CASE REPORT
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Mononeuropathy Multiplex in a Patient with Chronic Active Hepatitis B

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Background Mononeuropathy multiplex is a rare complication during the course of chronic hepatitis B, despite various neuropathies following acute hepatitis B having been reported previously.

Case Report A 30-year-old man presented with sensorimotor symptoms in multiple peripheral nerves. The serological tests for hepatitis were consistent with chronic active hepatitis B. After treatment with oral prednisone combined with an antiviral agent, the sensory and motor symptoms improved and hepatitis B virus replication was reduced.

Conclusions We suggest that chronic immune-mediated neuropathy associated with hepatitis B virus infection should be considered in the differential diagnosis of patients with hepatitis B.

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Key Words chronic hepatitis B, mononeuropathy multiplex.

Introduction

Among the several types of hepatitis, chronic active hepatitis B can cause peripheral neuropathies by vascular- or immune-mediated pathology.[1,2] Previously reported neuropathies in patients with hepatitis B virus (HBV) infection include vascular neuropathies such as polyarteritis nodosa (PAN) and demyelinating neuropathies such as chronic inflammatory demyelinating polyneuropathy and Guillain-Barré syndrome.[3] However, chronic immune-mediated, nonvasculitic mononeuropathy multiplex (MM) in association with chronic hepatitis B has been reported only rarely. We report a case of HBV-related multiple axonal neuropathy that mimicked vasculitic MM, and was complicated by chronic active hepatitis B.

Case Report

A 30-year-old, male HBV carrier complained of pricking and burning discomfort in the distal potions of the first to third fingers of the left hand, and dysesthesia of the left foot of 2 months duration. Despite treatment with medication for the pain at another hospital, the sensory symptoms progressed. By 5 weeks after the onset of the initial symptoms the patient had new complaints of difficulty with extension of the left ankle joint and flexion of all of the fingers on the left hand except for the fifth finger. Just prior to admission to the hospital, paresthesia of the right hand and foot developed. On admission to the hospital, his blood pressure was 120/80 mmHg. The patient had decreased deep tendon reflexes at all four extremities. The initial nerve conduction study (NCS) findings suggested a multifocal sensorimotor mononeuropathy of the axonal type (Table 1 and 2).

An extensive workup for the etiology of MM including fasting blood sugar, cerebrospinal fluid examination, and tests for cryoglobulin and immunoglobulins (IgM, IgG, IgA, and IgE) with serum protein electrophoresis, antinuclear, antineutrophil cytoplasmic, anti-SS-A/B, anti-centromere, anti-SCL70, anti-dsDNA, anti-SM, anti-cardiolipin antibodies, rheumatoid factor, proteins C and S, CH50/C3/C4 complement, lupus-anticoagulant, and thyroid function were negative. However, chronic active hepatitis B was diagnosed by hepatitis serology testing as follows: 1) positive HBsAg, HBeAg, HBV PCR, and anti-HBc, 2) markedly increased titers of HBV DNA (124 ng/mL), and 3) negative anti-HBs and anti-HBe. Aspartate aminotransferase and alanine aminotransferase levels were elevated (47 and 85 U/mL, respectively), but the eryth-

Table 1. Results of motor nerve conduction studies at baseline and follow-up

RT/LT nerve	Segment	Baseline			2-months follow-up		
		Latency (ms)	Amplitude (mV)	NCV (m/s)	Latency (ms)	Amplitude (mV)	NCV (m/s)
Median	TL	3.1/3.4	6.7/2.1		3.4/3.5	9.3/8.4	
	E-W		6.4/1.8	52.2/50.0		9.5/7.5	50.0/44.2
	AX-E		6.3/1.7	52.2/55.0		9.4/8.8	70.6/76.9
	F-wave	NP/NP			22.6/26.6		
Ulnar	TL	2.5/2.9	9.6/9.8		2.5/2.5		
	BE-W		9.4/8.8	56.8/62.1		11.1/17.4	67.6/48.6
	AE-BE		9.0/8.7	53.8/80.8		10.7/16.3	54.1/61.5
	AX-AE		8.6/8.7	58.8/61.5		10.4/16.2	60.2/60.8
	F-wave	26.0/27.2			27.0/25.3		
Tibial	TL	5.4/5.7	6.1/6.2		3.8/3.8	9.3/10.0	
	PF-A		5.5/4.8	46.5/45.7		8.5/8.0	44.8/45.5
	F-wave	55.1/53.1			50.2/51.3		
Peroneal	TL	4.2/4.6	8.0/1.3		3.3/3.4	6.0/4.6	
	FH-A		7.7/1.4	46.8/40.4		5.4/4.0	42.3/40.0
	PF-FH		7.8/1.2	39.7/45.0		4.8/4.0	58.8/60.4
	F-wave	47.3/NP			45.1/48.1		

RT: right, LT: left, NCV: nerve conduction velocity, TL: terminal latency, E: elbow, W: wrist, AX: axilla, BE: below elbow, AE: above elbow, PF: popliteal fossa, A: ankle, FH: fibular head, NP: no potential.

Table 2. Results of sensory nerve conduction studies at baseline and follow-up

RT/LT nerve	Segment	Baseline		2-months follow-up	
		Amplitude (uV)	NCV (m/s)	Amplitude (uV)	NCV (m/s)
Median	F-W	4.2/NP	44.8/NP	9.4/NP	46.4/NP
	P-W	13.0/NP	44.4/NP	16.0/NP	47.2/NP
	W-E	20.0/6.1	55.3/55.6	15.0/4.9	52.8/52.6
	E-AX	17.4/6.1	54.7/56.9	19.0/30.0	75.0/61.1
Ulnar	F-W	13.7/14.0	46.4/45.8	9.1/9.8	53.8/44.8
	W-E	19.0/11.0	56.1/54.3	15.0/36.0	49.8/62.9
	E-AX	14.7/14.0	62.1/60.3	13.0/31.0	45.5/68.4
Radial	W-F	5.5/12.0	47.4/46.2	11.0/10.5	53.8/51.6
Sural	MC-A	5.4/4.6	37.1/34.2	11.0/7.5	53.8/41.7

RT: right, LT: left, NCV: nerve conduction velocity, F: finger, P: palm, F: forearm, MC: middle calf.

rocyte sedimentation rate, and blood urea nitrogen, and serum creatinine levels were all within normal limits.

We initially thought that our patient had hepatitis-B-related PAN because he had three of the associated features (i.e., MM, chronic HBV infection, and myalgia), as per the American College of Rheumatology 1990 criteria for the diagnosis of PAN.[4] Treatment with methylprednisolone pulse therapy (1 g intravenously for three consecutive days) followed by oral prednisone (1 mg/kg/day) was started together with an antiviral agent (100 mg lamivudine).

A left sural nerve biopsy revealed no evidence of inflammatory cell infiltration or necrotic changes in the vessels walls. Semithin slabs of the sural nerve exhibited markedly reduced numbers of myelin fibers. We performed abdominal visceral angiography on the hepatic, renal, and superior mesenteric arteries to rule out systemic vasculitis. The results of the angiography were within normal limits and did not reveal multiple small aneurysms or arterial constrictions. The sensory and motor symptoms had improved 2 months later, and the HBV replication was reduced (follow-up HBV DNA: 2,230 pg/mL). The follow-up NCS showed improvement in the compound motor action potential and sensory nerve action potential (SNAP) amplitudes compared to the previous NCS findings, except for an absent SNAP over the finger-to-wrist segments of the left median nerve (Table 1 and 2).

Discussion

MM is a painful asymmetric sensory and motor peripheral neuropathy involving isolated damage to at least two separate nerve areas. It is a syndrome of diverse causes including diabetes mellitus, demyelinating, infectious, or neoplastic etiol-

ogy. In association with chronic active hepatitis B, MM associated with PAN is relatively common. Our case manifested with multifocal sensorimotor mononeuropathy accompanied by chronic active hepatitis B, similar to vasculitic neuropathies such as PAN. PAN is a necrotizing vasculitis of medium-sized arteries; its most prominent clinical manifestations include variable signs such as MM, weight loss, livedo reticularis, hypertension, abnormal renal blood tests, myalgia and arthritis, testicular pain, HBV infection, evidence of vasculitis on abdominal angiography, and abnormal nerve biopsy. The presence of three or more of these ten factors is associated with PAN with a sensitivity of 82.2% and a specificity of 86.6%.[4] Furthermore, HBV infection has been reported in around 30% of patients with PAN, although PAN is a rare complication of hepatitis B.[1,5] In our patient, a sural nerve biopsy did not disclose evidence of vasculitis, despite marked loss of myelinated fibers. However, the absence of vasculitis in the biopsy specimens dose not exclude vasculitis for several reasons: 1) multifocal vasculitis may occur in a more proximal part of the nerve (sampling bias), 2) the confirmative rate of specific vasculitis by biopsy is low,[6] and 3) sural nerve biopsy results may only provide information about the small arteries, thereby missing the vasculitis of medium-sized arteries (as in PAN). We therefore performed abdominal visceral angiography to seek evidence of vasculitis in the medium-sized to small arteries; the sensitivity and specificity of abdominal angiography in PAN are reported to be 89% and 90%, respectively. According to Hekali, 2- to 5-mm-sized and multiple (≥10) aneurysms on abdominal angiography are strongly supportive of a diagnosis of PAN.[7] Furthermore, the evidence of vasculitis in 80% of all patients with PAN may be established angiographically, although the clinical significance of angiography for investigation in suspected PAN might be controversial.[8] In our case, we thought that the diagnosis could be nonsystemic small-vessel vasculitic neuropathy associated with HBV infection, although negative hisotopathologic and angiographic results do not completely exclude the presence of localized PAN.

In general, an immune-mediated neuropathy should be considered if other causes of multifocal neuropathies, including diabetes mellitus and vasculitic neuropathies, have been excluded.[9] The beneficial response to steroid treatment also raised the possibility of a chronic immune-mediated neuropathy. The chronic immune-mediated neuropathies are a diverse group of disorders that result from immune-mediated damage to the peripheral nerves. Chronic hepatitis B is not only a recognized risk factor for the development of an immune-mediated neuropathy, but also a common infection, with it being estimated that there are more than 300 million sufferers worldwide.[10] The underlying pathology and mechanisms of the peripheral neuropathy following HBV infection have not been elucidated. However, immune-mediated neuronal damage secondary to the direct action of the virus itself on the nerve fibers, or deposition of immune complexes of HBsAg and HBeAg on the vasa nervorum can lead to peripheral neuropathies. In addition, viral replication might be an important factor in the disease activity or pathogenesis, as suggested by the high titers of HBV DNA and the improvement in clinical symptoms after the administration of antiviral agents.[11] Our patient improved clinically with the gradual attenuation of HBV replication after treatment with lamivudine.

In summary, we have presented an interesting case with steroid-responsive sensorimotor MM associated with chronic active hepatitis B that was not accompanied by any evidence of vasculitis. Early diagnosis and treatment in an immune-mediated neuropathy are very important for the control of disease activity and progression. If peripheral sensory or motor symptoms develop in patients with hepatitis B, chronic immune-mediated neuropathy associated with HBV infection should be considered in the differential diagnosis.

Conflicts of Interest

The authors have no financial conflicts of interest.

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