Clinical features, diagnosis, and management of enterovirus 71

Mong How Ooi, See Chang Wong, Penny Lewthwaite, Mary Jane Cardosa, Tom Solomon

Although poliomyelitis has been mostly eradicated worldwide, large outbreaks of the related enterovirus 71 have been seen in Asia-Pacific countries in the past 10 years. This virus mostly affects children, manifesting as hand, foot, and mouth disease, aseptic meningitis, poliomyelitis-like acute flaccid paralysis, brainstem encephalitis, and other severe systemic disorders, including especially pulmonary oedema and cardiorespiratory collapse. Clinical predictors of severe disease include high temperature and lethargy, and lumbar puncture might reveal pleocytosis. Many diagnostic tests are available, but PCR of throat swabs and vesicle fluid, if available, is among the most efficient. Features of inflammation, particularly in the anterior horns of the spinal cord, the dorsal pons, and the medulla can be clearly seen on MRI. No established antiviral treatment is available. Intravenous immunoglobulin seems to be beneficial in severe disease, perhaps through non-specific anti-inflammatory mechanisms, but has not been tested in any formal trials. Milrinone might be helpful in patients with cardiac dysfunction.

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Brain Infections Group, Institute of Infection and Global Health (M H Ooi MRCP, P Lewthwaite MRCP, Prof T Solomon FRCP) **and Department of Neuroscience,** (M H Ooi, Prof T Solomon), **University of Liverpool, Liverpool, UK; The Walton Centre NHS Foundation Trust, Liverpool, UK** (Prof T Solomon)**; Institute of Health and Community Medicine, University Malaysia Sarawak, Sarawak, Malaysia** (Prof M J Cardosa DPhil)**; and Department of Paediatrics, Sibu Hospital, Sibu, Sarawak, Malaysia** (M H Ooi, C Wong MRCP)

Correspondence to:
Prof Tom Solomon, Brain Infections Group, Institute of Infection and Global Health, University of Liverpool, Duncan Building, Daulby Street, Liverpool L69 3GA, UK
tsolomon@liverpool.ac.uk

Introduction

A global campaign has all but eradicated poliomyelitis from Europe, the Americas, and much of Africa and Asia. Over the past 10 years, however, the related enterovirus 71 (EV71) has emerged across Asia, where it threatens to become what has been coined the new polio.[1] The virus is a member of the enterovirus genus, which includes coxsackieviruses and echoviruses. EV71 first appeared in California, USA, in the 1960s, and caused sporadic cases or small outbreaks of hand, foot, and mouth disease (HFMD), neurological disease, or both (table 1). In 1997, the virus caused an unexpectedly large and severe outbreak in Sarawak, Malaysia, with high mortality. Regular epidemics have since been seen in countries across the Asia-Pacific region, including an epidemic in Taiwan in 1998 that was thought to involve millions of people, and an outbreak of HFMD in China, during which nearly 500 000 cases were reported.[13,14,17,18,22,25–30]

During outbreaks, thousands of children can develop HFMD, and although most will have self-limiting illness, a small proportion can rapidly develop neurological and systemic complications that can be fatal. EV71 is, therefore, of major interest to neurologists, paediatricians, and specialists in infectious diseases, virology, and public health. In this Review we discuss clinical management, diagnosis, and treatment of EV71 disease. In a companion article in *The Lancet Infectious Diseases*,[31] we examine the virology, clinical and molecular epidemiology, pathogenesis, and public health implications of this important emerging virus.

Clinical features

EV71 infection has a wide variety of clinical manifestations, although CNS infection and HFMD are the two features most frequently seen.[14]

Mucocutaneous and respiratory manifestations

HFMD is a common childhood exanthema that is characterised by a brief, generally mild, febrile illness with papulovesicular rash on the palms and soles, and multiple oral ulcers (figure 1). Herpangina, a closely related childhood enanthema, is characterised by febrile illness and the presence of multiple oral ulcers that predominantly affect the posterior of the oral cavity, including the anterior pharyngeal folds, uvula, tonsils, and soft palate. A classic course of HFMD generally occurs in older children with EV71, but in those aged 2 years and younger more-widespread and atypical rashes are frequently seen. Other features include upper respiratory tract infection, gastroenteritis, and non-specific viral rashes,[32] and, especially in young children, exacerbation of bronchial asthma, bronchiolitis, and pneumonia.[33] More than 20% of adult contacts in one Taiwanese outbreak had symptoms of an upper respiratory tract infection, but more than 50% of infected adults remained symptom free.[32]

Neurological and systemic manifestations

As for other enteroviruses, EV71 can cause aseptic meningitis, acute flaccid paralysis, encephalitis, and other rarer manifestations (table 2).[34] EV71 encephalitis is typically a brainstem encephalitis and, unlike most other enteroviruses, is frequently accompanied by severe cardiorespiratory symptoms, similar to those associated with poliomyelitis. These symptoms have been attributed to neurogenic pulmonary oedema, although the cause remains controversial.[31]

In a large prospective clinical study of several epidemics occurring over 7 years in Sarawak, 10–30% of children admitted to hospital with EV71-related HFMD also developed CNS complications.[17,23] Brainstem encephalitis was the most frequent presentation, accounting for 58% of neurological manifestations, followed by aseptic meningitis (36%), and brainstem encephalitis with cardiorespiratory dysfunction (4%). Most children with CNS involvement also had features of HFMD, but a small proportion presented only with neurological features.[17]

Myoclonic jerks are seen more often in EV71 than in other enteroviruses, and could be an early indicator of neurological involvement, particularly in the brainstem.[35] This symptom has, however, also been reported in other

	Number of EV71 cases reported	Number of fatal cases reported	Main clinical presentations
California, USA,1969–72[2]	20	1	Encephalitis, meningitis, coxsackievirus-like illness
New York, USA, 1972[3]	11	0	Aseptic meningitis, encephalitis, HFMD (only one case)
Sweden, 1973[4]	195	0	Aseptic meningitis, HFMD (some cases)
Bulgaria, 1975[5]	705	44	Aseptic meningitis, paralytic disease, including bulbar encephalitis
Japan, 1973, 1977, 1978[6]	1031	Some deaths, exact number unknown	HFMD (in most patients), cerebellar encephalitis, meningitis, acute flaccid paralysis
New York, USA, 1977[7]	12	0	CNS disease, HFMD, acute respiratory illness, acute gastroenteritis
Hungary, 1978[8]	323 laboratory confirmed	47 (unclear whether all due to EV71)	Meningitis, encephalitis, poliomyelitis, HFMD (only four cases)
Australia, 1986[9]	114	0	HFMD (in most cases), meningitis, encephalitis, encephalomyelopathy
Philadelphia, 1987[10]	5	0	Acute flaccid paralysis
USA, 1977–91[11]	193 laboratory confirmed	Unknown	1985–89: paralysis, meningitis, encephalitis, rash, Guillain-Barré syndrome
Sarawak, Malaysia, 1997[12]	2628	34	HFMD, aseptic meningitis, acute flaccid paralysis, cardiorespiratory dysfunction
Otsu, Japan, 1997[13]	12	0	HFMD, herpangina, meningoencephalitis, encephalitis, meningitis
Taiwan, 1998[14]	129 106	78	Encephalitis, aseptic meningitis, pulmonary oedema or haemorrhage, acute flaccid paralysis, myocarditis
Kenya, 1999[15]	8	0	Dermatitis, mucositis, myositis
Hyogo, Japan, 2000[16]	60	1	HFMD, aseptic meningitis, cerebellar ataxia, acute flaccid paralysis, brainstem encephalitis
Sarawak, Malaysia, 2000[17]	169 laboratory confirmed	2	HFMD, aseptic meningitis, acute flaccid paralysis, brainstem encephalitis
Singapore, 2000[18]	3790	5	HFMD, neurological disease
Korea, 2000[19]	Unknown	0	Aseptic meningitis, HFMD, herpangina, acute flaccid paralysis
Sarawak, Malaysia, 2003[17]	107 laboratory confirmed	1	HFMD, aseptic meningitis, acute flaccid paralysis, brainstem encephalitis
Fukushima, Japan, 1983–2003[20]	Unknown	Unknown	Unknown
Denver, USA, 2003[21]	8	1	Meningitis, acute flaccid paralysis, fever, cardiopulmonary dysfunction
Southern Vietnam, 2005[22]	173 laboratory confirmed	3	HFMD, aseptic meningitis, acute flaccid paralysis, brainstem encephalitis
Sarawak, Malaysia, 2006[23]	291 laboratory confirmed	6	HFMD, aseptic meningitis, brainstem encephalitis
Denver, USA, 2005[21]	8	0	Meningitis, acute flaccid paralysis, fever, encephalitis
Brunei, 2006[24]	1681	3	HFMD, neurological disease
Shandong, China, 2007[25]	1149	3	HFMD, brainstem encephalitis, aseptic meningitis
Anhui, China, 2008[26]	488 955	128	HFMD, neurogenic pulmonary oedema

HFMD=hand, foot, and mouth disease.

Table 1: **Enterovirus 71 outbreaks worldwide, by country and year**

viral CNS infections, including Japanese encephalitis, Nipah virus, subacute sclerosing panencephalitis, herpes simplex virus, HIV, and varicella-zoster virus. In addition, myoclonic jerks seen in many otherwise healthy young children, particularly when they are asleep, can occur spontaneously or be provoked by loud noises.

Seizures, if they occur at all in EV71 infection, are seen generally in children aged younger than 2 years and are short lived with good recovery of consciousness. Thus, they are likely to be febrile seizures rather than being caused by CNS involvement. Unlike other viral encephalitides, recurrent and sustained seizures are very rare, which probably reflects the fact that EV71 is associated with a brainstem rather than a cortical encephalitis.

Brainstem encephalitis with associated pulmonary oedema has been the hallmark of EV71 CNS infection in Asia since the late 1990s.[12,18,27,36] This distinctive clinical syndrome is characterised by prodromal HFMD followed by a sudden deterioration that typically occurs after 3–5 days of fever. Children then develop acute and rapidly progressing cardiorespiratory failure, which presents as shock and pulmonary oedema or haemorrhages. Without intensive care most children affected in this way will die before reaching hospital or within 24 h of admission.[12,18,27,36]

In the few studies where it has been possible to assess children with brainstem encephalitis, MRI and post-mortem findings have correlated well, with both showing frequent involvement of the medulla oblongata, reticular formation, pons, and midbrain (figure 2).[37–39] Acute flaccid paralysis is the primary presenting feature in several neurological syndromes caused by EV71, including poliomyelitis-like anterior horn cell destruction (anterior myelitis), Guillain-Barré syndrome, and transverse myelitis. Anterior horn cell destruction is probably the most frequently seen of these syndromes, although it is generally less severe than that caused by polioviruses and has a higher recovery rate.[34]

During the 1998 Taiwan epidemic the severity of brainstem encephalitis was categorised into three grades: grade I, myoclonic jerks, tremor or ataxia, or both; grade II, cranial nerve palsies evident from eye-

movement disorders (nystagmus, strabismus, or gaze paresis), facial weakness, and bulbar palsy (dysphagia, dysarthria and dysphonia); and grade III, acute onset of intractable, frequently fatal, cardiorespiratory failure.[36] A separate clinical staging system (stages 1–4) has been used to help monitor the clinical course of EV71 infection from febrile illness, to CNS involvement, to cardiorespiratory failure, and development of sequelae, and to aid management.[40,41] These systems are not, however, widely used, possibly because they are not always easy to remember and imply sequential progression, which does not always occur. The WHO Informal Consultation on Hand, Foot, and Mouth Disease, in Kuala Lumpur, Malaysia, in March, 2010, has proposed a simple clinical description of disease manifestation to describe the natural history of the disease, which will be published next year.

Diagnosis

During outbreaks of EV71, thousands of children develop symptoms (table 1). Most of them will have mild, self-limiting illness, but a small proportion of infected children rapidly develop severe and sometimes fatal neurological and systemic complications over days or even hours. In the past, many children with mild HFMD were originally cared for at home, but an increase in public awareness about the swift development of potentially fatal complications has led to many now being taken to hospital, and health services can easily become overwhelmed. A challenge for front-line clinicians is to recognise which patients are likely to deteriorate and to know which investigations give the best diagnostic yield.

Differential diagnosis

Childhood exanthema from a wide variety of causes can be confused with HFMD, particularly those seen with measles, rubella, and chicken pox (panel).[42] Two particularly important causes to consider are meningococcus, because of the need for antimicrobial treatments, and dengue, because of the risk of developing dengue haemorrhagic fever, as severe forms require careful fluid resuscitation. Herpangina can be confused with aphthous ulcer and herpetic gingivostomatitis.

Of the many enteroviruses that can cause HFMD or herpangina, EV71 and coxsackievirus type A 16 are the most frequent, and both can cause epidemic disease. Coxsackievirus type A 16 is not generally associated with neurological disease,[43] but the rash it causes is indistinguishable from that caused by EV71. However, other features can distinguish the two causes of HFMD. For example, studies from Sarawak and Taiwan show that children with EV71 are more likely to have a fever for longer than 3 days, with a peak temperature higher than 38·5°C, lethargy, and myoclonus.[23,44]

Aseptic meningitis, which is a frequent neurological manifestation of EV71, must be distinguished from a broad range of other viruses, especially echoviruses and other enteroviruses, adenoviruses, mumps, and occasionally Japanese encephalitis virus; partly treated bacterial meningitis and tuberculous meningitis should also be considered. Most patients with severe CNS disease due to EV71 also have features of shock and collapse. Septicaemia is, therefore, an important differential diagnosis. Other causes of encephalopathy might need to be excluded, particularly malaria. When acute flaccid paralysis is the predominant feature, the differential diagnosis includes poliomyelitis caused by wild-type polioviruses or vaccination, other enteroviruses, flaviviruses, rabies, Guillain-Barré syndrome, and bacterial toxins, such as diphtheria.

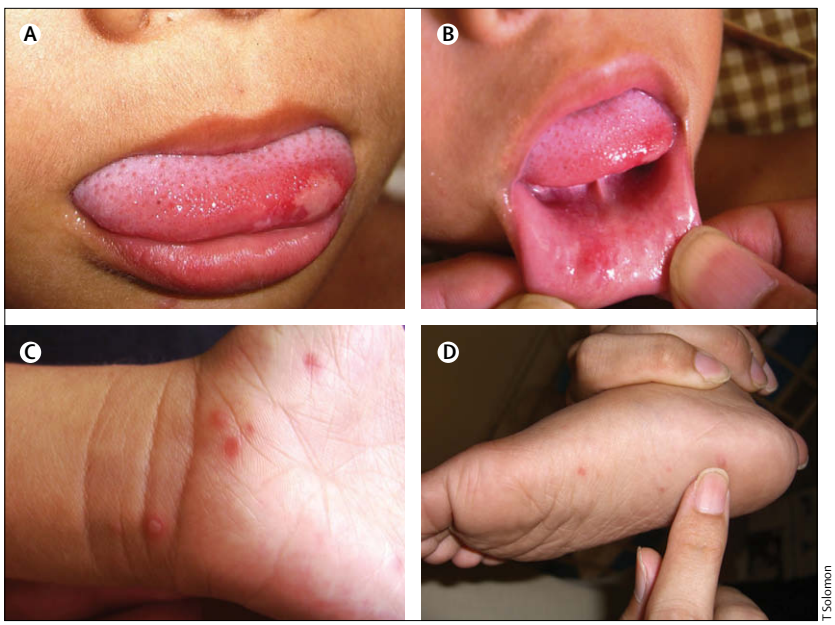

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Figure 1: **Mucocutaneous lesions in hand, foot, and mouth disease**
Ulcers on (A) the tongue and (B) inside the lip, and vesicular and macular lesions on (C) the wrists and (D) the soles of children with enterovirus 71.

	Frequency
Purely neurological manifestations	
Encephalitis, especially brainstem	Frequent
Acute flaccid paralysis (anterior myelitis)	Frequent
Encephalomyelitis	Frequent
Aseptic meningitis	Very frequent
Cerebellar ataxia	Infrequent
Transverse myelitis	Rare
Neurological and systemic manifestations	
Brainstem encephalitis with cardiorespiratory failure	Frequent
Manifestations indicative of immune-mediated mechanisms	
Guillain-Barré syndrome	Infrequent
Opsoclonus-myoclonus syndrome	Rare
Benign intracranial hypertension	Rare

Modified from McMinn,[34] with permission of John Wiley and Sons.

Table 2: **Neurological syndromes associated with enterovirus 71 infection**

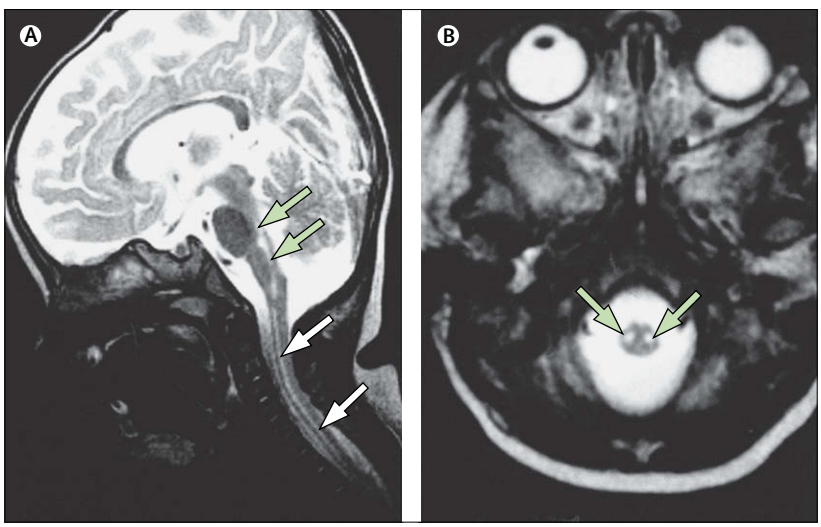

Figure 2: **MRI changes in enterovirus-71-associated encephalomyelitis**
T2-weighted images of a child aged 10 months who had presented 3 months earlier with somnolence, tachycardia, tachypnoea, and coma, and who recovered consciousness but remained dependent on a ventilator. High signal intensity can be seen in (A) the posterior portion of the pons and medulla (green arrows) and anterior cervical cord (white arrows) on a sagittal section, and (B) in the two anterior horns of the cervical cords (green arrows) on an axial section. Modified from Shen and colleagues,[39] with permission of the American Society of Neuroradiology.

Virological diagnosis

Laboratory diagnosis of EV71 is established primarily through virus isolation or molecular detection of the virus nucleic acid in appropriate clinical specimens. This approach is important to distinguish EV71 from other enteroviruses, such as coxsackievirus type A 16.

Choice of sample

Samples for laboratory investigation should be selected according to the disease manifestations. Possibilities include throat, rectal, and ulcer swabs, and samples of serum, urine, CSF, and fluid from vesicles. The sensitivity, specificity, and usefulness of findings vary according to the sample.[45] In particular, virus detection in samples from sterile sites, such as vesicular fluid, CSF, serum, urine, or those gathered at autopsy, is more reliable than that in samples from non-sterile sites, such as the throat or rectum, where the presence of the virus might merely indicate coincidental carriage.

Viral shedding from the gastrointestinal tract (via the throat or rectum or in stools) might continue after complete resolution of the symptoms of EV71 infection, as it does for other enteroviruses. A study in Taiwan showed that EV71 can be detected in the throat up to 2 weeks after recovery from HFMD or herpangina, and in stools it can be detected up to 11 weeks after recovery.[46] In addition, when an enterovirus is detected in non-sterile sites, it differs from that isolated in samples from sterile sites in 10% of throat swabs and 20% of rectal swabs.[45] In many of the sterile sites, however, the viral load is frequently very low, as for poliomyelitis; for example, virus is detected in 0–5% of CSF samples from patients with neurological disease.[6,8,17,23,47–51] The yield for serum is similarly low.[17] Vesicular fluid, when present, is more useful, although care must be taken during collection (figure 3). Given the potential number of samples, laboratories can become overwhelmed. One study showed the most efficient approach was to examine throat swabs for all patients, plus swabs from at least two vesicles or from the rectum for patients with no vesicles.[45]

Virus isolation, serotyping, and nucleic acid detection

The gold standard for diagnosis of enterovirus infection is virus isolation. Several human and non-human primate cell lines can be used, including rhabdomyosarcoma, which is most efficient, human lung fibroblast cells, and African green monkey kidney cells.[43] In rhabdomyosarcoma cells, a characteristic cytopathic effect is observed typically 7–10 days after inoculation. To improve the yield, blind passage might be necessary before cytopathic effects become apparent. Once a cytopathic effect is observed, the virus is identified by neutralisation tests in intersecting pools of type-specific antisera, EV71-specific antisera, or by an indirect immunofluorescence assay with EV71-specific monoclonal antibodies.[43] A molecular serotyping approach has been developed by amplification of part of the *VP1* gene of the cultured virus, use of PCR and pan-enterovirus EV71-specific primers, and sequencing of the product.[9] Several sets of primers directed at different regions of the *VP1* gene of EV71 have been developed.[5,9,52]

EV71-specific primers are used to perform PCR directly on clinical samples. The advantage of this approach is that it is quicker than virus culture. Speed can be especially important given the explosive nature of some EV71 outbreaks and the need for urgent public health interventions. The disadvantage is that only the virus looked for can be detected and, therefore, other unexpected causes will not be identified.[52–55] DNA microarray is a powerful, although expensive, tool designed to detect multiple pathogen targets by hybridisation of pathogen-specific probes. Two groups have reported its use to distinguish EV71 and coxsackievirus type A 16 infection in primary clinical specimens, with diagnostic accuracy of about 90%.[53,56]

Serology

Serological diagnosis of an acute virus infection classically relies on a fourfold increase being shown in the concentrations of a specific neutralising antibody between the acute and convalescent phases.[43] In the case of EV71, however, very high concentrations of neutralising antibodies are frequently detectable within the first few days of illness, and thus such a difference will not be seen.[49,51] Furthermore, although homologous antibodies are produced when young children encounter their first enterovirus infection, heterologous cross-reacting IgG and IgM antibodies are produced by older children and adults following repeated infection with different enterovirus serotypes. The usefulness of this test, therefore, decreases with increasing age.

A rapid IgM ELISA test for EV71 has been developed to try to overcome some of the current limitations of serological testing.[57] The possibility of cross reactivity still remains an issue,[58] and the duration of detectable EV71-specific IgM after an infection is also uncertain.

Other laboratory investigations

In mild EV71 disease, the full blood count and urea and electrolyte concentrations are generally normal, but in severe disease a raised white cell count with neutrophilia is frequently seen and hyperglycaemia might be present.[47] Creatine kinase concentration is sometimes raised in patients with cardiac involvement,[59] and an increased cardiac troponin I level has been reported as a predictor of imminent cardiopulmonary failure in children with brainstem encephalitis.[60] Pulmonary oedema, if present, will generally be obvious on chest radiographs; normal heart size indicates that the cause is not acute viral myocarditis or congenital heart disease. Electrocardiography frequently shows non-specific changes,[59] and continuous monitoring can demonstrate abnormal beat-to-beat variability, which can be predictive of imminent cardiovascular collapse.[61] In children who are haemodynamically unstable and have tachycardia, hypotension, or pulmonary oedema, echocardiograms show generalised left ventricular hypokinesia, which might be accompanied by mitral regurgitation;[57] pericardial effusion is seldom seen.

The lumbar puncture is essential in children who are unwell and who have suspected CNS involvement. In some patients the clinical features, such as meningism or myoclonic jerks, clearly point to the CNS. In other children, however, especially those younger than 2 years, there may just be high fever, vomiting, or lethargy, but a lumbar puncture shows CNS disease. Mild lymphocytic pleocytosis of 10–100 cells per μL is typical, but occasionally there might be none.[21] The ratio of glucose concentration in CSF to that in plasma is generally normal, but can be low.

Imaging

Although CT scanning can be helpful to exclude certain pathologies, it does not clearly identify EV71 encephalitis, where the pathology is mostly in the brainstem, as scans are almost always normal. Conversely, MRI shows characteristic high signal intensities on T2-weighted images in the dorsal pons and medulla, most of the midbrain, and the dentate nuclei of the cerebellum. Similar high-signal lesions can also be found in the anterior horn cells of cervical spinal cord (figure 2).[36,39] The usefulness of these changes in terms of sensitivity, specificity, and positive and negative predictive value, however, has yet to be demonstrated. In children with acute flaccid paralysis, MRI typically shows unilateral high-signal lesions in the anterior horn cells of the spinal cord on T2-weighted images, and contrast-enhancing ventral root on T1-weighted images.[36,62,63]

Panel: **Characteristics to consider in differential diagnosis of enterovirus 71 infection**

Rash

- Viral infections: coxsackievirus type A 16, and other enteroviruses,* measles,* rubella,* varicella-zoster virus,* human herpes viruses 6 and 7, parvovirus B19, dengue, flavivirus infections (especially haemorrhagic fever), alphavirus infections, Epstein-Barr virus, primary HIV infection, and non-specific viral rashes
- Bacterial infections: meningococcaemia (*Neisseria meningitides*), scarlet fever (*Streptococcus pyogenes*), leptospirosis, relapsing fever (*Borrelia recurrentis*), Lyme disease (*Borrelia burgdorferi*), syphilis (*Treponema pallidum*), and typhus and other rickettsial infections
- Other disorders: scabies (*Sarcoptes scabei*),* drug reactions, allergies, and paraneoplastic syndrome

Aseptic meningitis

- Viral infections: echoviruses,* coxsackieviruses and other enteroviruses, herpes simplex virus type 2, HIV, mumps, flaviviruses, alphaviruses, and bunyaviruses, lymphocytic choriomeningitis
- Bacterial infections: partly treated bacterial meningitis, tuberculous meningitis, parameningeal bacterial infections, listeria (*Listeria monocytogenes*), syphilis, Lyme disease (*Borrelia burgdorferi*), Weil's disease (*Leptospira* spp), *Mycoplasma pneumoniae*
- Other disorders: drug reactions, fungal infections (eg, *Cryptococcus* spp, *Candida* spp, *Aspergillus* spp)

Flaccid paralysis

- Viral infections: poliomyelitis and other enteroviruses,* vaccine-associated paralytic poliomyelitis, flaviviruses (Japanese encephalitis virus, West Nile virus, tick-borne encephalitis virus), rabies, adenoviruses
- Bacterial infections: botulism, diphtheria
- Other disorders: intramuscular injection into buttock causing sciatic nerve damage, Guillain-Barré syndrome (especially acute motor axonal neuropathy)

Brainstem encephalitis

- Viral infections: poliomyelitis and other enteroviruses,* flaviviruses,* Nipah virus
- Bacterial infections: listeria (*Listeria monocytogenes*), tuberculosis (*Mycobacterium tuberculosis*), brucellosis (*Brucella abortens*), Lyme disease (*Borrelia burgdorferi*)
- Other disorders: paraneoplastic syndromes

The importance of the infections listed varies greatly according to the age and geographic location of the patient. *Especially likely to be confused with symptoms of entervirus 71. Modified from Solomon,[42] with permission of Oxford University Press.

Predictors of severe disease

Several clinical features and laboratory abnormalities have been associated with neurological and fatal EV71 disease, but few have been prospectively validated.[47,60,64] Young age at disease onset is associated with increased risk of severe disease.[65] The results of a prospective clinical study of nearly 1500 children presenting to one hospital during three EV71 outbreaks in Sarawak over 7 years showed that neurological involvement was strongly predicted by the presence of at least two of the following: peak temperature of 38·5°C or more, fever for 3 days or longer, and a history of lethargy.[23] This study confirmed the findings from early retrospective studies. However, other early findings, such as an association between the absence of mouth ulcers and development of complicated or fatal disease,[17,66] were not confirmed. In a retrospective study, hyperglycaemia and leucocytosis

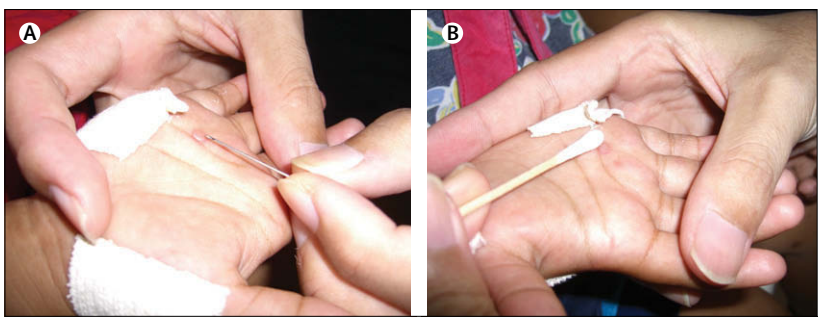

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Figure 3: **Collection of vesicular fluid from palmar lesions for virological diagnosis of hand, foot, and mouth disease**
(A) The hand should be gripped firmly to prevent movement, the skin stretched tight, and a small needle used to puncture the vesicle. (B) A clean swab is applied to collect the fluid released. The swab is placed into viral transport medium.

had been associated with fatal EV71 disease[47] and were confirmed prospectively,[23] but these are late symptoms that generally occur with fulminant disease and are not helpful clinical predictors of complications and death.[15]

Not all children with CNS involvement in EV71 infection will progress to cardiorespiratory collapse. The results of a small study involving 46 patients showed that children developed abnormal heart rate variability (an index of autonomic nervous system disease) about 7 h before the clinical onset of cardiorespiratory instability.[61] The researchers proposed that screening of children with CNS involvement for this feature should be done to predict impending cardiorespiratory failure and allow timely initiation of appropriate interventions. Cardiac troponin I is a cardiac-specific biomarker for myocardial injury and is measured in patients with suspected acute coronary syndrome in adults. Raised concentrations of this protein have been observed in children with EV71 infection, brainstem encephalitis, cardiac dysfunction, and pulmonary oedema,[60] in some cases before the development of cardiopulmonary failure.[60] Serial measurement of cardiac troponin I concentrations might, therefore, be helpful in identifying children at risk of left-ventricular failure. Measurement of heart rate variability and cardiac troponin I concentrations have not, however, become routine clinical practice in the management of EV71, probably because of the poor availability of technologically advanced equipment needed and the high cost, respectively. Even in wealthier Asian countries, such as Taiwan, these measures have not entered routine clinical practice. Overall, simple clinical parameters, such as length of illness, height of fever, and lethargy, are probably more useful indicators of potentially severe disease.

Treatment

No established antiviral treatments are available for EV71, and there are no specific clinical data on antiviral or ancillary treatments. Thus, recognition of which treatments might be appropriate remains a challenge for front-line clinicians.

Antiviral agents

Pleconaril is an antiviral drug that inhibits the entry of several enteroviruses into cells by blocking viral attachment and uncoating, and has been used in clinical trials of aseptic meningitis.[67–69] This drug it is not, however, active against EV71.[70] Several other capsid-function inhibitors have been investigated, and some have shown promising activities against EV71 in preclinical studies.[70] In-vitro and in-vivo studies show that both ribavirin and interferons might be useful,[71,72] and RNA interference approaches are being explored.[73–75]

Intravenous Immunoglobulin

During the initial large outbreaks of EV71 in Asia, clinicians in Sarawak and Taiwan used intravenous immunoglobulin on the presumptive basis that it would neutralise the virus and have non-specific anti-inflammatory properties.[17,44] Retrospective comparisons of patients who did and did not receive immunoglobulin suggest a benefit from this treatment if given early.[23,76] For example, among children with EV71 assessed in Sarawak over three seasons, 204 (95%) of 215 survivors who had severe CNS complications had received intravenous immunoglobulin treatment, typically once there was evidence of severe disease, such as tachycardia or poor perfusion or altered consciousness, compared with only one (11%) of nine fatal cases (odds ratio 148·36, 95% CI 16·34–6609·04, p<0·0001).[23] Analysis of cytokine profiles before and after immunoglobulin treatment showed substantial reductions in concentrations of some proinflammatory cytokines in patients with EV71 if they had encephalitis with autonomic dysfunction, but not if they had less severe disease.[76–80] Intravenous immunoglobulin has, therefore, become more routinely used for the treatment of severe EV71 disease, and in Taiwan has been introduced into the national treatment guidelines.[17,23,40,41,81] Uncertainty remains, however, over whether this expensive human blood product treatment is really effective, and randomised, placebo-controlled, phase 2 trials are needed. Such trials would be logistically and ethically challenging to establish because the treatment is so widely used, and would require careful design with surrogate endpoints of disease progression, such as failure of resolution of tachycardia.

Milrinone

Milrinone is a cyclic nucleotide phosphodiesterase inhibitor currently used in the treatment of congestive heart failure. Inhibition of phosphodiesterase subtype III by this cardiotrophic agent results in an increase in intracellular concentrations of cyclic AMP, which in turn leads to increased cardiac output and decreased peripheral vascular resistance. The results of a small, non-randomised, retrospective assessment of 24 children with EV71-induced pulmonary oedema showed that those treated with milrinone had reduced tachycardia and lower mortality than those who did not receive this

drug.[81,82] Peripheral white cell and platelet counts and plasma interleukin 13 concentrations were also lower,[82] which might indicate an immunomodulatory effect of the drug. A clinical study examining efficacy of milrinone is said to be ongoing.[83]

Fluid balance and inotrope support

In routine paediatric practice, the most common cause of shock and peripheral shut down is hypovolaemia and dehydration, for example after gastrointestinal infection. These disorders are treated with rapid fluid resuscitation. When similar approaches were used in the early EV71 outbreaks in Asia, however, they frequently precipitated pulmonary oedema. After it became clear that impaired cardiac function is an important contributor to shock, clinicians were more judicious in their use of intravenous fluids and used inotrope support. Fluid management should, whenever possible, be guided by measurement of central venous pressure. In Taiwan, management algorithms based on this approach seem to have improved outcome.[76]

Outcomes

Studies up to 7 years after infection show that children who present with aseptic meningitis generally have good outcomes, although parent and teacher reports indicate that the incidence of symptoms similar to those in attention deficit-hyperactivity disorder is 20% among children who have recovered from EV71 CNS infection, compared with 3% for matched controls.[84] Approximately a fifth of children with severe neurological disease, including encephalitis, poliomyelitis-like paralysis, and encephalomyelitis, have sequelae, particularly focal limb weakness and atrophy.[65,85,86] Cerebellar disorders are observed in about 10% of patients after moderately severe brainstem encephalitis, including cranial neuropathies, myoclonus, tremor, and ataxia. Of those, however, only a quarter with severe brainstem encephalitis associated with fulminant cardiorespiratory failure make a full neurological recovery.[65,86] Common sequelae include focal limb weakness and atrophy, swallowing difficulties requiring nasogastric feeding, central hypoventilation, facial nerve palsies, seizures, and psychomotor retardation.

Conclusions

Over the past 12 years, EV71 has evolved from being a rare and sporadic cause of HFMD to a cause of major and regular epidemics across the Asia-Pacific region and a disease frequently associated with severe and sometimes fatal neurological complications. Across Asia a range of diagnostic techniques is used. Standardisation via some form of laboratory network with proficiency panels to allow comparison of laboratory findings and ensure quality control might prove useful. Reliable ways of predicting who will develop HFMD and who will have neurological complications and which patients with CNS involvement are at risk of disease progression are still lacking. Intravenous immunoglobulin is now used presumptively for severe EV71 infection in many Asian countries, even though there are almost no data on its efficacy and this treatment is expensive. Evidence-based clinical practice guidelines for diagnosis and treatment would considerably help the management of this emerging neurological infectious disease.

Contributors

The Review was conceived by MHO and TS; all authors were involved in the design and drafting of the Review, and in revising it critically for important intellectual content.

Conflicts of interest

MJC joined Sentinext Therapeutics, a Malaysian biotechnology start-up company involved in the development of a vaccine against EV71, as Chief Scientific Officer in September, 2010, but was not employed by the company during the design or preparation of this Review. MHO, MJC, and TS have acted as informal advisers to WHO on hand, foot, and mouth disease and enterovirus 71 infection. SCW and PL declare that they have no conflicts of interest.

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