Case Report

Probable atomoxetine-associated acute hepatitis with hyperammonemia in a child with autism spectrum disorder and attention-deficit/hyperactivity disorder: A case report

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ABSTRACT

Drug-induced liver injury is an important cause of acute hepatic dysfunction in children receiving neuropsychiatric medications. Atomoxetine, a selective norepinephrine reuptake inhibitor used in the treatment of attention-deficit/hyperactivity disorder (ADHD), is generally well tolerated, although rare cases of hepatotoxicity have been reported. We describe a 5-year-old boy with autism spectrum disorder and ADHD who presented with fever, respiratory symptoms, and acute irritability. Laboratory evaluation revealed severe transaminitis with hyperammonemia, whereas bilirubin and coagulation parameters remained normal. The child had been started on atomoxetine, memantine, and piracetam 2 months before presentation. Withdrawal of the suspected medications and supportive therapy, including N-acetylcysteine, resulted in progressive clinical and biochemical improvement. This case highlights the importance of considering drug-induced liver injury in children presenting with sudden behavioral deterioration and abnormal liver function tests.

Key words: Atomoxetine, Attention-deficit/hyperactivity disorder, Autism spectrum disorder, Hyperammonemia, Induced liver injury, Pediatric hepatotoxicity

Drug-induced liver injury is an important cause of acute hepatitis and may mimic viral or metabolic liver disease [1]. Several medications used in neuropsychiatric disorders have been associated with hepatotoxicity. Atomoxetine, a selective norepinephrine reuptake inhibitor used in attention-deficit/hyperactivity disorder (ADHD), is generally considered safe; however, rare cases of severe hepatocellular injury have been reported in both adults and children [2,3]. Children with neurodevelopmental disorders frequently receive multiple medications, which may increase the risk of adverse drug reactions. Behavioral changes in such children may obscure underlying metabolic abnormalities, delaying diagnosis.

This case is reported because of the rare association of atomoxetine with acute hepatocellular injury along with hyperammonemia presenting as behavioral deterioration in a child with autism spectrum disorder.

CASE REPORT

A 5-year-old male child was brought in with complaints of cough, cold, and fever for 3 days, followed by breathlessness and increased irritability for 1 day. The child was a known case of autism spectrum disorder with ADHD and language delay. Two months before presentation, he had been started on atomoxetine, memantine, piracetam, and omega-3 supplementation by a pediatric neurologist.

On admission, the child was irritable but responsive. Physical examination revealed wheezing with chest retractions. Vital parameters were stable. Initial management included intravenous fluids, antibiotics, and nebulization.

Laboratory investigations revealed a hemoglobin level of 12.4 g/dL, total leukocyte count 3700/mm^3, and platelet count 247000/mm^3. C-reactive protein was normal. Liver function tests showed markedly elevated transaminases, with aspartate aminotransferase (AST) of 946 IU/L and alanine aminotransferase (ALT) of 1877 IU/L, whereas total bilirubin was within normal limits. Serum ammonia was significantly elevated at 450 mcg/dL. Coagulation profile revealed an international normalized ratio (INR) of 1.1, indicating preserved hepatic synthetic function.

In view of acute hepatitis with hyperammonemia, hepatic supportive therapy was initiated, including N-acetylcysteine infusion (100 mg/kg/day), Vitamin K,

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and L-ornithine. Suspected neuropsychiatric medications were withheld.

Serial investigations demonstrated progressive improvement. On day 3, AST decreased to 175 IU/L and ALT to 877 IU/L, whereas ammonia declined to 295 mcg/dL. By day 5, AST further decreased to 79 IU/L, ALT to 498 IU/L, and ammonia to 198 mcg/dL (Table 1).

The child showed gradual clinical improvement with a reduction in irritability and improved oral intake. He was discharged in stable condition with advice for follow-up and review of medications by a pediatric neurologist. On follow-up after 1 week, the child remained clinically stable with further improvement in liver enzyme levels.

Table 1: Trend of liver enzymes and ammonia levels

Day	AST (IU/L)	ALT (IU/L)	Ammonia (mcg/dL)
Admission	946	1877	450
Day 3	175	877	295
Day 5	79	498	198

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

DISCUSSION

Drug-induced liver injury is a significant cause of acute liver dysfunction and is often a diagnosis of exclusion [1]. Atomoxetine-associated hepatotoxicity is rare but has been documented in the literature [2,3]. The mechanism is believed to involve idiosyncratic hepatocellular injury related to hepatic metabolism of the drug [4].

Drug-induced liver injury may occur through idiosyncratic mechanisms involving immune-mediated or metabolic pathways [5]. The onset of hepatotoxicity typically occurs within several weeks to months after initiation of therapy. In the present case, symptoms developed approximately 2 months after starting atomoxetine, which is consistent with previous reports [3,5].

The biochemical pattern observed was hepatocellular, characterized by markedly elevated transaminases with normal bilirubin levels. Preservation of INR indicated intact hepatic synthetic function, thereby ruling out acute liver failure [6]. Hyperammonemia was a notable feature in this case and likely contributed to irritability and behavioral changes. In children with autism spectrum disorder, such symptoms may be misinterpreted as behavioral worsening rather than metabolic encephalopathy.

Similar cases of atomoxetine-induced hepatotoxicity in children have been reported, showing significant elevation of liver enzymes with improvement following withdrawal of the drug [3,7,8]. The temporal association between drug initiation and liver injury, along with clinical improvement after discontinuation, supports a probable causal relationship.

Hepatotoxicity has also been reported with various psychotropic medications, including those used in neurodevelopmental disorders [9]. Supportive therapy, including N-acetylcysteine, may be beneficial in non-acetaminophen-related liver injury due to its antioxidant properties and improvement in hepatic perfusion [7].

Differential diagnoses considered included viral hepatitis, autoimmune hepatitis, metabolic liver disorders, and other drug-induced liver injury. However, normal bilirubin levels, absence of coagulopathy, and rapid improvement following withdrawal of suspected medications favored drug-induced hepatocellular injury [10,11].

This case emphasizes the importance of considering drug-induced liver injury in children receiving neuropsychiatric medications and highlights the need to evaluate metabolic causes in cases of sudden behavioral deterioration.

CONCLUSION

Probable atomoxetine-associated acute hepatitis with hyperammonemia should be considered in children receiving neuropsychiatric medications who present with severe transaminitis. Early recognition and withdrawal of the suspected drug can lead to favorable outcomes. Behavioral deterioration in children with neurodevelopmental disorders should prompt evaluation for metabolic and hepatic causes.

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