Comprehensive analysis of patients with neuromyelitis optica spectrum disorder (NMOSD) combined with chronic hepatitis B (CHB) infection and seropositive for anti-aquaporin-4 antibody

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ABSTRACT

Previous research indicated the association between hepatitis B virus (HBV) infection/vaccination and the onset of demyelinating diseases. However, most of these studies were single case reports, and comprehensive data are still scarce. Here we present a comprehensive analysis of 10 patients with neuromyelitis optica spectrum disorder (NMOSD) combined with chronic hepatitis B (CHB) infection and seropositive for anti-aquaporin-4 antibody (AQP4-Ab). Demographic, clinical, laboratory, neuroimaging, outcome, and follow-up data of the 10 patients were retrospectively analyzed. The median age at the onset of NMOSD was 35 years (range 25-43). Nine patients were female (90%). All patients were positive for HBsAg and had been diagnosed with CHB earlier than with NMOSD. One patient had an autoimmune disease. All patients had normal thyroid function. Paresthesia and visual impairment were the most common clinical symptoms. The cerebrospinal fluid (CSF) parameters (protein and glucose) were normal in 10 cases, whereas slightly higher CSF white blood cell count was detected in 3 patients. The brain and spinal cord magnetic resonance imaging findings were abnormal in 8 patients. All patients were treated with hormone and immunosuppressive therapy, and anti-HBV agents. Patients with detectable serum HBV DNA were more prone to liver damage after receiving high doses of corticosteroids. In 8 patients, the symptoms improved before they were discharged. Two patients with optic neuritis (ON) maintained the symptoms. A month later, 1/8 patient had recurrence of symptoms, and one ON patient progressed to NMO. Overall, the characteristics of NMOSD patients with CHB and seropositive for AQP4-Ab are usually nonspecific. Abnormal liver function test results in NMOSD patients should be a warning of possible CHB infection, and the treatment should be modified accordingly.

KEY WORDS: Aquaporin-4; AQP4; neuromyelitis optica spectrum disorder; NMOSD; hepatitis B; HBV; CHB; liver function
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INTRODUCTION

Patients with hepatic disorders can develop neurological complications, involving both the central nervous system (CNS) and peripheral nervous system (PNS) [1]. Chronic hepatitis B (CHB) infection is a global health problem with more than 2 billion people infected worldwide, and among these people, 360 million are estimated to have chronic liver disease [2]. In China, with a high hepatitis B virus (HBV) prevalence, approximately 120 million people are chronically infected with HBV [3].

About 20% of HBV patients develop extrahepatic manifestations [4]. Different studies or case reports showed that HBV infection and vaccination are associated with the onset of CNS demyelinating diseases, such as multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), and transverse myelitis (TM) [5-9]. For example, Zhao et al. [6] showed that CHB infection may lead to ON worsening [6]. Heekin et al. [10] described a patient who developed seronegative neuromyelitis optica spectrum disorder (NMOSD) after the exposure to recombinant hepatitis B vaccine [10]. However, little attention has been given to the clinical features of anti-aquaporin-4 antibody seropositive (AQP4-Ab[+]) patients with NMOSD and CHB, and the current research has been limited to case reports. In this study, we present a comprehensive analysis of clinical and laboratory data, magnetic resonance imaging (MRI) results, treatment method and

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clinical outcomes of 10 Chinese patients with NMOSD combined with CHB infection, and seropositive for AQP4-Ab. To the best of our knowledge, this is the first clinical study analyzing the features of NMOSD combined with CHB infection.

MATERIALS AND METHODS

Clinical data collection and definitions

We retrospectively reviewed the clinical data of 275 patients with NMOSD hospitalized at the Third Affiliated Hospital of Sun Yat-sen University, from June 2006 to January 2016. A total of 10 patients with NMOSD combined with CHB infection were recruited in our study. The diagnosis of CHB was confirmed [11] if a patient was serologically positive for hepatitis B surface antigen (HBsAg) for more than 6 months, with or without positivity for hepatitis B e antigen (HBeAg). NMOSD was diagnosed according to the 2006 [12] and 2015 diagnostic criteria [13]. Physical disability in patients was measured by the Expanded Disability Status Scale (EDSS). Patients with human immunodeficiency virus (HIV), syphilis, hepatitis C, or other infectious condition that could affect the outcome were excluded from the study. The details of the enrollment process are presented in Figure 1. Demographic data, clinical and laboratory results, MRI findings, treatment method, and clinical outcome were recorded for the 10 patients (Tables 1-4).

Laboratory measurements

Venous blood samples were obtained from the patients after overnight fast. The following parameters were measured: anti-aquaporin-4 (AQP4) antibody (NMO-IgG), antinuclear antibody (ANA) titer, anti-double stranded DNA (anti-dsDNA), anti-Sm antibody, anti-Ro/Sjögren's-syndrome-related(SS)A and anti-La/SSB antibodies, anti-neutrophil cytoplasmic antibodies (ANCAs), rheumatoid factor (RF), thyroid markers, markers of HBV infection (HBsAg, HBeAg, HBeAb, HBcAb, and HBV DNA), and a marker of liver function alanine transaminase (ALT). Cerebrospinal fluid (CSF) differential cell count, glucose, protein, and chloride levels were also evaluated. All CSF samples were negative for oligoclonal bands (OCB).

NMO-IgG was detected with an anti-AQP4 antibody test using AQP4-transfected cell line from a commercial Biochip kit (Euroimmun, Lubeck, Germany).

MRI scans of the brain and spinal cord were performed using a GE 1.5 T MRI scanner (General Electric, Milwaukee, Wisconsin, USA). The slice thickness of the axial scans was 5 mm. All images were analyzed by experienced neuroradiologists.

Treatment

Intravenous high-dose methylprednisolone (IVMP, 1.0 g) was administered for 5 days to treat NMOSD, then gradually tapered by an oral steroid therapy for 2-8 weeks [14-16]. Azathioprine (AZA) or other immunosuppressive medications were used in combination [17]. Anti-HBV drugs, such as Entecavir Tablets or Heptodin, and other liver protective drugs (i.e. glutathione [GSH] or polyunsaturated phosphatidylcholine [Essentiale]) were included in HBV therapy.

Statistical analysis

Statistical analysis were performed using SPSS for Windows, Version 16.0. (SPSS Inc., Chicago, USA). Numerical

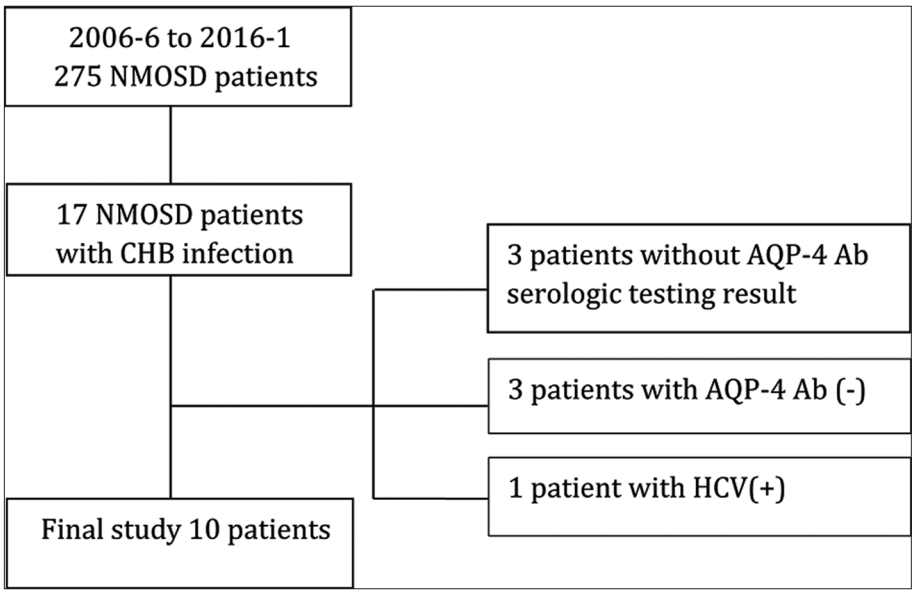

FIGURE 1. Inclusion and exclusion criteria for patient selection. From June 2006 to January 2016, 275 patients with neuromyelitis optica spectrum disorder (NMOSD) were identified at our hospital. There were 17/275 patients with NMOSD combined with chronic hepatitis B (CHB) infection. Out of the 17 patients, 3 patients had not undergone AQP4-Ab serologic testing, 3 patients were negative for AQP4-Ab, and 1 patient was positive for hepatitis c virus (HCV). The remaining 10/17 patients with NMOSD combined with CHB and seropositive for AQP4-Ab were enrolled in this study.

TABLE 1. Demographic and clinical characteristics of patients with NMOSD and HBV infection

Patients	1	2	3	4	5	6	7	8	9	10
Age/Gender	26/F	34/F	25/F	37/F	35/F	48/F	40/F	35/F	43/F	28/M
Age at HBV diagnosis	10	Preexisting	22	27	Preexisting	Preexisting	38	Preexisting	40	27
Age at the onset of NMOSD	26	32	25	37	35	43	40	35	43	28
Disease duration (months)	8	24	2	5	1	60	24	7	4	12
Onset						+				
ON only		+			+					+
TM only	+		+		+		+	+	+	
ON+TM				+						
EDSS										
Admission	5	7	5	4	3.5	5.5	3.5	4.5	4	3
Discharge	3.5	6	4.5	3.5	3	5.5	3	4	3	3
Clinical features										
Dizziness	+	+	-	-	-	-	-	-	+	-
Nystagmus	-	-	-	-	-	-	-	-	-	-
IHN	-	-	+	-	-	-	-	+	-	+
Bulbar paralysis	+	-	-	-	-	-	-	-	-	-
Bowel or bladder dysfunction	-	+	+	-	+	-	+	-	-	-
Visual impairment	+	+	+	+	-	+	+	+	+	+
Motor deficit	+	-	+	+	+	-	+	-	-	-
Sensory disturbances	+	+	+	+	+	-	+	+	+	-
Neuropathic pain	-	+	+	+	+	-	-	+	+	-
Pruritus	-	-	-	-	-	-	-	-	-	-
Vision										
OD	0.6	0.6	0.2	0.8	N	0.03	NA	1	Light perception	0.6
OS	0.6	0.8	0.8	1	N	0.09	NA	0.02	1	0.6
Diagnosis	NMO	NMO	NMO	NMO	NMO	ON AQP4-Ab(+)	NMO	NMO	NMO	ON AQP4-Ab(+)

NMOSD: Neuromyelitis optica spectrum disorder; HBV: Hepatitis B virus; EDSS: Expanded Disability Status Scale; F: Female; M: Male; ON: Optic neuritis; IHN: Intractable hiccup and nausea; NA: Not available; N: Normal; AQP4-Ab(+): Seropositive for anti-aquaporin-4 antibody; TM: Transverse myelitis; OD: Oculus dexter; OS: Oculus sinister

variables were presented as mean ± standard deviation (SD) or median (range), and categorical variables were expressed as percentages.

RESULTS

Clinical features of patients

From June 2006 to January 2016, 275 patients with NMOSD were identified at the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. Of these 275 patients, a cohort of 10 NMOSD patients with CHB (1 male and 9 females) were enrolled in this study (Figure 1 and Table 2). The mean age was 34.40 ± 6.60 years (range: 25-43) at the onset of NMOSD. CHB was diagnosed earlier than NMOSD in all patients. The duration of NMOSD ranged from 1-60 months, median was 7.5. The EDSS was 4.50 ± 1.18 at the time of admission, and declined to 3.90 ± 1.10 after the patient's discharge. The onset of vision loss was reported in 3 patients (i.e., in patient 2, 6, and 10), and 6 patients showed the onset of spinal cord symptoms. Only patient 4 had combined the onset of vision loss and myelitis. Paresthesia and visual impairment were the most common clinical symptoms. Almost all of the patients had visual impairment, except patient 5 who had normal binocular vision and patient 7 in which eye examination was not performed. Motor deficit and neuropathic pain were also relatively common symptoms among the 10 patients. Two patients (6 and 10) were diagnosed with ON and were seropositive for AQP4-Ab at the time of admission.

Serological and CSF findings

A mild inflammatory response was observed in the CSF of 3 patients (5, 8, and 9), in other cases, CSF and biochemistry values were normal. Only patient 5 had an autoimmune disease (SS). ANCAs and abnormal thyroid function were not detected in the 10 patients. Two patients (5 and 10) were HBeAg positive. Moreover, 5 patients (3, 4, 5, 7, and 10) who had detectable serum HBV DNA, showed different degrees of liver damage after receiving therapy with corticosteroids.

MRI findings

MRI was performed in all 10 patients. The brain and spinal cord MRI findings were normal in 2 patients with ON (6 and 10). Abnormal brain MRI results were found in 3 patients (1, 3, and 5). Lesions in the medulla oblongata were observed in 2 patients (1 and 5). Cervical or thoracic spinal cord lesions were detected in 3 patients (4, 5, and 8) and

TABLE 2. Biochemical parameters of patients with NMOSD and HBV infection

Patients	1	2	3	4	5	6	7	8	9	10
CSF index										
WBCs (106)	0	0	6	2	17	8	0	31	29	4
Protein (g/l)	0.14	0.06	0.32	0.52	0.31	0.28	0.01	0.144	0.1	0.12
Glucose (mmol/l)	3.39	3.8	2.81	2.87	2.57	3.67	4.39	3.49	3.45	4.01
Chloride (mmol/l)	120.6	133.2	127.9	121.7	121.1	127	125.2	122	125.9	123.8
OCB	-	-	-	-	-	-	-	-	-	-
Serum index										
NMO-IgG (AQP4-Ab)	+	+	+	+	+	+	+	+	+	+
anti-Ro/SSA	-	-	-	-	+	-	-	-	-	-
anti-La/SSB	-	-	-	-	+	-	-	-	-	-
ds-DNA	-	-	-	-	-	-	-	-	-	-
RF	-	-	-	-	-	-	-	-	-	-
ANCAs	-	-							-	
FT3 (pmol/l)	6.1	3.3	4.3	3.04	4.06	3.7	4	3.9	5.5	3.4
TSH	2.09	1.5	0.62	0.155	3.304	0.53	1.2	1.33	2.2	0.57
HBV infection condition										
HBsAg	+	+	+	+	+	+	+	+	+	+
HBeAg	-	-	-	-	+	-	-	-	-	+
HBeAb	+	+	+	+	+	+	+	+	-	+
HBcAb	+	+	+	+	+	+	+	+	+	+
HBV-DNA	<100 IUml	<100 IUml	2.94 E^{+03}	1.05 E^{+03}	7.86 E^{+02}	2.68 E^{+02}	1.04 E^{+02}	<100 IUml	<100 IUml	6.09 E^{+04}
Liver functionALT (U/l)										
After hormone therapy	24	28	70	56	120	34	45	20	20	207
Discharge	28	18	65	63	67	31	34	20	11	75

NMOSD: Neuromyelitis optica spectrum disorder; HBV: Hepatitis B virus; CSF: Cerebrospinal fluid; WBCs: White blood cells; OCB: Oligoclonal bands; NMO-Ig (AQP4-Ab): anti-aquaporin-4 antibody; anti-Ro/SSA: anti-Ro/Sjögren's-syndrome-related (SS) A antibody; anti-La/SSB: anti-La/Sjögren's-syndrome-related (SS) B antibody; ds-DNA: Double stranded DNA; RF: Rheumatoid factor; ANCAs: Anti-neutrophil cytoplasmic antibodies; FT3: Triiodothyronine; TSH: Thyroid-stimulating hormone; ALT: Alanine transaminase

TABLE 3. MRI features of patients with NMOSD and HBV infection

Patients	1	2	3	4	5	6	7	8	9	10
Brain lesions										
Brain lobes			+							
Basal ganglia	+									
Pons										
Medulla oblongata	+				+	-	-	-	Thoracic MR(+)	-
MRI activity	-	-	Brain MR(+),CervicothoracicMR(-)	-	Brain MR(-),CervicothoracicMR(+)					
Spinal cord lesions										
C	-	-	C5-6	C2-6	C4-C6	-		C2-5	-	-
T	-	T2-5	T2-L1			-		-	T7-8	-
C and T			+			-	C7-T12			

NMOSD: Neuromyelitis optica spectrum disorder; HBV: Hepatitis B virus; MRI: Magnetic resonance imaging; C: Cervical cord; T: Thoracic cord; C and T: Cervical and thoracic cord

TABLE 4. Treatment and outcomes of patients with NMOSD and HBV infection

Patients		1	2	3	4	5	6	7	8	9	10
Early standard corticosteroid therapy (<7 days of the onset)		NO	Yes	Yes	NO	Yes	Yes	Yes	NO	NO	NO
Azathioprine		75 mg qd	50 mg qd	50 mg qd	50 mg	50 mgqd	75 mg qd	100 mg qd	50 mg qd	50 mg qd	50 mg qd
Anti-HBV drugs		IFN	Entecavir Tablets	Entecavir Tablets	Entecavir Tablets	Entecavir Tablets	Entecavir Tablets	Entecavir Tablets	Entecavir Tablets	Entecavir Tablets	Entecavir Tablets
Discharge		Improved	Improved	Improved	Improved	Improved	Same	Improved	Improved	Improved	Same
Follow-up	1 month	Stable	NA	Stable	Stable	Stable	Stable	NA	Relapse	Stable	Progressed to NMO

NMOSD: Neuromyelitis optica spectrum disorder; HBV: Hepatitis B virus; qd: one a day; IFN: Interferon; NA: Not available

2 patients (2 and 9), respectively, while both types of lesions were detected in patient 3 and 7. Enhancement on MRI was observed in 3 patients (3, 5, and 9). Representative MRI scans of patients with NMOSD and CHB, and positive for AQP4-Ab are shown in Figure 2.

Response to corticosteroid therapy and clinical outcomes

Five patients received high-dose corticosteroids, in the first week following the admission. The remaining 5 patients delayed the therapy for various reasons. All the patients received an immunosuppressive therapy (AZA 50-100mg/day) and anti-HBV agents such as interferons (IFNs), Entecavir Tablets, or Heptodin.

In 8 patients, the symptoms improved before they were discharged. Two patients with ON maintained the symptoms. After 1 month, patients 2 and 7 lost to follow-up, patient 8 had recurrence of symptoms, and patient 10 progressed to NMO. Other patients maintained a stable condition.

DISCUSSION

CHB infection is still a significant medical problem in developing countries. HBV vaccination and infection have been associated with immunological and neurological disorders, such as MS, encephalomyelitis and ON [18]. Although the exact pathophysiological mechanisms remain unknown, it was proposed that molecular mimicry and immunological cross-reactivity between HBsAg and myelin antigens lead to the development of demyelinating diseases in the CNS and PNS [19]. HBsAg share high sequence homology with myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG), where the viral/protein mimicking sequences may become targets of antibody response, and consequently induce the degradation of the myelin sheath as well as lead to further neurodegeneration [20-26].

Other studies showed that T-cells that recognize specific epitopes of AQP4 protein could be detected in NMO patients, and indicated that the AQP4-specific T cells might be involved in the pathogenesis of NMO by enhancing/maintaining the autoimmune process or by initiating the inflammation and subsequent production of anti-AQP4 antibodies [27-31]. Molecular mimicry of infectious agents that involves T cells has also been suggested as a mechanism underlying the demyelination of the CNS following HBV vaccination. However, additional studies are required to confirm and explain the association between HBV vaccination and onset of demyelination [32,33].

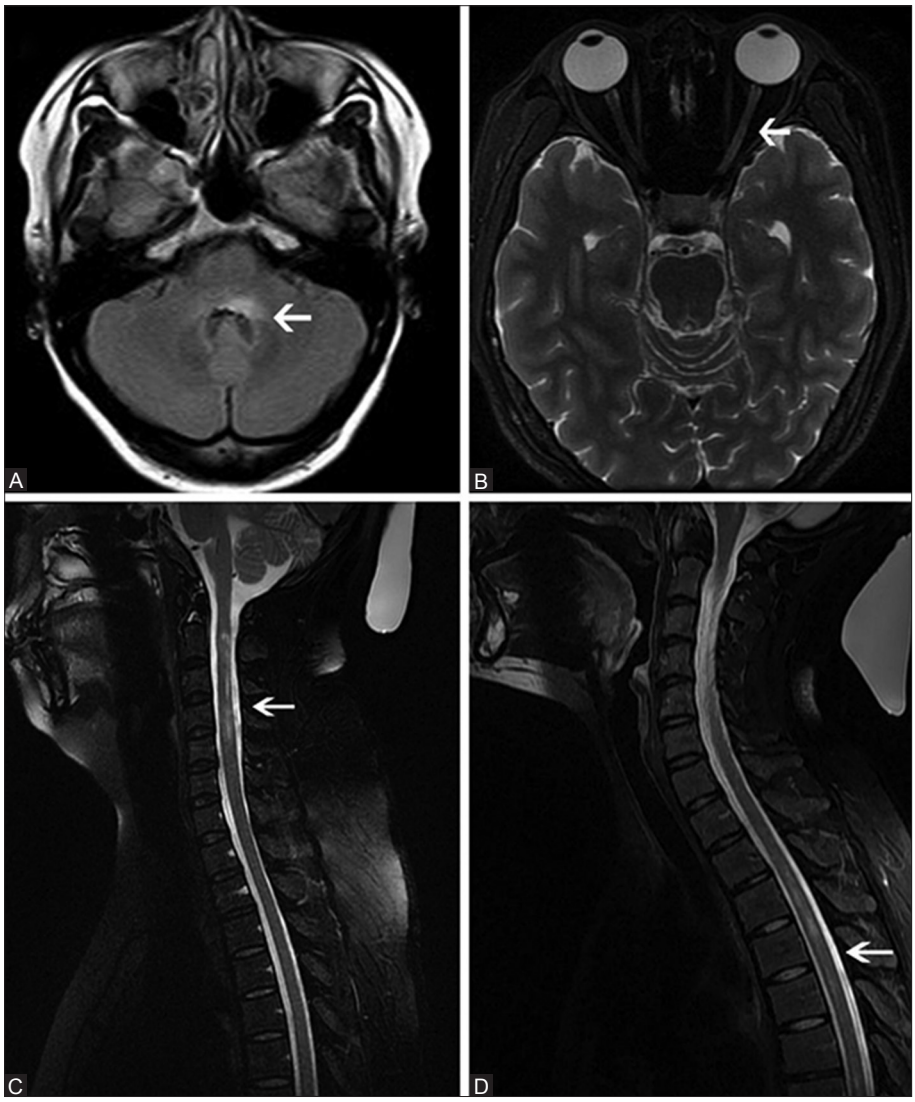

FIGURE 2. Representative magnetic resonance imaging (MRI) scans showing abnormalities in the brain (A and B) and spinal cord (C and D) of patients with neuromyelitis optica spectrum disorder (NMOSD) with chronic hepatitis B (CHB) infection, and seropositive for anti-aquaporin-4 antibody (AQP4-Ab). (A) Pons lesion; (B) bilateral optic nerve lesions; (C) transverse myelitis lesions in the cervical cord; (D) myelitis lesions in the thoracic cord.

In this study, 10 patients with NMOSD and CHB and seropositive for AQP4-Ab were evaluated. Two patients were diagnosed with ON. Female sex was predominant among the 10 patients. CHB was diagnosed earlier than NMOSD in all patients. The onset of vision loss was reported in 3 patients, 6 patients showed the onset of spinal cord symptoms, while only 1 patient had both, myelitis and the onset of vision loss. Paresthesia and visual impairment were the most common clinical symptoms among the 10 patients, followed by motor deficit and neuropathic pain. The CSF cell counts in 10 patients ranged from 0/mm^3 to 31/mm^3. Other CSF parameters were within the normal range. One patient was positive for anti-Ro/SSA and anti-La/SSB. All patients had normal thyroid function. The brain and spinal cord MRI findings were normal in 2 patients with ON. MRI of other patients showed abnormalities in the head or spinal cord, in line with the diagnostic criteria for NMOSD. The above-presented data suggest that the characteristics of NMOSD patients with CHB, seropositive for AQP4-Ab, are usually nonspecific.

Several points emerged in this study in terms of the treatment. IVMP are commonly used in the treatment of acute attacks in NMOSD. AZA, as a first-line steroid-sparing immunosuppressive drug, is generally introduced along with prednisolone [34-36]. In the course of treatment, all 10 patients in this study received a hormone therapy with high doses of corticosteroids. Some patients required multiple courses of pulse therapy. Previously, acute and severe liver damage were reported after IVMP pulse therapy [37]. In addition, the preexisting infection with viral hepatitis, such as HBV, was significantly associated with liver dysfunction [38]. In our study, patients who had detectable serum HBV DNA showed different degrees of liver damage after receiving therapy with high doses of corticosteroids. Although, it is not clear whether IVMP was a direct cause of the liver damage, it may be a

risk factor. Thus, the protection of liver function before and during pulse therapy in patients with HBV is very important. Similarly, AZA alone or in combination with prednisone has been effective in reducing relapse rates and improving EDSS in NMOSD patients [39]. However, the side effects of AZA, including bone marrow toxicity, gastric intolerance (GI), and hepatotoxicity, should be carefully monitored. In addition, a meta-analysis showed that thiopurine S-methyltransferase gene (*TPMT*) polymorphisms were associated with AZA-induced overall adverse drug reactions (ADRs) and bone marrow toxicity as well as with GI in one study, but not with hepatotoxicity. Nevertheless, they suggested that the presence of the normal *TPMT* genotype cannot preclude the development of ADRs during AZA treatment, and that *TPMT* genotyping cannot replace the regular monitoring of white blood cells and liver function [40].

CONCLUSION

The clinical, CSF, and neuroimaging characteristics of patients with NMOSD combined with CHB, and seropositive for AQP4-Ab, might easily be overlooked due to their non-specificity. The use of pulse therapy and immunosuppressive agents may lead to abnormal liver function or reactivation of HBV infection [41]. Therefore, we suggest regular monitoring of liver function in NMOSD patients with CHB infection, during their routine treatment.

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DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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