Recurrent High-Dose Intravenous Methylprednisolone Succinate Pulse Therapy-Induced Hepatopathy in a Patient with Multiple Sclerosis

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Introduction

Multiple sclerosis (MS) is an autoimmune disease of unknown etiology that invades the central nervous system (CNS) but does not involve liver tissue. MS is characterized by T-cell and macrophage infiltrates leading to demyelination of CNS. The well-known treatment of glucocorticoid pulse therapy using a short-acting agent such as methylprednisolone has become established as a standard therapy and is the first-line medical treatment in the acute relapsing period of MS.

Although this therapy is less toxic, various adverse effects of glucocorticoids have been recognized, including hiccups, insomnia, allergic skin rashes, myocardial ischemia, increased blood pressure in hypertensive patients and increased fasting glucose [1]. With regard to the liver, previous reports have indicated that glucocorticoid treatment can cause hepatomegaly, increased glycogen content, vacuolated/hypertrophied hepatocytes, or hemorrhagic hepatic necrosis in dogs and rabbits [2]. In humans, several cases with marked elevation of liver enzymes after high-dose intravenous glucocorticoid pulse therapy have been reported, although other steroids (particularly sex steroids) often induce chronic cholestasis [3].
We describe herein recurrent and reversible elevation of liver enzymes in a girl with MS after high-dose intravenous methylprednisolone succinate pulse therapy (IV-MP).

Case Report

An 11-year-old girl presented with low-grade fever and complaints of mild general fatigue for several days. She had been diagnosed with MS and was admitted to our hospital due to elevation of liver enzymes. In 1996, 40 days before the first episode of hepatopathy, she was treated with 1 g/day of methylprednisolone succinate (Solu-Medrol®, Pharmacia-Upjohn, N.J., USA) IV-MP over 3 days for acute exacerbation of MS (fig. 1). A general physical examination yielded normal results. Laboratory tests showed: alanine aminotransferase, 428 U/l (normal, 5–35 U/l); aspartate aminotransferase, 278 U/l (normal, 10–35 U/l); total bilirubin, 0.8 mg/dl (normal, 0.1–1.0 U/l); lactate dehydrogenase, 287 U/l (normal, 130–250 U/l); and γ-glutamyltransferase, 36 U/l (normal, 0.1–75 U/l). Complete blood count, prothrombin time, partial thromboplastin time, C-reactive protein level and erythrocyte sedimentation rate were normal. Antinuclear antibody was weakly positive with a titer of 1:80 (diffuse pattern). Serum immunoelectrophoresis was negative. Negative results were also obtained for hepatitis B surface antigen and antibodies to hepatitis A, C, D, and E. Thromboplastin time, C-reactive protein level and erythrocyte sedimentation rate were normal. Antinuclear antibody was weakly positive with a titer of 1:80 (diffuse pattern). Serum immunoelectrophoresis was negative. Negative results were also obtained for hepatitis B surface antigen and antibodies to hepatitis A, C, D, and E. Thromboplastin time, C-reactive protein level and erythrocyte sedimentation rate were normal. Antinuclear antibody was weakly positive with a titer of 1:80 (diffuse pattern).

Changes in serum alanine aminotransferase in our patient over a 2-year period. Arrowheads: IV-MP.

Discussion

This patient showed an adverse reaction due to high-dose methylprednisolone sodium succinate, but not to low-dose dexamethasone phosphate. The mechanisms and determinants underlying transient, reversible elevation of liver enzymes after IV-MP in this case remain obscure. Several cases with MS involving autoimmune hepatitis have been reported [4]. However, an association between liver injury and MS, including the coexistence of autoimmune hepatitis, is unlikely in our patient, as both anti-smooth-muscle antibody and antimitochondria antibody were negative and hepatopathy completely resolved.

Viral infectious diseases were unlikely because of the absence of several viral markers. Anaphylaxis is rarely induced following intravenous administration of succinate-containing corticosteroid preparations [5]. Administration of phosphate-containing corticosteroids (i.e. dexamethasone and betamethasone) is generally safe. Succinate ester has thus been suspected to be immunogenic. However, hepatopathy in this patient did not seem attributable to hypersensitivity or allergic reaction, as the skin test was negative to methylprednisolone sodium succinate and anaphylaxis reaction did not develop.

Another possible mechanism of hepatotoxicity in this patient could involve tumor necrosis factor (TNF)-α cytotoxicity. Anti-TNF antibody has been shown to attenu-
ate hepatotoxicity in an animal model of liver disease [6]. TNF-α is induced by the activation of nuclear factor (NF)-κB. Glucocorticoids lead to translocation of the glucocorticoid receptor into the nucleus. In the nucleus, the glucocorticoid receptor can modulate and effectively inhibit NF-κB activity. The reduction of NF-κB attenuates hepatocellular injury. Glucocorticoid pulse therapy reportedly leads to decreased levels of transcriptionally active proinflammatory NF-κB [7]. However, it is unknown whether NF-κB can be reactivated after IV-MP, leading to hepatotoxicity.

Little information is available concerning elevations in serum liver enzyme during and after short-term, high-dose exogenous glucocorticoid treatment. High-dose usage can increase the levels of liver enzymes and cause hepatic injury to liver metabolic function in culture hepatocytes [8]. Glucocorticoid-induced elevations in liver enzymes after suppression in the hypothalamic-pituitary-adrenal axis response have been described in animal models [9]. In humans, acute and severe liver damage has been reported, associated with glucocorticoid pulse therapy 3–17 weeks after the beginning of intravenous treatment [10]. The changes were more prominent with high-dose glucocorticoids than with low doses as in our patient. Similarities to our patient were identified in the absence of changes in bilirubin and γ-GTP. What remains unclear is the mechanism underlying steroid-induced hepatopathy.

**Conclusion**

The present case emphasizes the possible effect of high-dose glucocorticoids in the induction of transient hepatopathy. Corticosteroid-induced liver damage may be more frequent than commonly believed, and this case highlights the importance of adequate follow-up monitoring of liver tests after IV-MP.

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**References**