adverse drug reaction occurring in them is limited. Phenytoin has wide pharmacokinetic variability and has a narrow therapeutic range that can easily lead to drug toxicity. There are reports highlighting the association of long-term use of PHT and diffuse and reversible cerebellar atrophy. These changes have been reported only with the long-term use and at times even with normal drug levels.

Case History
A 15-year-old girl presented in August 2014 with sudden onset generalized tonic-clonic seizure (GTCS), multiple episodes in previous 4-5 days without associated history of fever or any neurological deficit although she did complained of headache prior to seizures and had vomiting also in this episode of illness. On examination child was drowsy (Blantyre coma scale), pupils were normal in size and reaction to light bilaterally. Tone was increased in all four limbs with power more than 3/5 in all joints. Deep tendon reflexes were brisk in all four limbs. Bilateral planters were extensors and signs of meningeal irritation were negative. All cranial nerve assessed were normal and there was no focal neurological deficit. Rest of the systemic examination was normal. Investigations revealed hemoglobin 11.2 g/dl, TLC was 9800 with 30% neutrophils and 65% lymphocytes, and ESR was 26mm in first hour. Chest X-ray was normal and Montoux test was strongly positive at 72 hours. MRI brain showed multiple tuberculoma which were conglomerate lesions in right frontal region (6.2 mm x 5.8 mm), left parietal (4.2 mm x 5.3 mm) and left occipital region (3.2 mm x 3.4 mm). There was mild basal meningeal enhancement and no evidence of hydrocephalus.

Child was started on ceftriaxone and was loaded with phenytoin besides other supportive measures. Sensorium improved after 3-4 days when the diagnosis of multiple tuberculoma with raised intra cranial tension was made and child was started on anti tubercular treatment (5 drugs, HRZES) along with prednisolone and phenytoin (100mg twice daily) besides Diamox and glycerol. Child was discharged after 2 weeks and was in regular monthly follow up for initial one year antitubercular drugs were given for 12 months while steroids were given for initial 2 months only. Decongestive drugs were given for initial 6 months. Child was advised to continue Phenytoin in same dose for one more year. But child was lost to follow up after that for next two years.

Again in August 2017 child presented with ataxia and difficulty in walking and holding objects for last 3 months. Child was bedridden, had difficulty in getting up from bed, doing daily activities like brushing teeth. There was no history of fever, cough, any seizures, loss of consciousness, trauma or focal deficits. On examination child was conscious, oriented. Vitals were stable. General physical examination showed hypertrichosis over forehead and gum hypertrophy (Fig. 1).
Fig. 1: Hypertrichosis (black arrow) and Gum Hypertrophy (red arrow)

Child was walking with ataxic gait. Cerebellar signs were positive, though there was no nystagmus. Rest of the neurological examination was normal. Other systemic examination was normal. Repeat MRI brain showed resolving tuberculomas in left parietal and occipital lobe with diffuse volume loss of cerebellum (Fig. 2 and 3).

Fig. 2: MRI Scans of Brain showing severe bilateral cerebellar atrophy

Fig. 3: Previous Brain MRI scans of same patient showing normal bilateral cerebellum

The diagnosis of diffuse cerebellar atrophy due to phenytoin was kept. Sodium valproate was started and phenytoin was tapered gradually. Follow up after 3 months showed improvement in ataxia she was able to get up from lying to sitting position, could walk with less swaying.

Discussion

Diffuse cerebellar degeneration due to phenytoin therapy has been reported previously by few researchers. The patho-mechanism of observed toxicity associated with chronic phenytoin administration is unclear but folate deficiency has been implicated due to the fact that low folate levels can impair hepatic drug metabolizing capacity or by impairing neural function directly.

In their case series in 1980, McLain et al reported about five patients who were on phenytoin, had developed clinical signs of cerebellar dysfunction and showed diffuse cerebellar degeneration in CT scan. These patients had high plasma phenytoin levels at the time of diagnosis but the cerebellar symptoms persisted even when phenytoin levels had returned to normal value in follow up.

Some studies have pointed out that the role of drug duration is as important as are the drug levels (even if in therapeutic range) in the causation of diffuse cerebellar atrophy. It was emphasized by some researchers that the prolonged phenytoin administration is associated with cerebellar ataxia. Leuf et al in their paper included eleven patients on phenytoin therapy who presented with relatively mild and short intoxication leading to cerebellar degeneration. They have mentioned that there is no correlation between serum phenytoin level and severity of clinical picture of cerebellar dysfunction or severity of cerebellar atrophy. Of these six patients had moderate to severe cerebellar atrophy while five patients had normal MRI brain.

However diffuse cerebellar degeneration is usually reversible in few months on discontinuing phenytoin unlike other cosmetic side effects like gingival hypertrophy and hyper-trichosis for which reversal might be very gradual. Kumar et al has reported a 16-year-old epileptic boy who was taking phenytoin for over ten years and manifested with phenytoin induced cerebellar atrophy. In this patient improvement both clinical and neuro-imaging was evident within three months of discontinuing phenytoin.

So, it’s very important for attending doctor to impress upon the parents of children (requiring long term phenytoin) at the outset about the absolute need of regular follow-up, explain them some common clinical manifestations suggestive of drug toxicity and also the importance of accurate drug dosing and avoiding drug substitutes themselves. The stringent need for regular monitoring of plasma drug levels should also be emphasized and clinicians should also be careful enough to diligently look for uncommon side effects in every follow up visits.

References