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CASE REPORT

Guillain-Barré syndrome following hepatitis E

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Abstract

Guillain-Barré syndrome (GBS) is often triggered by a preceding bacterial or viral infection. Occasionally, it has been observed in association with acute hepatitis A, B and C, and three cases have been previously described in India in which GBS was associated with acute hepatitis E. A molecular mimicry mechanism is supposed to be involved in the pathogenesis of GBS triggered by infectious agents, although the nature of the shared epitopes has not been characterized in most instances, including that in the case of hepatotropic viruses. We report a case of GBS following acute hepatitis E in a European individual. The presence of antiganglioside GM2 antibodies in this patient suggested molecular mimicry involving ganglioside GM2 in the pathogenesis of GBS associated with hepatitis E.

Key words: Gangliosides; Guillain-Barré syndrome; Hepatitis E; Molecular mimicry; Viral hepatitis

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INTRODUCTION

Guillain-Barré syndrome (GBS) is an acute polyradiculoneuropathy presenting, in its classical form, as a rapidly evolving symmetric and ascending motor paralysis with hypotonia and areflexia accompanied by an aleukocytic cerebrospinal fluid with elevated protein level. In over two-third of cases, an infection precedes the onset of neuropathy by 1 to 3 wk. Cytomegalovirus and Epstein-Barr virus account for a large proportion of virus-triggered cases. There are also many reports linking acute hepatitis A, B, and C, with GBS. Hepatitis E is a frequent cause of acute hepatitis in Asia, the Middle East, North Africa and South or Central America. Locally acquired hepatitis E in individuals who have not travelled to endemic areas is, however, becoming an emerging problem in European countries[1,2]. We report a case of Guillain-Barré syndrome in a patient sporadically contaminated in a Western country. This is the third report of GBS in a patient with hepatitis E[3,4], and the first occurring in a patient sporadically contaminated in a Western country. This is the first time, to our knowledge, that ganglioside molecular mimicry is suggested in the pathogenesis of GBS-associated with a hepatotropic virus.

CASE REPORT

A 66-year-old male general practitioner who worked in an urban area consulted due to an acute elevation of liver function tests (AST: 1062 IU/L, ALT: 1813 IU/L, γ-GT: 90 IU/L). Serum bilirubin and alkaline phosphatases were normal. The liver tests had been carried out during a routine check-up and the patient was completely asymptomatic at presentation. Three months prior to consultation his blood tests were normal. The patient had not recently received any hepatotoxic or neurotoxic drugs or vaccinations, and had not travelled abroad during the last year.

A few days later, the patient developed neurological symptoms, beginning with progressive loss of strength in both legs and paraesthesia of the lower limbs, mainly in the evening. Ataxia and neuropathic pain appeared a few days later. These symptoms led the patient to be hospitalized in the neurology department of our institution.

On physical examination, the patient was apyretic. Blood pressure was normal. Examination of heart, lungs and abdomen was unremarkable. There were no features of chronic liver disease and no signs of encephalopathy. The neurological examination showed a stance and gait ataxia with Romberg's sign and distal hypopallaesthesia. Symmetric hyporeflexia in the upper limbs and areflexia in the lower limbs were associated with a severe proximal weakness prominent in the lower limbs.

Routine blood examination showed an AST of 68 IU/L, ALT of 443 IU/L and γ-GT of 94 IU/L. Renal function, electrolytes, glucose, and haematologic values were normal.

Cerebrospinal fluid analysis showed a major increase in protein concentration at 1722 mg/L, associated with a high level of immunoglobulin G, without an increased number of leucocytes. Electrophysiological examinations of the lower limbs demonstrated an acute demyelinating polyradiculoneuropathy.

These findings were consistent with a diagnosis of GBS. Of note, serum antiganglioside antibodies GM2 IgM were positive (Dotzen ganglio profile Ab IgG and IgM by Zentech°). Other antiganglioside antibodies were negative (GM1, GM3, GD1A and GD1B, GD3, GQ1B, GT1A and GT1B). Antibodies to Purkinje cells, to neurons and to myelin were negative. Sulfatide antibodies were negative.

A serological study showed IgM antibodies to hepatitis E (two assays were used: HEV IgM ELISA by Genelabs, with a sensitivity of 93% and a specificity of 99%; and Recomblot HEV IgM by Mikrogen, with a sensitivity of 85.7% and a specificity of 100% in non endemic regions[5]).

Hepatitis B surface antigen, antibodies to hepatitis C, IgM anti-HAV were absent. The following serological tests were also negative: antibodies to HIV, Varicella-Zoster virus and cytomegalovirus. Serology for campylobacter was negative. IgG were positive, with negative IgM, for Epstein-Barré virus, adenovirus and herpesvirus.

A diagnosis of GBS associated with acute hepatitis E was made. Intravenous immunoglobulins were given at a dose of 0.4 g/kg per day for five days. This treatment significantly improved the patient's neurological condition with progressive recovery of walking perimeter and a reduction in neuropathic pain. Liver enzymes completely normalized. Four months later, a near-complete neurological recovery was noted.

DISCUSSION

Hepatitis E has become an emerging cause of acute hepatitis in western countries[1,2]. In most cases, acute hepatitis E in these regions is of autochthonous origin[6]. The most frequent risk factors for hepatitis E, reported in a French survey, were water consumption from a personal water supply, uncooked shellfish consumption, and the recent acquisition of a pet pig[7]. None of these risk factors were present in our patient. It is possible that the contamination was related to the patient's profession as a general practitioner. It has been shown that the clinical evolution of hepatitis E can be different in patients infected sporadically compared with patients infected in endemic areas. In autochthonous cases, the mean age is higher and the prognosis is more severe with a higher rate of fulminant liver failure[8].

Guillain-Barré syndrome is clinically defined as an acute inflammatory demyelinating polyradiculoneuropathy causing limb weakness[9]. Paralysis of muscles develops acutely over a period of days, but can take up to 4-6 wk. In most patients, after a brief plateau, improvement begins with a gradual resolution of paralysis which lasts from weeks to months. The syndrome is considered to be an autoimmune disease triggered by a preceding bacterial or viral infection. The most commonly identified triggering agents are *Campylobacter jejuni*, followed by cytomegalovirus, Epstein-Barr virus, and mycoplasma pneumonia. HIV, shigella, clostridium, haemophilus influenza, as well as hepatitis A, B and C were also identified as triggering agents[10]. In our case, the temporal association between acute hepatitis E and GBS strongly suggested a relation between both disorders.

The mechanism by which infection can trigger GBS is not completely understood. It is thought that the immune system mistakenly attacks myelin or axons by a molecular mimicry mechanism (in which the host generates an immune response against an infectious organism that shares epitopes with the host's peripheral nerves)[11]. The nature of the epitope, although still uncertain, is likely to be a glycolipid. The most attractive candidate targets are gangliosides, which are present in nodal and internodal membranes of nerve fibres[12]. Ganglioside antibodies may perturb nerve conduction and, in a complement-dependant fashion, disrupt the molecular topography of nodal and paranodal proteins and induce motor axonal degeneration[13]. It is postulated that infected cells can produce ganglioside-like epitopes that trigger the immune response. This mechanism of molecular mimicry has been observed for *Campylobacter jejuni* with the implication of several gangliosides (GM1, GD1B, and GQ1B)[14]. The implication of antiganglioside GM2 antibodies in the pathogenesis of GBS related to CMV has been described[15]. It has been demonstrated that CMV-infected fibroblasts express ganglioside-like epitopes that specifically recognize anti-GM2 antibodies[16]. These results suggest that, in CMV-infected GBS patients, infected cells with CMV can express epitopes inducing an immune response against gangliosides.

For GBS related to hepatitis A, B, C, or E, no homologous epitopes to a component of the peripheral nerves have been described to date. We report the first

description of the presence of antiganglioside GM2 antibodies in GBS associated with a hepatotropic virus, suggesting possible molecular mimicry involving gangliosides. This possible relationship should be further documented in the very rare cases of GBS associated with viral hepatitis to confirm the mechanism.

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