Future VIROLOGY

EDITORIAL

Hepatitis E virus-associated neuropathy: an emerging extrahepatic manifestation

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KEYWORDS
• Guillain–Barré syndrome • hepatitis E virus • HEV genotypes • neuropathy

Hepatitis E virus virus (HEV), the causative agent of hepatitis E, is an important public health issue, having water-borne, food-borne and zoonotic modes of transmission [1]. Hepatitis E infection may be symptomatic or asymptomatic, with a global mortality rate of approximately 2%, including cases of fulminant liver failure in pregnant women in developing nations [2]. HEV is a nonenveloped, plus-sense RNA virus that has four recognized genotypes, 1, 2, 3 and 4, which are infectious to humans. Of these, genotypes 1 and 2 are mainly restricted to humans and nonhuman primates, whereas genotypes 3 and 4 are infectious to swine, deer, boar and few other mammals in addition to humans [1]. While genotype 1 circulates in Asia, including the Middle East, genotype 2 is prevalent in African and Latin–American countries. By contrast, genotypes 3 and 4 are mainly confined to Eastern Asian countries, Eastern and Western Europe, and North America. Although HEV generally causes self-limiting acute infection, chronic cases of autochthonous hepatitis E in clinically immunocompromised patients has also emerged in high-income industrialized nations [3]. Most of these autochthonous-sporadic cases have been attributed to genotype 3 and 4, and a zoonotic association with the consumption of pork, deer and wild boar meat has been established [4].

Extrahepatic manifestation of HEV

HEV is inherently a hepatotropic virus. However, it is unclear how the virus reaches the liver and, therefore, an extrahepatic site(s) of replication is also possible. HEV replication has been demonstrated in the tonsils, small intestine, colon tissues and bile ducts of experimentally as well as naturally infected pigs [5,6]. Furthermore, the HEV-associated extrahepatic manifestations have been reported in cases of kidney injury, hematological disorders and, most importantly, neurological complications. Notably, in hepatitis E patients, cases of neurologic signs and symptoms, such as Guillain–Barré syndrome (GBS), neuralgic amyotrophy and acute transverse myelitis, have been widely reported from developing (five cases) as well as developed nations (13 cases) [7–19]. Although limited information on HEV-induced neurological manifestations are available, clinical cases of hepatitis E-associated GBS has received special attention across the world in recent years. Of note, the existing literature

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about HEV and neurologic symptoms is, however, mainly based on case reports or small case series, and there are no controlled trials/studies available to date.

Guillain–Barré syndrome

GBS is a rare, sporadically occurring disease that causes neuromuscular paralysis, with an annual incidence of 0.6–2.4/100,000 individuals worldwide [20,21]. GBS is defined as an acute inflammatory demyelinating polyradiculoneuropathy presenting, in its classical form, as a rapidly evolving symmetric and ascending motor paralysis with hypotonia and areflexia accompanied by an acellular cerebrospinal fluid response [22]. Symptoms of GBS typically peak within 4 weeks and then plateau before resolving. More than 50% of GBS patients experience severe pain and autonomic symptoms, such as cardiac arrhythmias, blood pressure instability or urinary retention. Of these, approximately 20% of patients continue to have severe disease despite treatment, and approximately 5% die of the syndrome.

Underlying mechanism(s)

In approximately 60% of cases, GBS is preceded by infections with bacterial agents (*Campylobacter jejuni*, *Haemophilus influenza* and *Mycoplasma pneumoniae*), as well as viruses from the Herpesviridae family (cytomegalovirus, varicella zoster virus and Epstein–Barr virus) [23]. Although uncommon, hepatitis viruses, such as HAV, HBV and HCV, have also been reported to be GBS-triggering agents [24]. Clinical evidence suggests that GBS is an organ-specific, immune-mediated disorder caused by synergistic interaction of cell-mediated and humoral immune responses targeting peripheral nerve antigens. However, the molecular or cellular mechanism(s) by which infection can trigger GBS is not completely understood. It is thought that the immune system mistakenly attacks myelin or axons by a molecular mimicry mechanism. It has been postulated that infected cells can produce ganglioside (GM1, GM2, GD1B and GQ1B)-like self-antigenic epitopes, which elicit the production of antiganglioside antibodies that may disrupt the molecular topography of nodal and paranodal proteins, and thus induce motor axonal degeneration [25,26]. The implication of anti-GM2 antibody in the pathogenesis of cytomegalovirus-induced GBS has been described [26]. However, for GBS related to hepatitis A, B and C, no homologous epitopes to components of the peripheral nerves have been described to date. Of note, very recently, the first description of the presence of anti-GM2 and anti-GM1 antibodies in HEV-induced GBS cases have been reported [13,16].

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Challenges to diagnosis & treatment

Diagnosis of GBS is based on clinical features, cerebrospinal fluid testing and nerve conduction studies. Although there is no specific drug for GBS, most patients have good outcomes without sequelae after conventional plasma exchange and intravenous immunoglobulin therapy. Moreover, the proper and timely diagnosis of HEV infection in general and in neurological cases remains technically challenging. Lack of an approved algorithm, consistency of serologic tests and viral load quantification, in terms of sensitivity and specificity, are the limiting factors. Extrahepatic symptoms may develop not only during active HEV infection, but also after clearance of the virus, and therefore the association of such symptoms with hepatitis E is usually overseen in clinics and the morbidity burden remains underestimated. In a very recent report, GBS was shown to be associated with autochthonous HEV-genotype 3 infection in European patients [16,17,19,27]. In industrialized nations, the actual incidence of HEV-associated GBS is unknown as autochthonous hepatitis E remains underdiagnosed. This is in part due to the fact that HEV infection is frequently subclinical, and because the neurological findings surpass liver injuries and hepatitis is not suspected. In the majority of such cases, HEV RNA is normally found only up to 4–6 weeks after onset of clinical symptoms. Therefore, the problem is that, if the onset of neurological symptoms is often >4–8 weeks after viral infection, serology is the only diagnostic tool. The hepatitis E serology is further complicated in European cases where approximately 20–60% of individuals are HEV-IgG positive in which tests for HEV-IgM might be false positive due to immune cross-reactions or negative after a few months.

Although there is no established treatment for HEV infection, ribavirin is the commonly used regimen in chronic cases that has been proven successful in spontaneous clearance of serum HEV RNA [4]. In most of such cases, the patients were given no specific treatment and neurologic signs and symptoms resolved fully in

3 months, and laboratory parameters returned to reference range within 6 months. However, a few were given intravenous immunoglobulin (0.4 g/kg once per day for 5 days), which rapidly improved neurologic signs and symptoms, and progressively returned liver enzyme levels to reference limits within 4 weeks [13,15,16]. Nevertheless, the recently developed HEV vaccine [28] would be protective in naive travellers or in high-risk population groups, such as transplant recipients, and people with underlying liver conditions or neurological disorders.

Conclusion & future perspective

HEV infection in GBS patients is often associated with abnormal levels of liver enzymes. It is thus recommended that clinicians should strongly consider the possibility of hepatitis E infection in patients with neurologic disorders, especially in peripheral nerve and liver complications. HEV diagnosis may be suggested by examining the patient's serology, which should be further confirmed by viral RNA detection in the serum and/or CSF. Nonetheless, further investigations are needed to assess the actual prevalence of HEV infections in cases of neurologic disorders, especially those of unknown etiology. Since other tested drugs for GBS, including corticosteroids, have not proved beneficial, there is an obvious need for developing more acceptable and efficacious therapies.

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