CASE REPORT

Brainstem encephalitis and acute polyneuropathy associated with hepatitis E infection

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SUMMARY

A 59-year-old man presented with feverish illness. His Glasgow Coma Scale was 15, had reduced visual acuity in the left eye with partial left ptosis and mild left hemiparesis with an extensor left plantar. Over 48 hours, he accrued multiple cranial nerves palsies and progressed to a flaccid paralysis necessitating admission to an intensive care unit.

Cerebrospinal fluid (CSF) study showed 20 lymphocytes and raised protein. Viral and bacterial PCRs were negative. Samples for Lyme, blood-borne viruses, syphilis and autoantibodies were also negative. MRI brain showed T2 abnormalities within the brainstem. Nerve conduction studies revealed an acute motor and sensory axonal neuropathy pattern of Guillian Barre Syndrome (GBS). The patient was treated for both infective and inflammatory causes of brainstem encephalitis and GBS. Retrospective studies confirmed the presence of hepatitis E virus (HEV) RNA in CSF and serum studies showed positive HEV IgG and IgM prior to intravenous infusion. After 3 months of intensive rehabilitation, the patient was discharged home walking with a frame.

BACKGROUND

Hepatitis E is rarely associated with neurological complications in the immunocompetent patient and, to our knowledge, this is the first report worldwide of brainstem encephalitis and acute polyneuropathy-associated with hepatitis E in an immunocompetent patient.

Hepatitis E is an emerging health concern worldwide and this case will be of interest to neurologists, infectious disease clinicians as well as general clinicians.

CASE PRESENTATION

A 59-year-old right-handed lorry driver presented acutely with a feverish illness associated with blurring of vision in left eye, subtle distal weakness in left leg and mild confusion. In the accident and emergency department, he was found to have a temperature of 39°C; otherwise, systemic examination was unremarkable. A documented neurological examination reported a Glasgow Coma Scale of 15, reduced visual acuity in left eye to finger counting and a partial left ptosis. Tone and reflex patterns were normal but there was a mild left side hemiparesis (Medical Research Council grade 4). There were no abnormal sensory or cerebellar findings. First-line and second-line investigations are summarised in [tables 1 and 2](#).

Collateral history from his partner revealed that he had been feeling unwell and feverish for 3 days prior to admission. He had no significant medical history, drug history nor family history of neurological disorders. He had no lifestyle risk factors for transmissible infections.

Investigations summarised in [tables 1, 2 and 3](#).

Six hours' postadmission, temperature increased to 40°C despite antipyretic agents and fluid resuscitation. He then complained of neck pain, worsening occipital headache, slurred speech and a further reduction in visual in the left eye. Pupillary light reflex on the left was commented to be 'diminished'; otherwise, funduscopy and cranial nerves examination was unremarkable. Tone was normal but power in left lower limb reduced to 3/5. Reflexes were brisk on the left but with flexor plantars bilaterally. The patient was commenced on intravenous ceftriaxone and acyclovir for presumed central nervous system (CNS) infection and a lumbar puncture was performed.

By 24 hours' postadmission, the patient had developed respiratory compromise and was becoming increasingly drowsy. His evolving neurology included a left relative afferent pupillary defect, nystagmus in all directions of gaze, left sixth nerve palsy and evolving muscle weakness to antigravity in his left leg, with MRC grade four in all other limbs. There was a left upper limb intention tremor with left extensor plantar. Sensory examination was still normal.

Arterial blood sampling demonstrated type 1 respiratory failure and, because of rapid progression, he was transferred to ICU for monitoring. Examination thereafter revealed progressive bulbar palsy and autonomic dysfunction including hyperhidrosis, sialorrhoea, tachycardia and hypertension. Amoxicillin was added to cover listeria infection.

Forty-eight hours after admission and patient's neurology progressed again. There was bilateral upper motor neuron (UMN) facial weakness, with progressive limb weakness in all four limbs. Reflexes were diminished throughout; however, the left plantar remained extensor. Shortly afterwards, he required invasive ventilation to protect airways.

Nerve conduction studies performed 36 hours after admission demonstrated absent sensory responses in lower limbs with reduced amplitude in upper limbs. Motor responses were normal in both upper limbs but conduction velocity was delayed in lower limbs; however, only tibial nerves were in the demyelination range. Needle electromyography (EMG) showed no evidence of active denervation.

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Table 1 First and second-line investigations

Test (units)	On admission	Transfer to neurology ward (27 days later)	Normal range
Hb (g/l)	161	99	135–180
MCV (fl)	87.9	95.3	80–100
WBC ($\times 10^9/L$)	8.8	7.0	4.0–11.0
Neutrophils ($\times 10^9/L$)	6.4	4.2	2.0–7.5
Lymphocytes ($\times 10^9/L$)	3.3	2.1	1.0–4.0
Platelets ($\times 10^9/L$)	101	486	150–400 ($\times 10^9/L$)
Urea (mmol/L)	8.4	9.2	2.5–7.8
Creatinine (umol/L)	111	51	60–120
Na (mmol/L)	132	138	133–146
K (mmol/L)	4.1	4.3	3.5–5.6
eGFR ml/min	>59	>59	>59
Bil (umol/l)	17	5	<20
ALT (U/L)	132	50	5–55
AST U/L)	32	21	10–45
ALP (U/L)	91	106	30–130
Albumin (g/l)	43	18	35–50
Adjusted Ca (mmol/L)	2.19	2.44	2.20–2.60 (mmol/L)
Phosphate (mmol/L)	0.82	1.46	0.8–1.5 (mmol/L)
CRP (mg/L)	6	10	0–10
lactate	1.8		0.6–2.4
TSH (mU/L)	0.29		0.20–5.00
B12 pg/ml	370.5		197.0–771.0
Folate (mU/L)	0.29		0.20–5.00
aPTT	21.9	30	23.0–31.0 s
PT	14.3	11	9–13 s
PT ratio	1.4	1.0	
Amylase	55		0–100 (U/L)
LDH	219		0–250
Immunoglobulin levels	Normal		
Hepatitis B Surface Ag	Negative		
Hepatitis C Antibody	Negative		
HIV screening	Negative		
Syphilis serology	Negative		
Lyme serology	Negative		
Pneumococcus urinary antigen	Negative		
Legionella urinary antigen	Negative		
ANA	Negative		
RF	Negative		
Gangliosides Screen	Negative		
Anti-MOG	Negative		
Aquaporin-4 Abs	Negative		

ALP, alkaline phosphatase; ANA, antinuclear antibodies; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; MCV, Mean corpuscular volume; MOG, myelin oligodendrocyte glycoprotein; PT, prothrombin time; RF, rheumatoid factor; TSH, thyroid-stimulating hormone; WBC, white blood count.

Table 2 Imaging on admission

Blood film	mild lymphocytosis with mature forms
Chest X-ray	No abnormality detected
CT Head	No intra or extra-axial haemorrhage, space-occupying lesion or vascular territory infarct.

Table 3 CSF results on admission

Item/unit	Results	Normal range
WBC ($\times 10^6/L$)	20 (100% lymphocytes)	<5
RBC ($\times 10^6/L$)	18	<5
Protein (g/l)	1.65	0.15–0.45
Glucose (mmol/L)	4.1 mmol/L	2.5–4.4
Serum Glucose	8.9 mmol/L	4.0–6.0
Pathology	No organisms seen	
Immunology	polyclonal bands in CSF only	
Viral and bacterial PCR	Results were awaited	

CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell.

On day 4, consciousness level rapidly deteriorated to E¹ V¹ M¹ though there was occasional spontaneous right eye opening. His only motor response at this stage was a weak right bicep reflex. There was marked persistent hypertension (BP >200/100) requiring labetalol infusion. Decision was made to start a course of intravenous immunoglobulins in a dose of 0.4 g/kg/day for 5 days for presumed atypical presentation of Guillian Barre Syndrome (GBS). At this stage, all treatable causes were believed to be covered.

Cerebrospinal fluid (CSF) viral PCR came back negative for herpes simplex viruses 1 and 2, varicella zoster virus, cytomegalovirus, Epstein-Barr virus, adenovirus, enterovirus and parechovirus so acyclovir was discontinued.

On day 7, MRI brain with gadolinium was done at the Institute of Neurosciences in Glasgow and it showed atypical T2 hyperintensities and restriction of diffusion within the Pons, proximal cervical cord and basal ganglia bilaterally. Brain MR angiogram was normal (see figure 1).

The patient was then commenced on intravenous methylprednisolone 1 g for 3 days followed by enteral prednisolone 40 mg daily. After discussion with microbiology dept, antibiotics were

Figure 1 Atypical T2 signal hyperintensities and restriction of diffusion within the pons and proximal cervical cord. (top left: axial T2 image, top right: axial T1 post gadolinium, bottom left: DWI and bottom right: axial T2 FLAIR). DWI, diffusion weighted images; FLAIR, fluid attenuation inversion recovery.

Table 4 Repeat CSF results 2 weeks later

Item/unit	Results	Normal range
WBC (*10 ⁶ /L)	<5	<5
RBC (*10 ⁶ /L)	<5	<5
Protein (g/l)	3.22	0.15–0.45
CSF and serum glucose	Normal	
Pathology	No organisms seen	
Cytology	No evidence of malignancy	

CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell.

stopped as blood cultures repeatedly showed no growth and the patient was afebrile with no clinical features of sepsis.

On examination, a flaccid tetraparesis was identified but horizontal eye movements were preserved. CT scan of chest, abdomen and pelvis showed no evidence of any underlying malignancy. Antimyelin oligodendrocyte glycoprotein and anti-aquaporin four antibodies were negative as well as Cryptococcus and full Enterovirus screen. Repeat CSF results are summarised in table 4.

Given the clinical suspicion of immune-mediated process despite lack of a definitive diagnosis, a trial of plasma exchange therapy was undertaken, and he responded well with gradual functional improvement.

Although patient was clinically improving, MRI brain scan at 4 weeks showed progression of the brain stem lesions, particularly the pontine swelling. Discussion with neuroradiology favoured inflammatory over ischaemic or osmotic demyelination disorders especially there was no significant fluctuation in plasma electrolyte levels (figure 2).

Nerve conduction studies were repeated 4 weeks later and it showed evidence of significant peripheral nerve involvement with profound axonal loss in both motor and sensory nerves in keeping with acute motor and sensory axonal neuropathy (variant of GBS).

Further MRI scan few weeks' postadmission showed significant reduction in size and signal intensity of the brainstem lesions with enlargement of the pons has completely resolved.

An extended virology screen was undertaken to include Zika, West Nile, Sandfly fever viruses and hepatitis E. Retrospective serum sample testing was positive for hepatitis E IgM and IgG prior to immunoglobulins infusion reflecting acute infection. Interestingly, CSF PCR was also positive for hepatitis E virus (genotype 3) on the first CSF sample raising an important question of whether such presentation was immune-mediated or also direct CNS invasion by the virus.

Figure 2 Sagittal and axial T1 MRI cross sections 4 weeks after initial presentation showing progression of brainstem lesion, particularly the pontine swelling. FLAIR, fluid attenuation inversion recovery.

OUTCOME AND FOLLOW-UP

Patient received continuous input from physiotherapy, occupational therapy, dietetic and speech and language teams during his hospital stay and his condition continued to improve. He was transferred to the rehabilitation unit and was discharged home 3 months later walking with a frame with a very good improvement in overall condition.

DISCUSSION

Hepatitis E virus and neurological disorders

All hepatitis E virus (HEV) genotypes have been associated with GBS, neuralgic amyotrophy and encephalitis/myelitis.¹ The association between GBS and HEV infection has been demonstrated worldwide with all four genotypes. A prospective Bangladeshi study found HEV IgM sero-prevalence in patients with GBS (11%) to be significantly higher than that of controls ($p < 0.01$).² Similarly, HEV IgM ranged from 5% in a Dutch case-control study to 8% in a Belgium study.^{3 4} None of the cases found to have HEV had antiganglioside antibodies detected. However, only the Belgium study systematically ruled out organisms known to cause GBS (*Mycoplasma pneumoniae*, CMV and EBV). These studies have also found that approximately a third of patients with HEV infection presenting with GBS have normal liver function tests. Another neurological complication of HEV is neuralgic amyotrophy, also known as Parsonage-Turner syndrome or brachial plexus neuritis, which is a distinct and painful peripheral neuropathy that causes episodes of multifocal paresis and sensory loss in a brachial plexus distribution.⁵ As with GBS, the aetiology is thought to be postinfectious and immune mediated; majority of cases reported in literature have been in Europe and associated mostly with genotype 3. Direct CNS infection, manifesting as encephalitis, meningitis or myelitis have also been reported but less commonly (12 published cases), half of them were immunocompetent.^{1 6–13} Often, the delineation between CNS and peripheral nervous system (PNS) infection is not clear and patients may present with a mix of symptoms. Other neurological presentations reported in literature include mononeuritis multiplex (asymmetric, asynchronous involvement of non-contiguous nerve trunks, usually painful), myositis, Bell's palsy and vestibular neuritis¹ but, to our knowledge, this is the first reported case worldwide of HEV presenting with a combination of brain stem encephalitis and acute polyneuropathy in an immunocompetent patient.

Learning points

- ▶ This case highlights that clinicians should remain vigilant to the possibility of hepatitis E-related neurological complications and have a low threshold for testing.
- ▶ Generally, the prognosis is good in immunocompetent patients.
- ▶ Importantly, it also highlights that intensive supportive treatment and aggressive management may result in an excellent outcome.

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REFERENCES

- 1 Dalton HR, Kamar N, van Eijk JJ, *et al*. Hepatitis E virus and neurological injury. *Nat Rev Neurol* 2016;12:77–85 <http://www.ncbi.nlm.nih.gov/pubmed/26711839>.
- 2 Geurtsvankessel CH, Islam Z, Mohammad QD, *et al*. Hepatitis E and Guillain-Barre syndrome. *Clin Infect Dis* 2013;57:1369–70 <https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/cit512>.
- 3 van den Berg B, van der Eijk AA, Pas SD, *et al*. Guillain-Barré syndrome associated with preceding hepatitis E virus infection. *Neurology* 2014;82:491–7 <http://www.ncbi.nlm.nih.gov/pubmed/24415572>.
- 4 Stevens O, Claeys KG, Poesen K, *et al*. Diagnostic Challenges and Clinical Characteristics of Hepatitis E Virus-Associated Guillain-Barré Syndrome. *JAMA Neurol* 2017;74:26 <http://archneur.jamanetwork.com/article.aspx?doi=>.
- 5 van Alfen N. Clinical and pathophysiological concepts of neuralgic amyotrophy. *Nat Rev Neurol* 2011;7:315–22 <http://www.nature.com/doifinder/>.
- 6 Mandal KCN. Indian Pediatrics - Editorial. 2006;43:1365 <https://indianpediatrics.net/apr2006/apr-365-366.htm>.
- 7 Joshi GG, Sircar S, Jain AK, *et al*. Acute viral hepatitis E and Japanese encephalitis: an unusual co-occurrence. *Indian J Gastroenterol*;26:102–3 <http://www.ncbi.nlm.nih.gov/pubmed/17558086>.
- 8 Kamar N, Izopet J, Cintas P, *et al*. Hepatitis E virus-induced neurological symptoms in a kidney-transplant patient with chronic hepatitis. *Am J Transplant* 2010;10:1321–4 <http://doi.wiley.com/>.
- 9 Dalton HR, Keane FE, Bendall R, *et al*. Treatment of chronic hepatitis E in a patient with HIV infection. *Ann Intern Med* 2011;155:479–80 <http://www.ncbi.nlm.nih.gov/pubmed/21969351>.
- 10 Despierrès L-A, *et al*. Neurologic Disorders and Hepatitis E, France, 2010. *Emerg Infect Dis* 2011;3.
- 11 Maddukuri VC, Russo MW, Ahrens WA, *et al*. Chronic Hepatitis E with Neurologic Manifestations and Rapid Progression of Liver Fibrosis in a Liver Transplant Recipient. *Dig Dis Sci* 2013;58:2413–6.
- 12 de Vries MA, Samijn JP, de Man R, *et al*. Hepatitis E-associated encephalopathy in a renal transplant recipient. *BMJ Case Rep* 2014;2014:bcr2014204244 <http://www.ncbi.nlm.nih.gov/pubmed/24789162>.
- 13 Deroux A, Brion JP, Hyerle L, *et al*. Association between hepatitis E and neurological disorders: two case studies and literature review. *J Clin Virol* 2014;60:60–2.

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