Acute Disseminated Encephalomyelitis Associated With Hepatitis C Virus Infection

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Background: Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease of the central nervous system that is frequently preceded by an acute viral infection. This is the first reported case of ADEM associated with hepatitis C virus (HCV) infection.

Case Description: A 46-year-old woman underwent a surgical procedure and received multiple blood transfusions, at which time serologic testing for HCV was negative. Fifty days later, she suddenly developed seizures, alteration of consciousness, right hemiparesis, hemianopsia, and urinary retention. Magnetic resonance imaging revealed symmetric multifocal changes on T2-weighted images in the cerebral gray and white matter and in the cerebellar white matter with some lesion enhancement after gadolinium administration. Blood testing showed a recent HCV infection with high titer of IgM early antigens and a strongly positive reaction for HCV RNA. All other microbiological and virological test results were negative both in serum and in cerebrospinal fluid. Treatment with high-dose dexamethasone was followed by a dramatic improvement of the clinical and magnetic resonance picture. Within a few months the patient recovered completely and there were no relapses during 2 years of follow-up.

Conclusions: Infection with HCV is associated with several autoimmune neurological manifestations. It is recommended the patients with ADEM be screened for HCV.

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Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease of the central nervous system (CNS) that usually develops after acute viral or bacterial infection or vaccination. It has also occurred after organ transplantation or administration of drugs such as gold and streptomycin, but in a few patients no precipitating cause could be found. Numerous infectious agents have been linked to ADEM, including varicella, mumps, measles, rubella, influenza, coxsackievirus B, human T-lymphotropic virus 1, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, herpes simplex virus, Legionella cincinnatiensis, Campylobacter, Borrelia burgdorferi, Salmonella typhi, Mycoplasma pneumoniae, and Chlamydia pneumoniae.1-4 Thus far, however, no association of hepatitis C virus (HCV) with ADEM had been reported. Acute disseminated encephalomyelitis is usually a monophasic disease with acute onset characterized by multiple foci of CNS damage, predominantly in the cerebral and cerebellar white matter, although basal ganglia and gray matter may also be involved. Lesions are frequently bilateral, large, and confluent.5

Effective therapy has included high-dose corticosteroids, and, more recently, intravenous immunoglobulins6 and plasmapheresis.7

A 46-year-old woman was admitted to the Department of Neurology, Policlinico of Modena, Modena, Italy, for the sudden onset of occipital headache and recurrent generalized seizures. Fifty days earlier, during a Billroth II gastroresection for a perforated duodenal ulcer, she had received multiple blood transfusions. Serologic testing for HCV was negative at the time of the surgery.

On admission, the patient was somnolent but arousable, and showed mild right hemiparesis and right hemianopsia. She had headache and vomiting, but no evidence of meningeal irritation.

On the first day of admission she had alternating stupor and psychomotor agitation and developed urinary retention.
Routine blood screening was normal. Findings of electrocardiographic and chest x-ray film examinations were normal. Levels of anticardiolipin antibodies, antinuclear antibody, antineutrophil cytoplasmic antibody, cryoglobulins, neoplastic markers (α-fetoprotein, carcinoembryonic antigen, cancer antigen [CA] 125, CA 19.9, CA 15.5, and neuron-specific enolase) were also normal. The CSF examination showed mild pleocytosis and increased total protein (65 mg/dL [reference range, 15-45 mg/dL]). Iselectrofocusing of paired CSF and serum samples showed a “mirror pattern” with numerous IgG oligoclonal bands in both CSF and serum.

Bacterial, mycobacterial, and fungal cultures from blood and CSF were negative. Results of serologic testing and CSF–polymerase chain reaction analysis for *Borrelia burgdorferi*, human immunodeficiency virus, adenovirus, Enterovirus, HSV types 1 and 2, cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, polyomavirus JC, and hepatitis B virus were also negative.

Anti-HCV IgG, tested by second-generation enzyme-linked immunosorbent assay, was mildly positive; serum IgM antibodies to structural antigens (c33, c22, N55) were strongly positive; and HCV RNA, detected by reverse transcriptase–polymerase chain reaction, was highly positive (2.800 MEq/mL), indicating recent HCV infection.

An electroencephalogram showed severe diffuse theta-delta activity, predominantly on the right hemisphere. Magnetic resonance imaging (MRI) of the brain revealed symmetrical multifocal changes on T2-weighted images that involved gray and white matter in parieto-occipital regions involving gray and white matter more prominently on the left; symmetric multifocal changes in frontal and periventricular white matter. C and D, Complete recovery of abnormal signal foci.
occipital regions, hemispheric white matter in frontal and periventricular regions, and the cerebellar white matter. Some lesions presented enhancement after gadolinium administration (Figure, A-B).

Treatment with intravenous dexamethasone, 0.6 mg/kg (30 mg) daily for 15 days was instituted. In the following days, the seizures ceased, her alertness increased, and both hemiparesis and hemianopsia improved. On the seventh day after admission, the foci of abnormal signal on brain MRI were remarkably reduced in number and size.

At discharge, 24 days after admission, neurological examination and brain MRI (Figure, C-D) had improved further. The intravenous dexamethasone regimen was tapered to a regimen of oral prednisone, 25 mg for 2 weeks, and then to 12.5 mg for 2 months.

Five months later, the patient showed complete resolution of clinical and neuroradiological signs. During the next 2 years, there were no relapses and the patient led a usual life.

**COMMENT**

Infection with HCV is often associated with neurological complications involving the peripheral nervous system and less frequently the CNS. It has been shown to cause profound alterations in the host immune system, resulting in immunological abnormalities such as autoantibodies production, especially cryoglobulins, immune complex formation, and deposition and development of collagen vascular disorders. Complications of the CNS result from direct action of the virus or from immune-mediated damage. However, CNS involvement was reported only in 1 patient with progressive cerebral lymphocytic meningitis, in whom HCV RNA was isolated from the CSF.

To date, HCV-associated CNS vasculitis has been described in some patients. This occurs late in the course of the disease, months or even years after the infection, and is usually associated with cryoglobulinemia and accompanied by multisystemic manifestations.

In our patient, CNS vasculitis was ruled out because she had no skin lesions, kidney abnormalities, peripheral nervous system involvement, or other signs of multisystemic disease. In addition, there were no cryoglobulins, autoantibodies, or circulating immune complexes. Moreover, the disease developed shortly after the HCV infection, as indicated by the fact that serologic test results were negative before the patient underwent surgery and transfusion, and seroconversion was noted on admission, 50 days later. Recent viral infection is typical of ADEM, whereas CNS vasculitis is usually associated with chronic infection.

Central nervous system lymphoma or metastatic malignant neoplasms were ruled out by clinical course and MRI, and acute CNS infections were excluded by negative microbiological and virological data. The diagnosis of multiple sclerosis was carefully considered, but the sudden, multifocal clinical onset and the extensive, symmetric, and confluent abnormalities on MRI, as well as the absence of clinical or neuroradiological relapses after 2 years, made this diagnosis unlikely. Therefore, it appears that our patient had immunemediated CNS damage associated with HCV infection, and directed mainly against myelin rather than against blood vessels, as in the cases with vasculitis.

The pathogenetic mechanism of ADEM is still obscure, and both humoral and cellular responses have been considered. A recent study identified Th2 cells reactive to myelin basic protein in peripheral blood of patients with ADEM. The response to plasmapheresis and intravenous immunoglobulin administration suggests a key role of autoantibodies, similar to other autoimmune neurological diseases, such as Guillaine-Barre syndrome or myasthenia gravis. Still, it is unclear how so many different agents may activate a common cascade of events leading to inflammation and demyelination in the CNS—further data are needed to elucidate these mechanisms.

In conclusion, we emphasize the importance of HCV screening in patients with ADEM because acute CNS demyelination might be the first manifestation of HCV infection.

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**REFERENCES**