Enteroviruses and Enterovirus Encephalitis

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What are enteroviruses?

Enteroviruses are small RNA (ribonucleic acid) viruses. Each year, a billion or more people worldwide are affected by enteroviruses. Enterovirus infections are more common in the hotter and wetter months, the time of maximum potential exposure. The clinical attack rates are highest in infants and children, but adult cases have also been reported.

Types of enteroviruses

Enteroviruses have been traditionally classified into two distinct classes: polioviruses (the common cause of polio) and non-polioviruses. Non-polio viruses include coxsackie A virus, coxsackie B virus, echoviruses, and the numbered enteroviruses (such as Human Enterovirus 71-HEV71). The human non polio enteroviruses may be further classified by their genetic code.

Clinical presentation

Clinical presentation varies. Most enterovirus infections are clinically silent. Others produce mild symptoms such as a short lived febrile illness with or without a sore throat, vomiting, and on occasions, diarrhoea. Only rarely do enterovirus infections result in severe disease in the heart (cardiomyopathy) or nervous system such as Meningitis (inflammation of the lining of the brain and spinal cord), Acute Flaccid Paralysis (limb weakness) or Encephalitis (inflammation of the brain). Severe enterovirus disease may cause symptoms such as muscle pain, headache, neck stiffness, lethargy, clumsiness, More often they too first present with fever, cough, abdominal pain and gastrointestinal upset and/or rash (especially of the hand, foot and mouth disease) and swollen glands.
**Diagnosis**

Based on the symptomatology and the risk factors (age, exposure, geographic locations) a doctor may clinically suspect enterovirus infection.

The diagnosis can be confirmed by identifying the virus genetic material in samples (faeces, nose or throat secretions, cerebrospinal fluid (CSF) and/or blood) using a polymerase chain reaction (PCR) assay.

Other tests that can be used to confirm enterovirus infection include growing the virus from samples in cell cultures and/or serology (demonstrating the development of antibodies in blood against enteroviruses).

Enterovirus infections of the brain or spinal cord may result in abnormal signals on imaging such as Magnetic Resonance Imaging (MRI).

**Treatment for non-polio enteroviruses**

Unfortunately, there is no specific antiviral medication for non-polio enterovirus infection. Treatment consists of supportive measures: antipyretic, analgesic medication or intensive care therapies in severe cases. Intravenous immune globulin therapy has been used in chronic enterovirus infections in immunocompromised patients with some success.

**Prevention**

Enteroviruses are very contagious. They spread through fecal-oral, respiratory and oral-to-oral routes in crowded environments. For example if you touch hands with an infected person, or touch objects that have the virus on them, or changing nappies or drinking infected water. Perinatal and post-natal transmission from mother to baby can occur.

The viruses are very resilient, able to survive exposure to the gastro-intestinal system. They can be killed with standard disinfectant and heat, but they are resilient to freezing and chlorine.

Enterovirus infections are very difficult to prevent, as many people do not know they are infected. Early diagnosis and effective management of identified cases are good measures of
prevention. Careful attention to hand and personal hygiene can help limit outbreaks particularly after contact with secretions from an infected individual.

Enteroviruses are a major public health concern given the increase in outbreaks of strains serious neurological disease, death on occasions and disability in survivors. Effective antiviral treatment and vaccination are still required. Candidate vaccines to prevent enterovirus infections and disease are in development with some showing promised in animal models and clinical trials in China.

Risk Factors

Risk factors associated with enteroviruses infections are:

- Environmental: poor sanitation and crowded living conditions
- Age: young children are at a greater risk because of poor hygiene and lack of prior immunity
- Health: the immuno-compromised also have a high risk for acute infection.

Enterovirus Encephalitis (EVE)

Encephalitis is a rare presentation of enterovirus infection. However, enteroviruses are one of the most common causes of Encephalitis in children. In a study of Encephalitis cases in the USA (California project) 4.6% of all cases of Encephalitis had EVE (confirmed or suspected). Patients with EVE were younger than those with other viral causes of Encephalitis and predominantly male. Only 27% of patients with EVE were adults over 18 years of age. Patients with confirmed EVE, with the exception of EVE due to EV71, presented with milder clinical illness than patients with Encephalitis caused by other infections.

Enterovirus Encephalitis in Neonates (newborns)
Neonates are at a particular risk of developing Meningoencephalitis after infection with enteroviruses. Enterovirus in infection in newborns may present with fever, poor-feeding, irritability, lethargy, jaundice, and ‘sepsis’. As well as Meningoencephalitis, neonates can develop Pneumonia, Hepatitis and Myocarditis.

In a neonate with clinical signs suggestive of possible enterovirus infection, a lumbar puncture should be considered to obtain and examine the CSF. Neonatal Enterovirus Encephalitis can result in significant brain injury and long-term neurological and developmental problems.

**Human Enterovirus 71 (HEV71)**

HEV71 was first identified in 1969, causing large epidemics in Bulgaria, Hungary, Malaysia and Taiwan. In the late 1990s, HEV71 emerged in eastern Asia causing large outbreaks of hand-foot-mouth disease (HFMD) and fever, and, in some children, Meningitis, Acute Flaccid Paralysis and a severe Brainstem Encephalitis with high mortality. Children with Brainstem Encephalitis usually present with myoclonus (quick, involuntary muscle jerk), tremor, ataxia (co-ordination, balance and speech difficulties), nystagmus (involuntary eye movement) and cranial nerve palsies. The outcomes of Brainstem Encephalitis are severe, only a few children recovering fully, most of them are left with permanent neurological sequelae.

HEV71 epidemics have caused great public health concern because of their size and the risk of children younger than five years old developing severe neurological disease and potentially death. The largest epidemic occurred in China, beginning in 2007, with reports of almost 500,000 cases in 2008, increasing to over 1.7 million cases in 2010, and close to 1000 deaths during the epidemic. Recent data from Malaysia supported by recent outbreak data from Australia suggest that disease occurs in 2-3 year epidemic cycles corresponding with new, naive birth cohorts.

HEV71 epidemics are seasonal, with the highest transmission rates occurring during warmer, wetter months. A comprehensive guide for clinical management of HFMD has recently been published by the World Health Organization. Infection control practices consist mainly of hand washing, disinfection, and isolation during epidemics.

A major effort has gone into developing vaccines for HEV71, particularly in China, with three large trials now completed and published in 2014. While this provides hope for future control HEV71 epidemics, at this stage, the trialled vaccines are proven to work only for one sub-type.
of the HEV71. There is a need to determine EV subtypes causing disease around the globe, to test the current HEV71 vaccines against other subtypes, and to develop vaccines with broader protection for the many sub-types of HEV71 and for the development of potent antiviral treatments for children and adults who acquire this potentially devastating infection.

FS042V1 Enteroviruses and Enterovirus Encephalitis; Created: February 2015/ Review Date: February 2018

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