Case Report

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A Case of Valproate Induced Hyperammonemic Encephalopathy in an Elderly Bipolar Patient Under Treatment With Sulphonylureas

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Abstract

Valproic acid induced hyperammonaemic encephalopathy (VPA-VHE) is a rare side effect of valproic acid. It is characterized by impaired consciousness and lethargy, focal neurological signs or symptoms with a serum level of ammonia above 40 mmol/L. This syndrome is often misdiagnosed, especially in psychiatricsetting. Wepresentthe case of a bipolar patient who developed VPA-VHE. He assumed also sulphonylureas to manage mild hyperglycemia. After three months of treatment with valproic acid patient had a depressive episode and acute onset of headache, disorientation, consciousness impairment, and psychomotor slowing. This presentation induced to make investigation and we have discovered hyperammonaemia with EEG alteration; a diagnosis of valproate induced hyperammonemic encephalopathy (VHE) was made. The patient recovered quickly after discontinuing valproic acid therapy. Valproic acid is a frequent treatment in psychiatricsetting and a betterknowledge of possibleadverseeffectsisimportant to prevent and manage rare conditions like VHE.

Keywords: Valproic acid; Hyperammonaemic encephalopathy; Bipolar disorder; Elderly

Introduction

Valproic Acid (VA) is a drug with a mechanism of action implying enhancement of GABA-mediated inhibition, through a presynaptic action on GABA metabolism, and/or a direct effect on ion channels in the postsynaptic neuronal membrane [1-4].

VA is largely used in neurological setting as an anticonvulsant, but it is also approved for the treatment of neuropathic pain, migraine headache prophylaxis, restless legs syndrome [5]. In the psychiatry setting, VA is widely used for the management of patients with bipolar disorder, dementia-related agitation, social anxiety and schizoaffective disorder [6, 7].

Although VA is generally considered a well-tolerated drug, it can nevertheless cause hyperammonemic encephalopathy (VHE) requiring treatment withdrawal. VHE represents a rare complication of the treatment with VA, characterized by elevation of ammonia serum levels above 40 mmol/L, often occurring in patients with no history of underlying liver disease.

The onset may be sudden within the first weeks, or slower, as it may occur up to one year from the beginning of the treatment. The symptoms include impaired consciousness and lethargy, focal neurological signs or symptoms, and increased seizure frequency [1]. Other reported symptoms include asterixis, vomiting, perseveration, aggression, ataxia, and, eventually, coma and death [8, 9]. EEG performed in a few patients with pre-existing epilepsy, show a pronounced general slowing, an increase in epileptiform discharges and possibly the presence of triphasic waves [1, 10]. Most cases have been reported in children and younger adults, although recent case reports supply growing evidence that this complication can also occur in elderly patients [11].

Here, we describe a case of VHE that occurred in an elderly bipolar patient treated with VA in the absence of liver failure.

Case Report

The case concerns a 62 years old male patient with diagnosis of Bipolar Disorder type I, according with DSM-IV-TR diagnostic criteria. He was affected by type II diabetes treated with sulphonylureas (glimepiride 3 mg/die). He reported no history of neurological disorders, such asseizures or unexplained changes in level of consciousness.

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Psychiatry history was characterized by a first depressive episode about two years ago (June 2010), treated with Citalopram 20 mg/day. After six months he was affected by a maniac episode that required hospitalization. He was put on VA 500 mg 2 cpr/day, so that his psychophysical condition was stabilized for the following three months.

In March 2011, there was a relapse in the sense of depression and this condition required a new hospitalization. At admission patient presented deflected mood, apathia, anedonia, low self-esteem and difficulties in daily performances; moreover he was considerably sedated, with evident psychomotor slowing and it was observed tremor of the upper limbs. We observed space-time disorientation, memory impairment and confabulation; the attitude was resigned, speech needs to be stimulated and was focused on somatic complaints. We maintained treatment with VA (dosage 1000 mg/die) and added quetiapine (upward titration until 300 mg/day in 4 days). There was no feed restriction or weight loss. Routine blood chemistry tests and urinalysis were in the normal range.

During hospitalization, the patient had claimed several headache episodes and had no benefits from Non-Steroidal Anti-Inflammatory Drug (NSAID). Persistence of headache, altered state of consciousness, difficulties to stand, as well as persistence of unintentional tremor required a neurological consultation, which resulted however negative. Then, further blood tests and EEG were required. EEG finding charted highlights anomalies of slow theta and delta waves widespread, prevalent on the left fronto-temporal regions. Laboratory tests resulted in hyperammoniemia (60 μmol/L, normal range11 - 35 μmol/L). Clinical presentation suggested the diagnosis of encephalopathy. Liver impairment was ruled out by abdominal ultrasounds and blood tests. The hypothesis of a VA VHE was considered, so that the treatment with VA was stopped.

As a consequence, maintenance of posture wassignificantly and gradually improved, as well as of headache and tremor.Wash out led to an improvement of consciousness, orientation and cognition after two weeks; the depressive symptoms were also improved, with no neurological signs, and stable general conditions. Hammoniemia levels were monitored: after five days of VA withdrawal values were slightly reduced (45 μmol/L), whereas after eleven days the values fell within the normal range (24 μmol/L). EEG was repeated after 12 days, and showed slow rhythms reduction and residual theta waves. Thus, the patient was discharged after 20 days of hospitalization. At follow up, blood tests showed normal ammonium level and EEG. Clinical improvement for both mood cycling and depression was maintained and the patient returned to his usual daily activities.

Discussion

This case report showed the importance of monitoring side effects due to VA administration, even in psychiatric setting. The first case of VHE, with otherwise normal hepatic function parameters, was described by Coulter and Allen in 1980 in a child with epilepsy [8]. This phenomenon was the object of a wide debate among Neurologists, while a first case in the psychiatric setting was reported by Settle only in 1995 [12].

Although the majority of literature case reports are mainly related to the onset of VHE in children and younger adults, recent evidence highlighted that this complication can also occur in elderly, but only four case reports have been published [11]. While there are several case reports on VHE due to acute overdose of VA [13], only a few case reports on VHE due to VA chronic use have been described to date [14, 15]. For this reason, we reported the case of 62 years old man without liver failure under chronic treatment with VA for a bipolar disorder.

Hyperammonaemic encephalopathy due to chronic treatment with valproic acid in the absence of liver failure is relatively uncommon [16]. The daily dosage of VA [3] and its plasma, as well as those of ammonia are not related to the degree of encephalopathy [1]. Moreover, asymptomatic hyperammonaemia is observed in 20 to 25% of those taking VA [3].

The mechanism by which VA and its derivatives produce hyperammonemia is unclear, although various mechanisms have been proposed [1]. VA is partly metabolized in the liver by oxidation, which in turngenerates active metabolites. Such metabolites inhibit hepatic enzymesinvolved in ammonia elimination through the urea cycle [1].

Hyperammonemia causes relevant alteration in GABAergic transmission, which substantially contributes for encephalopathy symptoms [1, 4].

An array of risk factors for symptomatic hyperammonemia have been proposed, including polypharmacy, complicated medical conditions, mental retardation, dietary restrictions such as an exclusively vegetarian diet, carnitine deficiency, concomitant use of other anticonvulsants such as topiramate, the presence of congenital abnormalities of the urea cycle [4, 15, 17]. Among less common causes are hyperinsulinemic hypoglycemia, malignancies, portosystemic shunts, urinary tract infections, major surgery, and parenteral nutrition [18-22].

These data could be of help in investigating the pathophysiology of VHE, as well as in the prediction of severe adverse reactions.

The patient did present none of the above risk factors, with the exception of type II diabetes controlled with sulphonylureas. In this case, the patient showed sedation, temporal space disorientation, psychomotor slowing, trembling and NSAID-resistant headache. Clinical signs were not associated with numerous clinical presentations, although EEG signs, (i.e. widespread slowed theta and delta activity prevalent in left fronto-temporal cortex), were in accordance to previously reported literature findings.

In light of such propensity of valproate to induce hyperammoniemia also through a hepatic N-acetylglutamate synthase inhibition, it is of interest that sulfonylureas are mainly metabolized by the hepatic enzyme CYP2C9, and thus interfere with the cytochrome p450 system [23]. Now, the presence of certain alleles of CYP2C9 significantly increases the risk of hypoglycaemia, meaning that the hypo-function of the enzyme may increase plasma levels of the drug [24]. For this reasons, it appears plausible, among other causes, that high levels of sulfonylureas may inhibit also metabolic enzymes of valproate and thus unmask eventual borderline hyperammonemia.

In the case of a patient taking VA, which is affected by encephalopathy, regardless of the duration of therapy, plasma ammonia levels should be always checked [16]. The treatment of choice in these cases consists in dose reduction or discontinuation of the drug, with or without L-carnitine supplement, providing, in addition, symptomatic treatment [11].

In our experience, 12 days after discontinuation of the treatment with VA, ammonia levels returned in thenormal range, concomitantly to symptom relief.

In conclusion, because of the large use of VA and other mood stabilizers in the clinicalmanagement of psychiatric disorders, it has become of relevance, with special regard to the elderly,that clinicians focus their attention onto uncommon adverse effects of valproate, such as VHE. Although the follow-up of the blood ammonia levels appears fundamental in hyperammonemia diagnosis, often patients with elevated ammonia levels are, on the other hand, asymptomatic [25, 26]. In fact, Raja and Azzoni [27] have reported that 51.2% of the patients receiving VA developed asymptomatic hyperammonemia (level > 97 μg/dL). Lewis et al. [28] also found a positive correlation between VA serum concentration and ammoniemia values.The Authors also note that it is quite difficult to distinguish mental status changes due to VA from worsening of psychosis or mania, or even from a failure in therapeutic response. They conclude by recommendingto monitor both liver function and serum ammonia in patients taking VA in order to possibly perform early detection of adverse effects [28].

This case report shows the relevance of monitoring side effects appearing in course of treatment with VA in patients with bipolar disorder. Our experience confirms and demonstrates the relevance of an early recognition of VA-induced hyperammoniemia, and underlines the necessity to institute a prompt treatment of this side effect of VA for successful and complete recovery of the patient.

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