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Case report

First reported case of Human Parechovirus encephalitis in an adult patient complicated by Refractory Status Epilepticus

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ABSTRACT

Human Parechovirus (HPeV) infections are common amongst children, particularly neonates. However, data in adult cases are lacking. We report a unique case of HPeV meningoencephalitis in an adult complicated by Refractory Status Epilepticus (RSE).

Introduction

HPeV is a viral genus classification within the family *Picornaviridae.* It is a RNA virus with 19 discovered genotypes. It is related to enteroviruses and in children can cause gastroenteritis, sepsis and encephalitis. In adults there are published reports of HPeV associated with myocarditis, muscle weakness, myalgia, orchiodynia and fasciitis [1–3].

Case description

A 63-year-old male presented to a regional Emergency Department with seizures preceded by four days of confusion. He had a background of alcohol use disorder, hypertension (on Indapamide) and Stage IV cholangiocarcinoma with metastases to the liver, ribs, and lungs. He had undergone radiotherapy, chemotherapy, and biliary stenting.

He experienced two witnessed generalised tonic-clonic seizures ten minutes apart at home, lasting 30 s and four minutes respectively. He reported no preceding meningism, history of seizures, head trauma or ill contacts (specifically young children).

The patient's vital signs, blood work and progress are summarised in Table 1.

He was disoriented and had difficulty following multi-stage commands. Physical examination was otherwise unremarkable with no neurologic deficits.

A Brain CT scan showed no intracranial haemorrhage or mass. Within 24 h, the patient went into Status Epilepticus manifesting as generalised tonic clonic seizures lasting for up to 25 min. Seizure termination was attempted by administration of Midazolam (IV 5 mg 2 aliquots), given five minutes apart. Therapy was escalated with a Phenytoin load (IV 20 mg/kg). He progressed into RSE warranting intubation with Propofol and Fentanyl and a second loading of Phenytoin. He was transferred to ICU for neurological monitoring and mechanical ventilation.

On Day 2 of admission, a lumbar puncture was performed and treatment for meningoencephalitis was commenced using Ceftriaxone (IV 2 g BD for 1 day), Acyclovir (IV 10 mg/kg TDS for 5 days) and a stat dose of Dexamethasone (IV 10 mg). Given the history of biliary stenting and increasingly cholestatic liver function tests, Metronidazole (IV 500 mg BD for 2 days) was added for potential biliary anaerobic sepsis. Thiamine (IV 300 mg

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Table 1
Clinical and Biochemical Summary of Events.

Day	Events and Management	Investigations	Antiepileptic and Antibiotic changes
Day 1	Presentation to ED via ambulance for 2x generalised tonic clonic seizures **Respiratory Rate:** 20 breaths/min **Heart Rate:** 110 bpm, sinus rhythm **Blood Pressure:** 140/85 mmHg **Temperature:** 37.3 °C **Oxygen Saturation:** 94% with 0.21 FiO2 Admitted to ward	**CT Brain:** No intracranial haemorrhage or mass. **Haemoglobin**: 126 g/L (130-180 g/L) **White Cell Count:** 8.9 × 109/L (4.0-11.0 × 109/L) **Platelets**: 198 × 109/L (150-450 × 109/L) **C-Reactive Protein**: 27.5 mg/L (<3.0 mg/L) **Sodium**: 128 mmol/L (135-145 mmol/L) **Potassium**: 3.3 mmol/L (3.5-5.2 mmol/L) **Corrected Calcium**: 2.54 mmol/L (2.15-2.55 mmol/L) **Magnesium**: 0.73 mmol/L (0.70-1.10 mmol/L) **Creatinine**: 56 umol/L (60-100umol/L) **eGFR**: >90 ml/min/ 1.732 (>90 ml/min/ 1.732) **Creatine Kinase**: 108 U/L (<201U/L) **Liver Function tests (LFTs):** **Bilirubin**: 58 umol/L (<25umol/L) **ALP**: 779 U/L (40-130 umol/L) **GGT**: 1532 U/L (<51umol/L) **ALT**: 49 U/L (<51umol/L) **AST**: 99 U/L (<41U/L) **Albumin**: 31 g/L (35-50 g/L) **Arterial Blood Gas:** **pH:** 7.37 (7.35-7.45) **pCO2**: 55 mm Hg (35-46 mmHg) **pO2**: 30 mm Hg (80-100 mmHg) **Lactate**: 1.3 mmol/L (<1.5 mmol/L)	Midazolam IM 10 mg with Ambulance Clonazepam PO 0.5 mg Levetiracetam IV 1 g Levetiracetam IV 500 mg BD ongoing
Day 2	**MET call** for partial tonic clonic seizure lasting >20 mins Transfer to ICU: Grade 1 intubation and mechanical ventilation with propofol and rocuronium. Metaraminol requirements post intubation for BP maintenance Titrated propofol and fentanyl to effect Thiamine and Lactulose commenced	**MRI Brain:** T2 hyperintense signal within the right medial temporal lobe and thalamus with minor diffusion restriction and vasogenic oedema suggesting viral encephalitis. Chronic small vessel ischaemia. **Lumbar Puncture:** performed, results pending **Hyponatraemia:** 124 **Hypercalcaemia:** 2.81 **Ammonia level:** 63 umol/L (11-45umol/L). **Bilirubin:** 58 **Creatinine:** 56 **eGFR:** >90	MET team gave Midazolam IV 10 mg Phenytoin loaded IV 20 mg/kg Phenytoin IV 300 mg daily ongoing Ceftriaxone IV 2 g BD Acyclovir IV 10 mg/kg TDS and single dose dexamethasone IV 10 mg commenced for potential encephalitis Metronidazole commenced for potential biliary sepsis
Day 3	Dexmedetomidine infusion commenced. Metaraminol required for 1 day. Internal jugular central venous line, vascular catheter and arterial line inserted	**Ultrasound Abdomen and Renal tract:** potential hydronephrosis	Increased levetiracetam to 1 g BD IV Midazolam infusion commenced Benzylpenicillin IV 1.8 g 4hourly commenced for potential Listeria infection
Day 4	Noradrenaline infusion commenced Developed Hypotension with a MAP of 55 **Sedation break:** 3-4 min of seizure activity, self-ceased. Acute kidney Injury (AKI)	**Lumbar Puncture:** Protein elevated 0.62, normal glucose 2.9. No bacteria seen and nil growth after 48hrs **CSF HSV/EBV/VZV/ Flavivirus PCR:** added on tests **CSF Paraneoplastic antibodies and anti-NMDA testing**: added on tests **HIV serology:** pending **Ammonia level** 44 **Creatinine peaked:** 269 **eGFR:** 21 **Blood cultures**: no growth	Administered phenobarbitone IV 60 mg single dose Decreased levetiracetam to 500 mg BD due to AKI Ceased ceftriaxone and metronidazole. Decreased acyclovir dose to IV 750 mg BD due to AKI
Day 5	Noradrenaline infusion ceased Hypotension resolving **Sedation break:** midazolam infusion ceased. Observed partial seizures in right lower limb	**EEG:** consistent with encephalitis **Hyponatraemia:** Na 128 with polyuria	Given Midazolam IV 5 mg 5 min after seizure activity. Midazolam infusion restarted. **Current regime:** Phenytoin 300 mg mane IV Levetiracetam 500 mg BD IV Carbamazepine 550 mg single dose IV
Day 6	IV dextrose given Vascular catheter removed	**Hypernatraemia**: Na 158 **CSF PCR**: Parechovirus detected **CSF HSV/EBV/VZV/ Flavivirus PCR:** negative **CSF Paraneoplastic antibodies and anti-NMDA testing**: negative **HIV serology:** negative	Sodium Valproate IV 800 mg BD commenced Benzyl penicillin and Acyclovir ceased
Day 7	Dexmedetomidine causing hypotension. Noradrenaline restarted Midazolam and fentanyl ceased Thiamine ceased Lactulose decreased	**Creatinine:** 138 **eGFR:** 47 **Bilirubin:** 11	Levetiracetam increased to 1 g BD
Day 8	Transferred to tertiary metropolitan hospital ICU		Sodium Valproate IV 800 mg BD Clonazepam IV 0.5 mg BD Phenytoin IV 500 mg daily Levetiracetam IV 1.5 g BD
Day 9		**EEG** : epileptiform discharge right hemisphere posterior quadrant and temporal region and contralateral occipital lobe **VRE swabs:** pending results	

Table 1 (*Continued*)

Day	Events and Management	Investigations	Antiepileptic and Antibiotic changes
Day 10	Episode of tachycardia HR 115 and febrile 38.5	**EEG**: mild encephalopathy, frequent epileptiform discharge from right hemisphere, poorly formed background rhythms and frequent delta slowing over right hemisphere suggestive of structural abnormality **Blood cultures:** pending results	Ceftriaxone started IV 1 g daily
Day 11	Increasing noradrenaline requirements	**EEG**: frequent focal epileptic activity over right hemisphere **CT Chest Abdomen Pelvis:** 6.1 cm liver mass, left biliary dilatation, right sided biliary stents, small right pleural effusion	Clonazepam IV 0.5 mg BD increased to TDS
Day 12	IV dextrose	**VRE vanB:** positive **Hypernatraemia:** 152	Ceftriaxone increased IV 2 g daily Metronidazole IV 500 mg BD and Teicoplanin started
Day 14	Extubated	**EEG**: right posterior quadrant and frontotemporal changes. Not in electrographic status epilepticus	
Day 15	Hypoactive delirium Lactulose commenced Quetiapine commenced	**Ammonia** 59 **LFT:** cholestatic profile worsening	
Day 16			Phenytoin changed from IV 500 mg daily to oral Levetiracetam IV 1.5 g BD changed to oral Sodium valproate changed from IV 800 mg BD to oral Ceftriaxone, Teicoplanin and metronidazole ceased Augmentin Duo Forte 500 mg/125 mg and Ciprofloxacin 500 mg BD commenced
Day 17			Clonazepam IV 0.5 mg TDS changed to oral Ciprofloxacin ceased
Day 18	Lactulose ceased		Clonazepam decreased to oral 0.5 mg BD
Day 20		**EEG**: right temporal discharges of broad field (less frequent than EEG on 9/10/17). Background is slow, consistent with mild encephalopathic process	
Day 24		**CT Brain**: nil new findings	
Day 27		**EEG**: nil epileptiform abnormalities, improved from EEG on 19/10/17. Mild diffuse slowing	
Day 30		**Ascitic tap:** performed. Cytology consistent with cholangiocarcinoma	
Day 31		**VRE vanB:** still detectable	
Day 35	**MET call:** post procedure tachypnoea and tachycardia Post-procedure pancreatitis	**ERCP**: intra-ductal stent stenosis, clearance of right anterior duct stent of distal stones/sludge, improved on cholangiogram **Lipase**: 1578	Levetiracetam, phenytoin and sodium valproate changed to IV in setting of fasting patient Augmentin Duo Forte ceased Tazocin IV 4.5 mg 8hourly and Teicoplanin IV 800 mg 24 hourly commenced
Day 38			Phenytoin changed from 500 mg IV daily to 300 mg IV daily
Day 39			Phenytoin reduced to oral 300 mg daily
Day 41		**EEG**: normal EEG	Clonazepam reduced from oral 0.5 mg BD to 0.25 mg BD Levetiracetam changed to oral
Day 42			Sodium valproate changed to oral 800 mg BD Teicoplanin and Tazocin ceased
Day 43			Changed to Augmentin Duo Forte
Day 44	Transferred to rehabilitation		**On transfer:** Clonazepam PO 0.25 mg BD Phenytoin PO 300 mg daily Levetiracetam PO 1.5 g BD Valproate PO 800 mg BD
Day 47			Clonazepam changed to PO 0.25 mg nocte
Day 51			Augmentin Duo Forte ceased
Day 52			Clonazepam ceased
Day 63	Discharged home		**On discharge:** Phenytoin PO 300 mg daily Levetiracetam PO 1.5 g BD Valproate PO 800 mg BD
	Out-patient	**Ascitic tap**: performed	
	Out-patient	**Ascitic tap:** performed	
	Oncology clinic follow-up	**CT Abdomen:** progressive omental disease and liver metastases	Discharged with GP follow-up for symptom management

TDS) and Lactulose (NGT 40 ml BD) were commenced, given an Ammonia level of 63 umol/L (11–45 u mol/L).

MRI Brain suggested right medial Temporal lobe and Thalamic Viral Encephalitis.

Ongoing Status Epilepticus mandated third line anti-epileptics: Levetiracetam (Loading IV 1 g, Maintenance NGT 500 mg BD) and regular Phenytoin (NGT 300 mg daily). A sedation break demonstrated ongoing seizure activity and so the Levetiracetam dose was increased (NGT 1 g BD).

On Day 4, lumbar puncture yielded a sterile CSF with elevated protein (0.62 g/L), normal glucose (2.9 mmol/L) and no white blood cells, hence antibiotics were ceased. At this time Parechovirus/viral PCR testing was suggested by Infectious Diseases and Acyclovir was continued for potential Herpes Simplex Virus (HSV). Blood

cultures collected prior to the commencement of antibiotics remained negative.

CSF enteroviral PCR detected Parechovirus RNA but no HSV. Genotyping could not be performed due to sample size. CSF Paraneoplastic antibodies were negative. Given Parechovirus infection is managed supportively, Acyclovir was ceased.

Phenobarbitone (IV 60 mg) was added for burst suppression and Sodium Valproate (IV 800 mg BD). Partial seizures during sedation breaks were refractory to a midazolam infusion and intermittent boluses. Ventilator dyssynchrony was managed with Dexmedetomidine and ensuing hypotension with Noradrenaline.

On Day 8, he was transferred to a tertiary ICU for twelve days for continuous EEG monitoring. EEG showed active epileptiform focus over the right posterior quadrant, temporal, and occipital lobes. Antiepileptics were rationalised to Sodium Valproate (IV 800 mg BD), Clonazepam (IV 0.5 mg BD), Phenytoin (IV 500 mg daily), and Levetiracetam (IV 1.5 g BD). Amelioration of seizure activity was demonstrated on serial EEGs over ten days with loss of the focal epileptiform pattern but persisting activity over the right hemisphere.

On Day 14, dysphagia complicated extubation, mandating nasogastric feeding.

His admission was complicated by biliary sepsis.

On Day 35, he underwent ERCP for biliary stasis/calculi and developed pancreatitis and ascites requiring drainage. Cytology was consistent with cholangiocarcinoma. On Day 44, antiepileptics were weaned and the patient was moved to rehabilitation with residual confusion and right-sided dyspraxia.

During rehabilitation seizure activity was minimal with ongoing bilateral arm tremors and Clonazepam was ceased. Neuropsychological assessment demonstrated ongoing executive cognitive deficit with reduced processing speed and attention.

On Day 63, he was discharged home with frontal lobe release features, driving restrictions, and epilepsy/oncology outpatient follow-up. He passed away 1 month later from progressive refractory malignant ascites.

Discussion

Status Epilepticus is defined as continuous clinical/electrographic seizure activity lasting five minutes or more, or recurrent seizure activity without return to baseline. RSE refers to seizure activity that fails to respond to first line anti-epileptics [4]. Timely seizure control limits neuronal injury and reduces cognitive and behavioural sequelae. The differential diagnoses for new-onset seizures in this patient included, but were not limited to: intracerebral haemorrhage, meningoencephalitis, autoimmune encephalitis, metabolic disturbance, metastatic or primary brain tumour, paraneoplastic encephalitis, alcohol-related seizures and hepatic encephalopathy.

HPeV is spread through contact with saliva, faeces or respiratory droplets from an infected person. This infection coincided with a concurrent outbreak of HPeV amongst children in Victoria, Australia from July 2017- November 2017 [5]. HPeV epidemics tend to occur in a two-yearly cycle with a similar outbreak in Spring 2015. Such epidemiological factors have not previously been associated with adult cases despite the biannual summer to autumn seasonal pattern of HPeV infection. This applies to the genotype HPeV 3, which is the most common cause of aseptic meningitis in North American infants younger than 90 days [6].

It is unclear why severe disease from HPeV infection is more common in paediatric populations. However, low maternally derived neutralizing antibody titers to HPeV3 are a risk factor for developing serious neonatal sepsis [7]. Gastroenteritis is a common presentation with illness severity being associated with different genotypes. One study describes seizures manifesting in 90% of HPeV-infected infants with meningoencephalitis. Individual cases of acute flaccid paralysis and acute disseminating encephalomyelitis in infants have been reported with the long-term sequelae of white matter injury, cerebral palsy and hypoxic-ischaemic encephalopathy [8].

As seen with this patient, CNS infections from HPeV 3 typically lack pleocytosis of the CSF [9]. In these cases, detection of RNA in CSF is not predictive of CNS infection and may be the result of spill-over from the blood [10]. As such, real-time reverse transcription-PCR assay testing on CSF fluid and serum may be the most effective tool for detecting this virus in a timely manner. Stool and nasopharyngeal samples may also be tested.

This is the first reported case of HPeV causing meningoencephalitis in an adult. This case highlights the devastating effect of RSE that can ensue from infection. It expands the epidemiological knowledge of HPeV and when testing should be performed in adults. Supportive management is the standard of care for HPeV infection with no specific antiviral therapy hence rapid diagnosis will decrease antibiotics therapy.

Conflict of interest

No potential conflicts of interest to disclose.

Ethical approval

Ethical approval and patient consent gained.

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