Peripheral Neuropathy in Japanese Patients with Hepatitis C Virus Infection

Toshiharu Ijichi, Ichiyō Kono, Satoru Mori, Kenji Nakajima, Masanori Nakagawa and Takeshi Okanoue*

Abstract

Objective The aim of this study was to report a series of Japanese patients with neuropathic symptoms following HCV infection.

Patients and Methods Fifteen patients with neuropathic symptoms and HCV infection were studied retrospectively (neuropathy group). We evaluated clinical and electrophysiologic findings. As a control group, we investigated prospectively 11 patients with chronic HCV hepatitis without neuropathic symptoms.

Results In the neuropathy group, the peripheral neuropathy was a multiple mononeuropathy (MM) in 8 patients, a polyneuropathy in 4 patients, a single cranial neuropathy in 2 patients, and a cervical radiculopathy in one patient. Five patients with MM had relapsing symptoms. Two patients showed a progression of neurologic symptoms following varicella zoster virus infection. Mixed cryoglobulinemia was noted in 4 of 13 tested patients. Circulating immunocomplexes were detected in 3 of 10 tested patients, and low complement (C3, C4, or CH50) levels were noted in 10 of 13 tested patients. Nerve conduction study (NCS) showed abnormal findings in 10 of 13 investigated patients. In the control group, only the frequency of low CH50 was significantly lower than that in the neuropathy group. NCS abnormalities were found in 3 of 11 patients.

Conclusion We showed the presence of various types of neuropathies in patients with HCV infection. Our results suggest that relapsing MM is common in HCV positive neuropathy with or without cryoglobulinemia, and that the virus may modulate neurologic manifestations of other viral infections. Subclinical neuropathy may be present in some patients with HCV infection without neurologic symptoms.

Key words: neuropathy, hepatitis C virus (HCV), cryoglobulinemia, immunocomplex, complement

Introduction

Hepatitis C virus (HCV) infection is recognized as a major public health problem. Extrahepatic manifestation including polyarteritis nodosa, membranoproliferative glomerulonephritis, Sjögren’s syndrome and peripheral neuropathy can occur in 40% to 75% of patients with HCV infection (1, 2). Although many studies have reported various types of peripheral neuropathy such as polyneuropathy (PN), multiple mononeuropathy (MM), and Guillain-Barré syndrome (GBS) in patients with chronic HCV infection in Western countries (3–6), there are only a few case reports describing an association between neuropathy and HCV infection in Japan (7, 8).

On the other hand, peripheral neuropathy associated with mixed cryoglobulinemia (MC) has been widely recognized (1, 9–11) and a strong association is established between chronic HCV infection and MC (12–16). Many studies have reported peripheral neuropathy in patients with chronic HCV infection and MC (17, 18); however, other studies reported peripheral neuropathy in HCV infected patients without MC (7, 19, 20).

The aim of this study was to conduct a clinical and electrophysiologic evaluation of Japanese patients with chronic HCV infection and neuropathic symptoms and signs with or without MC.

For editorial comment, see p 377.
Patients and Methods

Fifteen patients were retrospectively selected in the Department of Neurology of our university hospital on the basis of symptoms and signs consistent with peripheral neuropathy and a history of chronic HCV infection confirmed with a presence of anti-HCV antibodies and viral RNA using polymerase chain reaction (neuropathy group). Patients with chronic HCV infection, with normal serum levels of liver enzymes, and without abnormal findings on abdominal ultrasonography were diagnosed as HCV carriers.

We previously reported the details of Patient 6 (8). Transfusion of HCV infection was by blood transfusion in 5 patients. The diagnosis of liver involvement was chronic active hepatitis in 12 patients, liver cirrhosis with hepatoma in one patient, and HCV carrier in 2 patients. The diagnosis of liver involvement was chronic active hepatitis in 12 patients, liver cirrhosis with hepatoma in one patient, and HCV carrier in 2 patients. The diagnosis of liver involvement was chronic active hepatitis in 12 patients, liver cirrhosis with hepatoma in one patient, and HCV carrier in 2 patients.

As a control group, we investigated prospectively 11 chronic HCV hepatitis patients admitted to the Department of Gastroenterology of our university hospital for interferon therapy.

Non-parametric analysis (Mann-Whitney U test) was used to compare laboratory data and abnormal findings in a nerve conduction study between the two groups.

Results

Clinical findings of the neuropathy group (Table 1)

There were 15 patients in the neuropathy group (seven males, eight females, mean age: 64.6 (SD 9.6); range 39–76 years). The diagnosis of liver involvement was chronic active hepatitis in 12 patients, liver cirrhosis with hepatoma in one patient, and HCV carrier in 2 patients. The diagnosis of liver involvement was chronic active hepatitis in 12 patients, liver cirrhosis with hepatoma in one patient, and HCV carrier in 2 patients. The cause of transmission was unknown in the other 10 patients. The duration between HCV transmission and the onset of neuropathic symptoms in known cases was relatively long (mean 24.2; range 15–38 years). The peripheral neuropathy was a MM in 8 patients, a PN in 4 patients, a neuropathy restricted to a single cranial nerve in 2 patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/ gender</th>
<th>Transmission</th>
<th>Duration between HCV transmission and the onset of neuropathic symptoms (y)</th>
<th>Type of neuropathy</th>
<th>Liver disease</th>
<th>MC</th>
<th>Low level of C3</th>
<th>Low level of C4</th>
<th>Low level of CH50</th>
<th>High level of C1q</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>63/M</td>
<td>Unknown</td>
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<td>CAH</td>
<td>ND</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
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<td>Chronic MM, SM, relapsing</td>
<td>CAH</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
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</tr>
<tr>
<td>3</td>
<td>57/M</td>
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<td>Chronic PN, S</td>
<td>CAH</td>
<td>ND</td>
<td>-</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>57/M</td>
<td>Transfusion</td>
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<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>Subacute MM, SM</td>
<td>CAH</td>
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<td>LC, hepatoma</td>
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<td>-</td>
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<td>-</td>
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<td>CAH</td>
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<td>+</td>
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<td>CAH</td>
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<tr>
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<td>Acute myeloradiculoneuropathy, SM</td>
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<td>ND</td>
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<tr>
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<td>Subacute MM (CSS), SM</td>
<td>HCV carrier</td>
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Table 2. Nerve Conduction Study of Patients in the Neuropathy Group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Increase in Motor DL</th>
<th>Decrease in CMAP</th>
<th>Decrease in MCV</th>
<th>Decrease in SNAP</th>
<th>Decrease in SCV</th>
<th>Increase in F wave latency</th>
<th>Reduction of percentage of F wave recording</th>
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<td>ND</td>
<td>ND</td>
<td>ND</td>
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</tr>
<tr>
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<td>+ (MN)</td>
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<td>-</td>
</tr>
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<td>6</td>
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<td>+ (UN)</td>
<td>+ (MN, SN)</td>
<td>NE (MN, TN)</td>
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<td>+ (MN)</td>
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<td>+ (MN, UN, TN)</td>
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<td>NE (MN, UN, SN)</td>
<td>NE (MN, TN)</td>
<td>NE (MN, TN)</td>
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<tr>
<td>15</td>
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<td>+ (UN, SN)</td>
<td>+ (UN)</td>
<td>ND</td>
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</tr>
</tbody>
</table>


and a cervical radiculopathy in one patient. Sensory symptoms such as paresthesia, numbness and burning were found in all patients and were always initial neuropathic symptoms except 2 patients with single cranial neuropathy.

In patients with MM, the mode of onset was chronic in 4, and subacute in 4. Notably, five had relapsing symptoms. One patient with subacute onset MM developed multiple cranial neuropathy (Patient 6). Another patient with subacute onset MM was diagnosed as having Churg-Strauss syndrome (CSS) with histologic evidence by skin biopsy. Three of four patients with PN developed chronic sensory polyneuropathy. One developed unilateral facial paresthesia (Patient 8). Another patient with PN developed severe acute polyradiculoneuropathy with motor and sensory involvement following herpes zoster in a lower limb (Patient 13). One patient with acute onset unilateral peripheral facial nerve palsy was diagnosed as Bell’s palsy. Another patient with single cranial nerve involvement developed acute onset unilateral oculomotor palsy without internal ophthalmoplegia. A patient developed myeloradiculoneuropathy following herpes zoster in the neck (Patient 14). Her symptoms were so severe that mechanical ventilation was needed for a few weeks.

Laboratory findings of the neuropathy group (Table 1)

MC was positive in 4 of 13 tested patients (30.8%). Other associated findings included a low C3 complement level in 2 of 13 tested patients (15.4%), a low C4 complement level in 7 of 13 tested patients (53.8%), and a low hemolytic complement activity (CH50) in 10 of 13 tested patients (76.9%). A high level of circulating immunocomplex (C1q) was noted in 3 of 10 tested patients (30.0%).

Nerve conduction study in the neuropathy group (Table 2)

We performed motor and sensory NCS in 13 patients. F wave recording was conducted in 12 patients. Various types of abnormal findings were noted. In the motor conduction study, we observed an increase of motor DL at least in 1 nerve in 4 patients (30.8%), a decrease in CMAP at least in 1 nerve in 3 patients (23.1%), and a decrease in MCV at least in 1 nerve in 4 patients (30.8%). Abnormal findings in the sensory conduction study were also observed. The decrease in SNAP in at least 1 nerve was noted in 5 patients (37.7%), while a decrease of SCV in at least 1 nerve was observed in 7 patients (53.8%). An increase in F wave latency in at least 1 nerve was observed in 4 patients (33.3%), and the percentage of F wave recording was reduced in 6 patients (50.0%). As a whole, abnormal findings in NCS were noted in 10 of 13 patients (76.9%).

Treatment in the neuropathy group

Interferon-α (IFN-α) (3 million units 3 days/week) was administered to Patient 6. Although cryoglobulins became undetectable and the level of HCV RNA was markedly decreased, symptoms and signs of MM worsened.

A five-day course of high-dose intravenous immunoglobulin (IV Ig) (0.4 g/kg/day) was prescribed for Patient 6, followed by no clinical improvement in MM. Two patients with varicella zoster virus infection were also treated with IV Ig in addition to acyclovir (1,500 mg/day). A partial improvement was observed in acute polyradiculoneuropathy (Patient 13), whereas an equivocal effect was noted in myeloradiculoneuropathy (Patient 14).

Prednisolone (1 mg/kg/day) was administered to Patients...
Blood chemistry including serum levels of transaminase and All patients were diagnosed as chronic active HCV hepatitis 4 females, mean age: 48.6 (SD 11.7); range 32-76 years. We investigated 11 patients in the control group [7 males, Neuropathy group

<table>
<thead>
<tr>
<th></th>
<th>CG</th>
<th>Low C3 level</th>
<th>Low C4 level</th>
<th>Low CH50*</th>
<th>High C1q level</th>
<th>Abnormality of NCS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathy group</td>
<td>64.6±9.6</td>
<td>4/13 (30.8%)</td>
<td>2/13 (15.4%)</td>
<td>6/13 (46.2%)</td>
<td>9/13 (69.0%)</td>
<td>3/10 (30.0%)</td>
</tr>
<tr>
<td>Control group</td>
<td>48.6±11.7</td>
<td>3/11 (27.3%)</td>
<td>1/11 (9.1%)</td>
<td>3/11 (27.3%)</td>
<td>3/11 (9.1%)</td>
<td>3/11 (27.3%)</td>
</tr>
</tbody>
</table>

*p<0.05 (Mann-Whitney U test). CG: cryoglobulinemia, NCS: nerve conduction study.

Comparison between the neuropathy group and the control group (Table 3)

We investigated 11 patients in the control group [7 males, 4 females, mean age: 48.6 (SD 11.7); range 32–76 years]. All patients were diagnosed as chronic active HCV hepatitis according to liver biopsy. None of them complained of neuropathic symptoms. In this group, the findings of routine blood chemistry including serum levels of transaminase and HCV RNA were similar to those in the neuropathy group (data not shown). In the control group, MC was positive in 3 patients (27.3%), and other associated findings included low C3 complement level in one patient (9.1%), low C4 complement level in 3 patients (27.3%), low CH50 in 3 patients (27.3%), and high C1q level in one patient (9.1%). The frequencies of MC, and low C3 and C4 complement levels, were higher in the neuropathy group than in the control group, although the differences were not significant. Only the frequency of low CH50 was significantly higher in the neuropathy group (p<0.05).

Abnormal findings of NCS such as the increase in motor DL, the decrease in SNAP, and the decrease in the percentage of the F wave recording were found in 3 patients in the control group (27.3%), although their frequency was significantly lower than that in the neuropathy group (p<0.05).

Discussion

We presented various types of neuropathy in Japanese patients with chronic HCV infection. As reported previously in Western countries (4, 6, 17, 21), sensory dominant polyneuropathy (PN) and multiple mononeuropathy (MM) were common in the neuropathic patients with chronic HCV infection. Cacoub et al (4) showed two types of vasculitis as complications of HCV infection. One was an immune complex vasculitis involving preferentially small size vessels that causes PN, and another is a medium vessel vasculitis causing MM. Although histologic evidence was absent, these two types of vasculitis are suggested to be the main causes of the neuropathies in our patients. Five of 8 patients with MM had relapsing symptoms as reported previously concerning a patient with MM with HCV infection without mixed cryoglobulinemia (MC) (7). This may be a common symptom in HCV infected patients with MM as is sometimes seen in patients with MC (22).

Extrahepatic signs of HCV infection associated with MC are well known (23). MC is the most common immune disorder that occurs during chronic HCV infection, and peripheral neuropathy, such as sensory PN and MM, is recognized as its major manifestation (22). It is suggested that chronic HCV infection causes an abnormal immunologic response producing MC. In these conditions, immunocomplexes can be formed and induce inflammatory processes leading to the development of vasculitis by activation of the complement system (24). C3 and C4 complements are usually diminished in neuropathies of HCV infected patients with MC (6). Thus, the association between HCV infection and cryoglobulinemic neuropathy is well established. On the other hand, some studies (19, 20) reported various types of neuropathies in HCV infected patients without detectable MC. Paoletti et al (20) described a high prevalence of peripheral neuropathy in patients with HCV infection with genotype 1b without MC. Caudai et al (19) suggested intrathecal infection of HCV in a patient with chronic sensory neuropathy without MC. In the present study, MC was observed in only approximately one-third of the patients with neuropathic symptoms. These findings also support the possible association between neuropathies and HCV infection without MC. Since HCV can infect lymphocytes (25, 26), it may directly alter the cell process of immunomodulation leading to the development of neuropathies.

One patient in our study developed Churg-Strauss syndrome (CSS). CSS is defined as an eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium sized vessels and is associated with asthma and eosinophilia (27). In CSS, circulating immunocomplexes or rheumatoid factors are often detected, but MC is rarely found. The antigen responsible for CSS has not been identified (24). Although the relation between CSS and HCV infection is unclear, it is not surprising that such vasculitis occurs in patients with HCV infection considering the involved vessel size and immune profiles. Mercié et al (24) reported two patients with CSS and HCV infection. In their study, MC was present in one
patient and absent in another. The present case supports a possible relation between CSS and HCV infection although further epidemiological studies are needed.

In two patients in the present study, neurologic symptoms occurred following shingles. Neurologic manifestations were polyradiculoneuropathy with motor and sensory involvement in one, and myeloradiculoneuropathy in another. Symptoms were very severe in both patients. Varicella zoster virus (VZV) reactivation causing shingles sometimes occurs even in healthy subjects, however, severe neurologic complications are typically observed in immunocompromised hosts including those with cancer or retrovirus infection (28, 29).

Since the present patients showed no findings consistent with typical immunocompromised hosts, other factors modulating the immune mechanisms were postulated. Considering a lymphotropism of HCV (25, 26), it is suggested that chronic HCV infection is one of the factors causing immunemediated neurologic disorders. The symptoms and signs in one patient with polyradiculoneuropathy resembled those with a variation of Guillain-Barré syndrome (GBS). GBS is an inflammatory polyradiculoneuropathy, thought to be an aberrant response to an immunologic stimulus and mediated T lymphocytes (30). Interestingly, both VZV and HCV are recognized as causative agents of GBS (5, 31–33). We emphasize that HCV may have a broad spectrum of neurologic disease association similar to VZV and may modulate neurologic manifestations of other viral infections.

Cranial neuropathy with HCV infection has rarely been reported (34). Two patients in the present study developed single cranial nerve involvement. In one patient with unilateral oculomotor palsy, considering the absence of internal ophthalmoplegia, a vascular etiology was likely. Vasculitis related to HCV infection may be associated with this symptom.

In nerve conduction studies (NCS), an increase of distal latency (DL) and a decrease in conduction velocity (CV) suggest demyelinating neuropathy, while a decrease in the amplitude of the action potential (AP) suggests axonal neuropathy. Against expectation, here, we found an increase in DL and a decrease in CV in addition to the decrease in the amplitude of AP in the present patients. These findings suggest that the neuropathy was not only axonal, and therefore different from some previous studies reporting that neuropathies in patients with HCV infection are mainly axonal (6, 15). Although the precise reasons for those differences are unknown, some possibilities are suggested. First, some previous studies (6) used the term axonal, but the details of the findings in NCS were not shown; thus their diagnostic criteria were not completely consistent with those of the present study. Second, in some studies (18), the diagnosis was made not by NCS but mainly by histology. Finally, because those studies were performed in Western countries, different manifestations may be present in different races and regions. In the present study, abnormalities of the sensory conduction velocity and sensory nerve action potential were detected in half and one-third of the patients investigated, respectively.

Motor conduction abnormalities were less frequent. The abnormalities of the F wave recordings were noted in half of the patients investigated. These abnormalities were observed predominantly in nerves of the lower limbs such as the sural and tibial nerves. The findings of our NCS resembled those of MC (22). According to these findings, HCV may have an association with various types of neuropathies including typical cryoglobulinemic neuropathy.

We treated some patients in this study. It is important to note that IFN-α worsened the neuropathy in Patient 6. Although a few studies have reported an improvement in neuropathy after IFN-α therapy (34, 35), the majority of case reports describe the worsening of neuropathy by IFN-α therapy (36, 37). Care should be taken regarding IFN-α therapy in patients with HCV infection and neuropathy, because immunosuppressive agent such as IFN-α can induce autoimmune responses.

We investigated 11 patients with chronic HCV infection without neuropathic symptoms as a control group. The frequency of MC, low complement level, and high level of C1q were not significantly different although they tended to be lower than in the neuropathy group. These findings suggest that not only MC and its related proteins but also other immunomodulating factors play a role in making lesions causing neuropathies although the frequency of low CH50 was significantly lower in the control group. Furthermore, because a few patients in the control group showed mild abnormal findings in NCS, subclinical neuropathy may be present at least in some patients with HCV infection without neurologic symptoms.

In conclusion, HCV infection may be associated with various types of neuropathies in Japan as well as in Western countries. Our results suggest that relapsing MM is common in HCV positive neuropathy with or without MC, and that the virus may modulate neurologic manifestations of other viral infections.

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