

SEVERE COMPLICATIONS OF ENTEROVIRUS OR HUMAN PARECHOVIRUS INFECTION

Abstract

Our knowledge of these rare but very severe enterovirus and parechovirus infections is very limited. Between July 2014 and July 2015, we conducted a BPSU study to estimate the burden of enterovirus and parechovirus meningitis in young infants: we identified almost 400 cases, substantially more cases than we had expected.¹ Reassuringly, though, most infants recovered without any long-term complications. During the course of our surveillance, however, we were contacted by a number of paediatricians and neonatologists requesting advice on the management of infants and children of all ages who had developed rare and severe complications associated with these viruses. This led us to establish a team of specialist paediatric infectious diseases consultants, neurologists and cardiologists to provide clinical advice on a case-by-case basis. A major problem faced by the team was the lack of any data on how common such severe complications were, which children were most at risk or what would be their likely outcome. We tried to answer the question by working with paediatric intensive care colleagues and, using anonymised data from PICANET (www.picanet.org.uk), we found that there had been 104 enterovirus-related intensive care admissions in United Kingdom and Ireland during 2010-14 (5 years) and 8% died of their illness. This is quite high, given that these infections are generally viewed to be mild and self-limiting. We know that these numbers are likely to be at the lower range because we only included the sickest children who were diagnosed with an enterovirus infection whilst in the intensive care unit. Babies who are admitted to neonatal units, and children with complications related to the heart, nerves or spinal cord, may not necessarily be admitted to the paediatric intensive care, but would be captured in a BPSU study.

Principal Investigator

Dr Shamez Ladhani
Paediatric Infectious Diseases Consultant, St. George's Hospital, London
Consultant Epidemiologist, Public Health England, London NW5 5EQ.
E-mail: shamez.ladhani@phe.gov.uk

Co-investigators

Prof Paul Heath, Paediatric Infectious Disease Consultant, St George's University of London
Prof Mike Sharland, Paediatric Infectious Disease Consultant, St George's University of London
Dr Ming Lim, Consultant Paediatric Neurologist, Evelina Children's Hospital
Dr Jonathan Round, Consultant Cardiologist and Intensivist, St George's University Hospital
Dr Juan Kaski, Consultant Paediatric Cardiologist, Great Ormond Street Hospital
Dr Serena Braccio, Paediatric Infectious Disease Clinical Research Fellow, Public Health England, St George's University of London
Dr Kate Templeton, Consultant Clinical Scientist, University of Edinburgh
Dr Catherine Moore, Principal Clinical Scientist, Public Health Wales
Dr Christopher Williams, Consultant Epidemiologist, Public Health Wales
Dr Niamh O'Flaherty, Microbiologist, Republic of Ireland
Prof Deirdre Kelly, Hepatologist, Birmingham Children's Hospital

Website

<http://www.rcpch.ac.uk/bpsu/severeenterovirus>

Background

Enterovirus and human parechovirus are two related viruses that commonly cause mild, self-limiting illnesses in children, mainly flu-like syndromes or diarrhoea and vomiting. Rarely, however, these viruses can cause very severe infections including meningitis, encephalitis, myocarditis, hepatitis and septic shock. These severe conditions can lead to permanent damage to the brain and spinal cord, liver or the heart, and even death. Our knowledge of these rare but very severe complications is very limited. Through this BPSU study, we hope to collect more robust data on the epidemiology, clinical course and outcomes of children who develop these rare manifestations.

Coverage

United Kingdom and Republic of Ireland

Duration

February 2019 to February 2020 (inclusive). Follow-up until February 2021 (1 year follow-up).

Research Questions	<ul style="list-style-type: none"> ▪ Estimate the age-specific incidence of severe manifestations of childhood enterovirus (EV) and human parechovirus (HPeV) infections in the UK and Ireland ▪ Describe the clinical presentation, laboratory features, disease severity, complications and outcome at hospital discharge ▪ Describe the investigation and management of severe EV/HPeV infection (method and timing of diagnosis; management; medications) ▪ Describe any specialist support required (intensive care, referral to a tertiary centre) ▪ Describe survival and rates of long-term complications of severe EV/HPeV infections at 12-months using a follow-up questionnaire ▪ Assess any associations between clinical disease or outcome with viral subtypes and/or viral loads
Case definition	<p>Any child aged <16 years with laboratory-confirmed enterovirus or human parechovirus infection (from any site) who develops any severe complication, including (but not restricted to):</p> <ul style="list-style-type: none"> ▪ Cardiovascular collapse requiring inotropes (sepsis-like syndrome), or leading to myopericarditis, arrhythmias or cardiomyopathy; OR ▪ Neurological complications lasting >48 hours: including cranial/peripheral nerve palsy/paralysis (including acute flaccid paralysis) +/- seizure +/- coma +/- intracranial damage on imaging; OR ▪ Fulminant or acute liver failure requiring specialist hepatology advice/referral: including deranged liver function tests, coagulopathy and encephalopathy ▪ Intensive Care admission for management of enterovirus/parechovirus infection.
Reporting instructions	To report any cases seen within the last month that meet the case definition
Methods	<p>Each paediatrician reporting a child who meets the above case definition of FPIES will be sent a clinical questionnaire by the study team.</p> <p>Throughout the study, all patient data will be dealt with in strict confidence, and affected children and their families will not be contacted directly by the FPIES study team at any stage</p>
Ethics approval	<p>The study has been approved by London - London Bridge Research Ethics Committee (reference: 17/LO/1518) and Public Benefit & Privacy Panel, Scotland (reference: 1718-0330) . Public Health England has approval under Section 251 of the NHS Act 2006 to process confidential patient information for public health purposes. See The Health Service (Control of Patient Information) Regulations 2002 (http://www.legislation.gov.uk/ukxi/2002/1438/contents/made).</p>
Support group	<p>Meningitis Research Foundation (MRF) (www.meningitis.org) Meningitis Now (www.meningitisnow.org)</p>
Funding	This study is funded by Public Health England
References	<ol style="list-style-type: none"> 1. Kadambari S, Braccio S, Ribeiro S, Allen DJ, Pebody R, Brown D, Cunney R, Sharland M, Ladhani S. Enterovirus and parechovirus meningitis in infants younger than 90 days old in the UK and Republic of Ireland: a British Paediatric Surveillance Unit study. Arch Dis Child. 2018 Dec 8. pii: archdischild-2018-315643. 2. Harvala H, Broberg E, Benschop K, et al. Recommendations for enterovirus diagnostics and characterisation within and beyond Europe. J Clin Virol. 2018 Apr;101:11-17. 3. Braccio S, Kapetanstrataki M, Sharland M, Ladhani SN. Intensive Care Admissions for Children With Enterovirus and Human Parechovirus Infections in the United Kingdom and The Republic of Ireland, 2010-2014. Pediatr Infect Dis J. 2017 Mar;36(3):339-342. 4. Oades PJ, Ladhani S. Enteroviral meningoencephalitis in an infant: an increasingly recognised infection. Arch Dis Child. 2015 Feb;100(2):208. doi: 10.1136/archdischild-2014-307372. Epub 2014 Sep 22. 5. Kadambari S, Bukasa A, Okike IO, Pebody R, Brown D, Gallimore C, Xerry J, Sharland M, Ladhani SN. Enterovirus infections in England and Wales, 2000-2011: the impact of increased molecular diagnostics. Clin Microbiol Infect. 2014 Dec;20(12):1289-96.