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Valproic Acid and Hepatic Steatosis: A Possible Link? About a Case Report

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ABSTRACT ~ **Background:** *Valproic acid is a mood-stabilizing anticonvulsant. Hepatic injuries are among the occasionally observed adverse effects of this medication.* **Case presentation:** *We present the case of a 47-year-old man who had bipolar disorder for ten years and treated with valproic acid. He demonstrated elevated serum aminotransferases and ultrasonography revealed that hepatomegaly was suggestive of hepatic steatosis.* **Conclusion:** *This case report stresses the importance of a complete drug history and the need for clinicians to be aware of the delayed onset of hepatic injuries.* Psychopharmacology Bulletin. *2016;46(2):59–62.*

Introduction

Valproic acid (VPA) is a widely prescribed treatment in the management of epileptic seizures, bipolar and schizoaffective disorders, social phobias, and neuropathic pain.[1] In Tunisia, VPA occupies an important place in the treatment of bipolar disorder. Despite its clinical benefits, patients receiving VPA chronically may develop hemorrhagic pancreatitis, bone marrow suppression and, more frequently, hepatic injury.[2] Another typical clinical finding of VPA intoxication was the development of nonalcoholic fatty liver disease (NAFLD). It affects 20%–25% of the general population including children. The term NAFLD covers a wide spectrum of hepatic diseases. These diseases include simple hepatic steatosis in 80% of patients, inflammation, cirrhosis and the development of hepatocellular carcinoma.[3,4]

Case Report

A 47-year-old man, with 10 years history of bipolar disorder treated with VPA, presented at our hospital on June 2012. There was no past history of significant illness. His remaining medication was: VPA 1500 mg daily, amisulpiride 600 mg daily and Lorazepam 3.75 mg daily. His body mass index was 32.

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Investigations included routine blood tests, thyroid and renal function test were normal. Serum level of VPA was within the therapeutic range (100 μg/mL). Laboratory results were compatible with liver dysfunction: aspartate aminotransferase (AST) 70 IU/l, alanine aminotransferase (ALT) 123 IU/l. Serum bilirubin was normal. The patient was completely asymptomatic. One month later, AST and ALT levels rose to 10 times normal values. The patient was referred to the Gastroenterology department for further investigation. Tests revealed no evidence of acute viral hepatitis, autoimmune, metabolic or alcohol-related liver disorders. Feeding habits were normal, there was a negative history of contact with chemical and/or toxic products and fecal flow was regular. Ultrasonography revealed that hepatomegaly was suggestive of hepatic steatosis. A diagnosis of Nonalcoholic fatty liver disease (NAFLD) was made. The imputability of VPA was considered strong and the collegial decision between the pharmacovigilance and psychiatry services maintained the drug-induced origin and consequently interrupted the valproic acid that we replaced with Lithium: 1gr/day. Seven months later, serum liver enzymes returned to normal values and hepatic steatosis disappeared, suggesting a certain causal relationship between drug intake and hepatic damage.

Discussion

Based on the histological findings and laboratory results, our patient was diagnosed with Nonalcoholic fatty liver disease (NAFLD), despite being asymptomatic. Nonalcoholic fatty liver disease (NAFLD) is a group of diseases characterized by steatosis and the absence of a secondary cause for hepatic fat accumulation. Steatosis must be documented histologically or with sonography, serum aminotransferases are commonly elevated in patients on VPA therapy; however, this elevation is generally mild (1–3x ULN) and does not involve a rise 7 in serum bilirubin.[5] Patients are mostly asymptomatic or suffer mild symptoms (malaise, lethargy, and anorexia).[6] This form of acute idiosyncratic liver injury is characterized by microvesicular steatosis and cell necrosis of varying degree.

This presentation of VPA hepatotoxicity has a delayed onset from weeks to months, and in some cases even years, following initial exposure and is frequently transient and resolves with dose reduction or drug discontinuation.[3,7–9] In recent years, the association between VPA treatment and NAFLD has been further studied and it is well recognized that long-term use of this drug can induce features of the metabolic syndrome consistent of substantial weight gain, insulin resistance, and lipid abnormalities.[10]

Despite the rich literature regarding NAFLD, VPA has been investigated as a contributing factor for the development of NAFLD, but his role in the development of this liver disease is poorly understood.[4] The authors hypothesized that even if there is a clear association between NAFLD and VPA-treatment, the development of NAFLD may not be the consequence of the action of the VPA-metabolites per se.[11] Similar to many studies, in this case, it may be the consequence of the weight gain and metabolic syndrome induced by VPA.[12–15]

This notion is also supported by results from a rat model of high fat diet and VPA administration, demonstrating increased hepatic steatosis and hepatotoxicity, as well as exacerbation of VPA-induced impairment of mitochondrial β-oxidation.[16] Other mechanisms of VPA induced hepatic steatosis are possibly related to the drug's metabolism, as VPA is primarily metabolized in the liver. One of the major metabolic pathways, accounting for 30%–50% of VPA metabolism, is conjugation, predominantly with glucuronic acid but also other minor conjugation reactions with glutathione, carnitine, coenzyme A, and other amino acids, while the other main metabolic pathway is mitochondrial oxidative reactions, especially β-oxidation, which typically accounts for about 40% of its metabolism.[9] As in other conditions characterized by microvesicular steatosis, it appears that interfering with fatty acids mitochondrial β-oxidation plays a key role in VPA induced hepatic toxicity. Formation of valproyl-CoA causes depletion of intra mitochondrial CoA affecting fatty acid β-oxidation, impairment of ATP production, and inhibition of Carnitine-palmitoyl-transferase I (CPT1) as well as depletion of carnitine stores.[17,18]

Conclusion

Results from the literature indicate that the association is particularly strong in patients who are initially overweight with presenting features of metabolic syndrome. The pathogenic mechanisms through which VPA leads to obesity, metabolic syndrome and increased risk of NAFLD are still an issue for debate. This case report stresses the importance of a complete drug history and the need for clinicians to be aware of the delayed onset of hepatic injuries. This leads us to think of bipolar patients who are found within weak grounds, such as alcoholics, cancer and HIV positive patients. ✤

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