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Valproate induced myopathy-a different presentation of an uncommon condition

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Case Report

Valproate induced myopathy-a different presentation of an uncommon condition

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Abstract

We report the case of an 11-year-old girl, who presented with weakness of legs for 20 days at presentation. The symptoms started soon after the initiation of sodium valproate for generalized seizures. The patient was found to have carnitine deficiency. Majority of the reports suggest that valproate induced myopathy occurs months after the onset of treatment. We report this case where the myopathy developed within days of onset of treatment with valproate. This may have been the reason why the patient showed no changes in EMG. The patient also showed no significant risk factor for the predisposition to the carnitine deficiency secondary to valproic acid therapy. No other complication of the carnitine deficiency was noted in our patient.

Key words: Carnitine deficiency, valproate induced myopathy, valproate side effects

Introduction

Sodium valproate, a significant antiepileptic drug is known to cause common side-effects like nausea, vomiting, weight gain, alopecia etc. This may include myopathy, which occurs after a few months of therapy. We present a case developing within days of initiation of therapy.[1]

Case report

An 11-year-old girl was presented to the hospital with complaints of difficulty in walking upstairs, observed initially while climbing the bus to school, for past 20 days. The weakness was experienced in both the legs. Additionally, there was an associated history of difficulty in getting up from the squatting position. There was no history of slippage of slippers and no symptoms in the upper limbs. Further, no similar family history was recorded. After an examination, the patient was found to have normal reflexes and mild neck flexor weakness was noted. No sensory symptoms or signs were detected. The patient's prior medical history referred to episodes of generalized seizures for which, she had been initiated on sodium valproate. The mother insisted that the symptoms had begun one day after the initiation of the antiepileptic medicine. The patient was found to have normal electrolytes, liver function test, renal function tests and thyroid function tests. The patient was found to have a normal creatine kinase, nerve conduction study and electromyography (CPK, NCS, EMG respectively). Serum carnitine levels were 16 μmoles/L (normal range 25-54 μmoles/L). In view of the onset of weakness after the initiation of sodium valproate, the medicine was changed. Thereafter, she recovered in 3 to 4 days. Carnitine supplementation was initiated as well.

Discussion

Interestingly, the cases similar to the aforementioned case are relatively few. All the cases reported exhibited mostly lower limb symptoms compared to upper limb symptoms. All cases had normal

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CPK and NCS reports.[1,2] In both the reports, the presentation of the weakness was comparatively late and noticeable after months. In the aforementioned case, the presentation occurred within days. In contrast with the reports in other cases, our patient had a normal EMG. This may be attributed to an early presentation of the weakness as compared to the other reports. [3]

Similar to the other reports, our patient also showed a low carnitine levels.[1,2] Carnitine, a protein synthesized from lysine and methionine, acts as a transmembrane carrier in the mitochondria for the long chain fatty acids. It plays a significant role in utilizing fats as a source of energy in muscles.[2] Carnitine physiology is the basis of metabolic deficits, predominantly in the type 1 skeletal muscle fibres. The type 1 fibres are slow twitch oxidative fibres. Carnitine deficiency results in a lipid storage myopathy involving the type1 fibres and leads to hypotonia and weakness. There is also associated myolysis and atrophy of type 2 fibres.[4]

Most often, decreased carnitine levels have no pathological significance. In many instances, children show no symptomatic manifestations due to carnitine deficiency.[2] A state of carnitine insufficiency may exist between frank deficiency of carnitine and normal levels of carnitine. Obesity, cancer, renal disease (and its treatment-dialysis) and endocrine conditions (diabetes mellitus and hypothyroidism) are amongst the conditions that lead to carnitine insufficiency.[4] Our patient showed none of these conditions.

Valproic acid is a commonly used antiepileptic drug, useful for a broad range of seizures such as idiopathic generalized epilepsy, symptomatic seizures, Lennox Gastaut syndrome, West syndrome, Landau Kleffner syndrome, etc. It has also been used in the management of the painful diabetic neuropathy and peripheral nerve injury. Treatment of migraine and its prophylaxis also involve the usage of valproate. Moreover, valproate has found its use in tardive dyskinesia and chorea. Due to its effectiveness in anticancer activity, its usage was permitted in suppression of tumour growth, metastasis and induction of tumour differentiation for ovarian carcinoma. It inhibits toxoplasma gondii, mycobacterium smegmatis and staphylococcus aureus. Valproic acid has a mood stabilizing effect as observed in cases of Alzheimer's disease and in panic attacks (not responsive to antidepressants).[5,6,7] However, it has its share of side effects (Table 1).

Table 1: Side effects of Valproate

1	**Gastrointestinal side effects-** Nausea, vomiting, diarrhoea, abdominal cramps Hepatotoxicity and pancreatitis especially in children
2	**Hematological side effects-** Neutropenia, coagulation disorders, pseudolymphoma syndrome
3	**Pediatric population-** Hepatotoxicity and pancreatitis - therefore, it should be avoided in children. Reduced bone mass and growth. Significant increase in weight and BMI with reduced height. Fetal valproate syndrome (developmental delay, typical facies, and malformations)
4	**Oncological-** Endometrial adenocarcinoma and breast cancer
5	**Obstretics and Gynecological effects** Teratogenic effects- limb defects, neural tube defects and spina bifida, cardiovascular deformities, craniafacial defects and skeletal defects- avoid valproate as far as possible in fertility period. Menstrual abnormalities, polycystic ovarian syndrome, increased testosterone levels in women (often without features of hyperandrogenism).
6	**Neurological side effects** Paradoxical aggravation of seizures (in overdoses) Iatrogenic parkinsonism, dementia and cognitive decline, metabolic encephalopathy Pseudoatrophy of the brain. Reversible neurotoxic symptoms Acute confusional state, myoclonus and non convulsive status epilepticus
7	**Others** Anticonvulsant hypersensitivity, toxic epidermal necrolysis, Steven Johnson syndrome. Onychomadesis, hyperpigmentation, onycholysis. Subclinical hypothyroidism, increased serum insulin levels and impaired glucose homeostasis. Dyslipidemia, metabolic syndrome, and raised LDL.

Valproate and some other drugs e.g. nucleoside analogues (antiretroviral therapy) and chemotherapy can lead to reduction of carnitine levels. Valproic acid can deplete carnitine by several synergistic mechanisms that include the following-

a. Valproic acid is a branched chain fatty acid. It combines with carnitine to form

valproylcarnitine. This compound is excreted in urine. Thereby reducing the levels of carnitine.

b. During an ongoing treatment with valproic acid, the tubular reabsorption of carnitine and acyl carnitine is reduced, resulting in further excretion of carnitine.

c. Valproic acid inhibits the action of butyrobetaine hydroxylase, which in turn is significant in the endogenous production of carnitine.

d. The uptake of carnitine by the cells and mitochondria is inhibited by both, valproic acid as well as valproylcarnitine.

e. Valproic acid combines with mitochondrial CoA-SH. This inhibits the restoration of acylcarnitine from the stores of mitochondrial carnitine. Reduction of CoA-SH levels further reduces the oxidation of fatty acids and impairs Adenosine Triphosphate (ATP) production thereby affecting the action of carnitine transporter.[8]

Therefore, valproic acid affects the production, transport as well as the excretion of carnitine. Thus so, it reduces the carnitine levels by several mechanisms. Carnitine deficiency induced by sodium valproate also causes cardiac problems, encephalopathy, cerebral edema, hepatotoxicity and fatigue. Risk factors that predispose to carnitine deficiency include young age, non-ambulatory status, underweight children, diet and tube feeding, neurological disabilities and use of anticonvulsant drugs etc.[2,8]

The carnitine deficiency affects the skeletal as well as cardiac muscles which show a ragged red appearance on biopsy and increased number of mitochondria and lipid droplets on electron microscopy. In relation to this, there is hepatic steatosis, raised serum glucose and ammonia and reduced levels of ketones.[4] The treatment of carnitine deficiency is carnitine supplementation, which results in significant improvement as the carnitine concentration improves.[2]

Conclusion

Majority of the reports suggest that valproate induced myopathy occurs months after the initiation of treatment. The case discussed so far is significant precisely because of the fact that myopathy developed within few days after the initiation of treatment. This may have been the reason why the patient exhibited no changes in EMG. Further, the patient showed no significant risk factor for the predisposition to the carnitine deficiency secondary to valproic acid therapy. No other complication of the carnitine deficiency was noted in our patient.

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