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Valproate induced hyperammonemic encephalopathy: a rare adverse effect of a common drug

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ABSTRACT

Introduction. Sodium valproate or Valproic acid (VPA) is routinely used in management of epilepsy in neurology practice. It is a well-tolerated drug with mild side effects. Valproate induced encephalopathy (VPE) is a rare but serious adverse effect of this commonly used drug.

Presentation of the case. We present a case of a 42-year-old female with valproate-induced encephalopathy. She had history of development of subacute onset of Parkinsonism followed by decreased sensorium after initiation of sodium valproate. On examination, she had tremor of both upper limbs and asterixis. Her serum ammonia was raised and valproate level was mildly raised. There was improvement in her symptoms after stoppage of valproate.

Conclusion. We report a case of reversible Valproate induced encephalopathy (VPE) managed by stopping the offending drug. Clinical suspicion for VPE should be considered in any patients developing new neurological symptoms while on sodium valproate.

Keywords: valproate, valproic acid, encephalopathy, hyperammonemia, carnitine

INTRODUCTION

Sodium valproate or Valproic acid (VPA), is a commonly used drug in neurology as it is widely used for the treatment of epilepsy and migraine [1]. VPA is a safe drug with few side effects which are mild, including nausea, vomiting, tremor, ataxia, hair loss and weight gain. Valproate induced encephalopathy (VPE) is a rare but serious side effect which may lead to adverse outcome if left untreated [2]. There are few reported cases of valproate induced non hepatic hyperammonaemic encephalopathy from India.

CASE PRESENTATION

A 42 year old female admitted with known history of hypertension and focal epilepsy. She had history of recurrent episodes of focal to bilateral tonic clonic seizure 7 months back. On neuroimaging, she was found to have ring enhancing lesion suggestive of neurocysticercosis (NCC). She was started on sodium valproate 500 mg thrice daily. She had no recurrence of seizure since then. She started developing slowness in her activities of daily living since last 3 months. Progressively she had difficulty in walking and worsening of sensorium. On physical examination she was found to be in drowsy, somnolent state. She was wheelchair bound and could not walk. She was found to have tremor of both upper limbs along with asterixis.

On evaluation, laboratory reports revealed normal routine biochemistry including liver function test. Her serum ammonia was found to be raised. Her serum valproate level was also found to be mildly raised. Electroencephalogram showed generalized background slowing. Ultrasonography of abdomen revealed normal liver size and echotexture with chronic cholelithiasis. Magnetic resonance imaging (MRI) brain with contrast showed small ring enhancing lesion in right superior frontal region suggestive of NCC. She was managed with lactulose syrup, L-carnitine and switching of antiepileptic from valproate to levetiracetam. She started showing clinical improvement from next 2-3 days after admission to ward. Serum ammonia repeated after 1 week showed a declining pattern. She was discharged from the hos-

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pital in ambulatory stage with absence of asterixis and persistence of postural tremor.

DISCUSSION

Sodium valproate is a commonly prescribed drug in neurology clinics. Valproate encephalopathy is rarely reported in literature with low incidence of 0.1–2.5% [2]. It mostly occurs during initial days of administration of valproate, but few people develop valproate encephalopathy after long term treatment as seen in our case. Acute or sub-acute onset of worsening sensorium while on valproate with normal liver enzymes and raised levels of serum ammonia, possibility of valproate encephalopathy should be considered [3]. Valproate encephalopathy is under diagnosed condition as serum ammonia level as well as valproate level may be normal. Reversal of encephalopathy after withdrawal of valproate should be diagnostic of VPE. EEG in VPE shows features of encephalopathy such as diffuse background slowing with a predominance of delta or theta activity as shown in our patient. Triphasic waves can also be found in patients of VPE [4].

The pathogenesis of valproate encephalopathy is not fully understood. Various mechanisms have been proposed, most importantly hyperammonemia, L-carnitine deficiency and urea cycle defect [5]. The elevation of serum ammonia level occurs either due to hepatic or renal dysfunction. Valproate causes activation of glutaminase activity in kidney leading to release of ammonia causing raised serum ammonia level. Clinical presentation of encephalopathy is due to edema in brain caused by raised glutamine levels in astrocytes leading to raised osmotic pressure. Glutamate levels are noted to be elevated in both CSF and serum in VPE patients with normal serum ammonia level. Valproate increases the renal excretion of carnitine leading to L-carnitine deficiency. Carnitine plays a very important role in VPA metabolism and renal release of ammonia, so its deficiency leads to decreased metabolism of valproate and raised ammonia level thus exacerbating occurrence of VPA encephalopathy. Carnitine supplementation usually reverses VPE which is a supportive evidence regarding role of carnitine deficiency in VPE [6].

Various factors associated with Valproate toxicity are genetic factors, concomitant use of other drugs, liver dysfunction, ornithine transcabomylase (OTC) deficiency and dose of valproate. Concomitant use of antiepileptics particularly levetiracetam and topiramate is associated with increased risk of VPE [2].

The line of management in a case of VPE includes discontinuation of offending drug, L-carnitine supplementation, hydration and laxatives such as lactulose [7]. Carnitine deficiency in VPE causes hyperammonemia so supplementation with carnitine improves the neurological symptoms in VPE. It can be given intravenously or orally at a dose of 50–100 mg/kg/day. Extracorporeal treatment is another important treatment modality for severe valproate toxicity causing cerebral edema, shock, or very high levels of ammonia or valproate [8]. Other treatment options include use of meropenem, carglumic acid and naloxone [9]. Our patient responded well with discontinuation of valproate and substitution with levetiracetam. She was also given intravenous hydration, carnitine supplementation and lactulose.

CONCLUSION

To conclude, any patients while on valproate therapy developing new neurological symptoms should be evaluated and treated for VPE as it is a treatable entity with reversal of neurological symptoms as seen in our case.

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