

Hepatitis C virus infection with peripheral neuropathy is not always associated with cryoglobulinaemia

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Abstract

Objectives—To describe cases of peripheral neuropathy associated with chronic hepatitis C virus infection without mixed cryoglobulinaemia.

Methods—Four cases of peripheral neuropathy associated with chronic hepatitis C virus infection with persistent negativity of mixed cryoglobulinaemia were found.

Results—All patients had small increases of transaminase levels and a positive viraemia. Liver biopsy showed chronic active hepatitis in all but one case (Knodell 4–9, Metavir A0F0–A3F3). Neuromuscular biopsy showed axonal neuropathy associated with lymphoid infiltrates around small vessels in two cases. Rheumatoid factor was always negative and C4 complement level was always normal. In three patients, neuropathy improved with interferon α , interferon α + ursodesoxycholic acid, or steroids + plasma exchange.

Conclusion—Peripheral neuropathy may be associated with hepatitis C virus infection without mixed cryoglobulinaemia.

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Chronic hepatitis C virus (HCV) infection may be associated with numerous extrahepatic manifestations, such as mixed cryoglobulinaemia, membranoproliferative glomerulonephritis, sicca syndrome, or porphyria cutanea tarda.¹ Peripheral neuropathy (PN) may also be associated with HCV infection and it is usually related to mixed cryoglobulinaemia. Before HCV was discovered, PN was known to be associated with type II or type III, rather than type I cryoglobulinaemia.² PN associated with mixed cryoglobulinaemia was described as subacute and asymmetrical neuropathy.^{3,4} Most mixed cryoglobulinaemia described as “essential” is now known to be related to HCV

infection.⁵ In prospective studies, sensory or motor PN has been found in up to 9% of patients chronically infected with HCV.^{6,7} However, the presence of a PN in a patient positive for HCV may be due to other causes,⁸ including PN without mixed cryoglobulinaemia, as reported here.

Case reports

Tables 1 and 2 summarise the main characteristics of the patients. Three men and one woman, mean age 56 years (range 40–78), had a chronic HCV infection without hepatitis B virus or HIV infection. All patients had a moderate increase of transaminase levels at diagnosis. HCV viraemia by polymerase chain reaction (PCR) was positive in each case and genotypes were 2, 4, 1b, and 1b. Genotype distribution was similar to that of a French population infected by HCV. Liver biopsy was performed in each case (Knodell 4–9, Metavir A0F0–A3F3). Extrahepatic manifestations were arthralgia (n=3), myalgia (n=1), sicca syndrome (n=1), and Raynaud's phenomenon (n=1). Cryoglobulinaemia was searched for from four to 11 times during a two to eight year period and was never found to be positive. Rheumatoid factor was also always negative on multiple determinations. C4 complement level was always normal. No patient had cirrhosis at diagnosis of HCV infection.

PN was a sensory polyneuropathy (n=1) or mononeuropathy multiplex (n=3), associated with motor involvement in two cases, confirmed by electromyography in each case. Neuromuscular biopsy was always performed before treatment, showing an axonal neuropathy, associated with perivascular lymphoid infiltrates in two cases. In these two cases, no necrotising vasculitis “periarteritis nodosa like” aspect was seen, even when the clinical findings were compatible. No granuloma, fibrinoid necrosis, leucocytoclastic, or extravasation of erythrocytes was mentioned on

Table 1 Main characteristics of four patients with chronic hepatitis C virus infection and peripheral neuropathy without mixed cryoglobulinaemia

Characteristic	Patient No 1	Patient No 2	Patient No 3	Patient No 4
Age/sex	78/M	40/M	62/F	46/M
Mode of infection	?	Intravenous drug user	?	?
HCV infection				
Diagnosis	1991	1997	1997	1997
PCR*	+	+	+	+
Liver biopsy	Knodell 9, Metavir A3F3	Knodell 4, Metavir A0F0	Knodell 6, Metavir A1F1	Knodell 5, Metavir A1F1
Genotype	2	4	1b	1b
Extrahepatic manifestations	Sicca syndrome	Arthralgia, myalgia, Raynaud's phenomenon	Arthralgia	Arthralgia
Cryoglobulinaemia (No of determinations)	11 (1991–1999)	6 (1997–1999)	4 (1998–2000)	8 (1998–2000)
Rheumatoid factor	–	–	–	–
C4 level	Normal	Normal	Normal	Normal

*PCR = HCV viraemia by polymerase chain reaction.

Table 2 Main characteristics of the peripheral neuropathy in four patients with hepatitis C virus without mixed cryoglobulinaemia

Characteristics	Patient No 1	Patient No 2	Patient No 3	Patient No 4
Peripheral neuropathy	Sensory polyneuropathy of legs	Severe motor and sensory multiplex mononeuropathy of three limbs	Mild sensory multiplex mononeuropathy of four limbs	Sensory multiplex mononeuropathy of four limbs
Initial electromyographic study	Axonal sensory polyneuropathy	Severe neuropathy with low motor and sensory velocities	Axonal sensory neuropathy	Axonal sensory neuropathy
Neuromuscular biopsy before treatment	Muscular atrophy with mild denervation; axonal sensory nerve involvement	Normal muscle; axonal sensory nerve loss with perineural, venular, and arteriolar inflammatory infiltrates	Muscular atrophy; inflammatory axonal neuropathy with perivenular and arteriolar lymphoid infiltrates	Normal muscle; axonal sensory neuropathy without inflammatory infiltrate
Treatment	Interferon α (3 mIU three times a week) + Ursodesoxycholic acid (400 mg/day) for 24 months	+ Prednisone 1 mg/kg/day during 2 months*	Not treated	Interferon α (3 mIU three times a week)† for 10 months†
Outcome after treatment	Progressive improvement	Improvement	Stable	Improvement

*Interferon was contraindicated because of depressive status.

†Interferon had to be stopped because of severe depressive status.

histopathological studies. Three patients were treated. Patient 1 received interferon α (IFN α) and ursodesoxycholic acid for hepatitis and neuropathy. PN progressively improved under the IFN α regimen with lower paraesthesia after 28 months. Patient 2 was treated because of PN. He did not receive IFN α because he was severely depressed, but PN, arthralgia, and myalgia dramatically improved after three months' treatment with prednisone and a plasma exchange regimen. Prednisone was stopped seven months later. More than one year later, the patient is free of neurological symptoms. In these two patients, clinical improvement was associated with electromyographic improvement. Patient 3 was not treated because a liver biopsy indicated that the hepatitis was mild and the neurological symptoms did not worsen during the two year follow up period. Patient 4 was treated with IFN α and his PN improved after eight months. However, IFN α has been stopped recently because he is severely depressed.

Discussion

We report four cases of PN with HCV infection in the absence of cryoglobulinaemia. None of the patients had other factors associated with PN, such as excessive alcohol consumption, renal insufficiency, or neurotoxic treatment. No patient had evidence of either cryoglobulinaemia or indirect signs suggestive of cryoglobulinaemia, such as purpuric skin lesion, rheumatoid factor, and an abnormal C4 level. In two cases, vasculitis of small vessels was found in neuromuscular biopsy specimens. PN progressively improved during treatment with IFN α in two cases or with prednisone and plasma exchange in one case.

In HCV infected patients the possible causes of the presence of PN must be analysed cautiously.⁸ Small vessel vasculitis associated with mixed cryoglobulinaemia is by far the most common cause. It is often associated with purpura and arthralgia. Its hallmark is the presence of mixed cryoglobulinaemia in the serum, mainly of type II IgM κ , associated with rheumatoid factor activity and a low C4 level. None of these clinical or biological signs was found in the four patients reported on here. Only one account of PN and HCV infection without cryoglobulinaemia has been reported

previously, if we exclude one case with positive rheumatoid factor.⁹ In a series of nine patients with neurological symptoms associated with HCV infection, Tembl *et al* found two patients without cryoglobulinaemia.¹⁰ Symptoms were an anterior optic neuropathy and restless legs syndrome with small fibre neuropathy. The number of cryoglobulinaemia determinations was not mentioned in this study. Moreover, previously undetectable cryoglobulinaemia was noticed after IFN α treatment in the first patient, suggesting that cryoglobulinaemia was positive before treatment. Even if the patient with restless legs syndrome was infected by HCV after transfusion, we do not know whether a search for HIV seropositivity, which may be associated with restless legs syndrome, was made. This condition may also be idiopathic.

The prevalence of mixed cryoglobulinaemia is about 50% in subjects infected by HCV,⁵ and the association of cryoglobulinaemia with PN might have been coincidental in some cases. Our observations showed that cryoglobulinaemia and indirect markers, such as the presence of rheumatoid factor or a low C4 level, were negative. However, we cannot exclude the possibility that cryoglobulinaemia was positive from time to time, even though the methods we used had a proved sensitivity.¹¹ Recently, Japanese authors have reported the presence of mixed cryoglobulinaemia in up to 90% of patients with HCV using other methods.¹² Because age and extensive liver fibrosis are commonly associated with extra-hepatic manifestations of HCV infection,⁷ patients 2, 3, and 4 may develop mixed cryoglobulinaemia in the future. On the other hand, an eight year follow up of patient 1 has not shown an outbreak of mixed cryoglobulinaemia despite development of cirrhosis.

In a large cohort of patients, PN was found to be associated with skin vasculitis, but not with cryoglobulinaemia.⁷ Five patients with PN and HCV-type II mixed cryoglobulinaemia have been reported to have high concentrations of anti-HCV antibodies and HCV RNA in the cryoprecipitates. HCV RNA was also found in epineural cells using reverse transcriptase-polymerase chain reaction (RT-PCR), suggesting a role for HCV itself in type II mixed cryoglobulinaemia-associated neuropathy.¹³

The high prevalence of PN in HCV patients without other symptoms related to mixed cryoglobulinaemia is also compatible with a role for HCV itself in the pathogenesis of damage.¹⁴ Since the study of Feiner published in 1983—before HCV was discovered—it has been known that vasculitic lesions in patients with cryoglobulinaemia are not identical in each organ.¹⁵ The first case described in this pathological report is certainly an HCV-mixed cryoglobulinaemia (type II mixed cryoglobulinaemia with IgMk component) vasculitis with purpura and glomerulonephritis, with identical deposits in normal cutaneous vessels and kidney. In the second case with peripheral neuropathy, the monoclonal component of cryoglobulinaemia was IgA and was probably not related to HCV infection. Purpura seems to be a typical type II cryoglobulinaemia related lesion with vascular and tissue deposition of HCV-RNA, monoclonal IgM, and complement components. In PN with HCV associated cryoglobulinaemic vasculitis, HCV related proteins or RNA have been demonstrated in only a few cases,¹³ and immune complexes are found less often.¹⁶

As reported by Lamprecht *et al*, different pathogenic mechanisms in different organs are at work in the presence of cryoglobulinaemia.¹⁷ Cryoglobulinaemic vasculitides are immune complex mediated vasculitides that predominantly affect small vessels. They should only be diagnosed in the presence of clinical signs of vasculitis and cryoglobulinaemia and histological proof of an immune complex mediated vasculitis by immunohistochemistry or electron microscopy.

From the clinical data of our patients, it was not possible to distinguish between neuropathy and polyarteritis nodosa. A pathological study showed that neurological vasculitides were probable in two cases, even if not clearly defined. Unfortunately, immunohistochemistry or electron microscopy was not carried out in our patients. PN in HCV positive patients may be due to another type of vasculitis—namely, polyarteritis nodosa.^{18–21} Occlusion of vasa nervorum with the “periarteritis nodosa like” aspect has been seen in some cases,^{2 18 19} but this aspect was not associated with perineural vasculitis in our cases.

Finally, it has been reported that IFN α may cause a worsening of PN in patients with HCV-mixed cryoglobulinaemia, despite improvement of hepatic parameters.^{22 23}

In view of the causative factors that may play a part in patients with HCV infection and PN,

treatment has to be considered individually, taking into account the clinical features, neuromuscular biopsy sampling, and liver damage, and it must be regularly monitored.

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