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 (CNS) 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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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]). Isoelectrofocusing 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, NS5) were strongly positive; and HCV RNA, detected by reverse transcription–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 in- creased, 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 resolu- tion 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 neurologi- cal complications involving the peripheral nervous sys- tem and less frequently the CNS. It has been shown to cause profound alterations in the host immune system, resulting in immunological abnormalities such as auto- antibodies 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 involve- ment was reported only in 1 patient with progressive en- cephalomyelitis, in whom HCV RNA was isolated from the CSF.

To date, HCV-associated CNS vasculitis has been de- scribed 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, peripher- al nervous system involvement, or other signs of multisystemic disease. In addition, there were no cryo- globulins, autoantibodies, or circulating immune com-plexes. Moreover, the disease developed shortly after the HCV infection, as indicated by the fact that sero- logic test results were negative before the patient under- went surgery and transfusion, and seroconversion was noted on admission, 50 days later. Recent viral infec- tion is typical of ADEM, whereas CNS vasculitis is usu- ally associated with chronic infection.

Central nervous system lymphoma or metastatic malig- nant neoplasms were ruled out by clinical course and MRI, and acute CNS infections were excluded by nega- tive microbiological and virological data.

The diagnosis of multiple sclerosis was carefully con- sidered, but the sudden, multifocal clinical onset and the extensive, symmetric, and confluent abnormalities on MRI, as well as the absence of clinical or neuroradiologi- cal relapses after 2 years, made this diagnosis unlikely.

Thus, it appears that our patient had immune- mediated 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 obs- cure, and both humoral and cellular responses have been considered. A recent study identified T and B cells reactive to myelin basic protein in peripheral blood of patients with ADEM. The response to plasmapheresis and in- travenous immunoglobulin administration suggests a key role of autoantibodies, similar to other autoimmune neu- rological diseases, such as Guillaine-Barre syndrome or myasthenia gravis. Still, it is unclear how so many dif- ferent 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 infec- tion.

**REFERENCES**