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CASO CLÍNICO

Drug-Induced Hepatitis Caused by Methylphenidate: A Case Report

Hepatite Medicamentosa por Metilfenidato: Um Caso Clínico

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ABSTRACT

Methylphenidate (MPH) is a widely prescribed psychostimulant for the management of attention deficit hyperactivity disorder (ADHD). Although most adverse effects of MPH are transient and reversible, hepatotoxicity remains a rare but potentially serious complication. We present the case of a 12-year-old female patient with ADHD who had been receiving MPH treatment since the age of 8. After three and a half years of therapy, she did blood tests that showed a marked elevation in transaminases and gamma-glutamyl transferase. Extensive evaluation ruled out alternative causes of liver disease, and liver biopsy findings were consistent with drug-induced hepatitis. Discontinuation of MPH resulted in progressive normalization of liver enzyme levels. This case underscores the importance of regular laboratory monitoring during long-term psychostimulant therapy, particularly regarding liver function. Early recognition of abnormal biochemical findings allows for prompt discontinuation of the offending drug, reversal of hepatic injury, and prevention of more severe complications such as liver failure.

Keywords: Adolescent; Attention Deficit Disorder with Hyperactivity/drug therapy; Chemical and Drug Induced Liver Injury/diagnosis; Chemical and Drug Induced Liver Injury/etiology; Methylphenidate/adverse effects

RESUMO

O metilfenidato (MTF) é um psicoestimulante amplamente utilizado no tratamento da perturbação de défice de atenção e hiperatividade (PDAH). Embora os efeitos adversos mais comuns sejam ligeiros e transitórios, a hepatotoxicidade é uma complicação rara, mas potencialmente grave. Apresenta-se o caso de uma adolescente de 12 anos com PDAH, medicada com MTF desde os 8 anos. As análises após três anos e meio do início do tratamento detetaram uma elevação significativa das transaminases e gama-glutamil transferase. A investigação excluiu outras causas de doença hepática e a biópsia hepática revelou alterações compatíveis com hepatite medicamentosa. A suspensão do MTF levou à normalização progressiva das enzimas hepáticas. Este caso reforça a necessidade da vigilância laboratorial durante a terapêutica prolongada com psicoestimulantes, particularmente da função hepática. A identificação precoce de alterações analíticas permite a suspensão atempada do fármaco e a reversão do quadro clínico, prevenindo complicações mais graves, como a insuficiência hepática.

Palavras-chave: Adolescente; Doença Hepática induzida por Produtos Químicos e Fármacos/diagnóstico; Doença Hepática induzida por Produtos Químicos e Fármacos/etiologia; Metilfenidato/efeitos adversos; Perturbação De Hiperatividade e Défice de Atenção/tratamento farmacológico

INTRODUCTION

Methylphenidate (MPH) is a widely prescribed psychostimulant for the treatment of attention deficit hyperactivity disorder (ADHD),[1] one of the most common neurodevelopmental disorders in childhood and adolescence.[2,3]

Hepatotoxicity is a recognized adverse effect, with clinical presentations ranging from asymptomatic elevations in serum aminotransferases to severe liver injury, potentially progressing to acute liver failure requiring transplantation.[1,4]

Drug-induced liver injury (DILI) is defined as acute or chronic hepatic damage attributable to drugs, herbal products, or dietary supplements.[5] It may be classified by clinical phenotype (hepatocellular, cholestatic or mixed), pathophysiological mechanism (intrinsic or idiosyncratic), and histopathological profile.[5,6] Management usually centers on immediate discontinuation of the offending agent (or administration of a specific antidote when available), and prognosis is often favorable with drug withdrawal.[5] However, as DILI is fundamentally a diagnosis of exclusion, exhaustive clinical and laboratory evaluation is required to eliminate competing etiologies.

CASE REPORT

A 12-year-old female patient with ADHD and learning disabilities initiated intermediate-acting MPH 20 mg (0.6 mg/kg) at the age of eight. According to family preferences, medication was suspended on weekends and holidays. After approximately three years, treatment was modified to long-acting MPH 27 mg (0.6 mg/kg) to optimise it.

Three and a half years after treatment initiation, routine laboratory testing (first determination) revealed elevated liver enzymes: alanine aminotransferase (ALT) 375 U/L, aspartate aminotransferase (AST) 239 U/L, and gamma-glutamyl transferase (GGT) 69 U/L. Four weeks later, repeat testing demonstrated further increases (ALT 672 U/L, AST 354 U/L,

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GGT 102 U/L), prompting the immediate cessation of MPH. Bilirubin, alkaline phosphatase, lactate dehydrogenase, prothrombin time, and international normalized ratio remained within normal limits. The patient remained clinically asymptomatic. Past medical history and family history were otherwise unremarkable. Potential toxic agents, including prescribed and non-prescribed substances, were denied.

Physical examination disclosed hepatomegaly extending 3 cm below the right costal margin, without splenomegaly or cutaneous stigmata of chronic liver disease.

Extensive laboratory investigations yielded negative or normal results, including: serum creatine kinase, serologies (hepatitis A, B, C; adenovirus; varicella-zoster virus; parvovirus B19; herpes simplex virus; cytomegalovirus; Epstein-Barr virus; human immunodeficiency virus), toxoplasma, syphilis, alpha-1 antitrypsin (1.14 g/L; reference 0.90 - 2.0 g/L), serum ceruloplasmin (0.26 g/L; reference 0.21 - 0.46 g/L), autoimmune hepatitis antibodies (antinuclear; anti-smooth muscle; anti–liver kidney microsome; anti-mitochondrial; anti-liver cytosolic antigen type 1, anti-soluble liver antigen), gamma globulins, celiac disease serology, ammonia, and plasma amino acids.

Abdominal ultrasound with Doppler confirmed hepatomegaly with increased parenchymal echogenicity but no additional abnormalities. Due to persistent enzyme elevation four months after MPH discontinuation, a percutaneous liver biopsy was undertaken. Histopathology showed preserved parenchyma architecture, portal expansion with mixed inflammatory infiltrate and interface activity, without plasma cells, steatosis, or fibrosis. Lobular findings included mild anisocytosis and scattered mononuclear infiltrates. Hepatic copper concentration was 16.1 µg/g (reference < 250 µg/g).

Over six months, liver enzymes gradually normalized (AST 34 U/L, ALT 27 U/L). The patient remained asymptomatic. A cautious rechallenge was suggested but declined by the mother, despite noting modest deterioration in academic efficiency.

DISCUSSION

Attention deficit hyperactivity disorder has an estimated global prevalence of 7.2% and constitutes one of the most challenging neurodevelopmental disorders.[2,7] Pharmacotherapy remains the cornerstone of management, with MPH widely recognized as first-line treatment.[3] It is generally considered safe, but has also been associated with rare cases of hepatotoxicity, even at therapeutic doses. It most often presents as mild, transient, and asymptomatic increases in aminotransferase levels.[1,4,8]

Only a few cases of clinically significant MPH-induced liver injury have been reported. To our knowledge, only three of these occurred in children.[1,9,10] Unlike our case, all of the reported cases developed symptoms, including pruritus, malaise, anorexia, vomiting, or abdominal pain.

Two published cases involved intravenous MPH.[11,12] The latency period between MPH initiation and hepatotoxicity is clear, but highly variable. It typically occurs within weeks to months. The literature cites timeframes ranging from two hours to a few days,[11,12] two weeks,[13] and one to two months.[1,9,10,14] In our case, the absence of early monitoring precluded precise determination of onset.

Typically, MPH-induced liver injury is self-limiting, resolving within weeks to a few months of drug discontinuation. However, one pediatric patient required liver transplantation.[1] Our patient exhibited enzyme normalization only after six months, suggesting an unusually prolonged course. Potential explanations include severity of the injury (which was not the case), the patient's baseline liver health, and the presence of any additional liver damage. The authors speculate that the PiSS phenotype of α1-antitrypsin may act as a cofactor that prolongs liver injury. This case may represent persistent DILI, defined as hepatic injury lasting beyond three months.[15]

Abdominal ultrasound was performed in five cases.[1,9-11,14] Hepatomegaly, present in this case, was also described in a prior report.[11]

Liver biopsy was obtained in three cases.[1,11,14] In two of these, histopathology revealed portal or periportal inflammation with lymphocytes, plasma cells and eosinophils.[11,14] Our case also showed portal inflammation, but lacked plasma cells. While not mandatory for diagnosis,[5] the biopsy was important for establishing a differential diagnosis and for assessing the extent of the lesion, as it ruled out other causes. The histological signatures of DILI – such as necrosis and apoptosis, cholestasis, neutrophilic portal inflammation, and fibrosis[5,6] – are heterogeneous and lack pathognomonic specificity.[15]

The differential diagnosis between idiosyncratic DILI and autoimmune hepatitis is particularly challenging,[6] given clinical and histological overlap. In this case, the absence of circulating antibodies (although rare, seronegative cases do exist), the liver biopsy not being strongly suggestive (although not entirely exclusionary), and resolution without use of immunosuppressants, favoured DILI. Alternative causes of hepatopathies were rigorously excluded.

A positive rechallenge represents the strongest evidence for causality, but it entails substantial risk, including fulminant

hepatic failure. Therefore, rechallenge should be reserved for indispensable drugs, which was not applicable here. Conversely, spontaneous recovery following discontinuation of MPH is an important criterion in the causality assessment of DILI.

As psychostimulant treatment is typically long-term, we recommend routine biochemical monitoring, particularly of liver enzymes, ideally before treatment initiation and periodically throughout therapy, since most cases of DILI are asymptomatic. Clinicians should be aware that, although rare, MPH-associated hepatotoxicity can progress to subacute liver failure. Drug withdrawal should be promptly considered in cases of unexplained elevation of transaminases or suspected acute liver injury. Comparing the clinical presentation with reported cases in open access pharmacovigilance resources, such as LiverTox, may also support clinical decision-making.

PREVIOUS AWARDS AND PRESENTATIONS

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AUTHOR CONTRIBUTIONS

DVG, MB: Data collection, writing of the manuscript.
SA, SF, SR: Critical review of the manuscript.
All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Legal guardian consent obtained.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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