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NCC WITH KINSBOURNE TYPE OMAS (OPSOCLONUS, MYOCLONUS AND ATAXIA SYNDROME) SECONDARY TO PHENYTOIN TOXICITY

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ABSTRACT

Background: OMS is a rare neurological disorder affects approximately 1/1,000,000 of the worldwide population without gender, generic or ethnic predilection1. The most common causeof OMS in children is paraneoplastic, especially due to neuroblastoma, parainfectious, congenital, metabolic or drug toxicity. The exact pathophysiology of OMS is not known2, Although opsoclonus and myoclonus both are adverse effect of phenytoin but opsoclonus– myoclonus syndrome (OMS) as a consequent effect of phenytoin toxicity has rarely been reported in the literature 3.
Objective: The purpose of reporting this case is to emphasize that as phenytoin has narrow therapeutic window and myriad of side effects even a minor increase in dose leads to toxicity like in our patient there was appearance of OMS after increment of dose of phenytoin. Methods: We present the case of a 19 years old male who was a known case of seizure disorder and presented to us with generalized tonic clonic seizure, opsoclonus, myoclonus and ataxia.
Results: A 19 years old male who was diagnosed with? NCC? Tuberculoma on basis of brain imaging around and was started on tab phenytoin, presented to us with generalized tonic clonic seizure. Dosage of phenytoin was increased around one and half month back due to one episode of GTCS and tablet valproate was added in treatment recently for intermittent abnormal jerky movement but there was no improvement in his symptoms. Patient presented in drowsy state and was found to have exaggerated deep tendon reflexes. Subsequently, dysarthria, difficult walking, jerky movements of upper limb, urinary incontinence, slurred speech, opsoclonus with evidence of myoclonic jerks involving all four limbs, face and eyelids. He had severe trunk as well as gait ataxia, incoordination and dysmetria. Hematological, biochemical and cerebrospinal fluid examinations were normal. Brain magnetic resonance imaging revealed likely possibility of neurocyticercosis and serum phenytoin level was markedly increased (56 mg/L). Phenytoin was stopped and tab clobazam 5mg HS was started along with valproate. All his symptoms including opsoclonus–myoclonus and ataxia gradually disappeared over next 10 days. Therefore, phenytoin induced opsoclonus–myoclonus ataxia syndrome was the final diagnosis. The repeat estimation of serum phenytoin level was within normal limits (18 mg/L).
Conclusion: This case report of phenytoin toxicity will help to alert physicians about the toxic manifestations of phenytoin in patients on long as well as short term therapy. Treatment with phenytoin should be individualized based on the patient's clinical response, plasma drug levels and signs of toxicity and regular follow up to evaluate compliance and response to therapy. Monitoring of serum phenytoin levels and adverse drug reactions should be done even when the seizure is under control and especially when there are doubts of early toxic effects. We should also educate the patients and caregivers about the clinical manifestations of phenytoin toxicity, so that it can be recognized early and treated appropriately.

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INTRODUCTION

OMS is a rare neurological disorder affects approximately 1/1,000,000 of the worldwide population without gender, generic or ethnic predilection (Brien and Siatkowski, 2016). It is also known as the dancing eye-dancing feet syndrome, Kinsbourne syndrome, myoclonic encephalopathy, Kinsbourne type OMAS, opsoclonic encephalopathy which is characterized by opsoclonus (rapid, irregular, horizontal and vertical eye movements), myoclonus that may affect trunk, limbs or face, and cerebellar ataxia (Pranzatelli and Tate, 2010). OMS may be associated with ataxia (OMAS), tremor, dysarthria and psychiatric symptoms and is more common in children. The most common cause of OMS in children is paraneoplastic, especially due to neuroblastoma, parainfectious, congenital, metabolic or drug toxicity. The exact pathophysiology of OMS is not known (Verma *et al*., 2014). Baets*et al*. had demonstrated loss of cerebellar purkinje and granular cell layer in autopsy of OMS of paraneoplastic origin. Since OMS is a rare disease, so there are no guidelines regarding its management (Baets *et al*., 2006; Klaas *et al*., 2012).

As Phenytoin is an antiepileptic drug that continues to be used widely for treatment of focal and generalized tonic-clonic seizures and has narrow therapeutic window and myriad of side effects. Therefore, even a minor increase in dose leads to toxicity like in our patient there was appearance of OMS after increment of dose of phenytoin. Although opsoclonus and myoclonus both are adverse effect of phenytoin but opsoclonus–myoclonus syndrome (OMS) as a consequent effect of phenytoin toxicity has rarely been reported in the literature (Verma et al., 2014; Dehaena and Van Vleymen, 1987). A 19 years old male was presented to us with acute onset abnormal, episodic intermittent involuntary jerk movement of all four limbs, trunk and eye lids followed by loss of consciousness from 1day. Patient was a known case of generalized tonic-clonic seizure for past two and half months when he was diagnosed to have? NCC? Tuberculoma on basis of brain imagingand was started on tab phenytoin. Dosage of phenytoin was increased around one and half month back due to oneepisode of GTCS and Tablet Valproate 500mg BD was added in treatment recently for intermittent abnormal jerky movement but there was no improvement in his symptoms. There was a history of low grade fever (undocumented), 10 days back for 5-7 days without any history of cough , burning micturition, loose stools , pain abdomen, rash, jaundice, blurring of vision, weakness of any extremities , trauma. There was no history of weight loss, loss of appetite. Personal history and family history was non-significant.

Initially patient was drowsy and on examination his vitals were stable (BP- 110/70 mm Hg, PR – 88/min. RR- 20/min. sPO2- 94%. RBS, 190). There was no pallor, icterus, lymphadenopathy, cyanosis, edema, rash, gum hypertrophy. During CNS examination bilateral planters were mute and all deep tendon reflexes were exaggerated. Power and sensory couldn't be assessed as patient was drowsy initially so he was given anti- edema and antiviral treatment. On subsequent days patients GCS improved and became oriented, but started developing personality changes in form of abnormal behaviour, which thought to be secondary to location of granulom a in frontal lobe. Subsequently patient developed alternating conscious level, dysarthria, difficult walking, jerky movements of upper limb, urinary incontinence, slurred speech. Neurological examination revealed opsoclonus with evidence of myoclonic jerks involving all four limbs, face and eyelids. He had severe trunk as well as gait ataxia, in coordination and dysmetria. Rest of neurological and systemic examination was normal. Hematological, biochemical and cerebrospinal fluid examinations were normal. The immunological study for HIV, HCV and HBV was negative. Brain magnetic resonance imaging revealed hyper intense lesion (7.4*7.2mm) with eccentric hypoitense nodule in right posterior superior frontal region with peripheral contrast enhancement likely neurocyticercosis. Electroencephalography was normal. Ultrasonography of abdomen, B-scan of eye, Xraythigh and chest was normal. Serum phenytoin level was markedly increased (56mg/L). Phenytoin was stopped and tab clobazam 5mg HS was started along with valproate. All his symptoms including opsoclonus–myoclonus and ataxia were gradually disappeared over next 10 days. Therefore, phenytoin induced opsoclonus–myoclonus ataxia syndrome was the final diagnosis. The repeat estimation of serum phenytoin level was within normal limits (18 mg/L).

DISCUSSION

The toxic effects of phenytoin form a myriad of various deleterious and erratic cerebellar-vestibular side effects which are primarily dose related. It may also cause other central nervous system effects, behavioural changes, increased seizure activity, gastrointestinal symptoms, hirsutism, gingival hyperplasia, osteomalacia and megaloblastic anemia. There are several reports of phenytoin induced ataxia, nystagmus, gingival hypertrophy, nodular skin lesions and hirsutism on phenytoin ingestion. Chronic phenytoin ingestion leads to its accumulation in the cerebral cortex, resulting in atrophy of cerebellum, causing ataxia and nystagmus. Gingival hypertrophy may be attributed to altered collagen metabolism.Altered metabolism of sex steroid hormones by phenytoin can induce hyperandrogenic symptoms like hirsutism and nodular skin lesions (Menon et al., 2015; Gosavi et al., 2012; Solanki and Kumar, 2013).

Our patient presented with altered consciousness level, dysarthria, gait ataxia, opsoclonus , myoclonus, slurred speech which defined asopsoclonus myoclonus ataxia syndrome (OMAS). The leading hypothesis for the cause of OMAS is an autoimmune, inflammatory reaction targeting central nervous system tissues, triggered by either a paraneoplastic or an infectious event. Antineuronal and antiPurkinje cell antibodies have been associated with OMS and neuroblastoma in some patients, although many patients have no detectable autoantibodies. The exact pathophysiology of OMS is unknown. However, there are two proposed mechanisms. The first is that oculomotor neurons of the caudal fastigial nucleus of the cerebellum become disinhibited secondary to Purkinje cell dysfunction in the cerebellar vermis. Purkinje cells normally relay inhibitory signals to cells of the fastigial nucleus. Histopathologic examination of patients with OMS has demonstrated gliosis and inflammation in the cerebellar vermis, supporting this theory. A second potential mechanism is disinhibition of burst neurons, which are cells that normally generate saccadic eye movements. Burst neurons are normally under tonic inhibition from omnipause cells except during saccades. Disruption of this inhibitory signal may cause the saccadic intrusions seen in ocular flutter or opsoclonus. The clinical features of OMS have led to the name "dancing eyesdancing feet" syndrome. It has been described in both

pediatric and adult patients. In the pediatric population, OMAS is associated with an underlying diagnosis of neuroblastoma in approximately half of cases but there have been post infectious associations reported in the literature, particularly with viral pathogens. Examples of viruses associated with OMS include influenza, West Nile virus, varicella, cytomegalovirus, human herpes virus 6, human immunodeficiency virus, and hepatitis C. There are also reports of antecedent bacterial infections including *Mycoplasma pneumoniae*and salmonella. Post immunization associations have been reported following varicella, measles, and diphtheria pertussis tetanus vaccine administration. Despite these associations, no clear etiology has been identified. In older children beyond the typical age range forneuroblastoma, OMAS as a postinfectioussyndrome may usually also occur.OMS has also been attributed to toxic or metabolic abnormalities. Examples reported include phenytoinoverdose, hyperosmolar nonketoticdiabetic coma, and cocaine intoxication. Posttraumatic opsoclonus hasalso been reported in the setting of severe head injury and coma (Brien and Siatkowski, 2016; Klaas et al., 2012).

Signs of phenytoin toxicity usually manifest at phenytoin levels above 20mg/L. Serum phenytoin levels were 56 mg/L in our patient. Although toxic effects may develop at therapeutic concentrations in some patients which can be attributed to the unpredictable relationship between serum levels of phenytoin and their side effects. Previous studies point out that phenytoin toxicity may develop over months to year after starting the drugprobably due to gradual accumulation of phenytoin over the time period as a result of non-linear pharmacokinetics but in our patient symptoms presented after a relatively short duration of 3 months of drug intake which may be a clue that pharmacokinetics not only vary as per dose but as well as per patients too. These effects can be reversed by withdrawing or reducing the dose of phenytoin. In our patient there was history of appearance of OMS after increment of dose of phenytoin. There was significant response and complete resolution after withdrawal of phenytoin and addition of clobazam with evidence of significant raised phenytoin level suggests that OMAS was attributed to phenytoin toxicity. Although phenytoin is known to aggravate myoclonic jerks in most of myoclonic epilepsies but to best of our knowledge phenytoin toxicity presenting as OMAS has been reported only a few times till date.

Conclusion

This case report of phenytoin toxicity will help to alert physicians about the toxic manifestations of phenytoin in patients on long as well as short term therapy. Treatment with phenytoin should be individualized based on the patient's clinical response, plasma drug levels and signs of toxicity and regular follow up to evaluate compliance and response to therapy. Monitoring of serum phenytoin levels and adverse drug reactions should be done even when the seizure is under control and especially when there are doubts of early toxic effects. We should also educate the patients and caregivers about the clinical manifestations of phenytoin toxicity, so that it can be recognized early and treated appropriately.

Conflict of interest

There are no conflict of interest as per this case report is concerned.

Author's contribution

All the authors have worked together to come to diagnosis and writing this report so that there can be contribution in diagnosing and detecting rare diseases which can help in making medical fraternity more helpful than it ever was.

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