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CASE REPORT

Hepatotoxicity after high-dose intravenous methylprednisolone in multiple sclerosis patients

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Key Clinical Message

Hepatotoxicity is a rare adverse event of methylprednisolone that should be considered in clinical practice. In patients at risk, we propose liver function surveillance, by measuring hepatic enzymes concentration 15–30 days after methylprednisolone administration. Additionally, we propose ACTH, dexamethasone, or plasma exchange as alternate treatment options for these patients.

Keywords

Exacerbations, glucocorticoids, hepatotoxicity, methylprednisolone, multiple sclerosis.

Introduction

Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system [1]. Corticosteroids are the most used and highly effective treatment of MS relapses, as they target the autoimmune inflammatory response, and have proven to hasten recovery [2]. Among them, high-dose intravenous methylprednisolone (IVMP) is the conventional corticosteroid therapy used for MS and other autoimmune disease exacerbations, with 500–1000 mg/day dosage, during three or five days [3].

Corticosteroid adverse events, such as hyperglycemia related to insulin resistance, tachycardia, insomnia, gastric damage, facial flushing, high blood pressure, and myocardial ischemia, are well known [3]. However, hepatotoxicity of IVMP has not been usually described, and it is not clearly mentioned in the fact sheet. Being a relatively rare condition, liver damage in MS patients after IVMP infusion has been usually related to immunomodulator drugs, autoimmune or viral agents [4]. Lately, some cases report describing the relation between methylprednisolone therapy and hepatotoxicity have been published [5].

In this report, we describe clinical, laboratory, and histological data from three MS patients who developed idiosyncratic hepatotoxicity after IVMP administration. All three patients were hospitalized in the department of Gastroenterology of our tertiary Spanish hospital, and followed by MS division faculty neurologists.

Cases

Written informed consent was obtained from all three patients.

First case

A 28-year-old woman, without any personal or familiar history of hepatopathy. Laboratory work-up was made prior to this episode, showed no alterations. In February 2012, she was diagnosed with relapsing-remitting MS

(RRMS). She was treated with 1000 mg IVMP for 3 days and 500 mg IVMP for additional 3 days, with complete recovery. Considering the patient's request, no disease modifying therapy (DMT) was initiated. Two months later, she experienced a new relapse. She was treated with 1000 mg IVMP for 5 days, and 500 mg IVMP for additional 4 days, with full recovery. Again, due to patient's request, treatment with DMT was postponed. Seven weeks after the last MTP bolus infusion, the patient developed jaundice, choluria, acholia, nausea, and vomiting. Although previous laboratory analysis had been normal, laboratory work-up performed during the episode showed high concentration of liver enzymes, iron, ferritin, and transferrin saturation. Hepatic sonography did not show significant alterations and hepatic biopsy demonstrated only mild architectural damage. Viral and autoimmune hepatitis were ruled out, alternative therapies (naturopathic treatments, nutritional supplements) and alcohol abuse were excluded. One month later, after clinical and laboratory improvement, she was discharged. In February 2013, after a subsequent relapse, she was treated again with IVMP 1000 mg for 3 days (laboratory analysis was not altered prior to this infusion). One month later she developed another severe acute hepatitis episode. Laboratory work-up, sonography, and clinical evolution resembled those from the previous episode. Hepatic biopsy showed a lymphocyte–edematous background and fibrotic changes related to mild chronic hepatitis. DMT with glatiramer acetate was initiated, because of its low hepatotoxicity rate, and IVMP was proposed to be avoided in following MS relapses. Thereafter, she has not experienced any subsequent hepatic symptoms or liver enzyme elevations.

Second case

A 37-year-old male patient, diagnosed with active progressive MS in 2006. In September 2012, he presented an acute episode of transverse myelitis and was treated with 1000 mg IVMP for 5 days with partial improvement. DMT was not initiated. Previous and subsequent blood test did not show any alterations. In September 2013, he experienced a new acute activation, and he was treated with 1000 mg IVMP for 5 days. Six weeks later, laboratory work-up revealed that the liver enzyme levels have been increased 18 times from the physiological concentration. Additionally, there was observed prolonged INR, with no other alterations or clinical manifestations. Viral, autoimmune, and other toxic hepatotoxicity causes (alcohol, counter drugs, etc.) were excluded. Two months later, when the coagulopathy had resolved, an ultrasound-guided liver biopsy showed no inflammatory findings. Regarding the first episode, and the presence of similar cases in the literature, IVMP was avoided in following clinical worsening or relapses. To date, he has not experienced subsequent acute hepatitis episodes.

Third case

A 35-year-old woman, diagnosed with RRMS in April 2014. After a clinical relapse, she was treated with 1000 mg IVMP for 5 days. Previous laboratory work-up showed no alterations. Three days after IVMP infusion, a routine analysis showed 42-fold increase in liver enzyme levels from the physiological concentration. The patient was clinically asymptomatic. Viral, autoimmune, and other toxic hepatitis causes were excluded. When blood tests were again normalized, treatment with glatiramer acetate was initiated. To date, the patient has remained asymptomatic, without further neurological or hepatic exacerbations.

Discussion

Herein, we describe three MS patients who developed severe acute hepatotoxicity after methylprednisolone infusion. Exposure to any other possible etiological agents was discarded. All three patients were classified in the "probable adverse drug reaction" category of the Naranjo scale and the WHO causality assessment criteria. Therefore, it was reasonable to hypothesize that IVMP was the possible cause of hepatotoxicity.

Pharmacological hepatotoxicity is usually idiosyncratic, and is based on individual and genetic susceptibility [1]. It is not related to drug dosage and imitates every possible presentation of acute or chronic hepatitis [1, 6]. Latency period has been described from few days up to six months [1, 2]. Prognosis varies from complete recovery to death [5]. It is determined based on a strong suspicion of the clinician, an accurate anamnesis and the exclusion of other causes [1]. It is confirmed by: (1) the improvement of clinical and laboratory tests after the cessation of the administration of the drug and; (2) in selected cases, the relapse of abnormalities indicative of hepatotoxicity during subsequent exposures [2]. There has been identified as risk factors the presence of viral hepatitis antibodies, age above 50 years, female gender, and smoking history [5]. Unlike, through our patients, only female gender was present as risk factor.

To our concern, a limited number of cases of IVMP-induced hepatotoxicity in MS patients have been reported [2, 7–10]. In patients at risk, there has been proposed a strict monitoring of liver function once a week during pulse therapy, and once a month for the subsequent 12 months [4]. Considering our cases, and the literature review, we propose an additional liver surveillance in

patients that are not at risk. Consequently, we suggest to perform a liver enzymes determination 15–30 days after the last IVMP infusion.

Regarding treatment options, there have been described patients who received dexamethasone in subsequent exacerbations without laboratory alterations or clinical manifestations [2], while others did not receive any treatment or remained asymptomatic in the follow-up period [2]. These different approaches are related to the absence of consensus regarding alternate treatment options for these patients [1]. Our patients did not experience additional exacerbations, but adrenocorticotropic hormone (ACTH), dexamethasone or plasma exchange would have been proposed as treatment options, according with the published data [3] and clinical findings.

Practice Key Points

Hepatotoxicity is a relatively unknown, rare, and potentially fatal, adverse event of methylprednisolone administration. It should be considered thoroughly in day by day clinical practice.

To prevent fatal outcomes or severe permanent liver damage, we propose liver function surveillance, by measuring hepatic enzymes concentration 15–30 days after the last methylprednisolone administration.

In patients at risk (presence of viral hepatitis antibodies, age above 50 years, female gender, and smoking history), a strict monitoring of liver function should be considered: once during pulse therapy, and periodically for the subsequent 12 months.

There is no guideline consensus regarding alternate treatment or medical procedures for these patients. We propose ACTH, dexamethasone, or plasma exchange as alternate treatment options.

Conflict of Interest

The authors declare no conflicts of interest.

Authorship

MHC: involved in manuscript concept and design; clinical assessment; acquisition of data; drafting the manuscript; final approval of the version to be published. JAMA: involved in clinical assessment; acquisition of data; drafting/revising the manuscript; final approval of the version to be published. ALR: involved in clinical assessment; acquisition of data; drafting/revising the manuscript; final approval of the version to be published. MVC: involved in clinical assessment; revising the article for important intellectual content; final approval of the version to be published. ESP: involved in anatomopathological assessment; revising the article for important intellectual content; final approval of the version to be published. GCR: involved in clinical assessment; revising the article for important intellectual content; final approval of the version to be published. CDAF: involved in manuscript concept and design; clinical assessment; drafting/revising the manuscript; final approval of the version to be published; also, acted as supervisor. MLMG: involved in manuscript concept and design; clinical assessment; drafting/revising the manuscript; final approval of the version to be published; also, acted as supervisor.

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