THE NORTHERN HOSPITAL

PARECHOVIRUS

"The children up in the sky", Elves and Fairies, Ida Rentoul Outhwaite, Lithographic print, 1916

"Although we know that after such a loss the acute state of mourning will subside, we also know we shall remain inconsolable and will never find a substitute, no matter what may fill the gap, even if it be filled completely, it nevertheless remains something else. And actually this is how it should be…it is the only way of perpetuating that love which we do not want to relinquish."

Sigmund Freud, letter to his friend Ludwig Binswanger, following the death of his daughter Sophie, 1929

PARECHOVIRUS

Introduction

Human parechovirus (HPeV) occurs commonly in the general population, and usually causes only a mild respiratory and/or gastrointestinal illness in young children.

Children are more likely to develop symptoms, and **neonates** and **young infants** (< 6 months) are at risk of more **severe disease**.

Most HPeV infections cause **no** or mild **symptoms** in similar manner to other **echovirus** infections that manifest as:

- Gastroenteritis
- Influenza-like respiratory illness.

Characteristically, young infants present with:

- Fever
- Irritability
- On occasions also a diffuse erythematous rash ("red, hot and angry" babies).

However some strains can cause **severe illness** manifesting as:

- **Sepsis-like syndrome (including septic shock)**
- **Seizures**
- **Meningoencephalitis**

HPeV should be considered as a differential diagnosis in neonates and young infants presenting with a picture of **meningoencephalitis, seizures** or a **sepsis-like syndrome**.

Testing for HPeV by PCR testing is indicated in children younger than 6 months of age with characteristic presentations without another confirmed diagnosis.

There is no specific anti-viral therapy available for HPeV infection and so treatment is supportive. There is currently no vaccine available.

History

HPeV1 and HPeV2, originally known as echovirus 22 and 23 of the EV genus, respectively, were reclassified in 1999 as a separate genus (Parechovirus) on the basis of genetic and biologic differences.

Since the reclassification, the number of known HPeVs has increased to 16 genotypes

Epidemiology

Most cases occur in young children (< 2 years) and infants.

Recent epidemics of human parechovirus causing disease in young children in Australia have occurred in, 2013, 2015 and 2017 [2]

HPeV genotype 3 caused the epidemic from late 2017 to early 2018.

Serological data from Europe and Japan show that 90% of infants have been infected with at least one HPeV subtype by the age of 2 years. [2]

There is as yet insufficient data to define seasonal periods of elevated risk.

Pathology

Organism

Human parechovirus belongs to the **Picornaviridae** *family* of viruses.

It is a small **RNA virus**.

HPeVs were formerly considered to be part of the echovirus genus in the 1960s but were assigned their **own genus** in the 1990s.

The **enteroviruses** have been traditionally divided into five sub-genera, each with a number of serotypes:

1. Enteroviruses
2. Polioviruses
3. Group A coxsackie viruses
4. Group B coxsackie viruses
5. Echoviruses

The parechoviruses are closely *related* to the enteroviruses and share many of the same biological, clinical, and epidemiologic characteristics with the them, but they do differ sufficiently in genomic sequence to be classified as a separate genus.

Human enteroviruses (EVs) and more recently parechoviruses (HPeVs) have been identified as leading viral causes of neonatal sepsis-like disease and meningitis.

HPeV **serotypes** that have been demonstrated to cause human disease include:

- HPeV type 1 (tends to cause milder gastroenteritis symptoms in children > 6 months).
- HPeV type 2
- HPeV type 3 (tends to be the cause more serious disease).
- HPeV type 6 (tends to cause milder gastroenteritis symptoms in children > 6 months).

Transmission

- HPeV is usually spread from person to person through contact with **respiratory droplets, saliva** or **faeces** from an infected person.
- It can also be spread through inanimate objects and surfaces that have been contaminated with infected secretions.

Incubation Period

- About 2 - 7 days.

Reservoir

- Human

Period of Communicability

- this has not been clearly defined.

  HPeV3 has been shown to be shed in the stool for a median of **58 days**, although the risk of transmission is probably highest during **acute symptomatic illness**. [2]

Susceptibility and Resistance

- Anyone can be infected with parechovirus, however adults are usually immune and children, especially very young children are at the greatest risk.

  Young infants < 3 months and ex-premature babies are at the highest risk.

Clinical Features

Children:

Most infected with HPeV are asymptomatic (50 - 80 %).

Some may develop illness in the form of:

1. A gastroenteritis

2. A respiratory influenza-like illness

Some strains of HPeV however can lead to more **severe disease** particularly in **infants, under the age of 3 months**:

More severe presentations can include:

1. A sepsis-like syndrome (including septic shock):

    - Fever
    - Irritability
    - Tachycardia
    - Drowsiness / lethargy
    - Poor peripheral perfusion (**see Appendix 1 below**).

2. A diffuse erythematous skin rash is occasionally seen .

3. A neurological illness:

    Manifestations may include:

    - Meningitis/ encephalitis
    - Flaccid paralysis
    - Seizures
    - Apnoea

4. Less commonly significant GIT complications may be seen, including:

    - Hepatitis, (including fulminant liver failure).
    - Intussusception
    - GIT perforation.

Some infants with severe HPeV infection may have subsequent abnormal neurodevelopment.

Adults:

In adults, HPeV is associated with:

1. Upper respiratory tract infection
2. Mild diarrhoeal illness
3. Less commonly myocarditis

Pregnancy:

There is currently no evidence to suggest particular concern regarding infection in pregnant women or the fetus.

Investigations

PCR:

Testing for HPeV by PCR testing is indicated in children younger than 6 months of age with characteristic presentations without another confirmed diagnosis.

Human parechoviruses are not currently detected using standard enterovirus tests used in most pathology services.

Parechovirus PCR should be *specifically* requested, and in Victoria is performed through the Victorian Infectious Diseases Reference Laboratory (VIDRL).

PCT testing can be performed on:

1. Nasopharyngeal aspirates
2. Stool specimens
3. Throat swabs
4. Cerebrospinal fluid
5. Urine
6. Whole blood (EDTA).

Stool and **CSF** have the highest sensitivity and so are the preferred samples.

MRI Scan:

Infants with proven HPeV infection and neurological symptoms should undergo magnetic resonance imaging (and not head ultrasound) to exclude encephalitis.

Magnetic resonance imaging of the brain is important to detect characteristic features of meningoencephalitis (**peri-ventricular white matter diffusion restriction**) that likely has **prognostic** significance.

Cranial Ultrasound:

Head ultrasound, widely used in the assessment for meningitis in neonates, is **not** sensitive to diagnose white matter changes due to parechovirus infection.

Management

Prevention:

The best way to prevent parechovirus infection is the same as for prevention of all viral gastrointestinal illnesses.

In hospital hand hygiene and contact precautions should be implemented (including gloves, gown, plastic apron, mask and eye protection).

In the community, non-hospitalised, confirmed cases should avoid contact with other young children (including childcare and school attendance) until symptoms have fully resolved.

Contacts of confirmed cases should be made aware that older children and adults may develop mild upper respiratory or diarrhoeal symptoms.

There are cases of transmission from mildly symptomatic children to adults resulting in severe acute illness, but these appear to be uncommon.

Hand hygiene, cough etiquette and staying away from childcare and school while unwell should be emphasised.

Treatment:

There is no specific therapy available and so treatment is supportive.

Empirical antibiotics should be administered in the first instance according to local and guidelines for possible bacterial sepsis or meningoencephalitis, especially in neonates, until this has been excluded by negative sterile site cultures.

Vaccination

- There is no current vaccine available for Human parechovirus.

  Unfortunately, the antigenic diversity of the **enterovirus/HPeV group** is a significant barrier to the development of a broadly protective vaccine.

Notification:

- Human parechovirus infection is not currently a notifiable condition in the state of Victoria.

Follow-up

Follow-up studies have shown adverse neurological outcomes in patients with meningoencephalitis, and developmental concern among patients with sepsis-like illness from the 2013 - 2014 epidemic.

A study of Australian infants hospitalised with HPeV3 in 2013 found that 19% showed significant concern in developmental attainment 12-16 months after infection and an additional 50% had some concern based on standardised tools.

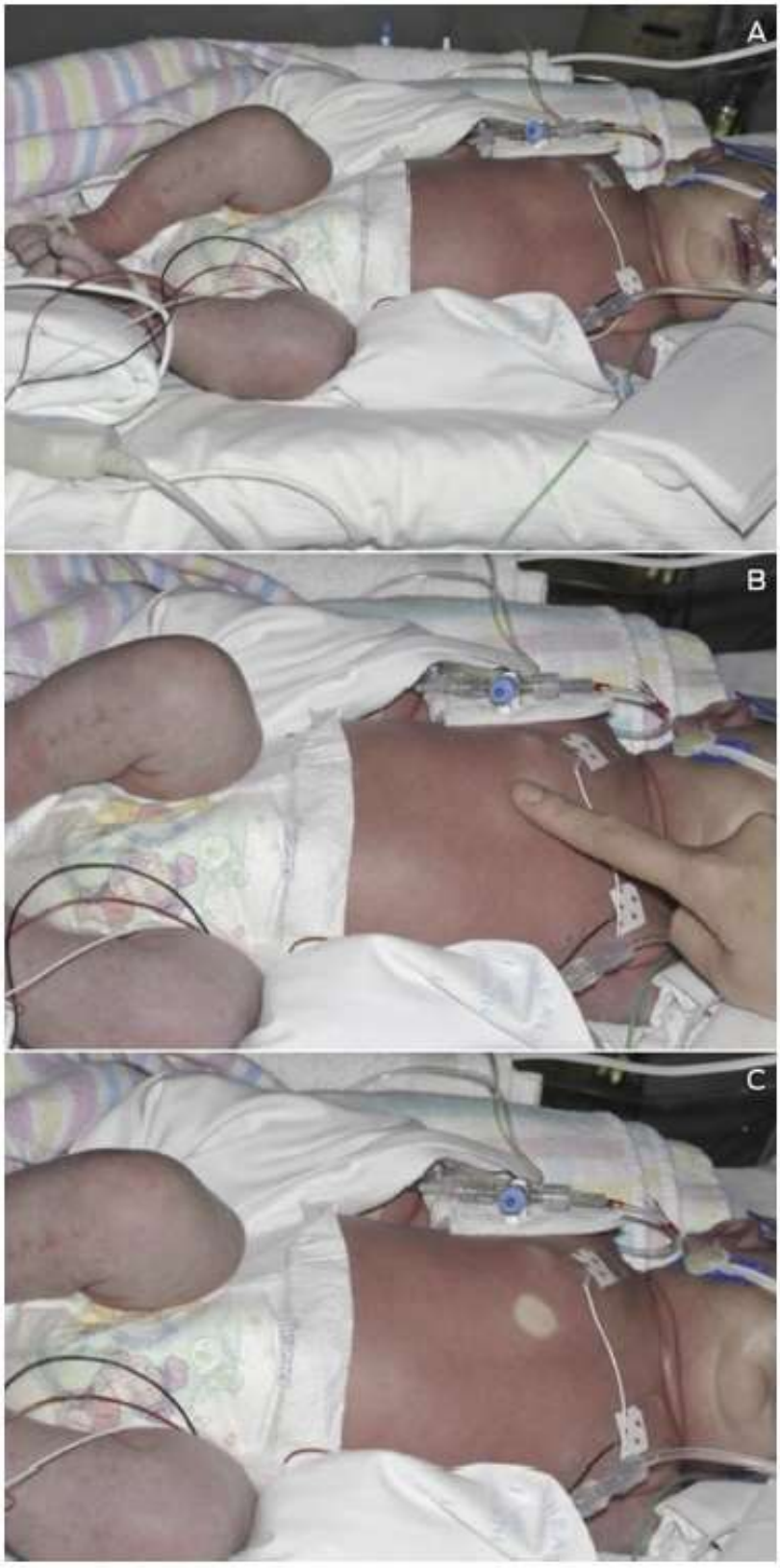
An earlier study documented severe neuro-developmental sequelae, including cerebral palsy, central visual impairment and gross motor impairment.

These findings are consistent with those from other countries, where 16% of children hospitalised with confirmed HPeV infection had significant neurological sequelae.

These data also appear to be consistent with outcomes from other causes of encephalitis.

Because of the evidence of adverse neuro-developmental outcomes following severe HPeV infection, we recommend that all children hospitalised with HPeV infection should be followed up by a **paediatrician** at least until school entry, and preferably afterwards, to monitor development and learning, and manage complications including seizures.

Appendix 1



Left: Infant with Parechovirus infection. This infant is significantly unwell, (note the presence of cardiorespiratory monitoring, multiple intravenous lines and a nasal mask for continuous positive airway pressure ventilation support).

Panel A: There is a confluent erythroderma of the trunk with an acral (i.e peripheral) erythematous maculopapular rash of the lower limbs

Panels B and C: Demonstrate an intense erythroderma with prolonged capillary return time indicative of poor perfusion.

(Photographs: Drs. Ameneh Khatami, Brendan McMullan and Julie Huynh).

References

1. Dr Simon Slota-Kan, Acting Chief Health Officer, Victoria: Human Parechovirus (HPeV) Alert; Bulletin 30 December 2015.

2. Philip N Britton et al. Parechovirus: an important emerging infection in young infants. MJA 208 (8) 7 May 2018.

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