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Methylprednisolone-induced Toxic Hepatitis After Intravenous Pulsed Therapy for Multiple Sclerosis Relapses

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Abstract: High-dose, intravenous methylprednisolone (MP) is the only recommended first-line treatment for multiple sclerosis relapses. However, there are increasing reports on liver toxicity induced by this treatment regimen. We report of 4 multiple sclerosis patients with no history of viral/metabolic liver disorders or alcohol/hepatotoxic drug intake, who developed hypertransaminasaemia following intravenous MP. In 2 of the patients, liver biopsy showed periportal fibrosis, piecemeal necrosis, and inflammatory cell infiltrates. A rechallenge test confirmed a causal association in 1 case. MP-induced liver toxicity may be more frequent than commonly thought and it is important to report this adverse reaction, which is potentially lethal, and to raise awareness on the potential hepatotoxicity of corticosteroid pulses.

Key Words: liver toxicity, steroid pulses, multiple sclerosis, relapse

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Cases of acute hepatitis related to intravenous methyl/prednisolone (IVMP) therapy have previously been described in patients treated for multiple sclerosis (MS) relapses,[1–5] in a patient with central nervous system vasculitis and in patients with Graves ophtalmopathy. Severe steatohepatitis and liver failure were fatal in another 3 patients treated with prednisolone for lupus erythematosus systemicus, dermatomyositis, and Graves ophtalmopathy (reviewed in Gutkowski et al[2]).

We report 4 cases of liver injury following IVMP therapy (1 g for 5 d) in patients treated for MS relapses for the first time. All patients had normal blood chemistry before treatment, they denied alcohol intake, and no concomitant medications were taken except for lisinopril in case 1. Diagnostic work-up was normal in all patients, except for case 3 (vide infra), and entailed serological tests for ~~HAV, HBV, HCV, EBV, CMV~~ and syphilis, dosage of antinuclear (ANA) and antismooth muscle antibodies (ASMA), antimitochondrial antibodies, liver-kidney microsomal antibodies, iron, serum ferritine, blood lipid profile, serum ceruloplasmin, and liver ultrasound.

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CASE REPORTS

Case 1 (50-y-Old Female, History of Arterial Hypertension)

Transaminases started increasing on day 4, peaked on day 8 [aspartate aminotransferase (AST): 136 U/L, alanine aminotransferase (ALT): 355 U/L, and γ-glutamyl transpeptidase (γGT): 346 U/L], and normalized by day 24.

Case 2 (30-y-Old Female)

Transaminases started increasing on day 3, reached a peak level on day 6 (AST: 157 U/L, ALT: 627 U/L), and returned to normal within 2 weeks.

Case 3 (38-y-Old Woman With Autoimmune Thyroiditis)

Transaminases peaked after 2 months (AST: 109 U/L, ALT: 260 U/L, γGT: 54 U/L) and normalized within another month. The diagnostic work-up revealed positive ANA (1:640) and ASMA (1:80).

Case 4 (24-y-Old Woman)

IVMP was administered in February (followed by a 1-mo oral taper), in July, and in September 2008. Transaminases were dosed before treatment in July (AST: 211 U/L, ALT: 494 U/L) and in September (AST: 315 U/L, ALT: 671 U/L, γGT: 89 U/L). Abdominal ultrasound showed liver steatosis. Liver enzymes gradually returned to normal by November, but newly transiently increased in December (AST: 37 U/L, ALT: 104 U/L), over the period of 1 week, following a rechallenge with IVMP for another MS relapse.

Liver biopsy was performed in cases 3 and 4 and showed, in both the cases, inflammatory infiltrates, focal piecemeal necrosis, periportal fibrosis, and numerous ceroid-laden macrophages.

DISCUSSION

Drug-induced liver injury is mediated by either an intrinsic, dose-dependent, and predictable mechanism, or by an idiosyncratic, dose-independent, and unpredictable mechanism. The clinical expression of drug-induced disease is highly variable, including minimal and asymptomatic liver enzyme elevations, acute or chronic hepatitis, cholestatic liver disease, and acute liver insufficiency. Criteria favorable to a diagnosis include exclusion of alternative causes of liver damage, demonstration of clinical and serological improvement after dechallenge, and the reappearance of alterations after rechallenge.[6]

The conjunction of clinical, laboratory, and histologic data; the exclusion of other causes of hepatic profile changes; and the rechallenge in 1 patient, suggest that hepatitis in our patients was probably related to an idiosyncratic reaction to IVMP treatment except maybe in patient 3. Patient 3 had a positivity for ANA and ASMA and we cannot rule out an autoimmune hepatitis (AIH), although the liver biopsy did not suggest this diagnosis, as there have been reports of AIH developing after methylprednisolone

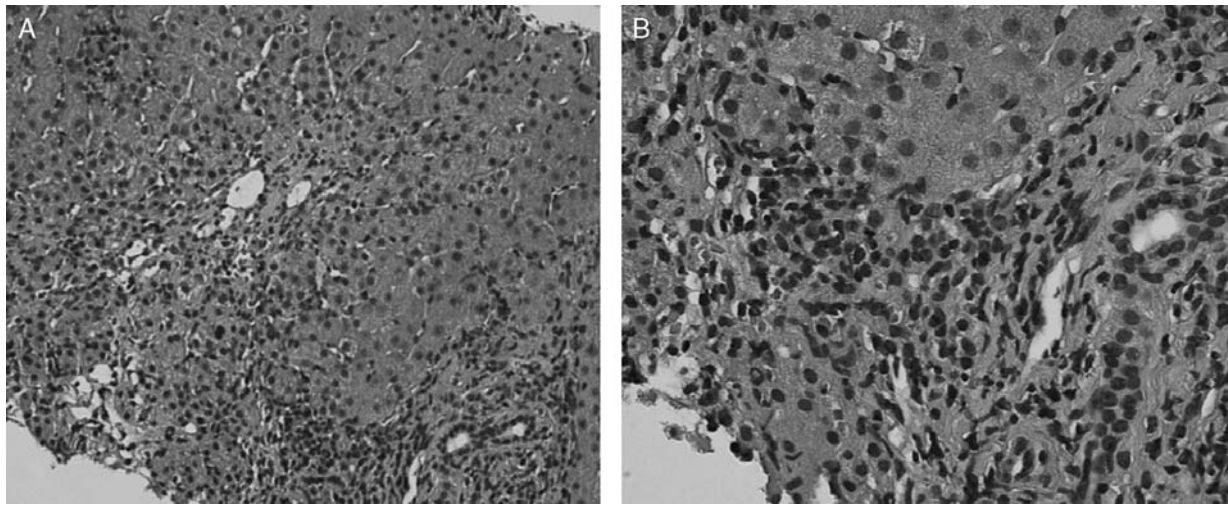

FIGURE 1. Liver biopsy of case 4 showing inflammatory infiltrates in the portal space and focal piecemeal necrosis. Hematoxylin and eosin stain, magnification: ×10 (A) and ×20 (B).

(MP) treatment,[7] the hypothesis being that of a rebound phenomenon after discontinuation of immunosuppressive regimens.

High-dose MP is the only recommended first-line treatment of MS exacerbations. Plasma exchange may be considered for patients who have not responded to MP, although only about one third of patients are likely to respond, and there is insufficient data to support the use of intravenous immunoglobulins as monotherapy for MS relapses.[8,9] As a consequence, treatment of MS relapses becomes challenging if IV steroids are not a safe choice. Further studies on current second-line and third-line treatments such as plasma exchange and intravenous immunoglobulins and on possible alternative treatment regimens are needed.

Glucocorticoid-induced liver toxicity is probably more frequent than it may appear and it is a known entity among hepatologists. However, neurologists and other specialists who are faced with exacerbations of autoimmune diseases may not be aware of the risk of high-dose corticosteroid therapy. Considering the widespread use of short-term high-dose regimens of corticosteroids, it is important to highlight the importance of this possible, potentially lethal, adverse reaction[10–12] ~~(Fig. 1)~~.

REFERENCES

1. Loraschi A, Banfi P, Mauri M, et al. Hepatotoxicity after high-dose methylprednisolone for demyelinating disease. *Clin Neuropharmacol*. 2010;33:52–54.
2. Gutkowski K, Chwist A, Hartleb M. Liver injury induced by high-dose methylprednisolone therapy: a case report and brief review of the literature. *Hepat Mon*. 2011;11:656–661.
3. Rivero Fernández M, Riesco JM, Moreira VF, et al. Recurrent acute liver toxicity from intravenous methylprednisolone. *Rev Esp Enf Dig*. 2008;100:720–723.
4. Das D, Graham I, Rose J. Recurrent acute hepatitis in patient receiving pulsed methylprednisolone for multiple sclerosis. *Indian J Gastroenterol*. 2006;25:314–316.
5. Hofstee HMA, Nanayakkara PWB. Stehouwer CDA. Acute hepatitis related to prednisolone. *Eur J Int Med*. 2005;16:209–210.
6. Lee WM. Drug-induced hepatotoxicity. *New Engl J Med*. 2003; 349:474–485.
7. Takahashi A, Kanno Y, Takahashi Y, et al. Development of autoimmune hepatitis type 1 after pulsed methylprednisolone therapy for multiple sclerosis: a case report. *WJG*. 2008;14: 5474–5477.
8. Sellebjerg F, Barnes D, Filippini G, et al. EFNS guideline on treatment of multiple sclerosis relapses: report of an EFNS task force on treatment of multiple sclerosis relapses. *Eur J Neurol*. 2005;12:939–946.
9. Elovaara I, Apostolski S, van Doorn P, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. *Eur J Neurol*. 2008;15:893–908.
10. Nanki T, Koike R, Miyasaka N. Subacute severe steatohepatitis during prednisolone therapy for systemic lupus erythematosis. *Am J Gastroenterol*. 1999;94:3379.
11. Weissel M, Hauff W. Fatal liver failure after high-dose glucocorticoid pulse therapy in a patient with severe thyroid eye disease. *Thyroid*. 2000;10:521.
12. Dourakis SP, Sevastianos VA, Kaliopi P. Acute severe steatohepatitis related to prednisolone therapy. *Am J Gastroenterol*. 2002; 97:1074–1075.