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SCIENTIFIC LETTER

Guillain-Barré syndrome following acute hepatitis E virus infection: A novel Indian case report with acute inflammatory demyelinating polyneuropathy pattern and anti-GM1 antibodies

Síndrome de Guillain-Barré tras una infección aguda por el virus de la hepatitis E: Un caso novedoso reportado de la India con un patrón de polineuropatía desmielinizante inflamatoria aguda y anticuerpos anti-GM1

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Dear Editor,

Hepatitis E virus (HEV) triggers a lot of extrahepatic manifestations, especially neurological disturbances.[1] The most common are neuralgic amyotrophy (Parsonage-Turner syndrome), Guillain-Barré syndrome (GBS), myelitis, and encephalitis.[2] Their exact pathophysiology remains obscure.[2]

The most common subtypes of GBS are acute inflammatory demyelinating polyneuropathy and acute motor axonal neuropathy. Some antibodies are associated explicitly with GBS subtypes and related neurological deficits concerning different gangliosides in human peripheral nerves. Patients with acute motor axonal neuropathy frequently have serum antibodies against GM1a, GM1b, GD1a, and GalNAc-GD1a gangliosides.[3] However, the nature of the shared epitopes has not been characterized in most instances, including hepatotropic viruses, especially HEV.[3–7]

As a phenotypic variant, we report a novel GBS case from rural India following acute HEV infection with acute inflammatory demyelinating polyneuropathy pattern and anti-GM1 antibodies.

A 50-year-old male from rural West Bengal, India, visited our clinic as an outpatient for acute onset flaccid weakness involving all four limbs for the last four days. Initially, he felt intense lower back pain with tingling and numbness in both

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lower limbs up to the ankles. The next day, the patient felt difficulties getting upstairs and getting up from a squatting position while using an Indian-style toilet. The following day, he needed assistance even for moving from bed to toilet, and the weakness ascended to involve both upper limbs similarly.

He was recently diagnosed with type 2 diabetes mellitus, receiving oral antidiabetic drugs, and was recently discovered to have jaundice. He also had controlled primary hypothyroidism, for which he took daily thyroid replacement. On examination, he had deep jaundice, tender hepatomegaly, was afebrile, and was hemodynamically stable. Neurological examination revealed normal cognitive abilities, cranial nerve, and sensory examinations. He had a flaccid areflexic type of quadriparesis with intact autonomic functions. Complete blood cell count was normal except for neutrophilic leukocytosis and raised erythrocyte sedimentation rate. Liver function tests revealed total bilirubin of 30 mg/dL (direct bilirubin 12 mg/dL), raised AST (1200 IU/L) and ALT (1400 IU/L), and ALP (580 IU/L). The albumin globulin ratio was normal. Prothrombin time and international normalized ratio were mildly raised. Renal and thyroid function tests, electrolytes, and urinalysis were normal. Abdomen ultrasonography revealed features suggestive of acute hepatitis. Serological tests for hepatotropic viruses revealed positive anti-HEV IgM and HEV-RNA detection by reverse transcription-polymerase chain reaction. Serological tests for SARS-CoV-2, HIV (1, 2), hepatitis B virus, hepatitis C virus, hepatitis A virus, Epstein–Barr virus, cytomegalovirus, herpes simplex virus (1, 2), varicella-zoster virus, Malaria, Leptospira, scrub typhus, syphilis, and Dengue were negative. Both history and urine toxicology screen were negative for offending drugs. Fasting blood sugar was 278 mg/dL, and postprandial blood sugar was 360 mg/dL. Magnetic resonance imaging of the brain and spinal cord revealed no abnormalities.

Nerve conduction studies on the seventh day of neurological symptoms onset disclosed an acute inflammatory demyelinating polyneuropathy pattern. Serum anti-GM1 IgM antibodies were positive. A cerebrospinal fluid study showed an increased protein level and normal cell count (albumin-cytological dissociation; cells 4, all lymphocytes, protein 213 mg/dL). A diagnosis of GBS following acute HEV infection was made.

He was put on subcutaneous insulin therapy (basal bolus regime), S-Adenosyl methionine (800 mg/day), pantoprazole (80 mg/day), lactitol fiber, rifaximin (1200 mg/day), adequate hydration, and rest. His symptoms showed remarkable improvement after intravenous immunoglobulin therapy. He was ambulatory with persistently reduced deep tendon reflexes.

Extrahepatic, primarily neurological, manifestations have frequently been reported in acutely and chronically HEV-infected patients.[1] The pathogenesis of GBS-related HEV infection could be immune-mediated or by direct infection of nerves.[8] Furthermore, mitochondrial apoptosis may be involved in HEV-induced neurological dysfunction.[8] The presence of anti-ganglioside GM1 or GM2 antibodies in the serum of some HEV-associated GBS patients indicates that HEV infection may trigger GBS by activating an autoimmune response to destroy myelin or axon mistakenly.[9]

Liver function is abnormal in 10–40% of patients and hyponatremia in 25%. Three case–control studies performed in the Netherlands,[5] Bangladesh,[6] and Japan[7] support the association of HEV infection with GBS. A critical limitation of these studies investigating the presence of only anti-HEV IgM (without HEV RNA determination) is the possibility of false-positive results in the context of autoimmunity. Conversely, false negative results cannot be excluded.[1] Anti-HEV IgM in GBS patients is unrelated to age, sex, disease severity, or clinical outcome.[5]

Management of HEV-associated GBS has no apparent difference from other GBS cases. It mainly consists of supportive therapy and immunotherapy.[9] Intravenous immunoglobulins or plasma exchange is the primary strategy for treating HEV-associated GBS.[10] Respiratory function should be monitored since respiratory failure can occur without symptoms of dyspnea.[10] Further study is required to determine whether antiviral therapy could be an additional strategy to shorten the length of the disease course.[9]

Following acute HEV infection, this would be the first reported Indian case of anti-GM1 antibody-positive GBS (acute inflammatory demyelinating polyneuropathy). It shows that these antibodies can also be present in this immune-mediated setting, being the probable immunological link between these two entities. This association has not been demonstrated in the previously communicated acute-HEV-infection-associated GBS cases from India.[11]

Our case highlights (1) the importance of including acute HEV infection in the differential diagnosis of entities causing GBS since HEV is a common infection worldwide and is an emerging disease in developed countries; (2) the presence of extrahepatic neurological manifestations of HEV infection is essential to take into account for avoiding misdiagnosis since HEV is not routinely tested for in acute hepatitis because of perceived rarity of this infection in non-endemic countries[2]; (3) It is essential to ask for NCS, anti-HEV-IgM, HEV-RNA (by RTPCR) and anti-GM1-IgM antibodies, and biochemical cerebrospinal fluid analysis looking for albumin-cytological dissociation in case of a strong clinical suspicion of GBS following acute HEV infection for diagnostic confirmation.

Early recognition of this clinical-microbiological-immunological scenario could help achieve prompt diagnosis and proper treatment before life-threatening complications (mainly respiratory failure). Finally, further and more extensive prospective studies need to be carried out to explore epidemiological data in India, the evolution and prognosis of this acute-HEV-infection-associated neurological complication, and the relationship between anti-GM1 antibodies and the acute inflammatory demyelinating polyneuropathy pattern.

Informed consent

Written informed consent was obtained from the patient participating in the study.

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Conflict of interest

The authors declare no conflict of interest relevant to this work.

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