

Acute transverse myelitis and hepatitis C virus

Mielite acuta trasversa e virus dell'epatite C

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In the last few years, hepatitis C virus (HCV) neurotropism has been established and reports mainly indicate peripheral nervous system involvement caused by a vasculitic process [1-5]. Here, we report a case of acute transverse myelitis developing 4 years after documented HCV seropositivity, associated with intrathecal anti-HCV protein IgG synthesis.

■ CASE REPORT

A 60-year-old woman, seropositive for HCV since 1996, was admitted to the Department of Infectious Diseases, University of Perugia, Italy, in July 2000 with persistent fever (38.5°C for more than 2 weeks), progressive leg weakness and gait imbalance. Neurological examination showed weakness of both legs, normal reflexes with bilateral Babinski sign and a sensory level at L₂ segment with pain hypoesthesia, slight reduction in vibration sensitivity and urinary retention. Blood parameters, including cryoglobulins, ANA and ANCA, were normal but there was serum positivity for HCV structural and non structural antigen antibodies (c33, c22-3, NS5, c100-3) detected by immunoblot assay. Serum HCV-RNA was found positive and genotyping characterization resulted, according to Simmonds classification, type 1.

Cerebrospinal fluid (CSF) analysis showed mild lymphocytic pleocytosis (40 cells/μl, normal range: <5 cells/μl) increased total proteins (116 mg/dl; normal range 15-50 mg) and isoelectrofocusing (IEF) evidence of oligoclonal

bands not found in serum. Neurotropic virus RNA and DNA including HSV-1 and -2, HHV-6, CMV, EBV, HIV-1, HTLV-1 and Varicella-Zoster (tested by PCR), were not found. Negativity for neurotropic viruses was confirmed in two other consecutive CSF examinations. Brain magnetic resonance imaging (MRI) revealed small T₂-weighted hyper intense signals in subcortical areas, suggesting old ischemic lesions. Spinal cord MRI showed T₂-weighted hyper intense signal extending over L2 to L4 lumbar segments with gadolinium enhancement of the surrounding pia arachnoid. The patient was treated with ampicillin, gentamicin and acyclovir for 3 weeks. Leg weakness slightly improved, normal pain sensory function was restored and lumbar segment vibratory sensation returned towards the end of August. At discharge, the patient was able to walk with bilateral assistance for a few meters and showed leg weakness, hyperreflexia with Babinski sign and moderate urinary retention.

In November 2001, she was admitted to the Department of Neurological Sciences, University of Siena, with worsening of leg weakness. She was treated with intravenous methylprednisolone (1 g for 3 days) responding with slight improvement in clinical parameters. In July 2002, due to renewed worsening of clinical parameters, a lumbar puncture was performed. CSF analysis showed normal protein levels (47 mg/dl) and no pleocytosis (2 cells/μl) but IEF confirmed several oligoclonal bands. PCR testing for HCV-RNA was negative but antibodies against HCV c22-3 protein were found by immunoblot assay. Brain MRI was unchanged

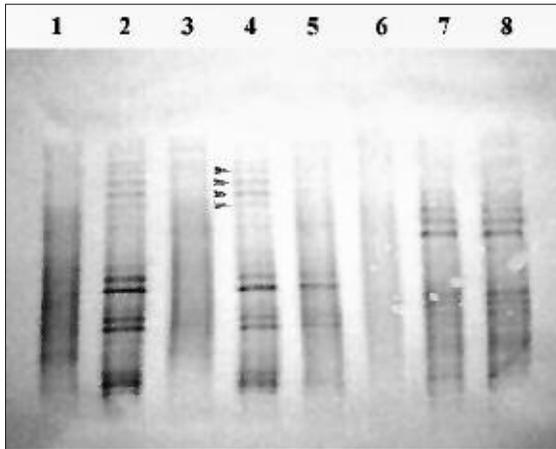


Figure 1 - Immunoblotting pattern of serum and CSF IgG from the patient with acute transverse myelitis (ATM) and a multiple sclerosis (MS) subject before and after immunoabsorption with HCV proteins. After several washes with PBS-0.05% Tween, the strips were blocked with PBS-5% BSA for 1 h at room temperature, then overlaid with 1 ml of undiluted CSF specimens for 1 h at room temperature. Afterwards, the CSFs were removed and 5 μ g IgG with a corresponding diluted serum sample was subjected to agarose IEF, transferred to a nitrocellulose membrane and immunoblotted with a sheep anti-human IgG, anti-sheep IgG peroxidase conjugate and 3-amino-9-ethyl-carbazole as colorimetric substrate.

Lanes 1-2: serum and CSF IgG from ATM patient (July 2000); lanes 3-4: serum and CSF IgG from ATM patient (July 2002) (arrow-heads indicate IgG bands that disappeared or were markedly faint after immunoabsorption); lane 5: CSF IgG from ATM patient after immunoabsorption; lanes 6-7: serum and CSF IgG from a MS patient; lane 8: CSF IgG from a MS patient after immunoabsorption.

and spinal cord MRI no longer showed hyperintense signal in lumbar segments. Further treatment with intravenous methylprednisolone was undertaken. The patient is currently unable to walk and shows hyperreflexia with Babinski sign and moderate urinary urgency.

Immunoabsorption and IEF study

In order to test for an intrathecal immune response to HCV, we performed IEF of the first and last serum and CSF specimens of the patient and a multiple sclerosis (MS) patient as control, before and after immunoabsorption with recombinant structural and non structural HCV proteins immobilized on nitrocellulose strips (Chiron, CA, USA). Identical patterns of oligoclonal IgG were found in the first and last CSF sample of our patient. After immunoab-

sorption with recombinant HCV proteins, some IgG bands disappeared or became markedly faint in the last CSF sample, whereas no change was observed in IgG oligoclonal pattern of CSF from the MS patient (Figure 1).

■ DISCUSSION

The clinical findings of our patient (the speed of clinical progression from the onset, the symmetry of clinical signs, the spinal cord MRI findings and the CSF pleocytosis) are all consistent with acute transverse myelitis of unknown aetiology [6-9]. Myelitis may also be an early clinical sign of MS but brain MRI repeated two years later the clinical onset was substantially unchanged and did not meet the recently proposed diagnostic criteria for MS [10, 11]. Spinal cord MRI repeated 1 year and half later did not reveal any new T2-weighted focal lesion. Furthermore, the CSF IgG oligoclonal pattern, although rare in acute transverse myelitis was different from that of MS patient and part of it was found to be directed against non structural HCV proteins [9]. Central nervous system involvement in the course of chronic HCV infection was found to be associated with cryoglobulinemia and causes cerebral ischemia [12]. Recently, a report of acute disseminated encephalomyelitis associated with recent HCV infection was also described but most neurological manifestations of chronic hepatitis show peripheral nervous system involvement caused by a vasculitic process [5, 13]. To our knowledge, this is the first report of acute myelitis developing some years after demonstration of HCV seropositivity and associated with intrathecal immune response against HCV proteins. In our patient, the absence of HCV RNA in CSF supernatants despite the presence of anti-HCV IgG oligoclonal could exclude a direct pathogenic role of HCV in spinal cord damage and, by contrast, supports the hypothesis of an immune-mediated mechanism. Although it remains to be established whether this response is of pathogenic importance, it is worthwhile testing CSF supernatants and cellular pellets for HCV-RNA and related antibodies in acute myelitis of unknown aetiology.

Key words: Acute transverse myelitis, hepatitis C virus, neurotropic viruses, autoimmunity, cerebrospinal fluid

SUMMARY

In the last few years, substantial evidence has been provided on peripheral nervous involvement in infection by hepatitis C virus (HCV), whilst central nervous involvement is rare. Here, we report a case of acute transverse myelitis in a woman developing 4 years after documented HCV seropositivity, associated with intrathecal anti-HCV protein IgG. Isoelectrofocusing of all CSF samples before and after immunoabsorption with recombi-

nant structural HCV proteins revealed disappearance or marked decrease of some oligoclonal IgG bands suggesting binding to HCV proteins. To our knowledge, this is the first report of acute myelitis associated with intrathecal immune response against HCV proteins. This finding suggests that in acute myelitis of unknown aetiology, testing CSF for HCV RNA and related antibodies is warranted.

RIASSUNTO

Negli ultimi anni numerose evidenze hanno dimostrato un coinvolgimento del sistema nervoso periferico ma raramente del sistema nervoso centrale in corso di infezione da virus dell'epatite C (HCV). In questo studio, riportiamo un caso di mielite acuta traversa insorta in una donna dopo 4 anni di documentata sieropositività al virus dell'epatite C ed associata alla presenza di IgG intratecali dirette contro proteine del virus. L'analisi all'isolettrofocusing delle proteine dei campioni di liquor cefalo-rachidiano raccolti durante i periodi di ricovero, prima e dopo immunoadsorbi-

mento con proteine strutturali ricombinanti del virus dell'epatite C, ha mostrato la scomparsa o una forte attenuazione di IgG oligoclonali suggerendo quindi la presenza di IgG intratecali anti-HCV. A nostra conoscenza, questa è la prima descrizione di mielite acuta associata ad una risposta immunitaria intratecale anti-HCV. Questo dato suggerisce inoltre che nei casi di mielite trasversa acuta ad eziologia virale sconosciuta la ricerca dell'RNA di HCV e di anticorpi anti-proteine strutturali del virus nel liquor debba essere effettuata.

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