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Acute-onset chronic inflammatory demyelinating polyneuropathy following hepatitis A virus infection

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An infection is less likely to elicit chronic inflammatory demyelinating polyneuropathy (CIDP) than Guillain-Barré syndrome. We here report a case of acute-onset CIDP following hepatitis A virus infection and briefly comment on the potential mechanisms regarding the induction and chronicity of autoimmunity after a viral infection.

Key words: Polyradiculoneuropathy, Chronic inflammatory demyelinating; Guillain-Barre syndrome; Hepatitis A virus

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Inflammatory neuropathies such as Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are well-known immune-mediated polyneuropathies sharing many common characteristics during the acute disease phase. Autoimmune disorders are believed to develop as a result of interplay between genetic and environmental factors.

GBS is often associated with preceding infections such as *Campylobacter jejuni (C. jejuni)*, *Mycoplasma pneumoniae*, Epstein-Barr virus, cytomegalovirus (CMV), and varicella zoster virus (VZV).[1] In contrast, it is challenging to find an antecedent infection as a specific triggering event for CIDP, even in acute-onset CIDP (A-CIDP).[2] This might be due to environmental factors influencing the development of GBS more than the development of CIDP, and the immune system of CIDP patients being genetically permissive to be activated and, once activated, letting autoreactive T-cells remain viable and activated to cause a chronic autoimmune disease.[3,4]

Here we describe a patient who had initially been diagnosed with GBS following hepatitis A virus (HAV) infection, but whose diagnosis was eventually changed to A-CIDP.

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CASE

A 28-year-old man presented with progressive quadriparesis of subacute onset. He had been healthy until contracting icteric hepatitis A 4 weeks before the onset of quadriparesis. He was treated for hepatitis conservatively, and recovered from the illness 2 weeks later. One week after the convalescence of hepatitis A, he felt paresthesia in the distal limbs, and then over the following 3 weeks he became quadriplegic with the inability to ambulate independently. A neurological examination at the admission revealed symmetric areflexic quadriparesis both in the proximal and distal limbs of Medical Research Council (MRC) grade 4 as well as reduced sensation of pinpricks, vibration, and joint position in a glove-and-stocking distribution. Cranial nerve abnormalities and cerebellar dysfunction were not present. The findings of laboratory studies, including blood electrolytes, urea, creatinine, liver function test, antinuclear antibody, anti-double-stranded DNA, and C3 and C4 complement levels were unremarkable, but positivity for HAV IgM confirmed the recent HAV infection. Monoclonal gammopathy was not found in serum protein electrophoresis and immunofixation. A cerebrospinal fluid examination revealed mildly elevated protein (0.51 g/L) without pleocytosis. The results of a nerve conduction study (NCS) were compatible with diffuse sensorimotor polyneuropathy and multifocal demyelination when the EFNS/PNS revised criteria were applied (Table 1).[5] Terminal latencies and the distal compound muscle action potential durations were strikingly delayed or prolonged. Consideration of all of the clinical and laboratory findings led us to diagnose GBS. Accordingly, intravenous immunoglobulin G (IVIgG) was administered at a total dose of 2 g/kg over 2 days. The patient recovered rapidly to become fully capable of performing routine daily activities. The findings of electrodiagnostic studies were improved compared to those in the previous NCSs (Table 1).

However, 2 months later he developed weakness (MRC grade 4) in both the proximal and distal limbs again, at which time the NCS parameters had worsened (Table 1). He was diagnosed as A-CIDP and treated with intravenous methylprednisolone at 1 g/day for 5 days, which resulted in him regaining nearly complete strength and no longer suffering from neuropathic pain or hypesthesia. He received low-dosage oral prednisolone (10 mg/day) and azathioprine (100 mg/day) thereafter, and remained in good health without any further relapse or worsening for more than 1 year after the initial two exacerbations.

DISCUSSION

Our patient had been initially diagnosed as GBS following acute HAV infection when he first presented with areflexic quadriparesis and paresthesia, although the progression over 3-4 weeks seemed rather protracted compared to typical GBS cases. Following the second development of weakness, the initial diagnosis of GBS was revised to A-CIDP. Although his disease course seemingly conforms also to recurrent GBS, as suggested by other studies,[6] we concluded that the diagnosis of A-CIDP was correct based on the following considerations: Firstly, the course of the initial episode had progressed over 4 weeks until IVIgG was administered, when the course appeared to be halted with no further progression. Secondly, the second episode was controlled successfully with corticosteroid pulse therapy, which is well known to be ineffective in GBS. Although one-fourth to one-third of CIDP patients report a history of illness in the preceding weeks before the onset of CIDP, most of the reported illnesses are nonspecific upper respiratory infections[2] and, unlike GBS, no specific infections have ever been confirmed to be associated with the development of CIDP. Thus, the association between HAV and the onset of A-CIDP in the present case is especially noteworthy.

Two sequential but distinct immunological events are required for the development of chronic tissue-specific autoimmune disorders such as CIDP: 1) induction of autoreactivity and 2) maintenance of aberrant immunological memory due to defective immune regulation.[3,4] The two main proposed mechanisms by which pathogens incite autoimmune disorders are molecular mimicry and bystander activation.[3] Cross-reactivity due to molecular mimicry between pathogens related to GBS and gangliosides of the peripheral nerve is well known to be the pathomechanism of GBS related to *C. jejuni, Hemophilus influenza*, and CMV. By contrast, for many other pathogens such as VZV, influenza virus, and *M. pneumoniae* that have been reported to incite GBS, no molecular mimicry to peripheral nerve antigens has been reported. This suggests that preceding infection and

Table 1. Findings of nerve conduction studies (NCSs) at admission, hospital day 14, and hospital day 120

Nerve and stimulation site	TL (ms)	CMAP duration[a] (ms)	CMAP amplitude (mV)	NCV (m/s)
Motor NCSs				
Median (right)				
Wrist–APB	31.2/32.3/28.5 (≤ 3.6)	22.7/17.9/16.8 (≤ 6.6)	1.8/5.0/1.4 (≥ 5.0)	
Wrist–elbow		22.1/19.0/23.9	1.5/4.3/1.7	37/37/53 (≥ 50.0)
Ulnar (right)				
Wrist–ADM	11.7/11.9/9.9 (≤ 2.5)	13.3/14.4/12.7 (≤ 6.7)	1.6/3.3/7.8 (≥ 5.0)	
Wrist–elbow		11.4/13.6/15.1	1.5/3.1/1.7	28/28/60 (≥ 50.6)
Peroneal (right)				
Ankle–EDB	23.3/20.0/19.2 (≤ 4.8)	11.8/14.0/18.2 (≤ 7.6)	0.8/0.9/1.0 (≥ 4.0)	
Ankle–fibula		15.6/25.4/37.0	0.2/0.4/0.3	44/42/18 (≥ 41.7)
Tibial (right)				
Ankle	11.8/11.6/16.2 (≤ 5.1)	13.3/25.9/55.8 (≤ 8.8)	0.7/0.6/0.5 (≥ 5.0)	
Popliteal fossa		17.6/32.5/33	0.7/0.5/0.5	52/44/25 (≥ 40.6)

Nerve and stimulation site	SNAP amplitude (μV)	NCV (m/s)
Sensory NCSs		
Median (right), orthodromic method[b]		
Finger	NP/NP/NP (≥ 10)	-
Wrist	17.5/12.1/ND (≥ 10)	55/52/ND
Elbow	41.7/40.8/ND (≥ 10)	55/55/ND
Ulnar (right), orthodromic method[b]		
Finger	NP/NP/NP	-
Wrist	10.7/9.4/ND	55/56/ND (≥ 47.5)
Elbow	25.4/28.9/ND	55/54/ND (≥ 39.1)
Sural (right), antidromic method		
Lower leg	5.5/3.2/NP (≥ 6.0)	34/34/ND (≥ 34.7)
Dorsal sural (right), antidromic method		
Lower leg	NP/NP/NP (≥ 3.0)	-

Triplets indicate the values at admission/hospital day 14/hospital day 120. Numbers in parentheses are normal reference values.
TL, terminal latency; CMAP, compound muscle action potential; NCV, nerve conduction velocity; APB, abductor pollicis brevis; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; SNAP, sensory nerve action potential; NP, no potential; ND, not done.
[a]CMAP duration is defined as the interval between the onset of the first negative peak and the return to baseline after the last negative peak.
[b]The third sensory NCSs of the median and ulnar nerves were performed using the antidromic method.

resultant inflammation could disturb the immune regulation of the host with proinflammatory milieu to activate otherwise dormant autoreactivity against peripheral nerve antigens, rather than causing an antigen-specific autoimmune

reaction.[7] The absence of an epidemiological association of *C. jejuni* with CIDP leads us further to the hypothesis that bystander activation—and not molecular mimicry as for GBS—plays a major role in the induction of autoimmunity relevant to CIDP, with the permissive immunological setting of the host subsequently allowing its persistence.

There are several case reports of an association between HAV infection and GBS, but the causal relationship remains controversial.[8] In our case, it is plausible that the profuse clinical manifestation of hepatitis A triggered bystander activation of preexisting autoreactive T-cells against peripheral nerve antigens. Defective immune regulation such as reduced promotor activity for the inhibitory Fc-γ receptor FcγRIIB expression and defective Fas-mediated T-cell apoptosis have been found in CIDP patients, and these are thought to be contributing factors to chronic autoimmunity.[9,10]

In conclusion, the case reported here supports that bystander activation may be a common immunological pathomechanism underlying the induction of both CIDP and GBS, and that the chronicity of autoimmunity is dependent on genetic and immunological host factors. To our knowledge, this is the first case of HAV-associated CIDP. Further epidemiological and immunological data are needed to clarify the role of preceding infections in the development of CIDP.

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