

# High-dose methylprednisolone-induced hepatitis in a patient with multiple sclerosis: A case report and brief review of literature

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## ABSTRACT

Toxic hepatitis is a rare but serious complication of high-dose prednisolone treatment. We report a case of high-dose prednisolone-induced acute hepatitis in a 48-year-old woman suffering from multiple sclerosis that recurred after repeated administration. Timely recognition is paramount to avoid this complication. This report includes a brief review of the literature on methylprednisolone-induced hepatitis.

## KEYWORDS

Hepatitis, methylprednisolone, multiple sclerosis

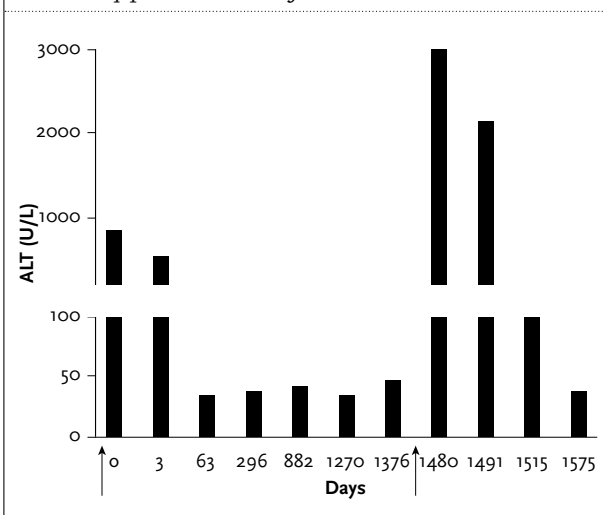
## INTRODUCTION

Multiple sclerosis is a chronic recurrent inflammatory disease of the central nerve system. It follows a heterogenic clinical course due to multifocal demyelination and inflammation resulting in frequent relapses.<sup>1</sup> First-line treatment of relapsing multiple sclerosis is high-dose intravenous administration of methylprednisolone.<sup>2</sup> The beneficial action of methylprednisolone is pleiotropic and most side effects such as truncal weight gain and osteoporosis occur after prolonged administration of the drug. Acute side effects include hyperglycaemia, fluid retention and mental changes such as euphoria and insomnia.<sup>3,4</sup> Methylprednisolone-induced hepatotoxicity is rare but recurs on repeated administration and may be associated with a poor outcome.<sup>5</sup> We describe a patient suffering from multiple sclerosis in whom repeated administration of methylprednisolone led to recurrence of hepatotoxicity.

## CASE REPORT

A 48-year-old woman was admitted to the emergency room in 2012 because of abdominal pain and nausea. In 1998 she was diagnosed with multiple sclerosis on the basis of clinical and radiological findings. In 2008, she was treated with a three-day course of methylprednisolone (1000 mg intravenously) because of a relapse of multiple sclerosis. This led to a pattern of grossly elevated liver enzymes (alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT)), two months following the treatment. The ALAT values returned to normal within four months. In 1998, 2001 and 2002 the patient was treated with a relatively low dose of dexamethasone orally (200 mg/day, 5 days) following a relapse of multiple sclerosis but this did not cause any elevation of the liver enzymes. On admission in May 2012, she reported similar symptoms to the earlier episode of hepatitis in 2008. Laboratory findings were now as follows: ALAT 3028 U/l (normal <35 U/l); ASAT 2384 U/l (<30 U/l); total bilirubin 29 µmol/l (normal <17 µmol/l); lactate dehydrogenase 1037 U/l (normal <490 U/l); gamma glutamyltransferase 182 U/l (normal <35 U/l); thrombocytes  $127 \times 10^9$  E/l (normal  $150\text{--}400 \times 10^9$  E/l); leucocytes  $4.5 \times 10^9$  E/l (normal  $4\text{--}10 \times 10^9$  E/l); haemoglobin 9.2 mmol/l (normal 7.5–10.0 mmol/l) and C-reactive protein 5.7 mg/l (normal <5 mg/l). Some 19 days prior to admission she had been treated with a three-day course of methylprednisolone because of an exacerbation of multiple sclerosis. She was admitted and with conservative management the pattern of elevated liver enzymes eventually resolved. A summary of the course of the ALAT levels with time is shown in *figure 1*. Alternative diagnoses for the onset of hepatitis were eventually ruled out. The patient denied any use of alcohol and was not taking any other medication. Serological

**Figure 1.** Relation between alanine aminotransferase and methylprednisolone infusion



The time course of alanine aminotransferase values in our patient. T values indicate time in days. The arrows indicate the timing of the methylprednisolone infusions. Note that ALAT increases in response to methylprednisolone infusions but returns to baseline values subsequently.

tests for hepatitis B, C, Cytomegalovirus, Epstein-Barr virus, Varicella Zoster and Herpes Simplex virus were all negative. Autoimmune hepatitis was excluded by a negative test of antinuclear antibodies, as well as negative tests for anti-smooth muscle antibodies. Tests for ferritin and transferrin saturation were normal. Abdominal ultrasound was compatible with mild liver steatosis.

Although histological confirmation is lacking, the combination of clinical and laboratory information suggested the diagnosis of methylprednisolone-induced toxic hepatitis. Indeed the unintended rechallenge four years after the first episode with ensuing hepatitis corroborates this hypothesis. We obtained a score of nine points (definitive drug reaction) using the Naranjo scale.

## DISCUSSION

We report a severe idiosyncratic toxic hepatitis from high-dose methylprednisolone. The side effect in this patient was specific for methylprednisolone but not for other steroids such as dexamethasone. An unintentional rechallenge test in 2012 confirmed the association between methylprednisolone and the onset of toxic hepatitis.

In order to obtain a comprehensive overview of high-dose methylprednisolone-induced hepatitis in multiple sclerosis we performed a literature search for PubMed articles for the years 1966-2012 using the keywords: multiple sclerosis, high-dose prednisolone intravenously,

high-dose intravenous methylprednisolone, methylprednisolone, glucocorticosteroid, toxic hepatitis, liver toxicity, hepatotoxicity, acute hepatitis, hepatitis and the MESH terms: hepatitis and multiple sclerosis. Additional articles were obtained through citation snowballing to locate primary sources. A total of five case reports were identified (table 1). It is remarkable that all the case reports written about this topic involve women. This could be explained by the higher incidence of multiple sclerosis in women (3.6 cases per 100,000 person-years) compared with men (2.0 per 100,000 person-years). In addition, the female-to-male multiple sclerosis ratio has increased over the last years.<sup>2</sup> In the reported cases, hepatotoxicity occurred three days to six weeks after intravenous methylprednisolone therapy. ALAT normalised in two weeks to four months after discontinuation of the drug. One patient was treated with glycyrrhizin in addition to withdrawal of methylprednisolone. Glycyrrhizin is an agent that is thought to protect against acute liver injury.

Drug-induced hepatotoxicity is usually idiosyncratic by nature. This reflects tissue injury that occurs without warning and is determined by individual susceptibility.<sup>5</sup> There are two types of idiosyncratic reactions: immunoallergic and non-allergic (metabolic). Immunoallergic reactions are dose-dependent and have a short latency period. Metabolic reactions seem to be dose-independent and have a variable latent period (days to months) to inception of injury.<sup>6,7</sup> Patients may develop hepatotoxicity even six months after discontinuation of a drug.<sup>8</sup> A non-allergic reaction occurs in 0.01% to 1% of patients exposed to the drug. Genetic as well as environmental factors play a role in the occurrence of an idiosyncratic reaction.<sup>9</sup> According to the literature, rechallenge after recovery of hepatotoxicity might not consistently reproduce the injury.<sup>8</sup> This supports the fact that environmental factors play an important role and explains why not all patients included in this review developed hepatitis after the first course of methylprednisolone therapy.<sup>9</sup> Interestingly, some suggest that the interval between pulsed methylprednisolone treatment and onset of elevated ALAT declines after the second episode of hepatitis. This has not been reported in other case reports and is difficult to understand given the non-allergic nature of the side effect (table 1).

Toxic hepatitis due to high-dose methylprednisolone therapy is a rare adverse event. It requires exclusion of alternative diagnoses and timely recognition of this drug-related reaction is important to allow stopping of the drug.<sup>5</sup> According to a survey of all liver transplantations in the USA between 1990 and 2002 (n=2.291) some 15% (n=375) were due to drug-induced acute hepatic necrosis.<sup>10</sup> There are no cases in the collated literature that document liver transplantation resulting from methylprednisolone-induced hepatitis.

**Table 1.** *Methylprednisolone-induced hepatitis in multiple sclerosis patients: review of five cases*

Reference	Age/ Sex	Type of steroid	Course	Dose and duration of treatment	Max. ALAT <sup>a</sup> / ASAT <sup>a</sup> (U/l)	Max. GGT <sup>a</sup> / ALP <sup>a</sup>	Time between treatment and elevation of liver tests	Histology	Conco- mitant treat- ment	Follow-up	Rechal- lenge
Furutama et al. <sup>13</sup>	11/F <sup>a</sup>	MP <sup>a</sup>	1st	1g iv/daily, 3 days	800 / 278	36/NM	1-5 weeks	NM	No	Normalisation of liver tests 2 weeks after MP discontinuation, bed rest and treatment with glycyrrhizin	Yes, twice
		MP	2nd	NM	800/NM	NM/NM	1-5 weeks	NM	No	NM	
		MP	3rd	NM	820/NM	NM/NM	1-5 weeks	NM	No	NM	
Das et al. <sup>14</sup>	48/F	MP	3rd	NM	1600/1450	NM/200	6 weeks	Striking infiltration of parenchyma by lympho- cytes, eosino- phils and plasma cells	No	Normalisation of liver tests after MP discontinuation	Yes, once
		MP	4th	NM	NM	NM	3 weeks		NM	Normalisation of liver tests after MP discontinuation	
Fernández et al. <sup>5</sup>	57/F	MP	1st	1g iv daily, 3 days	2685/1328	71/115	3 days	Acute hepatitis with lytic necrosis and ceroid-laden macrophage hyperplasia	no	Normalisation of liver tests 3 months after MP discontinuation	Yes, twice
		MP	2nd	1g iv daily, 3 days	41/883	NM/NM	5 days		NM	Normalisation of liver tests 3 months after MP discontinuation	
		MP	3rd	1g iv daily, 3 days	1328/2685	56/115	NM		NM	NM	
Gutkowski et al. <sup>6</sup>	24/F	MP	2nd	500 mg iv daily, 6 days	1740/900	50/186	4 weeks	No biopsy (low PT)	Beta- feron	Normalisation of liver tests 3 months after MP discontinuation	Yes, once
			3rd	500 mg iv daily, 6 days	1129/1488	168/164	4 weeks		No	Normalisation of liver tests after MP discontinuation	
Hofstee et al. <sup>15</sup>	46/F	MP	2nd	1g iv daily, 3 days	1095/755	156/140	6 weeks	No biopsy	No	Normalisation of liver tests 4 months after MP discontinuation	Yes, twice
			3rd	1g iv daily, 3 days	1600/900	NM/NM	Few weeks	No biopsy	No	<4 months	
			4th	1g iv daily, 3 days	2350/950	NM/NM	Few weeks	No biopsy	No	<4 months	

ALP = alkaline phosphatase; ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; F = female; GGT =  $\beta$ -glutamyltransferase; M = male; MP = methylprednisolone; NM = not mentioned.

Although hepatitis is a rare side effect, awareness of this toxicity is important so that repeated exposure to methylprednisolone can be avoided. In acute exacerbations of multiple sclerosis, pulsed methylprednisolone treatment has shown to have a short-term benefit on the speed of functional recovery.<sup>11</sup> Patients who fail to recover after methylprednisolone treatment could be treated

with therapeutic plasma exchange.<sup>12</sup> This might be an alternative therapy for patients developing acute hepatitis on methylprednisolone. Other options include IFN-beta which has been shown to reduce relapse rates.<sup>11</sup> There is no screening model that predicts idiosyncratic hepatotoxicity. Therefore, monitoring of serum ALAT following high-dose methylprednisolone treatment

should be considered in order to prevent idiosyncratic hepatotoxicity.

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