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CASE REPORT

Phenytoin induced Chorea: commonly used antiepileptic drug causing a rare movement disorder

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Abstract

Background: Phenytoin, a commonly prescribed antiepileptic drug, causes side effects like ataxia, tremor, hirsutism, gum hyperplasia, insomnia, confusion, headache and vertigo when used for longer duration. However, chorea is a rarely reported side effect of phenytoin and is completely reversible on stopping treatment.
Case presentation: A twenty-one-year-old Indian male patient, who had generalized epilepsy and had been on sodium valproate for 2 years, presented with acute onset chorea four days after starting phenytoin sodium. He had normal serum phenytoin levels. A thorough evaluation was done, which suggested phenytoin as a possible cause of chorea. Phenytoin was withdrawn, resulting in a dramatic subsiding of chorea. A rechallenge with the drug resulted in reappearance of choreiform movements. These disappeared again after drug withdrawal, implicating phenytoin as the possible etiological agent for chorea.
Conclusion: Phenytoin rarely induces involuntary movements as an adverse effect. During phenytoin therapy, if a patient develops involuntary movements, phenytoin toxicity should be suspected even with normal drug levels. This is important as drug withdrawal leads to complete symptomatic improvement thereby avoiding extensive workup for other secondary causes.

Keywords: chorea, phenytoin, anticonvulsants, epilepsy, generalized

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INTRODUCTION

Non barbiturate antiepileptics like Phenytoin, Valproate and carbamazepine are the most commonly used drugs in the treatment of epilepsy (1) Phenytoin is an older generation, relatively inexpensive and easily available antiepileptic drug. It is a sodium channel blocker that is metabolized predominantly in the liver via the CYP2C9 pathway (1) A variety of factors like genetic polymorphisms, drug interaction, and disease related impairment of this pathway predisposes individuals to various neurological and cutaneous adverse effects (2,3) However, chorea occurring as a side effect without other features of overt toxicity is a rare occurrence. Here, we describe a patient who developed chorea with phenytoin use.

CASE REPORT

A twenty-one-year-old Indian male patient, who was on sodium valproate for the past two years for generalized epilepsy, presented to us with a four-day history of acute onset generalized choreiform movements. There was no associated or preceding history of headache, fever, vomiting, trauma or other neurological complaints. Drug history revealed that the patient had been started on phenytoin 100mg TID 3 days before as an add on medication for 1 episode of generalized seizures which he had developed about four days before. There was no history of involuntary movements in family members.

On clinical examination, patient was conscious and well oriented to person, place, and time, and had normal vital signs. Neurological examination at our first consultation was remarkable for the presence of choreiform movements involving both upper and lower limbs (see video 1). There was no other focal neurological deficit. Routine biochemical and hematological investigations including ASO titres were all normal. Serum phenytoin levels were within normal range at 11.75 mcg/ml(10-20 mcg/ml). ECG and echocardiogram were normal. Cranial MRI and CSF study were normal. The chorieform movements were thought to be induced by phenytoin, so the drug was stopped with the results that the choreiform movements disappeared within 24 hours (see video 2) Five days later, with the rechallenge of phenytoin, the choriform movements reappeared and subsided when phenytoin was stopped again. Naranjo Causalty Assessment scale (4) was > 9, fitting into the criteria for definite ADR (adverse drug reaction).

DISCUSSION

Drug induced chorea is one of the most common causes of

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sporadic chorea, which can be can be acute or chronic (TD).Striatal denervation and dopaminergic stimulation is a causative factor. The most common drugs implicated are typical/atypical antipsychotics, DRBs, anti-Parkinson drugs, Ca+ antagonists, antidepressants, and anticonvulsants (Lamotrigine, CBZ, Valproate, PHT). Phenytoin rarely induces choreiform movements as an adverse effect. Involuntary movements induced by phenytoin are more likely to be seen in cases with a preexisting extrapyramidal lesion(5,6,7) Though there is no specific age predisposition, they occur more commonly in patients under the age of 20 years (*8*). They may last from several hours to even a few years and usually resolve with drug discontinuation. No correlation was noted between the serum levels of phenytoin and the appearance of involuntary movements(8). Our patient was already taking sodium valproate for the past 2 years for his seizures. Valproic acid leads to displacement of phenytoin from plasma proteins

and also inhibits phenytoin metabolism, thus increasing the concentration of free drug in the serum and leading to toxicity even with normal therapeutic drug levels. This has been well documented in children with refractory epilepsy on polytherapy.(9). Dysequilibrium of the basal ganglia output systems, caused by the differential effect of phenytoin on dopamine receptor subtypes, is proposed to be the probable pathophysiological mechanism behind these involuntary movements(*8*) Several reports of involuntary movements induced by phenytoin were published in literature (10,11,12).These involuntary movements have been reported even with normal drug levels(13,14). Phenytoin intoxication manifests predominantly as nausea, central nervous system dysfunction (particularly confusion, nystagmus, and ataxia), depressed level of consciousness, and coma and seizures in more severe cases(15) All of these features were absent in our patient.

Reports of a single patient with de novo chromosome 15 paracentric inversion developing chorea (16) and another patient with an isodicentric chromosome 15 syndrome with mental retardation and epilepsy developing chorea while on phenytoin, which subsided on withdrawal of phenytoin(17) implicate a possible genetic association of chromosome 15q which has been implicated as a candidate region for gene or genes of pathogenic importance for various hyperkinetic movement disorders. In our patient, who was on sodium valproate, there was a clear temporal relationship between the initiation of phenytoin and the onset of choreiform movements. It is possible that a drug interaction between the two led to phenytoin toxicity with normal therapeutic drug levels.

CONCLUSION

Here, we highlight an important but uncommon and reversible case of chorea. A detailed drug history must be determined in every patient presenting with chorea. During phenytoin therapy, if a patient develops involuntary movements, phenytoin toxicity should be suspected. Drug withdrawal leads to complete symptomatic improvement thereby avoiding extensive workup for other secondary causes.

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