HCV-Related Central and Peripheral Nervous System Demyelinating Disorders

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Abstract: Chronic infection with hepatitis C virus (HCV) is associated with a large spectrum of extrahepatic manifestations (EHMs), mostly immunologic/rheumatologic in nature owing to B-cell proliferation and clonal expansion. Neurological complications are thought to be immune-mediated or secondary to invasion of neural tissues by HCV, as postulated in transverse myelitis and encephalopathic forms. Primarily axonal neuropathies, including sensorimotor polyneuropathy, large or small fiber sensory neuropathy, motor polyneuropathy, mononeuropathy, mononeuropathy multiplex, or overlapping syndrome, represent the most common neurological complications of chronic HCV infection. In addition, a number of peripheral demyelinating disorders are encountered, such as chronic inflammatory demyelinating polyneuropathy, the Lewis-Sumner syndrome, and cryoglobulin-associated polyneuropathy with demyelinating features. The spectrum of demyelinating forms also includes rare cases of iatrogenic central and peripheral nervous system disorders, occurring during treatment with pegylated interferon. Herein, we review HCV-related demyelinating conditions, and disclose the novel observation on the significantly increased frequency of chronic demyelinating neuropathy with anti-myelin-associated glycoprotein antibodies in a cohort of 59 consecutive patients recruited at our institution. We also report a second case of neuromyelitis optica with serum IgG autoantibody against the water channel aquaporin-4. The prompt recognition of these atypical and underestimated complications of HCV infection is of crucial importance in deciding which treatment option a patient should be offered.

Keywords: Anti-aquaporin-4, anti-MAG neuropathy, demyelination, HCV, neuromyelitis optica, transverse myelitis.

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) affects approximately 170 million people worldwide and is associated with an array of extrahepatic manifestations (EHMs), including several neurological complications, whose pathogenic mechanisms are mostly driven by the immune system [1-3]. Both the innate immunity, as the first line of defence, and the subsequent activation of the adaptive immune system are essential for the control of HCV infection. However, HCV may evade host defences by resistance to neutralizing antibodies or reduction of its immunogenicity. As a result of the imbalance between viral activity and the defective immune response, chronic active hepatitis develops in about 80% of infected patients [4, 5]. This chronic dysregulation is also implicated in the persistence of HCV infection and in disease progression of many EHM that may arise during persistent infection. Many EHM are immunologic/rheumatologic in nature, being triggered by B-cell proliferation and ensuing production of monoclonal and polyclonal autoantibodies with rheumatoid factor (RF) activity or cryoglobulin (CG) properties. The spectrum of autoantibodies includes antinuclear antibodies (ANA), anti-SSA/anti-SSB, anti-smooth muscle antibodies (SMA), antineutrophil cytoplasmic antibodies (ANCA), anti-ganglioside GM1 and anti-sulfatide [6, 7]. In addition, possible mechanisms involved in a number of neurological EHMs, include bystander activation of autoreactive T cells and HCV-induced cross-reactive responses against structural neural and non-neural polypeptides. We here review known demyelinating disorders of the central nervous system (CNS) and of the peripheral nervous system (PNS) occurring in association with chronic HCV-infection. We also describe a case of HCV-related neuromyelitis optica (NMO) with circulating anti-aquaporin-4-IgG, an association previously reported in a single patient [8]. Finally, we call attention to the significantly increased prevalence of demyelinating neuropathy with monoclonal IgM anti-myelin-associated glycoprotein (MAG) antibodies, accounting for 5%, in a consecutive case series of 59 HCV-infected patients, as opposed to the estimated frequency of 0.001-0.005% in the adult population [9].

TRANSVERSE MYELITIS AND ENCEPHALOMYELITIS

Transverse myelitis (TM) encompasses a wide group of inflammatory spinal cord syndromes that occur as a result of infectious, para-infectious and postvaccinal events, or arise from granulomatous, vasculitic, systemic autoimmune disorders, and acquired idiopathic demyelinating diseases [10]. The etiology of TM remains unknown in up to 30% of cases, which are categorized as idiopathic. TM has an acute or subacute onset, clinically characterized by bilateral sensorimotor and autonomic dysfunction associated with a central spinal lesion involving most of the cross-sectional area, and spanning one-to-two vertebral segments; asymmetric neurologic signs are observed in partial TM, in association with a lesion involving less than half cross-sectional area. Short and asymmetrical lesions are highly

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suggestive of multiple sclerosis (MS), whereas symmetrical ones are typical of post-infectious myelitis. On the contrary, centrally located and symmetric lesions, affecting more than three vertebral segments, are classified as longitudinal transverse myelitis (LETM), a distinct neurological entity which is typical of NMO, but is also observed in MS, autoimmune systemic diseases, and acute disseminated encephalomyelitis (ADEM). In post-infectious forms, the course of TM is usually monophasic, albeit up to 25% of patients experience a recurrence; conversely, relapsing forms occur in multiple sclerosis, disease-associated myelitis, and in NMO spectrum disorders (NMOSD). At the neuropathological level, TM is characterized by predominant involvement of the white matter with focal accumulation of lymphocytes/monocytes, demyelination, axonal injury, and activated astrocytes and microglia [10]. The association between chronic HCV-infection and TM represents an apparently infrequent event, or, in alternative, an underreported EHM. In 1994, Sobukawa et al. described a 76-year-old man with a two-years-history of HCV-related liver cirrhosis, but no portosystemic shunts or concomitant hepatic encephalopathy, who developed gait disturbances over several weeks, rapidly evolving to progressive paraplegia [11]. At autopsy, demyelination of the lateral column of the spinal cord, especially at the thoracic level, in association with lipid-laden macrophages, gliosis and rare perivascular lymphocytic infiltrates were noted. The patient was diagnosed with “hepatic myelopathy”, a rare condition that usually evolves over several months to years and is preceded by overt hepatic encephalopathy. Given the above clinical atypical features, in addition to the presence of cellular inflammation, which is at variance with typical cases of hepatic myelopathy [12], a role for HCV is not excluded in this case. One of the earliest reports on spinal cord involvement in chronic HCV-infection described a patient with a reversible spinal cord syndrome, characterized by progressive sensory loss, normal spine MRI, prolonged central conduction times of somatosensory evoked potentials and normal nerve conduction velocities [13]. The CSF detection of HCV-RNA quasispecies, distinct from serum-derived HCV-RNA, suggested the possibility of both direct and immune-mediated viral damage to the CNS. The symptoms and somatosensory evoked potentials improved over a six-months period, after an initial 5-day-course of IV methylprednisolone, hence suggesting an autoimmune pathogenesis. A similar case of acute myelitis, rapidly evolving to paraplegia, has recently been reported in a chronically infected HCV patient with positive MRI and CSF HCV-RNA [14]. The condition improved following administration of methylprednisolone, a finding speaking in favor of immune-mediated mechanisms. While the pathogenesis of HCV-associated myelitis remains elusive, lines of evidence suggest that immune-mediated inflammatory processes involving autoreactive T cells and autoantibodies may play a role in a number of cases. The detection of viral quasispecies diverse between the CSF and liver supports an independent life of the virus at intrathecal locations, if not within the brain, and, in turn, autoantibody production may explain local or systemic autoimmune manifestations. In addition to CG, chronic HCV-infection is characterized by an augmented prevalence of circulating autoantibodies, such as antinuclear antibody, anti-SSA/anti-SSB antibody, and antineutrophil cytoplasmic antibody (ANCA), as an effect of activation and proliferation of B-lymphocytes. In these instances, in order to avoid inappropriate treatment, caution is required in assessing whether these serologic markers represent infection-related EHM or a co-existing autoimmune disorder. The first reported case of TM associated with serum positivity for antinuclear factor, dsDNA-antibodies, p-ANCA and c-ANCA was observed in a 34-year-old male with chronic HCV-infection [15]. This patient rapidly developed numbness, urinary retention and paraplegia, associated with MRI abnormalities spanning T4 and T5 vertebral segments of the spinal cord. Thereafter, only partial improvement was observed after 15-month-treatment with prednisone; while anti-HCV antibodies and HCV-RNA were not searched in the CSF, persistent circulating ANCA positivity was observed. In 2004, Grewal et al. described a patient with HCV-associated recurrent myelitis, in whom a spinal cord biopsy showed demyelination, marked tissue infiltration by macrophages and perivascular lymphocytes, in the absence of vasculitis [16]. In this patient neither HCV-RNA nor HCV antigens were found at a spinal cord biopsy, whereas anti-HCV antibodies, but not HCV-RNA, were detected in the CSF. Taken together, these findings suggested a prevailing antibody-mediated pathogenesis. Intrathecal anti-HCV IgG antibodies, but not CSF HCV-RNA, were also detected in a 60-year-old woman with a 4-year-history of HCV infection, who presented progressive paraparesis, reduced pain and vibratory sensitivity below L2 level, in association with T2-weighted hyperintense signal extending over L2-L4 vertebral segments [17]. The patient’s weakness improved after nonspecific treatment and the sensory function was restored. However, 14 months later she was admitted because of worsened leg weakness that partially responded to intravenous methylprednisolone; after 8 months, the patient had renewed worsening, in the absence of MRI changes, and again anti-HCV antibodies, but not HCV-RNA, were detected in the CSF. The presence of CSF anti-HCV antibodies in a patient with longitudinally extensive transverse myelitis, spanning from the lower medulla to upper thoracic segments, has been reported more recently, hence supporting a pathogenic role for antibody-mediated mechanisms [18]. In a retrospective investigation of 59 consecutive patients with idiopathic TM, Aktipi et al. obtained serological evidence of HCV infection in 7 patients, all with recurring myelitis [19]. At the first attack, only one patient was previously diagnosed with HCV infection, whereas the remaining cases were ascertained following a comprehensive screening, including a panel for viral/bacterial agents. Strikingly, the seven HCV-infected patients accounted for 12% of myelitis as a whole and 33% of recurrent variants; in one patient HCV-RNA was detected in the CSF. Taken together, the aforementioned reports highlight the importance of HCV screening in patients with idiopathic myelitis. A recurrent steroid-responsive LETM variant has been reported in a patient with HCV infection and sicca symptoms; at presentation, a spinal cord biopsy showed myelin loss in association with massive parenchymal and perivascular macrophage infiltration, swollen and irregular axons, diffuse T lymphocyte infiltration, and proliferation of small vessels with hyalinized wall [20]. A
repeat spinal cord biopsy, performed on the occasion of a relapse, revealed mild lymphocyte infiltration in association with vascular changes, hence suggesting a role for autoreactive T cells in the pathogenesis of tissue and vascular changes. As opposed to myelitis, only anecdotal cases of steroid-responsive encephalomyelitis (EM) have been reported in patients with either recent [21] or chronic HCV-infection with CSF anti-HCV antibodies [22]. In a patient with a fatal outcome, EM was preceded by optic neuritis, and postmortem brain examination disclosed perivascular lymphocyte infiltration, reactive astrogliosis, microglia activation, and the presence of HCV genome in the brain, but not in the CSF [23]. Although very limited experience is available for this condition, the response to corticosteroids supports an autoimmune pathogenesis.

NEUROMYELITIS OPTICA

NMO is an autoimmune brain-sparing demyelinating disorder preferentially affecting the spinal cord and optic nerves. NMO has been traditionally considered a restricted aggressive form of relapsing multiple sclerosis, until the discovery of complement activating NMO-IgG, targeting aquaporin-4 (AQP4), a water channel highly expressed in astrocyte foot processes. The presence of circulating autoantibodies against AQP4 is not unique to typical cases fulfilling diagnostic criteria of NMO, but includes a relatively large group of disorders, named as NMOSD [10]. NMOSD comprise limited forms of NMO, either idiopathic or in association with systemic autoimmune disorders, in addition to ON or myelitis associated with hypothalamic, corpus callosal, periventricular or brainstem lesions. Recently, an autoimmune AQP4-myopathy has been described within the NMOSD, as an effect of IgG targeting muscle plasmalemmal AQP4 [24]. Conversely, anecdotal reports describing the involvement of the peripheral nervous system in patients with NMOSD remain unclear, since AQP4 is not expressed in peripheral nerves. Kitada et al. reported an HCV-infected patient with simultaneous central and peripheral demyelination in association with anti-AQP4 antibodies and negative systemic autoimmune markers [8]. The clinical picture improved after sequential treatment with high-dose intravenous steroid and plasma exchange. At follow-up a marked decrease in anti-AQP4 antibody titer was observed. We recently studied a chronically HCV-infected 75-year-old-man, who, in 2011 developed difficulty walking, numbness below the T10 level and urinary retention. MRI revealed a spinal cord lesion extending from C5 to T1 vertebral segments and multiple confluent gadolinium-enhanced spinal cord lesions located within the T8 to T10 vertebral segments, in addition to supratentorial and brainstem T2-weighted hyperintense demyelinating lesions, not enhanced after gadolium administration. Analysis of the CSF showed a protein level of 60 mg per deciliter and a few oligoclonal IgG bands. An extensive rheumatological, paraneoplastic and infectious disease screening was negative. The patient partially recovered after high-dose intravenous methylprednisolone for 5 days. Five months later the patient had a relapse and spine MRI revealed contrast-enhancing T2-weighted hyperintense lesions extending from the T3 to the T8 vertebral segments. On readmission, physical examination revealed severe paraparesis, a bilateral extensor plantar response, and sensory disturbances over the lower trunk and legs; the patient also complained of numbness and tingling at the C8 level. Strength in all muscle groups in the lower extremities was rated 1 on the Medical Research Council (MRC) scale, which ranges from 0 (lowest score) to 5 (highest score). He also had weakness in distal muscles of arms, which rated 2 on MRC. A T5 truncal sensory level was detected with diminished sensation of touch, pinprick and joint position. The sense of vibration was impaired in the lower limbs; patellar and ankle reflexes were absent bilaterally. CSF examination showed a protein level of 78 mg per deciliter. Complement and RF were within normal limits; CG were present at low level (cryocrit <1%). Serum electrophoresis detected an IgGλ monoclonal protein (2 g/L). Visual evoked potentials showed a prolonged central latency on the right, while the left eye was not examinable because of an antecedent traumatic lesion. The serum sample was positive for anti-AQP4 antibodies, hence supporting a diagnosis of NMO. Immunosuppressive therapy with azathioprine was started and a gradual recovery was documented.

Taken together, the observation of the above cases suggests that HCV may activate anti-AQP4-producing B cells thus enlarging the spectrum of organ- and non-organ-specific autoantibodies associated with this condition.

DEMYELINATING PERIPHERAL NEUROPATHIES

The PNS is variably affected in HCV-infected patients, especially in cases with circulating CG [3]. In patients without CG, immune complexes or HCV-induced autoimmune mechanisms may play a pathogenic role in triggering vascular and perivascular inflammation [25], which may be driven by an intrinsic nerve population of immunocompetent and phagocytic cells [26]. Guillain-Barré syndrome (GBS), the most frequent cause of acute flaccid paralysis, is a post-infectious disorder that encompasses three main variants, including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and the Miller Fisher syndrome. Among uncommon infectious pathogens causing GBS, only hepatitis E virus has been consistently associated with this condition. AIDP has been associated with HCV infection only in a single case with subclinical HCV infection during the pre-convalescent phase [27]. However, previous evidence has been reported on the association between GBS and non-A, non-B hepatitis [28, 29], before the discovery of hepatitis C virus, and, more recently, in patients with chronic HCV infection, either untreated or treated with ribavirin [30] or interferon [31].

The spectrum of acquired demyelinating neuropathies also includes chronic forms, such as chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy, and neuropathy with monoclonal IgM anti-MAG antibodies. In a minority of cases, atypical forms of CIDP occur, with distal demyelination of sensory large fibers, or multifocal asymmetric involvement of sensory and motor nerves, such as the Lewis-Sumner syndrome. Only few reports have been published on CIDP in the course of HCV infection. Although some patients with CIDP and HCV
infection have been reported to improve after treatment with IFN-α alone or in combination with ribavirin [32, 33]. CIDP has been described also as an uncommon side effect in patients treated with IFN-α. The relationship between HCV, CIDP and treatment with IFN-α was first described by Marzo et al. [34]. Hirotani and coll., and Meriggioli and coll. reported two cases of IFN-α treatment-triggered CIDP who improved, respectively, after IVIg administration [35] and plasma exchange [36]. Finally, Couto et al. described a patient with active chronic HCV, under treatment with IFN-α and ribavirin, who developed CIDP and electrophysiological features of multifocal motor neuropathy; the condition was refractory to IVIg, but promptly responsive to steroids [37].

As emerging from these reports, IFN-α could have immunomodulating effects, such as reduction of proinflammatory cytokines, and, at the same time, a major role in favoring immune-mediated mechanisms. A single case of the Lewis-Sumner syndrome has been described in the setting of HCV infection [38]. This patient improved after IVIg and methylprednisolone treatment, although a relapse occurred following administration of INF-α and ribavirin; discontinuation of INF coupled with IV methylprednisolone led to complete remission.

ANTI-MAG NEUROPATHY

In about half of the patients with neuropathy and IgM monoclonal gammopathy the M protein reacts with MAG, a major component of noncompact myelin. Anti-MAG neuropathy is a distal demyelinating disorder [39], with a prevalence of 1–5 per 100,000 [9], occurring in patients older than 60 years. Owing to the involvement of large fibers, the clinical picture is characterized by sensory ataxia, mild motor involvement, and hand intention tremor. Significant weakness or small fiber neuropathy are encountered in a few atypical case. The majority of patients with anti-MAG neuropathy have monoclonal gammopathies of undetermined significance (MGUS), whereas Waldenström macroglobulinaemia or B-cell lymphoma are found in less than 30% of cases. In a few patients, anti-MAG neuropathy has been described in association with primary amyloidosis, cryoglobulinaemic vasculitis, CMT1 or ALS [40]. We studied a cohort of 59 consecutive patients with neuropathy and chronic HCV infection, recruited at our Institution from January 1996 through December 2010, who underwent sural nerve biopsy. CGs were detected in 39 subjects, including 18 cases with axonal polyneuropathy, 11 with overlapping mononeuritis multiplex, and 10 with mononeuritis multiplex. Fourteen patients without circulating CGs had a positive test for RF; 10 of them had an axonal polyneuropathy, 1 an overlapping form, and the remaining 3 cases a mononeuritis multiplex. Finally, among the 6 patients, who tested negative for CGs and RF, an IgM monoclonal gammopathy with anti-MAG activity was detected in 3 subjects with a demyelinating polyneuropathy. One of these patients had a clinical presentation typical of MGUS-associated anti-MAG neuropathy. Conversely, in a 70-year-old woman a mixed sensory and motor involvement was observed with impaired heel and toe walking. Neurophysiological investigations revealed a sensorimotor demyelinating neuropathy, whereas analysis of CSF showed 10 lymphocytes per cubic milliliter, 0 red cells, and a protein level of 98 mg per deciliter. Nerve biopsy showed loss of fiber and ongoing segmental demyelination with onion bulb formation. Perivascular infiltrates of lymphocytes and monocyte were observed at the epineurial level (Fig. 1). The third case regards a 62-year-old woman with chronic HCV

Fig. (1). Sural nerve biopsy in HCV-related anti-MAG neuropathy. Transverse semithin section showing decreased density of myelinated fibers (toluidine blue stain, 10x magnification, A). Paraffin-embedded sections disclosing perivascular infiltrates of lymphocytes and monocytes around epineurial arterioles and venules (haematoxylin and eosin stain, 20x magnification, B). Electron micrograph showing uncompacted myelin lamellae around a small remyelinating axon (C). D: Electron micrograph showing a myelinated axon with widening of external lamellae of the myelin with increased distance between major dense lines (D).
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infection and HBV coinfection, treated with IFN-α and Ribavirin 10 years earlier. Over the preceding two years, she developed a rapidly progressing sensorimotor neuropathy, with mixed axonal and demyelinating features at electrophysiological studies. At sural nerve biopsy, endoneurial edema and microangiopathy were found, in the absence of inflammatory infiltrates. In all three cases, IgM and complement deposition was observed on myelin sheaths. Taken in consideration that anti-MAG neuropathy has a prevalence of 1-5 per 100,000 [9], the finding of three patients with this condition among a population of 59 HCV-infected patients, seems more than casual. It is well known that HCV induces B-cell expansion, with production of monoclonal and polyclonal immunoglobulins, with or without CG features or RF activity. On the other hand, anti-MAG neuropathy, with M protein exhibiting CG properties, has been reported in two cases of Waldenström macroglobulinemia, characterized by IgM deposition on myelin sheaths in association with necrotizing vasculitis [41] or endoneurial CG deposition [42]. Recent evidence of a significant association between anti-GM1 and anti-sulfatide antibodies and HCV-related peripheral neuropathy provides additional support to the role of the virus in activating B-lymphocytes and inducing anti-neuronal immune response [43].

CONCLUSION

The enlarging spectrum of HCV-related immunemediated central and peripheral demyelinating conditions further confirm the important role of the immune system in the pathogenesis of these neurological conditions. Therefore, the recognition of these forms and the clarification of their molecular mechanisms are of crucial importance for an early diagnosis and appropriate treatment.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

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