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Enterovirus Infections of the Central Nervous System in Children

An Update

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With an estimated incidence in high-income countries of 12–19 cases per 100,000 population per year, viral meningitis is almost 3-fold more frequent than bacterial meningitis.^{1,2} Non-polio enteroviruses (NPEV) are the main cause of viral meningitis worldwide, and young age is an important epidemiological risk factor.^{1–3} Although the acute phase is often mild, NPEV infections can cause severe central nervous system (CNS) disease and result in fatal outcome. Transmission of enteroviruses (EVs) occurs mainly via the fecal-oral route and to a lesser extent by respiratory droplets.¹ Therefore, enhancing hand hygiene can diminish viral spread. Although the peak seasonality occurs in summer and fall in temperate climates, enteroviral infections occur perennially in tropical and subtropical areas.^{1,3}

Improved molecular typing and several EV surveillance programs (primarily geared toward the detection of poliovirus outbreaks)

have led to higher detection rates of enteroviral infections worldwide. Currently, there are more than 100 serotypes of NPEV identified that are subdivided into 4 species (A to D).⁴ Since the 1970s, there have been a number of reports of NPEV outbreaks with human EV 71 (EV71) with sometimes fatal outcomes especially in eastern Europe and the Asia-Pacific region.^{5–7} The World Health Organization reports more than 2000 deaths of an estimated 6 million infections.⁷ There are large differences in the case fatality rate between the different outbreaks, which might be related to differences in the pathogenic effect on the CNS of different genogroups of EV71.^{5,6,8}

In this review, typical CNS manifestations of EVs and recent outbreaks in children are summarized, and diagnostic tools and possible treatment and prevention strategies are presented.

CNS MANIFESTATIONS OF INFECTIONS WITH NPEV

Meningitis

Aseptic meningitis is defined as a syndrome with acute onset of meningeal symptoms, fever and cerebrospinal fluid pleocytosis with bacteriologically sterile cultures and absence of parenchymal brain involvement. It is caused by EVs in 48–95% of the cases in which a causative virus is identified in high-income settings.^{1,2} In contrast, the frequency was considerably lower (6%) in a recent but rare report from a resource-poor setting.⁹ However, children in resource-poor

settings are susceptible to a wider range of prevalent pathogens such as rabies, HIV or cytomegalovirus as well as other neurotropic viruses included in vaccination schedules in high-resource countries, such as mumps and measles. Known predisposing host factors for enteroviral meningitis are young age, immunodeficiency and to a lesser extent male gender and physical exercise.^{1,10}

Typical for the clinical course is biphasic fever with the onset of neurological symptoms during the second fever peak.^{1,3} Nonspecific findings in patients with enteroviral meningitis include nausea, headache, exanthems and respiratory tract symptoms, which are found among all age groups. With increasing age of the patients, characteristic findings of meningitis such as nuchal rigidity and photophobia may be present, whereas in the neonatal age irritability, lethargy and bulging fontanelle may be the only features.^{1,3} Cerebrospinal fluid pleocytosis, sometimes with a predominance of polymorphonuclear leukocytes, is typical at the early stages of disease.^{1,3} The following NPEV have been associated with causing aseptic meningitis: CVB2, CVB3, CVB4, CVB5, CVA5, CVA7, CVA9, CVA16, E4, E6, E9, E11, E14, E16, E25, E30, E31 and EV71.⁴ The short-term prognosis of enteroviral meningitis is good.^{1,3} However, systematic analyses of short-term and long-term clinical outcome are lacking.

Encephalitis

Encephalitis with parenchymal brain involvement is less frequent than meningitis.¹

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Symptoms range from mild features such as headache and drowsiness to altered sensorium, flaccid muscle weakness, focal neurological findings and mental status changes and coma.^{3,11} Rash and diarrhoea are important clinical features that help to distinguish enteroviral encephalitis from other forms of encephalitis.¹¹ In contrast to enteroviral meningitis, encephalitis caused by EVs is more likely to have a fatal outcome especially if diagnosis and symptomatic treatment are delayed.¹¹ Young children (<4 years) displaying high leukocyte counts (>13,000/mm³), seizures and myoclonic jerks among other symptoms are at high risk for death or neurological sequelae.¹¹ Encephalitis has been described in infections with EV71, EV75, EV76, EV89, CVA2, CVA9, CVA10, CVB1, CVB5 and echoviruses E4, E5, E6, E9, E11, E19, E17, E21 and E30.^{4,11}

Chronic Enteroviral Meningoencephalitis and Brainstem Encephalitis

Uncommon variants of encephalitis caused by EVs are chronic enteroviral meningoencephalitis, in patients with humoral immunodeficiencies, and brainstem encephalitis. Because of the lack of viral clearance, chronic meningoencephalitis may last for many years and can ultimately have a fatal outcome.¹ Brainstem encephalitis is the primary cause of death related to enteroviral infections in Asia and has replaced aseptic meningitis as the leading neurological manifestation in EV71 infection.⁸ After a mild febrile onset, patients (especially children) can develop cardiopulmonary symptoms leading to cardiopulmonary arrest.^{8,12} Typical clinical features of brainstem encephalitis are ataxia; tremor; myoclonic jerks; oculomotor problems such as nystagmus, strabismus or gaze paresis and bulbar palsy with dysphagia, dysarthria, dysphonia and facial weakness.¹¹

Acute Flaccid Paralysis

Formerly predominately seen in patients with paralytic poliomyelitis, in the era of widespread polio vaccination acute flaccid paralysis (AFP) has recently emerged in association with EV68 outbreaks in the US and Canada.^{4,13} Additionally, EV71 is associated with AFP.⁴ The clinical course is characterized by an acute onset of reduced muscle strength, hypomyotonia and weak or absent tendon reflexes in 1 or more limbs.⁴

RECENT AND CURRENT OUTBREAKS

In recent decades, there have been increasing reports of outbreaks caused by NPEV.^{5-7,11} Before an outbreak occurs it appears that the causative strain, often a new genomic lineage, is circulating already

“silently” for some years within the same geographical area.¹⁴⁻¹⁶ Nonetheless, only a small proportion of the NPEV detected, for example, in sewage water causes symptomatic infections.¹⁷ Lower herd immunity because of the lack of neutralizing antibodies in a new birth cohort may also facilitate the emergence of periodic viral activity.¹⁴⁻¹⁶

In temperate climates, NPEV serotypes endemically circulate with some serotypes being responsible for large outbreaks, such as echoviruses E9, E13, E18 and E30 and CVB5.¹⁷ In Europe within the last decade, E30 was the cause of the majority of outbreaks associated with CNS infections.¹⁷ Genome sequence analysis is increasingly employed as an important tool to analyse outbreaks of enteroviral infections and has revealed that E30, which has been circulating in Europe since 2012, belongs to a unique sublineage within the circulating EV genotype VII.^{15,17} Thus, new genomic lineages largely replace previous ones.¹⁵

Although known for its neurovirulence and devastating effects for more than 40 years, EV71 is considered as an emerging virus associated with large-scale epidemics especially within the Asia-Pacific region.^{4,5,11} The typical clinical presentation of infection with EV71 is hand foot and mouth disease with a benign outcome. However, neurological infections can occur in the absence of cutaneous manifestations and can cause either neurological sequelae or death, as observed during recent outbreaks in the Asia-Pacific region.⁶ The majority of severe EV71 infections occur in young children, presenting with fever, vomiting and hyperglycaemia.⁵ In China, the biggest recorded outbreak in 2009 involved 1.1 million cases and 353 deaths, and in similar extensive outbreaks in 2010 and 2011, there were more than 1.5 million cases, 27,000 neurological complications and a total of 905 deaths, primarily in young children.¹⁹

LABORATORY DIAGNOSTICS SPECIFIC FOR ENTEROVIRAL INFECTIONS

To date, reverse transcriptase PCR (even available as outbreak-strain-specific reverse-transcriptase-quantitative-PCR) is a sensitive and fast technique to detect EV infections and has a greater diagnostic yield compared with cell culture testing.^{10,12} Additionally, especially during outbreaks, genotyping with phylogenetic analysis of EVs is already widely used.¹⁶ Serological testing performs poorly in acute infections and is of limited utility in chronic infections.²⁰

TREATMENT AND PREVENTION STRATEGIES

Transmission of EVs occurs mainly via the fecal-oral route and to a lesser extent

by respiratory droplets.¹ Therefore, enhanced focus on hygiene can diminish viral spread. The prevention of infection through hygiene measures and vaccines should be the main focus.

For cases of severe CNS manifestations, treatment with intravenous immunoglobulin (IVIG) is currently the only therapy in widespread clinical use.²¹ Recently, studies demonstrated both the presence and the in vitro effectiveness of virus-specific antibodies within currently available IVIG preparations.^{22,23} However, there are currently no high-quality clinical studies to prove the effectiveness of IVIG in EV CNS disease. Also, varying amounts of virus-specific neutralizing antibodies can lead to complete ineffectiveness of IVIG in some cases, which leaves the use of IVIG in enteroviral infection controversial to date.²¹ Passive immunotherapy based on monoclonal antibodies—ie, similar to the humanized monoclonal antibodies used to prevent respiratory syncytial virus infection—could be 1 option to improve therapy in the future.²¹

Currently, there are no specific treatment options available. The only 2 agents that inhibit viral attachment or cell entry tested so far in vivo are pleconaril and lactoferrin, whereas newer drugs such as pyridyl imidazolidinones, soluble anti-SCARB2/PSGL-1 antibodies, Suramins and SP40-peptides are still under investigation.²¹ Pleconaril is well absorbed after oral administration and has shown the ability to prevent virus attachment to cells.²¹ In neonates with suspected enteroviral sepsis, enhanced viral clearance and increased survival among pleconaril recipients was recently demonstrated.²⁴ Unfortunately, because of cytochrome P-450 induction and side effects such as nausea and diarrhea, pleconaril has not been licensed by the US Food and Drug Administration. Lactoferrin has also not been licensed as the mechanisms of its antiviral effects are as yet unknown and it has only been tested in mouse models.²¹ Among the drugs that inhibit viral replication and cell signaling such as Rupintrivir, Dtrip-22, Aurintricarboxylic acid, NITD008 and Sorafenib, there has been no candidate identified so far that is both efficient in viral clearing and has a favorable side-effect profile.²¹

Within the Asian-pacific region, formalin-inactivated whole cell vaccines against EV71 have been developed and tested in phase III trials.^{6,18} Levels of neutralizing antibodies after 2 consecutive vaccinations were sufficient to likely convey protection up to 60 months. No safety concerns were identified, and the efficacy was greater than 90% against hand foot and mouth disease caused by EV71 and greater than 80% against severe disease manifestations of EV71.^{6,18} Co-administration studies with a pentavalent vaccine did not detect any negative effects on respective antibody titers.¹⁸ The disadvantage

of these vaccines is that co-circulation of divergent isolates as well as genotype switching of EV71 and circulation of CVA16 may lead to ineffectiveness of the vaccines as no cross-protection is generated.¹⁸ Still, especially in China, the established vaccination is recommended as a 2-dose regimen for children at 6–7 months of age, with a third dose at 18–24 months. Potentially more clinically effective and also more cost-effective vaccination strategies, including subunit vaccines, synthetic peptides and virus-like particles, are currently under investigation.^{18,21}

CONCLUSION

CNS infections with NPEV are reported increasingly, both because of higher detection rates and potentially rising numbers of outbreaks. Young children are at particular risk of severe infections. Typical CNS manifestations in decreasing frequency are meningitis, encephalitis, AFP and rarely encephalomyelitis. The public health burden of EV71 in the Asia-Pacific region is a major challenge with EV71 replacing poliovirus as the predominant neurotropic virus globally. Molecular tools now offer rapid and sensitive detection of NPEV infections in individual patients and facilitate the tracking of outbreaks. Treatment is limited to symptomatic management and enhanced hygiene measures, as there are no effective, currently licensed antiviral drugs against NPEV. Concerted efforts on a global basis should be made on surveillance to detect outbreaks with newly emerging strains (ie, genotypes and subgenotypes) early. Additionally, further research on the pathogenesis of enteroviral CNS infections, as well as the development of more effective vaccination strategies and antiviral drugs with activity against NPEV are needed.

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