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Clinical Report

A case of relapsing Guillain-Barré syndrome associated with exacerbation of chronic hepatitis B virus hepatitis

Elisabeth Chroni,[1] Constantinos Thomopoulos,[2] Spiridon Papapetropoulos,[1] Christos Paschalis,[1○] and Chrisoula Labropoulou Karatza[2]

[1]*Department of Neurology and* [2]*Department of Internal Medicine, University of Patras, School of Medicine, Patras, Greece*

A patient with two episodes of acute polyradiculoneuropathy (Guillain-Barré syndrome) that both occurred during exacerbation of chronic hepatitis B and separated by a 2-year asymptomatic interval is described. The possible causative relation between the neuropathy and the chronic hepatitis B is discussed. *Journal of NeuroVirology* (2003) **9,** 408–410.

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Guillain-Barré syndrome (GBS) has been reported to occur during the incubation period or the icteric phase of acute hepatitis B virus (HBV) hepatitis (Tabor, 1987). However, there is scant information about the development of GBS during the course of chronic HBV infection. We present a patient with relapsing GBS in close temporal relation to exacerbation of chronic hepatitis B.

Case report

A 65-year-old man presented with a 10-day history of numbness in both feet followed by distal leg weakness that gradually extended over a 5-day period to the upper limbs. His past medical history was negative except for well-controlled diabetes mellitus type II. On neurological examination in March 1996, the cranial nerves were intact, all his limbs were symmetrically weak, the tendon reflexes were absent bilaterally, and joint position as well as pinprick sensation was symmetrically diminished in a glove and stocking distribution. The expanded Medical Research Council (MRC) sum score, which was the summation of MRC scores of three pairs of individual muscles in the upper limbs and four pairs in the lower limbs, was 48 (maximum score in healthy individuals: 70). Cerebrospinal fluid (CSF) was acellular with 125 mg/100 ml protein. Blood counts, serum electrophoresis, and testing for porphyria were unremarkable. Neurophysiological study, performed 2 days after his admission, revealed reduced amplitudes of compound muscle and sensory action potentials and prolongation of F-waves for the ulnar and tibial nerves. The patient was started on prednisolone (50 mg daily and tapering-off). He gradually improved being able to walk normally by 1 month, whereas the reflexes returned normally in the arms and remained suppressed in the legs. Six weeks later, in June 1996, the patient again developed numbness and weakness in all his limbs and, in addition, difficulty in swallowing and respiratory failure requiring ventilatory support. The tendon reflexes disappeared whereas the CSF, examined 2 days after the readmission, showed 40 mg/100 ml protein and no cells. A repeat neurophysiological study showed prolongation of distal latencies and generalized slowing of motor conduction velocity in the ulnar and tibial nerves. Needle examination showed no evidence of denervation potentials but poor recruitment of motor units potentials. The patient improved considerably with a course of five plasmaphereses followed by prednisolone and was able to walk with support when discharged home 20 days later. Three months later, the symptoms reappeared and the

Address correspondence to Elisabeth Chroni, Department of Neurology, Medical School, University of Patras, P.O. Box 1045, 26500 Rion, Greece. E-mail: echroni@yahoo.com
○Deceased.
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patient was treated with intravenous immunoglobulin (0.4 g/kg for 5 days) followed by oral administration of prednisolone, finally resulting in complete recovery by March 1997.

Liver biochemistry was slightly abnormal from the beginning of his illness. The alanine aminotransferase (ALT) value gradually mounted to threefold the normal value at 6 months. The serological profile of the patient at that time was as follows: HBsAg (HB surface antigen) positive, HBeAg (HB e antigen) negative, anti-HBe positive, anti-HBc immunoglobulin M (IgM) negative, anti-HBc IgG positive, anti-HDV (hepatitis D virus) negative, anti-HCV (hepatitis C virus) negative, and HBV DNA by the molecular hybridization method at 2235 pg/ml. Antibodies for hepatitis A virus (HAV), Epstein-Barr virus (EBV), cytomegalovirus (CMV) and toxoplasma, as well as anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), anti-mitochondrial antibodies (AMA), and anti-neutrophil cytoplasmic antibodies (ANCA) were not detected. During the next few months the patient developed gradual deterioration of the liver function studies and he presented a decline of albumin, prolongation of prothrombin time, jaundice, and ascites (Table 1). In June 1997, given that the neuropathy was in remission and the danger of developing terminal liver failure was high, it was decided to discontinue the immunosuppressive treatment. There was a gradual improvement of synthetic liver function, with almost normal biochemical indices and no symptoms of liver disease 1 year later (Table 1).

The patient remained asymptomatic with normal liver biochemistries until 2 years later, when the transaminases raised to seven times the upper limit of normal, the HBV DNA was found positive (4 pg/ml) and the anti-HBc IgM showed low-grade positivity (Table 1). Lamivudine was given for the reactivation of the HBV infection. After 1 month and while transaminases were still elevated to five times the upper limit of normal, the patient developed slowly progressive difficulty in ascending stairs, using the intrinsic hand muscles and numbness in the distal limbs. In April 2000, the clinical examination showed symmetrical muscle weakness, which was more prominent in the distal parts of all four, limbs (expanded MRC sum score 42/70), with unobtainable tendon reflexes and distal sensory impairment of all modalities. CSF examination showed 70 mg/100 ml protein and no cells. The patient' s neurological status improved after a course of immunoglobulin and he continued to recover over a period of several months without further immunosuppressive treatment. Two years later, while continuing lamivudine for 20 months, the patient was free of any symptoms, all tendon reflexes had returned, the liver function was normal, and the HBV DNA was negative.

Table 1 Serial measurements of biochemical and virological parameters

Date	*AST (U/l)*	*ALT (U/l)*	*Albumin (g/dl)*	*Total bilirubin (mg/dl)*	*HBV DNA (pg/ml)*
3/1996○	26	57	NR†	NR†	NR†
8/1996	125	154	NR†	0.9	2235
2/1997	105	86	3.4	1.5	12450
6/1997◎	82	60	2.9	3.2	2700
2/1998	36	34	3.6	1.5	Negative
2/1999	33	31	4.8	1.3	Negative
2/2000	29	31	4.5	1.6	Negative
3/2000	89	125	4.4	1.2	4
6/2000#	156	308	3.6	1.2	NR†
10/2000	19	29	4.3	1.0	Negative
2/2002##	18	12	4.0	0.8	Negative
Normal values	5–40	5–40	3.5–5.5	0.1–1.3	

AST: aspartate aminotransferase.
○Diagnosis of Guillain-Barré syndrome.
◎Discontinuation of immunosuppression therapy.
#Reappearance of neurological symptoms—start of lamivudine.
##Twenty months on lamivudine.
†NR: not recorded.

Discussion

The neuropathic clinical features and laboratory findings of the presented patient were compatible with relapsing GBS. On the other hand, the liver function testing was suggestive of exacerbation of chronic HBV hepatitis. Guillain-Barré syndrome has been reported during the course of acute HBV hepatitis (Tabor, 1987; Tsukada *et al*, 1987). Neurologic symptoms typically begin from 3 to 9 weeks after the onset of acute hepatitis, although they can develop before the presentation of hepatitis (Berger *et al*, 1981). CSF analysis might disclosed the presence of HbsAg, elevated protein, and local synthesis of immunoglobulins (Feutren *et al*, 1983). Moreover, HbsAg-positive labeling of immunofluorescence was found around the endoneural small blood vessels and the endoneurium (Tsukada *et al*, 1987). High levels of circulating HbsAg-containing immune complexes were evident in serum and in a comparable titer in the CSF during the acute neurologic syndrome; these complexes were no longer detected after HBsAg clearance and neurologic recovery (Tabor, 1987; Tsukada *et al*, 1987; Feutren *et al*, 1983). Although hepatitis B vaccine was also implicated in causing GBS, it has been shown that the incidence is not higher than the background incidence in the general population. In our patient, the two clearly separated attacks of GBS were synchronous to the active phases of his liver infection. Interestingly, however, the first active phase of liver disease in this case was not compatible with acute HBV hepatitis, because anti-HBc IgM and HBeAg were not detected and decompensated cirrhosis was already evident after a period of 12 months only. Although HBV DNA or HbsAg estimations in the CSF were not available, the high serum HBV DNA at the time of the first GBS attack and the positivity of HBV DNA by molecular hybridization at the second attack indicate active viral replication.

The strong temporal link between exacerbation of GBS and chronic HBV hepatitis and the absence of further neurological relapses once the HBV infection was turned to inactive make possible a causal relationship. Moreover, the time sequence of the neurological manifestations in the presented case did not differ from that reported in acute HBV hepatitis, which is known to be related to GBS. Acute exacerbation of chronic hepatitis, as those seen in this patient, show immunological responses that are quantitatively and qualitatively quite similar to those of acute HBV hepatitis. We have no evidence to suggest the reverse relationship, i.e., that in some way GBS activated the chronic hepatitis as reported in two previous cases (Han *et al*, 1999), because the second GBS attack preceded by the reappearance of liver function abnormalities.

Exacerbation of hepatitis due to immunosuppression is certainly another possibility, given that initiation of immunosuppressive treatment was related to the dramatic increased of ALT and the severity of the first exacerbation of the HBV infection. However, this hypothesis was not supported by the fact that the second attack of GBS occurred shortly after an apparently spontaneous exacerbation of the hepatitis, in the absence of any immunosuppressive treatment.

The initial triphasic course of GBS in our patient should be related to the steroids, which have been shown to modify the natural course of the syndrome, rather than to spontaneous reactivation (Hughes *et al*, 1978). Acute relapses of GBS after asymptomatic intervals of a few or many years, as occurred in this patient, have rarely been reported (Wijdicks and Ropper, 1990). This case had several features that distinguished it from chronic inflammatory demyelinating polyneuropathy (CIDP). These are a) short evolution time with muscle weakness peaked in less than 4 weeks; b) full and rapid recovery with return of tendon reflexes after each attack; c) paralysis of respiratory muscles requiring mechanical support, which is unusual for CIDP; and d) improvement without long-term immunosuppressive medication at the second attack of neuropathy (Wijdicks and Ropper, 1990). Vasculitic neuropathy associated with HBV immune complexes is an unlikely alternative explanation, because this is typically asymmetric (mononeuropathy multiplex) rather than distal symmetrical one, usually accompanied by normal CSF protein, and more importantly axonal and not demyelinative in nature (Chalk *et al*, 1993).

It has been suggested that the association between GBS and viral hepatitis probably reflects an underlying dysimmune mechanism that may be triggered by the virus and can lead to damage through immune complexes (Tsukada *et al*, 1987). The coexistence of two separate attacks of GBS with exacerbation of chronic HBV, irrespective of the underlying pathogenesis, expand further the spectrum of hepatitis-related demyelinating neuropathies, implying perhaps an individual predisposition of the presented patient.

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