Letter to the editor

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Neuroleptic-induced Toxic Hepatitis

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We present the case of a 25-year old male diagnosed with Paranoid Schizophrenia. He was admitted to Internal Medicine with symptoms consistent with toxic hepatitis. He had no medical background of interest, with sporadic consumption of alcohol and cannabis. The patient was being treated with clozapine 600 mg/day, topiramate 400 mg/day, escitalopram 10 mg/day, biperiden retard 4 mg/day, resperdal consta (risperidone) 50 mg and omeprazole 20 mg/day.

The first psychotic episode was within the context of toxic consumption. Since then, he has been admitted seven times due to relapse in spite of good therapeutic compliance.

Given the poor pharmacological response, a regime was initiated with clozapine in addition to maintaining the administration of risperidone, a maintained improvement being observed. Four months later, the patient was admitted due to the presentation since two weeks earlier of mesogastric colic pain, nausea, abdominal distension and constipation. Normotensive, afebrile and without signs of encephalopathy. The initial analysis showed high levels of GOT (472), GPT (1222), GGT (174) and alkaline phosphatase (116), with bilirubin, protrombin, platelets, amylase and lipase being normal. The abdominal ultrasonography was informed as consistent with toxic hepatitis. Given the suspicion, the medication was withdrawn, the patient being maintained with lorazepam. Two days after his admission, he had a clinical picture of hepatic encephalopathy, with elevated levels of ammonia. A brain CT scan was requested and informed as normal. From the psychiatric point of view, the patient was calm, with a fluctuating sensation of derealization. Neurologically and analytically, he improved in the subsequent days. In the autoimmunity study, HIV, EBV, CMV and anti-HCV Ab were negative. Ceruloplasmin, copper in blood, alpha-1-antitrypsin and TSH levels were normal. Very elevated levels of ferritin (2622) were observed, possibly secondary to the sinusoidal hepatic histolysis.

The most likely cause of hepatic cytolysis is drug-related. Clozapine, olanzapine and quetiapine are the antipsychotics that elevate the transaminases and bilirubin the most while risperidone and ziprasidone have the least effect on them. The neuroleptic-induced toxic hepatitis diagnosis is mainly based on the chronology between the introduction of the hepatotoxic agent and the appearance of the clinical picture and on the exclusion of other causes. If elevation of transaminases is present, the differential diagnosis must be proposed between the transient enzyme elevation, cholestatic or cytolytic hepatitis, or hypersensitivity reaction. Screening must always be made for the hepatic condition of viral, alcoholic or immunoallergic origin.

Up to date, one case of fulminant liver failure,[1] three of cholestatic jaundice hepatitis with eosinophilic elevation,[2-6] and four cases of cholestatic hepatitis[8] have been reported. Markowitz[8,9] presented two cases of elevation of transaminases, alkaline phosphatases and bilirubin. Clozapine-induced hepatotoxicity seems to be idiosyncratic and unpredictable. The hepatotoxicty mechanism is unknown, although risk factors have been described, among them treatment with high doses of clozapine, obesity, alcohol consumption, elderly age, Gilbert's syndrome, concomitant medication with hepatotoxic substances and cocaine abuse. Initiation of the hepatic alteration is variable based on the antipsychotic. It most frequently begins in the first week of the treatment but can be delayed until 17 months after the initiation of risperidone. In the case of clozapine, studies have been published of its initiation between the first and eighth weeks.

In most of the cases treated with clozapine, the hepatic alteration was reversible when the drug was withdrawn. If there are clinical repercussion of the hepatotoxicty, its reintroduction must be avoided. It is recommendable to monitor the hepatic profile during antipsychotic treatment and even more so in those having a risk profile or when there is any significant health problem. Plasma determination of the antipsychotic levels could be useful to detect slow metabolizers.

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