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Case Report

Reversible Hyperammonemic Encephalopathy in a Patient with Schizophrenia

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Abstract

Introduction: Valproate acid (VPA) is a very common treatment in neurology and psychiatric pathologies. Valproate-associated Hyperammonemic Encephalopathy (VHE) is a rare and serious side effect of the VPA treatment.

Case report: We present the case of an adolescent with a recent diagnosis of schizophrenia, hospitalized for psychotic decompensation and generalized epileptic seizures, with no personal or family history of epilepsy. After progressive introduction of VPA, the patient developed an acute mental state characterized by lethargy, cognitive deceleration, confusion and verbal response lentification, suggestive of encephalopathy. Laboratory tests showed a hyperammonemia with normal hepatic function, and the electroencephalogram (EEG) showed severe diffuse slowing with bifrontally predominant triphasic waves, a characteristic pattern of metabolic encephalopathies.

Conclusion: This case shows an important and infrequent secondary effect of VPA, as well as the importance of EEG in the study of patients with altered state of consciousness.

Introduction

Valproate acid (VPA) is an antiepileptic drug effective in treatment of focal and generalized epilepsy, also used as a therapy and mood stabilizer in psychiatric disorders. It is usually well-tolerated, toxic effects and interactions with other drugs have been reported [1]. There are dose-related and idiosyncratic side effects, among these; hyperammonemic encephalopathy is a rare but serious side effect, which should be considered in patients under polytherapy who developed acute behavioural disorders. Frequently is accompanied without clinical or laboratory evidence of hepatotoxicity, and the pathophysiologic mechanisms are not completely understood.

Case Report

A 14-year-old girl with a recent diagnosis of schizophrenia was admitted to Psychiatry Service presenting psychotic decompensation with auditive hallucinations (hearing voices), behaviour disorder, hetero and auto-aggressivity, difficult contention, and no response to the previous drugs prescripted. There is no known family history of diagnosed psychiatric illness, patient had problems in education and was under special educational program. During Hospital course, toxicology screen was negative, physical examination revealed no abnormal findings other than the mental status examination. Once admitted to the inpatient unit was restarted on Clozapine 600 mg/day and started treatment with Risperidone Consta and Clonazepam (0-0-5 mg). MRI was normal. Seven days after being admitted to Hospital patient developed generalized epileptic seizures, without previous history of epilepsy, and with significant EEG changes in routine video-EEG studies performed after clinical seizures (occasional generalized spike and wave discharges with normal background activity). Neurology service decided to introduce progressively VPA, until valproate level reached therapeutic range. After a few days under VPA 1200 mg/day, patient developed a significant clinical worsening with conscious level oscillations, confusion, mental slowing, sleepiness and verbal response lentification. The EEG showed a severe diffuse slowing with bifrontally predominant triphasic waves (Figure 1). Laboratory tests including hepatic and renal function were normal. Serum Ammonia showed levels two times over the normal values (62.90 µmol/L; NV= 5-33 µmol/L). Patient was diagnosticated of Valproate-associated Hyperammonemic Encephalopathy (VHE), VPA was gradually withdrawn and patient was placed on Levetiracetam. One week after VPA withdrawn, patient developed clinical improvement, ammonia serum levels were normal, and EEG showed her basal activity.

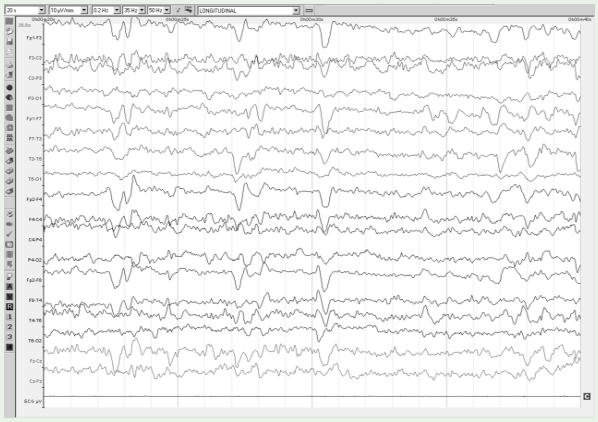

Figure 1: EEG showing severe diffuse slowing with bifrontally predominant triphasic waves.

Discussion and Conclusions

Chemically, VPA is a branched chain carboxylic acid (2-propylpentanoic acid or di-n-propylacetic acid) and is therefore very similar to short-chain fatty acids, making VPA a substrate for the fatty acid oxidation pathways [2]. VPA increases ammonia levels probably through both hepatic (urea cycle) and renal mechanisms. Ammonia is produced by the conversion of glutamine to glutamate, at the renal level, by the enzyme glutaminase. Some authors consider that VPA increases transport of glutamine across the mitochondrial membrane, making glutamine more available for the production of ammonia [3]. Hyperammonemia associated with encephalopathy can be observed in the context of normal liver function (urea cycle disorders), with altered liver function, or related to other factors.

Our case report is an encephalopathy with normal liver function, and with polytherapy as predisponent factor. The neurology literature identifies urea cycle disorders, immature hepatic function, carnitine deficiency, poor nutritional intake, polypharmacy, increased protein load, hypercatabolic state and co-morbid medical illness as risk factors for developing VPA-induced hyperammonemia [4,5]. Although VHE is an uncommon adverse effect, VPA can frequently lead to hyperammonemia. There are papers published showing increased ammonium levels in patients under VPA without clinical expression [6], which highlights the diagnostic value of electroencephalography findings in suspected VHE. The pathogenesis of VHE is not completely understood. Some authors observed ultrastructure alterations of astrocytes in the cortex of hippocampal gyrus and temporal lobe in VHE rats after chronic administration of VPA [7]. There are also reported MRI and proton MR spectroscopic findings in cerebellum white matter and globus pallidus in a patient with VHE [8]. Biochemically, a high ammonium level leads to an increase of glutamine, these raised glutamine levels augments intracellular osmolarity of astrocytes [3], which produces cerebral edema and higher intracranial pressure. Ammonia crosses the blood-brain barrier rapidly and inhibits intracellular glutamate uptake. Excessive NMDA receptor activity triggered by elevated extracellular glutamate increases risk of encephalopathy and also reduces seizure threshold [9]. Recent theories propose that VPA and Topiramate action on GABA receptors leads to excessive inhibition resulting in a clinical encephalopathy [10], and also increased spike and waves from excessive GABA-mediated thalamic inhibition. In agreement with this, Cauli et al demonstrated that increased GABAergic tone in the cerebellum contributes to cognitive impairment in hyperammonemic rats [11]. Furthermore, Palomero-Gallager group reported a neurotransmitter receptor imbalance in motor cortex and putamen in hepatic encephalopathy human post-mortem brain samples [12]. Therefore, these findings suggest that GABA seems to be the mediator of encephalopathy situation, on one hand due to the VPA action on GABA receptors, and on the other hand through hyperammonemia, accordingly, there are VHE cases reported with normal serum ammonia levels [10].

Regarding to EEG findings, tryphasic waves reported in this case, seem to arise from subcortical gray matter [13], in an inhibited cerebral cortex by excessive GABAergic tone in hiperammonemic encephalopathy. Previous cases of VHE in psychiatric patients have been described, but without EEG correlation [14].

In conclusion, physicians should consider valproate-induced hiperammonemic encephalopathy in psychiatric patients under VPA, whom developed acute changes in their mental status. It is important to highlight the diagnostic value of electroencephalography in a patient with acute toxic-metabolic encephalopathy, organic delirium, normal laboratory tests and cerebral MRI. We emphasize the importance of a correct diagnosis of VHE due to its low incidence, due to reversibility, which makes it pathology of obligatory diagnosis. It is basic the withdrawal of AV, being able to associate other treatments in function of the etiology of the process [15].

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