Hepatitis E virus and neurological injury

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Abstract | Hepatitis E is hyperendemic in many developing countries in Asia and Africa, and is caused by hepatitis E virus (HEV) genotypes 1 and 2, which are spread via the faecal–oral route by contaminated water. Recent data show that HEV infection is also endemic in developed countries. In such geographical settings, hepatitis E is caused by HEV genotypes 3 and 4, and is mainly a porcine zoonosis. In a minority of cases, HEV causes acute and chronic hepatitis, but infection is commonly asymptomatic or unrecognized. HEV infection is associated with a number of extrahepatic manifestations, including a range of neurological injuries. To date, 91 cases of HEV-associated neurological injury — most commonly, Guillain–Barré syndrome, neuralgic amyotrophy, and encephalitis/myelitis — have been reported. Here, we review the reported cases, discuss possible pathogenic mechanisms, and present our perspectives on future directions and research questions.

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Hepatitis E virus (HEV) is the causative agent of hepatitis E. HEV is a small (27–34 nm) non-enveloped, single-stranded RNA virus of the genus *Hepevirus*. Four genotypes (HEV1–4) are generally recognized. For many years, HEV was thought to be restricted to countries in Asia and Africa. In these areas, infection is caused by HEV1 and HEV2, which are obligate human pathogens. Transmission occurs through ingestion of faecally contaminated water in areas with poor sanitary infrastructure. As well as sporadic cases, outbreaks, which may involve thousands of cases, can occur. The resulting illness predominantly affects young adults, and is characterized by a short-lived hepatitis. In pregnant women, however, infection is often severe, leading to 25% mortality[1].

In developed countries, locally acquired hepatitis E is caused by HEV3 and HEV4, and is a porcine zoonosis[2,3]. The illness differs in a number of important respects from that caused by HEV1 and HEV2 (TABLE 1). Most infections (>90%) are asymptomatic. Patients with symptomatic hepatitis tend to be older males, who generally have a self-limiting hepatitis[4–12]. Cases are sporadic, and large outbreaks and excess mortality in pregnant women have not been observed[2]. In immunocompromised individuals, HEV3 can cause chronic infection with rapidly progressive cirrhosis[13–16]. Consumption of infected pork products is thought to be the main route of infection, but transfusion-related infection has also been reported[1,2]. In a number of countries, HEV has been found in the human blood supply with surprisingly high frequency[5–34] (TABLE 2), and several cases of transfusion-transmitted infection have been reported[26].

Hepatitis E is now known to be common in numerous developed countries, but in many places the exact incidence is uncertain or unknown. The incidence of infection varies geographically (TABLE 2) and over time, and has been estimated at 0.2% in the UK, 1.1% in the Netherlands, 0.7% in the USA, and 2–3% in Southern France[18,28,35,36]. These estimates equate to very large numbers of infections: >100,000 infections are thought to occur per year in England alone[26]. Recently, there has been a dramatic (4.5-fold) increase in prevalence in the Netherlands, with 1 in 600 blood donors found to be viraemic in 2014 (REF. 17).

In addition to hepatitis and liver cirrhosis, a number of extrahepatic manifestations, including various types of neurological injury, have been reported in individuals with HEV infection (BOX 1; FIG. 1). To date, 91 cases of HEV-associated neurological injury have been documented[4,37–78] (see Supplementary information S1 (table)), from both developed and developing countries (genotypes 3 and 1, respectively). A broad spectrum of neurological injury has been described, the most common manifestations being Guillain–Barré syndrome (GBS), neuralgic amyotrophy, and encephalitis and/or myelitis. In this article, we review the reported cases, discuss the possible pathogenic mechanisms, and outline future directions and research questions.

HEV-associated neurological injury

HEV is the commonest cause of acute hepatitis worldwide, but the burden of disease is unclear because testing is variable and new clinical presentations are still emerging.

Key points

- Hepatitis E virus (HEV) is the commonest cause of acute viral hepatitis worldwide
- HEV is hyperendemic in many developing countries, where it is spread predominantly by contaminated water, and endemic in developed countries, where it is mostly a porcine zoonosis
- HEV is associated with a range of subacute monophasic neurological injuries, in particular, Guillain–Barré syndrome, neuralgic amyotrophy and encephalitis/myelitis
- In patients with HEV-associated neurological injury, the neurological features dominate the clinical picture, and hepatitis is either mild or absent
- The incidence, clinical phenotype, pathophysiology and treatment of HEV-associated neurological injury remain to be determined

Table 1 | **Comparison of HEV genotypes**[1,3,104]

Characteristic	HEV 1 and 2	HEV 3 and 4
Geographical distribution	Asia (HEV1) Africa (HEV1 and HEV2) Mexico (HEV2)	Worldwide, including developed countries (HEV3) Japan, China and Europe (HEV4)
Source of infection	Obligate human pathogen	Zoonotic Blood supply
Route of infection	Faecal–oral via infected water	Oral via consumption of infected pork Parenteral, iatrogenic (blood supply)
Risk of infection from blood supply	Low	High
Outbreaks	Yes	No
Intrafamilial spread	Rare	No
Clinical attack rate	1:5 (REF. 105)	<1:10
Demographics	Mainly affects young adults	Mainly affects older men (median age 63 years, male:female ratio 3:1)
Chronic infection	No	Yes, in immunocompromised individuals Rapidly progressive liver disease if untreated: 10% of cases are cirrhotic within 2 years Viral clearance is usually achieved with a 3-month course of ribavirin monotherapy
Occurrence of second HEV infections	Yes (but poorly documented)	Yes Poorly documented for HEV3 Well documented in HEV4, more likely in women who have a milder hepatitis than is generally seen in primary infections
Clinical course	Self-limiting hepatitis in most cases	Self-limiting hepatitis in most cases
Effects during pregnancy	Mortality 25%	No evidence of increased mortality
Effects on individuals with underlying chronic liver disease	Increased mortality	Increased mortality
Neurological sequelae	Yes (but poorly documented	Yes

HEV, hepatitis E virus.

The first reported case of hepatitis E-associated neurological injury, in 2000, was an immunocompetent GBS patient from India[37], and 91 cases of HEV-associated neurological injury have now been published[4,37–78] (see Supplementary information S1 (table)). Cases have been described on three continents (66 in Europe, 23 in Asia, and one in the USA) in association with HEV1 and HEV3. In general, the cases from Asia have been less well documented — HEV genotyping was performed in only one Asian report. However, these cases were likely to be related to HEV1, as it is the predominant genotype in these countries.

The mean age at presentation was 50 years (range 2–92 years), and 58 of 77 patients (75%) were male. All cases were sporadic, and no infections were described in household contacts. The majority of patients (85 of 91, or 93%) were immunocompetent and had acute hepatitis E, from which most made a hepatological recovery without specific treatment. Cases were generally anicteric with a mild hepatitis, and the neurological symptoms and signs dominated the clinical picture. The reports describe HEV-associated cases of GBS ($n = 36$), neuralgic amyotrophy ($n = 30$), encephalitis/myelitis ($n = 12$), and miscellaneous conditions including mononeuritis multiplex, myositis, vestibular neuritis and Bell palsy ($n = 14$). All reports describe a single episode of neurological illness.

Guillain–Barré syndrome

GBS is a subacute disorder of the peripheral nerves and nerve roots, which results in rapidly progressive weakness and sensory deficits of the limbs, and can progress to respiratory failure[79]. Symptoms of preceding infection are reported by two-thirds of patients with GBS. Various types of infection — in particular, enteric *Campylobacter jejuni* — have been related to GBS, and these infections are believed to trigger an immune response that results in GBS[80]. In about half of the cases, the type of preceding infection is unknown, but studies have found unexplained mild liver function disturbance in one-third of patients with GBS[81]. Many individual case reports and series of HEV-associated GBS have been published (see Supplementary information S1 (table)), which include a total of 36 patients aged between 2 and 73 years from Europe (HEV3) and Asia (HEV1). 26 (72%) of the affected individuals were male, and all but one were immunocompetent.

In a recent case–control study, we investigated 201 Dutch patients with GBS in comparison with 201 healthy controls with a similar distribution of age, sex and year of blood sampling[67]. This study showed that 5% of patients with GBS had positive IgM serology indicative of a recent or current locally acquired HEV infection. This proportion was 10 times higher than in the control population. The association with HEV was further supported by the demonstration of HEV3 RNA in the blood of three of these patients. All cases of HEV-associated GBS were anicteric and most had only mildly elevated liver enzymes, but in three cases the liver function tests (LFTs) were normal. The affected patients had typical GBS with respect to disease severity and outcome, and none had detectable antiganglioside antibodies. Interestingly, a

Table 2 | **HEV viraemia and seroprevalence by country**

Country	Reference	Prevalence of HEV RNA positivity among blood donors	HEV IgG seroprevalence (%)
Highly endemic countries*			
Netherlands	Zaaijer *et al.* (2014)[17]	1:600	NR
	Slot *et al.* (2013)[18]	1:2,671	27.0
Midi-Pyrénées, South West France[‡]	Gallian *et al.* (2014)[19]	1:1,595	NR
	Mansuy *et al.* (2011)[20]	NR	52.5
France[§]	Gallian *et al.* (2014)[19]	1:2,218	NR
Germany	Vollmer *et al.* (2012)[21]	1:1,200	NR
	Baylis *et al.* (2012)[22]	1:4,525	NR
	Wenzel *et al.* (2013)[23]	NR	29.5
Japan	Fukuda *et al.* (2004)[24]	1:1,781	NR
Countries of intermediate or low endemnicity*			
England	Hewitt *et al.* (2014)[26]	1:2,848	NR
	Ijaz *et al.* (2012)[27]	1:7,000	NR
	Beale *et al.* (2011)[28]	NR	12.0
	Dalton *et al.* (2008)[5]	NR	16.0
Sweden	Baylis *et al.* (2012)[22]	1:7,986	NR
Austria	Fischer *et al.* (2015)[29]	1:8,416	13.5
USA	Baylis *et al.* (2012)[22]	Nil	NR
	Xu *et al.* (2012)[30]	Nil[§]	16.0
	Stramer *et al.* (2015)[106]	1:9,500	9.5
Scotland	Cleland *et al.* (2013)[31]	1:14,520	4.7
Australia	Shrestha *et al.* (2014)[32]	Nil[‖]	6.0
New Zealand	Dalton *et al.* (2007)[33]	NR	4.0
Fiji	Halliday *et al.* (2014)[34]	NR	2.0[¶]

HEV, hepatitis E virus; NR, not reported. *'Highly endemic' has been arbitrarily defined as an incidence of HEV viraemia in blood donors >1:2,500 and/or seroprevalence of >20%. 'Intermediate or low endemnicity' has been arbitrarily defined as an incidence of HEV viraemia in blood donors of <1:2,500 and/or seroprevalence <20%. Seroprevalence studies have been restricted to those employing the highly sensitive and partially validated Wantai anti-HEV IgG assay, as other assays have been shown to have very poor sensitivity. [‡]Deconstructed solvent–detergent-treated mini-pools. [§]Only 1,939 donors tested. [‖]Only 3,237 donors tested. [¶]Healthy adults and children.

recent HEV infection was also demonstrated in 10% of a cohort of patients with GBS from Dhaka, Bangladesh[60]. Taken together, the cases and controlled studies indicate that HEV is a trigger of GBS worldwide. However, a limitation of most studies was that other infections and co-infections were not excluded.

Neuralgic amyotrophy

Neuralgic amyotrophy is characterized by attacks of severe neuropathic pain of the arm and shoulder, followed by patchy weakness, atrophy and sensory disturbances[82]. The disease is largely localized to the brachial plexus, although other peripheral nerves can be involved. Neuralgic amyotrophy is considered to be a postinfectious, immune-mediated neuropathy; 50% of patients report an antecedent trigger with nonspecific 'infectious' symptomatology, and LFTs are mildly raised in 25% of cases[68]. 30 cases of HEV-related neuralgic amyotrophy have been reported (see Supplementary information S1 (table)), all but one of which were in European patients. The infecting virus was HEV3 in all cases where genotyping was performed. The mean age of the affected patients was 49 years, and 21 of 24 individuals (87.5%) for whom we have details were male.

The association of HEV with neuralgic amyotrophy was demonstrated by a recent observational cohort study of 38 Dutch and 28 Cornish patients with neuralgic amyotrophy, which showed that five (10.6%) of the 47 patients tested for HEV had serological evidence of recent HEV infection[68]. All patients had locally acquired HEV infection and had severe, bilateral brachial plexus involvement (FIG. 2), with a classic disease course of slow recovery over several months with marked residual deficits. Four of these patients were tested within 15 days of symptom onset and had detectable HEV viraemia. Three of the four patients had abnormal liver function.

Some years ago, a large consecutive neuralgic amyotrophy case series identified a subgroup of patients with mildly elevated LFTs of unknown cause (HEV was not tested for at the time of the study), who had a similar phenotype to the patients with HEV-associated neuralgic

Box 1 | **Extrahepatic manifestations of HEV infection**

Neurological
- Guillain–Barré syndrome
- Neuralgic amyotrophy
- Encephalitis/myelitis
- Mononeuritis multiplex*
- Myositis*
- Vestibular neuritis*
- Bell palsy*

Haematological[4,98]
- Thrombocytopenia
- Lymphopenia
- Monoclonal immunoglobulin*
- Cryoglobulinaemia*[99]

Nephrological
- Glomerulonephritis[100]

Other
- Acute pancreatitis[101]
- Arthritis*[102]
- Autoimmune thyroiditis*[103]

HEV, hepatitis E virus. *Causal association not proven.

amyotrophy, including severe bilateral brachial plexus involvement, and phrenic nerve or lumbosacral involvement in some cases[83]. 86% of the reviewed cases showed bilateral brachial plexus or phrenic nerve involvement. These findings suggest that HEV is associated with a sizeable proportion of neuralgic amyotrophy cases that display a distinct, more symmetric phenotype (FIG. 2), with involvement of the phrenic nerve in a substantial number of patients.

CNS infection

There are 12 published cases of CNS infection with HEV[38,41,42,46–48,51,59,61,64,66] (see Supplementary information S1 (table)). The patients were from Europe ($n = 7$), Asia ($n = 4$) and the USA ($n = 1$), had a mean age of 42 years, and five (56%) were male. Five of the affected individuals were immunocompromised as a result of solid organ transplantation. HEV infection was confirmed in six patients by demonstrating viral RNA (HEV3) in both serum and cerebrospinal fluid (CSF) at the time of the acute neurological illness. In one case, a different RNA sequence was found in the CSF[47], and this 'quasispecies compartmentalization' led to the suggestion of a link to emerging neurotropism. Five patients with encephalitis had a prominent ataxic syndrome, which is recognized in other viral infections, most notably acute varicella zoster virus infection. Two cases were characterized by meningitic features, and two of the patients had myelitis. Only one case of a pure myelitis has been reported. This case had MRI findings suggestive of a longitudinally extensive myelitis; however, antibodies to aquaporin-4, which are associated with neuromyelitis optica, were not reported. Five of the 12 patients also had evidence of a peripheral nerve component, including a GBS-like syndrome, demyelinating sensorimotor polyneuropathies, and a painful sensory neuropathy. Thus, PNS and CNS manifestations can coexist in HEV-associated illnesses.

No clear relationship exists between peripheral viral load and illness severity. Five patients were transplant recipients, some of whom had chronic HEV infection and, as is typical of such patients, the liver function tests were only mildly deranged (alanine aminotransferase (ALT) 100–200 IU/l; normal range 10–35 IU/l). Cases with acute hepatitis E had higher ALT levels, but those presenting later with the disease had more-modestly raised or normal levels. Four of the five transplant recipients developed an ataxic encephalopathy, all had an incomplete recovery, and two of the patients died. Individuals who were not immunocompromised were most likely to fully recover.

Other neurological disorders

The literature contains accounts of a variety of other HEV-associated neurological disorders that are not covered by the preceding categories. The most frequently reported of these disorders is mononeuritis multiplex, a condition that is characterized by asymmetric, asynchronous involvement of non-contiguous nerve trunks, which is usually painful. Mononeuritis multiplex is a common complication of immune and viral diseases in which vasculitis is the main pathophysiological process. Numerous viruses, including HIV, cytomegalovirus and hepatitis B virus, have been associated with this condition. In a recent observational study, six patients from France (mean age 53 years; three males and three females) presented with painful asymmetric neuropathy temporally associated with HEV infection[70]. Nerve conduction studies confirmed mononeuritis multiplex. HEV RNA was detected in serum obtained at the time of onset of neurological symptoms in four of the six cases, and was identified as genotype 3. The underlying pathological process could not be confirmed, as none of the patients underwent nerve biopsy.

Two cases of severe myositis associated with HEV have been reported[4,52]. In both cases, the patients had limb girdle weakness and significantly elevated serum creatine kinase levels (191,603 IU/l and >21,000 IU/l, respectively; normal range 60–175 IU/l). One patient was given the antiviral drug ribavirin, which resulted in a rapid decrease in both HEV RNA concentration and creatine kinase level. The authors speculated that HEV-associated myositis could be attributable to direct viral invasion of skeletal muscle.

Three cases of Bell palsy and another of vestibular neuritis that occurred concomitantly with HEV infection have been reported[4,73,84]. However, insufficient information was available to prove a causal association in these cases.

Pathogenesis

HEV is associated with a number of neurological presentations, but the pathogenic mechanisms are unknown and may differ between the various disorders. A common characteristic of the disorders is a monophasic disease course with subacute onset and rapid progression,

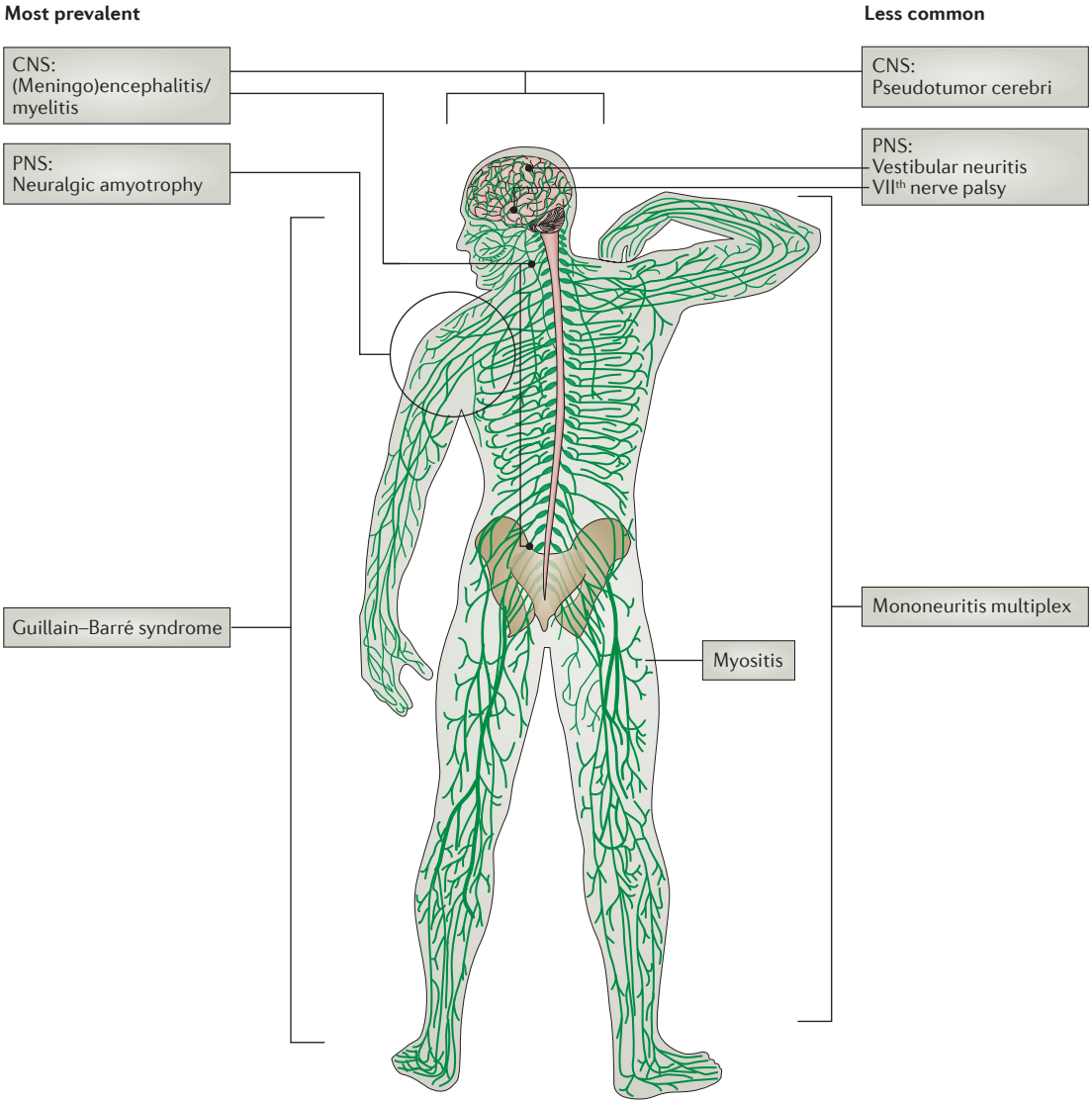

Figure 1 | **The range of neurological injury associated with hepatitis E virus.**

followed by a plateau phase and slow recovery. Some patients recovered completely, whereas others had considerable residual symptoms or disability. The majority of patients had involvement of the PNS, in particular, GBS and neuralgic amyotrophy. The epidemiology of the neurological presentations is similar to that of acute hepatitis E, with most cases being adult males. However, the mean age of neurological cases (49 years) is lower than for symptomatic hepatitis E in European populations (around 60 years).

A causative role for HEV in the cases that we have reviewed cannot be proven, as other infections were not systematically ruled out in the majority of the studies. However, the temporal association between neurological illness and HEV infection, the detection of viral RNA in CNS specimens, and the similarity of the clinical presentations make HEV infection a plausible causative factor for neurological illness. The features of HEV strains that might cause these illnesses are unknown, but our review of the literature has identified some suggestive data. Of note, 22 of the 27 HEV3 strains that were subtyped belonged to the HEV3f subtype. However, all 22 strains were from French patients, and the vast majority of French strains are known to be of this subtype[85]. Without more data from other geographical areas, the relevance of this finding is uncertain.

The mechanisms by which particular HEV strains might cause neurological disease are equally unclear. Other hepatitis viruses such as hepatitis C are associated with neurological disorders that are attributable to cryoglobulinaemia, systemic vasculitis or ischaemia[86–88], but there is little evidence of these aetiologies among HEV-associated disorders. There are at least three other possibilities. First, HEV quasispecies that are able to infect nervous tissues might be selected for during the course of infection. As noted above[47], this phenomenon has only been described in one patient. Second, the virus might acquire host RNA sequences that confer the ability to infect multiple cell types and, thus, potentially infect the CNS. These insertion sequences have been detected in

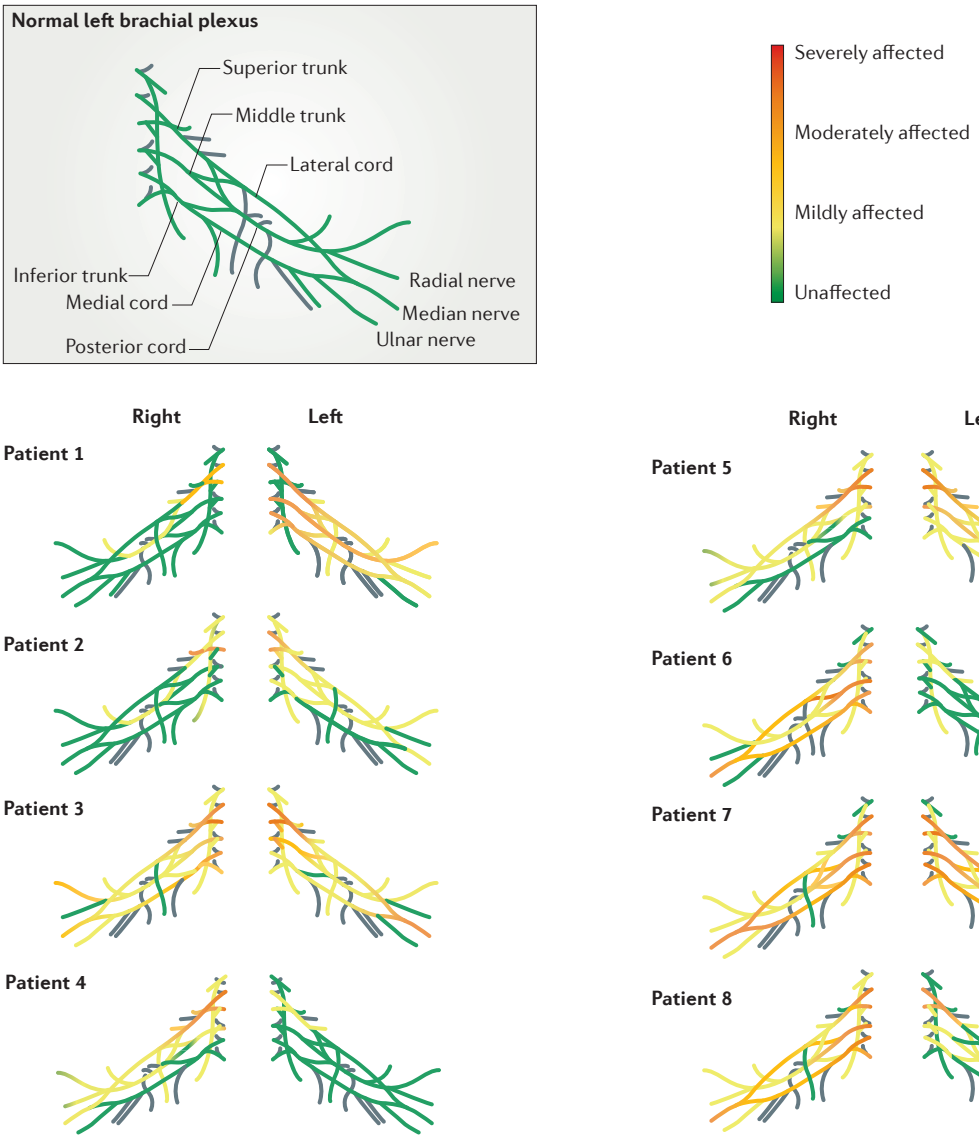

Figure 2 | **Brachial plexograms of eight patients with hepatitis E virus-associated neuralgic amyotrophy.** Clinical and electrophysiological data were used to generate these brachial plexus plots. Unaffected areas of the brachial plexus are shown in green. The most severely affected parts of the brachial plexus are shown in red, with moderately affected areas in orange and mildly affected parts in yellow. As these plots illustrate, the brachial plexus is typically affected bilaterally in a patchy manner.

isolates from two patients, one of whom had a neurological illness[85,89]. Both of these putative mechanisms have only been detected in immunocompromised patients with chronic HEV infection, and their relevance to HEV-related neurological illness in immunocompetent patients is debatable. A third possibility is that some HEV strains code for antigens that induce an immune response that attacks neural targets in susceptible patients.

In the case of GBS, the HEV-associated disease resembles GBS due to other causes in which the pathogenesis is thought to be immune-mediated. In HEV-associated GBS, circulating HEV RNA could not be detected in most patients, despite positive serology. This finding supports an immune-mediated pathogenesis for HEV-associated GBS, as it probably reflects the time taken for the immune system to respond to the infection and initiate the nerve damage. In five of 17 patients (29%) with HEV-related GBS, antibodies to the gangliosides GM1 and GM2 were demonstrated, providing further evidence of an immune-mediated process[39,44,50]. Similar antibodies in *C. jejuni*-associated GBS are induced by molecular mimicry, and cause complement-mediated neuronal injury[90,91]. Further studies are needed to determine whether crossreactive antibodies are responsible for HEV-associated GBS.

HEV-related neuralgic amyotrophy seems to have a more limited geographical distribution than GBS. All but one of the neuralgic amyotrophy cases occurred in Europe, where HEV3 is endemic, and HEV3 was the infecting genotype where tested. Patients with

Box 2 | **HEV-associated neurological injury: research questions**

- What other neurological conditions are associated with HEV?
- How commonly do HEV-associated neurological conditions occur?
- What are the pathogenic mechanisms of neurological injury?
- Can antiviral therapy (for example, ribavirin) improve the natural history?
- Do HEV genotypes differ in their neurological sequelae?
- Is neurological injury more common in locations that are hyperendemic for HEV, such as the Netherlands?
- Are some people more susceptible than others to neural injury after HEV infection?
- How important is quasipecies compartmentalization in the cerebrospinal fluid, and what are the mechanisms of neurological damage?
- Does the incidence and range of HEV-associated neurological damage vary with HEV genotype?
- Are second infections with HEV more likely to be associated with neurological injury, and does the clinical phenotype differ?

HEV, hepatitis E virus.

neuralgic amyotrophy were mostly HEV RNA-positive at symptom onset. This finding is consistent with neuralgic amyotrophy being an immune-mediated illness, with circulating HEV providing the antigenic drive. Alternatively, however, HEV could be neurotropic, with neuralgic amyotrophy resulting from direct infection of the brachial plexus. Nearly all HEV-associated neuralgic amyotrophy cases were male and had bilateral brachial plexus involvement. Lumbosacral and phrenic nerve involvement were observed in some cases. It is possible that HEV3 causes a specific phenotypic variant of neuralgic amyotrophy with these features. Recent data suggest that the incidence of neuralgic amyotrophy in primary care could be as high as 1 per 1,000 per year, which is 30–50 times more frequent than previously thought[92]. The prevalence of HEV among milder cases of neuralgic amyotrophy remains an open question.

HEV-related encephalitis and other CNS disorders might reflect direct viral infection, as viral RNA was detected in the CSF, and was associated with CSF pleocytosis. Host immune status seems to be important in this setting, as a disproportionate number of the case reports are in solid organ transplant recipients. Interestingly, many of these CNS infections coexisted with peripheral features, suggesting either that intrathecal viral replication was damaging peripheral nerve roots, or that an immune-mediated process, as described above, coexisted with active CNS infection. If the former hypothesis is correct, intrathecal infection might cause GBS in some cases, and might be the portal of entry in neuralgic amyotrophy.

It is difficult to draw any conclusions from the other neurological conditions that have been associated with HEV, because the numbers are small. Mononeuritis multiplex and Bell palsy are inflammatory disorders of peripheral nerves and could, conceivably, share a pathogenic mechanism with GBS or neuralgic amyotrophy, but the evidence is lacking.

In summary, we cannot be sure that HEV is truly a neurotropic virus. Evidence exists, however, of direct invasion of the CNS by HEV, viral replication within the CNS, and compartmentalization of CNS infection with selection of CNS-derived quasispecies. All of these features suggest a neurotropic potential for HEV. Such neurotropism could be strain-specific, which might explain why reports of HEV-associated neuralgic amyotrophy are geographically and genotypically restricted.

Box 3 | **Has HEV been misnamed?**

Evidence supporting HEV as a hepatotropic pathogen

- The currently recognized clinical phenotype of HEV is primarily hepatological
- HEV causes significant hepatological injury in both developing countries (HEV1 and HEV2) and developed countries (HEV3 and HEV4)
- HEV RNA has been found in the liver, bile and stool of patients with acute and chronic infection
- Liver histology improves in patients with chronic infection who are treated successfully with ribavirin
- The range and incidence of HEV-associated neurological symptoms is unknown

Evidence supporting HEV as a neurological pathogen

- >95% of all patients infected with HEV have no symptoms of hepatitis
- LFTs are commonly normal in infected asymptomatic blood donors
- Patients with HEV-associated neurological injury commonly have a mild hepatitis, and sometimes the LFTs are normal
- HEV is difficult to culture on liver cell lines, but can be cultured on a range of neurological cell lines
- HEV RNA is found in serum and CSF in some cases of HEV-associated neurological injury
- HEV quasispecies compartmentalization has been observed between serum and CSF
- Clearance of HEV from serum and CSF with antiviral therapy has been associated with improvement of neurological symptoms in a patient with chronic HEV infection and a painful peripheral neuropathy[48]

CSF, cerebrospinal fluid; HEV, hepatitis E virus; LFT, liver function test.

Diagnosis

Diagnosis of hepatitis E in patients with neurological symptoms is not straightforward. The hepatitis is mild, patients are usually not jaundiced, and LFTs may be normal, particularly in patients who present at a late stage. The timing of neurological symptoms associated with the onset of HEV infection is uncertain. On the basis of the combination of LFT abnormalities, serological responses and the presence or absence of viraemia, immune-mediated neurological symptoms are likely to follow HEV infection by approximately 2–4 weeks.

Minor abnormalities in LFTs are easily overlooked in patients presenting with neurological illnesses. We recommend that patients with GBS, neuralgic amyotrophy or meningoencephalitis should be tested for HEV at presentation. It might also be worth testing patients with other neurological conditions whose LFTs are raised. Testing should ideally include HEV serology (IgM and IgG) and PCR (blood, stool and CSF). PCR provides the best proof of infection, but may be negative because the viraemia is brief[1,2]. In the majority of studies to date, HEV RNA was either absent from the serum or not tested. Serological assays should be chosen with care, as their performance is variable and many are insensitive[93]. It is also important to exclude infections with other microorganisms that are known to trigger neurological injury, particularly in GBS.

Treatment

The current standard treatment for severe GBS or neuralgic amyotrophy is immune modulation. Treatment with either intravenous immunoglobulin (2 g/kg body weight over 5 days) or plasma exchange is of proven efficacy in GBS[94,95]. There is also circumstantial evidence to support the treatment of neuralgic amyotrophy with prednisolone 60 mg per day for 1 week, tapering to 0 mg in the second week[96,97]. Although some individuals respond well, these treatments are only partly effective in a sizeable proportion of patients with GBS or neuralgic amyotrophy. Various studies have demonstrated HEV RNA in the blood or CSF from patients with GBS or neuralgic amyotrophy[67,68]. This finding indicates that replicating HEV is present in these patients after hospital admission, challenging the concept of neuralgic amyotrophy and GBS as strictly postinfectious disorders. If HEV is still present in the patient at this stage, it might cause further nerve injury by sustaining immune activation and/or through direct neurotoxicity.

It is interesting to note that 15% of patients with GBS have progressive neurological injury after standard immune modulatory treatment, and a further 10% experience a relapse within the first 8 weeks[79]. We do not currently know how many of these patients have HEV-associated GBS, but these observations raise the question of whether treatment of the HEV infection with ribavirin monotherapy should be considered in patients who are found to have HEV RNA in the blood or CSF. To date, we have used antiviral therapy to treat six patients with HEV-associated neurological injury (three with neuralgic amyotrophy, and one each with myositis, encephalitis and peripheral neuropathy)[52,70], with variable outcomes. Owing to the small numbers and lack of controls, the efficacy of the treatment is currently uncertain. Antiviral treatment carries a potential risk of viral destruction with release of viral antigens that might sustain or enhance the immune reaction, thereby causing further neurological injury. The issue of use of antiviral therapy in these patient groups can only be resolved by appropriately designed placebo-controlled studies.

Conclusions and future perspectives

Many research questions regarding HEV-related neurological injury remain unanswered (BOX 2). For instance, the range of neurological illness associated with HEV is unknown, and a prospective pilot study currently being conducted in the UK, France and the Netherlands is addressing this issue. We also need to understand the pathogenic mechanisms underlying these disorders. It is particularly important to determine the conditions in which HEV might be neurotropic, because direct neural infection could respond to antiviral therapy. Ribavirin is a promising agent, as HEV seems to be sensitive to this drug, and it has been used successfully to treat chronic liver infection in immunosuppressed patients.

This Review has evolved out of multidisciplinary discussions. During this process, the neurologists asked the virologists and hepatologists the following question: "has this virus been misnamed (BOX 3)? These patients do not have much of a hepatitis, but they do have profound neurological injury." It may well transpire that most profound impact of HEV infection lies outside the organ that gave the virus its name.

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