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Review of the neurological manifestations of hepatitis E infection

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ABSTRACT

Hepatitis E (HEV) is a common infection worldwide and is an emerging disease in developed countries. The presence of extra-hepatic manifestation of HEV infection is important to bear in mind so that the diagnosis is not missed, since HEV is not routinely tested for in acute hepatitis due to perceived rarity of this infection outside of endemic countries. This article reviews the neurological presentations of acute and chronic HEV, and discusses the viral kinetics against symptomatology, and outcomes of specific treatment. Possible mechanisms of pathogenesis are considered.

Key words. Hepatitis E. Viral hepatitis. Neurological disease. Autochthonous infection.

Hepatitis E (HEV) is an under-diagnosed infection in developed countries, with the potential to cause significant morbidity as well as mortality.[1,2] The actual incidence of local HEV in developed countries is uncertain, especially as subclinical infection is common.[1]

Clinical manifestations of HEV typically include jaundice, fever, malaise, abdominal pain and vomiting, lasting 2 to 18 weeks with a median of 4 weeks.[1] As with other viral hepatitises, extra-hepatic manifestations can occur,[3] and the spectrum of clinical disorders is still emerging.[4-6] In particular, neurological disorders with a predominance of peripheral nerve disorders have been described.[6] A literature review found 25 cases reporting neurological manifestations of HEV in both acute and chronic infections[4,6-24] (Tables 1 and 2). Guillain-Barre syndrome and brachial neuritis are most frequently reported. Other reported disorders include transverse myelitis, cranial nerve palsies, seizure and intracranial hypertension.[17,21-24]

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Neurological disease occurred in sporadic and endemic infection within this cohort. Most case reports come from developing countries, reflecting the geographical distribution of HEV. All genotyped cases showed genotype 3 infection, which is found in developed countries. Cases from the Indian subcontinent are likely to be genotype 1.

A recent case series from Southwest England and Toulouse found a 5.5% prevalence (7 out of 126 over five years) of neurological complications in locally-acquired HEV infections.[6] Most of the reported cases of acute HEV were evidenced only by positive serology (anti-HEV IgM), which persists after viral clearance and therefore does not indicate duration of infection.[1] However the temporal relationship between development of transaminitis and neurological symptoms with evidence of HEV infection, and exclusion of other hepatotrophic causes, suggest this association is causal. Moreover, the presence of similar cases which were confirmed by RNA isolation substantiates a true association between HEV infection and neurological disorders.

Acute HEV infection is self-limiting. In cases of Guillain-Barre, where intravenous immunoglobulin and plasma exchange both have established effectiveness,[25] its use was associated with complete resolution of symptoms, but benefit over supportive treatment cannot be concluded. Cases of brachial neuritis were comparatively slower to resolve and none received specific therapies.

Table 1. Summary of acute hepatitis E with neurological manifestation.

Country	Age/gender	Significant co-morbidity	Neurological manifestation	Preceding jaundice or other symptoms	Diagnosis	Viral clearance from serum	Normalisation of liver function tests after presentation	Specific treatment	Neurological outcome	Ref.
France	60/female	Type 1 diabetes	Guillain-Barre syndrome	7 days	Serum RNA (genotype 3 f) CSF negative for HEV	4 weeks	4 weeks	IVIG 0.4 g/kg/day for 5 days	Residual motor deficit at 18 months	6
India	50/male	None	Guillain-Barre syndrome	5 days	HEV IgM	NA	1 month	None	Resolution by 1 month	7
India	58/female	None	Guillain-Barre syndrome Cranial nerve palsy 5 days later	7 days	HEV IgM	NA	3 weeks	IV IG for 5 days Plasmapheresis with albumin 40 mL/kg/day 3 days	Improvement in cranial nerve palsy after 5 days IVIG and resolution of all neurological symptoms in 7 days	8
Belgium	51/female	None	Guillain-Barre syndrome (anti-GM1 positive)	3 days	NA	NA	NA	IVIG	Resolution	9
Belgium	66/male	None	Guillain-Barre syndrome (anti-GM2 positive)	< 1 week	HEV IgM	NA	1 week	IV IG 0.4g/kg/day for 5 days	Resolution in 4 months	10
Ireland	40/male	NA	Guillain-Barre syndrome (anti-GM2 positive)	2 weeks	HEV IgM	NA	1 month	IVIG 0.4 g/kg/day for 5 days Plasmapheresis	Resolution after 1 month	11
Bangladesh	20/male	NA	Guillain-Barre syndrome	7 days	HEV IgM	NA	NA	None	Resolution in 2 weeks	12
India	35/male	None	Guillain-Barre syndrome	20 days	HEV IgM	NA	2 weeks	IVIG 0.4 g/kg/day for 5 days	Resolution with residual weakness in 2 weeks	13
United Kingdom	56/male	None	Bilateral brachial neuritis	1 day	Serum RNA (genotype 3) 1,000,000 copies/mL	6 week	10 days	None	Residual pain and weakness at 10 months	14
United Kingdom	53/male	None	Bilateral brachial neuritis	Nil	HEV IgM	NA	2 weeks	None	Resolution in 2 years	15
United Kingdom	38/male	Type 1 diabetes	Bilateral brachial neuritis	5 days	Serum RNA (genotype 3e)	6 weeks	6 months	None	Residual motor deficit at 18 months	6
United Kingdom	42/male	None	Polyradiculoneuropathy	NA	Serum RNA (genotype 3e) CSF negative for HEV	NA	6months	None	Resolution in 3 months	6
France	49/male	None	Polyradiculoneuropathy	Nil	Serum RNA (genotype 3) CSF negative for HEV	2 months	NA	None	2 weeks	16
France	54/female	None	Peripheral neuralgia with meningitis	Nil	Serum RNA CSF RNA (genotype 3)	3 weeks	2 weeks	None	2 weeks	16
India	12/female	None	Transverse myelitis	20 days	HEV IgM	NA	Normal at time of Neurological presentation	None	Resolution within 10 days	17
Hong Kong	NA	NA	Guillain-Barre syndrome	NA	NA	NA	NA	NA	NA	18
France	NA	NA	Neuralgic amyotrophy (brachial neuritis)	NA	NA	NA	NA	NA	NA	19
Thailand	NA	NA	Neuralgic amyotrophy	NA	Serum RNA (genotype 3)	NA	NA	NA	NA	20
India	NA	NA	Occulomotor nerve palsy	NA	NA	NA	NA	NA	NA	21
India	NA	NA	Seizure	NA	NA	NA	NA	NA	NA	22
India	Paediatric	NA	Pseudotumor cerebri (intracranial hypertension)	NA	NA	NA	NA	NA	NA	23
India	NA	NA	Bell's palsy	NA	NA	NA	NA	NA	NA	24

IVIG: intravenous immunoglobulin. CSF: cerebrospinal fluid.

Table 2. Summary of chronic hepatitis E with neurological manifestation.

Country	Age/Gender	Duration of HEV infection before neurological symptoms	Neurological manifestation	Significant comorbidity	Diagnosis	Specific treatment	Viral kinetic and liver parameters	Neurological outcome	Ref.
NW Europe	60/male	30 months	Ataxia, confusion, frontal dysfunction, proximal lower limb weakness	Kidney-pancreas transplant (infection acquired 27 months post-transplant)	Serum RNA (genotype 3f) 1572 copies/mL CSF RNA	Immunosuppression change	Serum viral clearance in 4 months	Resolution of higher function, residual motor deficit at 10 months	6
NW Europe	35/male	3 years	Acute encephalitis	Kidney transplant (infection acquired 48 months post-transplant)	Serum RNA (genotype 3f) 2,154,000 copies/mL CSF RNA	Immunosuppression stopped, IV IG 2 g/kg, Foscarnet 6 g/d	Serum and CSF viral clearance at 1 year	Complete resolution in 2 months	6
France	44/male	33 months	Polyradiculoneuropathy, ataxia, sphincter dysfunction	Kidney transplant	Serum RNA (genotype 3f) 260,000 copies/mL CSF RNA (viral sequence different to serum)	Immuosuppression change, IV IG 0.4 g/kg/day for 5 days		Death from decompensated liver disease	4, 6
United Kingdom	48/male	Preceeded HEV diagnosis by 2 years	Painful sensory peripheral neuropathy	HIV-1 (CD4 30 x 10^9/L)	Serum RNA (genotype 3a) CSF RNA	Peg-interferon α 2α/ribavirin	Serum viral clearance on symptom resolution; CSF RNA level approximately halved	Complete resolution on completion of antiviral therapy (duration unclear)	6

IVIG: intravenous immunoglobulin. CSF = cerebrospinal fluid.

Severity of HEV infection is related to viral load[1] but the number of cases with established level of viraemia is too small to ascertain if HEV has a dose effect on neurological symptoms and outcomes. There is no clear correlation between viral clearance, liver enzyme tests and duration of neurological symptoms.

Four reports exist of neurological symptoms in chronic HEV in immunosuppressed patients following organ transplant or HIV infection.[4,6] The temporal relationship between viral kinetics and symptom onset and resolution is variable in chronic HEV. The duration of infection before onset of neurological symptoms ranged from 18 months to 3 years. Chronic infection was evidenced by liver biopsy showing chronic hepatitis or cirrhosis and detection of RNA; serology in these patients may be unreliable. Demonstration of HEV RNA in cerebrospinal fluid (CSF) may account for involvement of the central nervous system, however, two patients with virus in CSF did not display disturbance of higher functions. Development of liver cirrhosis and decompensation are potential confounding factors. Despierres, *et al.* suggested the presence of HEV in the CSF may be related serum viral load,[16] but in Kamar's case there was low serum viral low but detectable virus in CSF and marked central nervous system disturbance (60). Therefore this is insufficient explanation for the selective occurrence of central nervous system symptoms.

There is no established treatment for chronic HEV; lowering of immunosuppression therapy is recommended[26] and pegylated interferon alpha has been used successfully in liver transplants.[26,27] In one case the use of pegylated interferon alpha with ribavarin resulted in viral clearance and neurological symptom resolution.[6]

Several mechanisms of HEV causing neurological disease have been proposed. In neuropathies following infections such as Guillain-Barre syndrome after Campylobacter, influenza and cytomegalovirus, anti-ganglioside antibodies are thought to play a pathogenic role.[28] Anti-ganglioside antibodies were positive in 3 out of 6 cases of HEV-GBS where they were measured, with one case of GM1 antibody and remainder of GM2.[9-11] Their production may be triggered by HEV infection which in turn leads to autoimmune inflammatory polyneuropathy via molecular mimicry. Treatment with immunoglobulin targets the autoimmune nature of GBS but due to the small number of HEV-associated cases, it is difficult to comment on treatment response.

Brachial neuritis is also thought to be autoimmune in origin in genetically susceptible individuals.[29] More than half of patients develop an immune event preceding neurological symptoms, such as viral infections (HIV, coxsackie, EBV), vaccination and pregnancy.[29] HEV may cause brachial neuritis by precipitating such an autoimmune response.

The isolation of different viral sequences within CSF and serum of the same patient suggest the possible emergence of neurotropic quasispecies which can directly affect the nervous system.[4,6] However in acute infection which can resolve within days, this mechanism is less probable.

The pathogenesis of HEV causing peripheral neuropathy and other neurological disorders may involve multiple mechanisms, predisposing and host immune factors, to account for the variety in manifestations, but the small number of cases and distribution in developing countries makes further investigations difficult.

CONCLUSION

Hepatitis E infection has well-documented neurological manifestations which can lead to significant morbidity. The spectrum of disease is wide and natural history variable. Specific therapies targeting the potential autoimmune aetiology did not produce consistent responses in the few cases used. Clinicians are challenged with uncertainties in prognosis and management. Hepatitis E is increasingly seen in developed countries as locally-acquired infections, and should be tested for in acute hepatitis, especially in seronegative or suspected drug-related cases. In addition, HEV infection should be considered in neurological disturbance associated with abnormal liver function tests.

CONFLICT OF INTEREST

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REFERENCES

1. Dalton HR, Bendall R, Ijaz S, Banks M. Hepatitis E: an emerging infection in developed countries. *Lancet Infect Dis* 2008; 8: 698-709.
2. Purcell RH, Emerson SU. Hepatitis E: an emerging awareness of an old disease. *J Hepatol* 2008; 48: 494-503.
3. Amarapurkar DN, Amarapurkar AD. Extrahepatic manifestations of viral hepatitis. *Ann Hepatol* 2002; 1: 192-5.
4. Kamar N, Izopet J, Cintas P, Garrouste C, Uro-Coste E, Cointault O, Rostaing L. Hepatitis E virus-induced neurological symptoms in a kidney-transplant patient with chronic hepatitis. *Am J Transplant* 2010; 10: 1321-4.
5. Fourquet E, Mansuy JM, Bureau C, Recher C, Izopet J, Peron JM. Severe thrombocytopenia associated with acute autochthonous hepatitis E. *J Clin Virol* 2010; 48: 73-4.
6. Kamar N, Bendall RP, Peron JM, Cintas P, Prudhomme L, Masuy JM, Rostaing L, et al. Hepatitis E virus and neurologic disorders. *Emerg Infect Dis* 2011; 17: 173-9.
7. Sood A, Midha V, Sood N. Guillain-Barre syndrome with acute hepatitis E. *Am J Gastroenterol* 2000; 95: 3667-8.
8. Kamani P, Baijal R, Amarapurkar D, Gupte P, Patel N, Kumar P, Agal S. Guillain-Barre syndrome associated with acute hepatitis E. *Indian J Gastroenterol* 2005; 24: 216.
9. Maurissen I, Jeurissen A, Strauven T, Sprengers D, De Schepper B. First case of anti-ganglioside GM1-positive Guillain-Barre syndrome due to hepatitis E virus infection. *Infection* 2011 [Epub].
10. Loly JP, Rikir E, Seivert M, Legros E, Defrance P, Belaiche J, Moonen G, et al. Guillain-Barre syndrome following hepatitis E. *World J Gastroenterol* 2009; 15: 1645-7.
11. Cronin S, McNicholas R, Kavanagh E, Reid V, O'Rourke K. Anti-glycolipid GM2-positive Guillain-Barre syndrome due to hepatitis E infection. *Ir J Med Sci* 2011; 180: 255-7.
12. Khanam RA, Faruq MO, Basunia RA, Ahsan ASM. Guillain-Barre syndrome associated with acute HEV hepatitis. *Ibrahim Med Coll J* 2008; 2: 32-4.
13. Kumar R, Bhoi S, Kumar M, Sharma B, Singh BM, Gupta BB. Guillain-Barre syndrome and acute hepatitis E: a rare association. *JIACM* 2002; 3: 389-91.
14. Cheung MC, Maguire J, Carey I, Wendon J, Agarwal K. Hepatitis E-an unexpected problem at home. *Scand J Gastroenterol* 2012; 47: 253 [letter to editor].
15. Fong F, Illahi M. Neuralgic amyotrophy associated with hepatitis E virus. *Clin Neurol Neurosurg* 2009; 111: 193-5.
16. Despierres LA, Kaphan E, Attarian S, Cohen-Bascrie S, Pelletier J, Pouget J, Motte A, et al. Neurologic disorders and hepatitis E, France, 2010. *Emerg Infect Dis* 2011; 17: 1510-2.
17. Mandal K, Chopra N. Acute transverse myelitis following hepatitis E virus infection. *Indian Pediatr* 2006; 43: 365-6.
18. Tse ACT, Cheung RTF, Ho SL, Chan KH. Guillain-Barre syndrome associated with acute hepatitis E infection. *J Clin Neurosci* 2012; 19: 607-8.
19. Inghilleri ML, Grini Mazouzi M, Juntas Morales R. Neuralgic amyotrophy as a manifestation of hepatitis E infection. *Rev Neurol (Paris)* 2012; 168: 383-4.
20. Rianthavorn P, Thongmee C, Limpaphayom N, Komolmit P, Theamboonlers A, Poovorawan Y. The entire genome sequence of hepatitis E virus genotype 3 isolated from a patient with neuralgic amyotrophy. *Scan J Infect Dis* 2010; 42: 395-400.
21. Yadav KK, Rohatgi A, Sharma SK, Kulshrestha M, Sachdeva S, Pardasani V. Oculomotor palsy associated with hepatitis E infection. *J Assoc Physicians India* 2002; 50: 737.
22. Kejariwal D, Roy S, Sarkar N. Seizure associated with acute hepatitis E. *Neurology* 2001; 57: 1935.
23. Thapa R, Mallick D, Biswas B. Psudotumor cerebri in childhood hepatitis E virus infection. *Headache* 2009; 49: 610-1.
24. Dixit VK, Abhilash VB, Kate MP, Jain AK. Hepatitis E infection with Bell's palsy. *J Assoc Physicians India* 2006; 54: 418.
25. Van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barre syndrome. *Lancet Neurol* 2008; 7: 939-50.
26. Haagsma EB, Riezebos-Brilman A, Van den Berg AP, Porte RJ, Niesters HG. Treatment of chronic hepatitis E in liver

transplant recipients with pegylated interferon alpha-2b. *Liver Transpl* 2010; 16: 474-7.
27. Kamar N, Rostaing L, Abravenel F, Garrouste C, Esposito L, Cardeau-Desangles I, Mansuy JM, et al. Pegylated interferon-alpha for treating chronic hepatitis E virus infection after liver transplantation. *Clin Infect Dis* 2010: 50: e30-e33.
28. Kusunoki S, Kaida K. Antibodies against ganglioside complexes in Guillain-Barre syndrome and related disorders. *J Neurochem* 2011; 116: 828-32.
29. Van Alfen N. Clinical and pathophysiological concepts of neuralgic amyotrophy. *Nat Rev Neurol* 2011; 7: 315-22.