ORIGINAL ARTICLE

Deaths in Children During an Outbreak of Hand, Foot and Mouth Disease in Peninsular Malaysia – Clinical and Pathological Characteristics

K Shekhar****, M S Lye**, O Norlijah**, Flora Ong*****, L M Looi******, R Khuzaiah**** and I Marzuki***** for the Outbreak Study Group*, *Members of the outbreak study group: I Hussein*, S L Wong********, Jai Mohan*******, M Sinniah*****, S Abu Bakar******

*Pediatrics Institute, Kuala Lumpur Hospital, Kuala Lumpur, **Institute for Medical Research, Kuala Lumpur, ***Faculty of Medicine and Health Sciences, University Putra Malaysia. ****Faculty of Medicine, International Medical University, *****Ministry of Health Malaysia, ******State Health Department, Kuching, Sarawak, *******University of Malaya, Kuala Lumpur, ********Ipoh Hospital, Perak, Malaysia, *********Hospital Seremban, Negeri Sembilan

Summary

From July through December 1997, 11 previously healthy children in Peninsular Malaysia succumbed to an illness clinically characterised by an acute severe refractory left-ventricular failure, following a brief prodromal illness, in the midst of an outbreak of hand, foot and mouth disease (HFMD), similar to the reported experience in Sarawak and Taiwan. Retrospective reviews of the clinical features and results of laboratory, pathological and virological investigations of cases were conducted. The median age of the 11 case-patients was 31 months (range, 13 to 49 months); 6 were males. A brief prodromal illness of 3 days (range, 2 to 5 days) was characterised by fever (axillary temperature > 38°C) (100%), oral ulcers (72%), extremity rashes (45%) and significant vomiting (55%). Upon hospitalisation, 7 of 11 case-patients had features suggestive of cardiogenic shock, while 4 of 11 case-patients developed shock during hospitalisation as evidenced by marked sustained tachycardia (heart rate ≥ 180 beats per minute), poor peripheral pulses and peripheral perfusion, mottled extremities, pulmonary oedema (haemorrhagic pulmonary secretions in 8 of 11 cases during tracheal intubation, often precipitated by conservative crystalloid boluses, and radiographic evidence of acute pulmonary oedema in 5 of 7 cases) and markedly impaired left ventricular function on echocardiographic examination (7 of 7 cases). Three of 4 case-patients had aseptic meningitis while one case-patient also had an acute flaccid paraparesis. Despite supportive therapy, death occurred within a median of 13.4 hours following hospitalization. Post-mortem findings (all 8 specimens examined) consistently demonstrated brain-stem encephalitis with foci of neuronal necrosis and micro-abscesses. None of the 11 specimens examined revealed histological evidence of myocarditis. Enterovirus 71 (EV71) was detected in 10 of 11 case-patients, many (7) from various sterile tissue sites (5 from central nervous tissues). No other viruses were isolated or identified. Clinical features and pathological studies closely paralleled the reported experience in Sarawak and Taiwan. The uniform necropsy findings of necrotizing brain-stem encephalitis coupled with essentially normal myocardial histology, in concert with the concurrent and consistent detection of EV71 points to a primary EV71 encephalitis; as yet unclear neurogenic mechanisms may account for the cardiovascular manifestations.

Key Words: Hand, Foot and Mouth Disease, Pulmonary oedema, Myocarditis, Acute flaccid paralysis, Aseptic meningitis, Encephalitis, Enterovirus 71, Peninsular Malaysia

This article was accepted: 3 January 2005

Corresponding Author: Norlijah Othman, Paediatric Unit, Department of Human Growth and Development, Faculty of Medicine and Health Sciences, University Putra Malaysia, 50586 Jalan Masjid, Kuala Lumpur

Introduction

In the wake of an outbreak of hand, foot and mouth disease in Sarawak[1], Peninsular Malaysia experienced a similar outbreak in 1997 with 4,625 admissions reported between 2nd June 1997 to 3rd January 1998. The distribution of reported cases admitted to hospitals in the various states is as follows: Perak (633 cases), Kedah (599 cases), Federal Territory (567 cases), Penang (533 cases), Pahang (492 cases), Johore (481 cases), Selangor (430 cases), Kelantan (340 cases), Trengganu (236 cases), Negri Sembilan (172 cases), Malacca (121 cases), and Perlis (20 cases).

The first death during this outbreak occurred on 6 July 1997 in the state of Selangor, followed by 10 more deaths in the other states comprising Kedah (2), Penang (2), Selangor (2), Kuala Lumpur (2), Johore (1), Malacca (1), over a period of 6 months. Four of the fatal cases were below 2 years of age while 7 were between 2 to 5 years of age. These comprised of 7 Chinese, 2 Malays, 1 Indian and 1 Sikh.

The following is a description of the clinical and pathological features of those 11 fatalities encountered in Peninsular Malaysia.

Materials and Methods

Following recognition in Sarawak in mid-1997 [1,2], of a cluster of sudden deaths in children attributable to acute left-ventricular failure often concurrently presenting with hand, foot and mouth lesions, aseptic meningitis and/or acute flaccid paralysis/paresis, all health-care centres throughout Peninsular Malaysia were put on high alert to recognize and report similar presentations.

Children who had the following clinical features were included as "cases": (a) brief febrile illness rapidly deteriorating to refractory shock of an apparent cardiac origin; (b) severely depressed myocardial contractility on echocardiography; (c) poor tolerance of conservative fluid boluses; and, (d) clinical and/or radiographic evidence of pulmonary oedema, with or without evidence of hand, foot and mouth lesions, aseptic meningitis and/or acute flaccid paralysis/paresis, in the absence of other causes that may explain these manifestations (such as bacterial septicaemia, dengue fever and Japanese encephalitis).

Two reviewers independently abstracted information from medical records using a standard data-collection form. This information along with results of pathological, microbiological and laboratory studies was subsequently reviewed by an Outbreak Study Group to identify those children who definitively fulfilled the case-definition.

Autopsy examinations were performed in 8 of the deceased patients at hospitals in Peninsular Malaysia, while percutaneous tru-cut myocardial biopsies were obtained in 3. The histopathological slides made were subsequently reviewed by a senior pathologist (LLM) at the University Hospital in Kuala Lumpur. Tissue specimens, and samples of stool, cerebrospinal fluid (CSF), throat and rectal swabs, vesicle fluid from hand and foot lesions and sera were inoculated into HEp 2 and Vero cell lines. Agents inducing cytopathogenic effects in these cultures were then characterised by agent-specific antigen detection, virus neutralization or polymerase-chain reaction (PCR). Reference laboratories processing specimens for virological investigations included those at the Institute for Medical Research in Kuala Lumpur and the University of Malaya.

Results

Demographic Characteristics

Eleven patients fulfilled the case-definition. Their median age was 31 months (mean, 33 months; range 13 to 49 months). Seven (64%) of the 11 case-patients were males. Two-thirds (66%) of the children were Chinese; the rest were Malay (2), Indian (1) and Sikh (1). Three children (27%) were from the state of Selangor; 2 each were from Kuala Lumpur, Kedah and Penang and 1 each from Malacca and Johore. All these states are on the West coast of Peninsular Malaysia.

Clinical Presentation

Following a brief prodromal illness of a median duration of three days (range, 2 to 5 days), that often consisted of fever (100%), oral ulcers (72%), extremity rashes (45%) and significant vomiting with poor oral intake (55%), several of these children (7 case-patients, 63%) were hospitalized with features suggesting shock (see Table I). Four other case-patients deteriorated to refractory shock at some point during hospitalization.

Shock, noted in the 7 case-patients on admission, was characterized by marked and sustained tachycardia out of proportion to the associated fever (median axillary temperatures 38°C; range 37.3 to 38.3). Heart rates (sinus tachycardia) consistently exceeded 180/min

(median 205/min, range 180 to 220) associated with poor distal capillary refill (exceeding 2 seconds), weak peripheral pulses, and skin mottling. Conservative crystalloid fluid boluses (10 to 20 ml/kg) were poorly tolerated and resulted in increasing respiratory distress with lung crackles. Echocardiographic examinations (all 7 case-patients examined) revealed markedly depressed left-ventricular contractility, the left ventricle appearing dilated and globular. Lung crackles were noted in 4 of the 7 case-patients presenting with shock on admission, while hemorrhagic pulmonary secretions suggesting pulmonary oedema were noted in 8 of 11 (72%) case-patients during tracheal intubation. Chest radiographs suggested acute pulmonary oedema in 5 of the 7 (71%) case-patients, while 2 other chest radiographs suggested pneumonitis.

Case-patients were also noted to have oral ulcers (63%) and palmoplantar rashes (36%) on admission; extremity rashes consisted of scanty papular or papulovesicular lesions that often needed to be actively sought for. Neurological features were not prominent on admission; notably one child presented with flaccid areflexic paraparesis while vomiting was a significant prodromal symptom. No other clinical findings of note were recorded (Table II). All case-patients were previously well, with age-appropriate development, nutrition and immunization status.

Laboratory findings were notable for neutrophilic leucocytosis (4 of 6 case-patients; median 20,657/μL; range 10, 900 to 35,100 with neutrophils forming 52% to 88% of leucocytes); thrombocytosis (2 of 7 case-patients, exceeding 500,000/μL) and sterile cerebrospinal fluid (CSF) with a predominance of lymphocytic pleocytosis (3 of 4 CSFs sampled). Results of coagulation screening, electrolyte levels and renal and hepatic function indices were often normal; mildly deranged blood urea and creatinine values were seen in 3 of 11 case-patients probably indicating moderate dehydration following prodromal vomiting in these patients. Bacteriological cultures of blood (9 case-patients tested) and CSF (5 children tested) were sterile. Levels of creatine kinase and lactate dehydrogenase as surrogate markers of myocardial injury were not significantly elevated (Table III).

Clinical Course

While 7 case-patients presented with overt shock, 4 other children deteriorated to refractory shock at some point during hospitalization (mean time, 4 hours). All 4 had sustained moderate sinus tachycardia (heart rates 120 to 150/minute) and were generally noted to be lethargic, unwell and mildly to moderately dehydrated (3 of 4 case-patients); one presented with flaccid, areflexic paraparesis.

Ten children subsequently required assisted ventilation for worsening respiratory distress; one case-patient developed sudden cardiac arrest prior to initiating ventilatory support. Eight of the 10 children ventilated had frothy hemorrhagic secretions during tracheal intubation. Ventilatory support involved moderately high settings with median peak inspiratory pressure of 28 mm Hg; (range 24 to 44 mm Hg), ventilator rate of 60 breaths/minute; (range 30 to 75/min), positive end-expiratory pressure of 8 mm Hg; (range 6 to 14 mm Hg) and fraction of inspired oxygen of 0.8. (range 0.4 to 1.0). Two patients developed brief generalized tonic-clonic seizures at some point during hospitalization. Three patients had CSF findings suggestive of aseptic meninigitis.

Despite assisted ventilation and supportive therapy comprising of inotropes [intravenous infusions of dobutamine (15 to 20 mcg/kg/minute, 10 of 11 case-patients), dopamine (5 to 20 mcg/kg/minute, 7 of 11 case-patients), Epinephrine (0.5 to 2 mcg/kg/minute, 3 of 11 case-patients), amrinone (loading dose of 750 mg/kg, followed by infusion of 5 to 10 mcg/kg/minute, 2 case-patients)], fluid restriction (half to two-thirds maintenance), diuretics and empirical intravenous immunoglobulin (single infusion doses, median 1g/kg, range 0.4 to 2 g/kg, 6 of 11 case-patients), cardiac arrest occurred within a median of 13.4 hours (range 0.8 to 28 hours), usually after a period of refractory bradycardia and hypotension. Cardiac dysrhythmia (refractory supraventricular tachycardia) preceding cardiac arrest was noted in one case-patient.

Pathological findings

Complete autopsy examinations were performed in 8 case-patients while 3 others had postmortem percutaneous tru-cut myocardial biopsies. Sections of the brain-stem consistently (8 of 8 examined) showed perivascular cuffing by lymphocytes and patchy neuronal degeneration often associated with microabscess formation. Cerebral cortical oedema and congestion, and meningeal inflammation were also noted in all cases with central nervous system tissues examined. Cervical cord myelitis was noted in 4 of 6 cases examined. Histological examination of all myocardial tissues (8 autopsies and 3 tru-cut biopsies) revealed patchy non-specific myocyte degeneration

(myocytolysis) without necrosis but no evidence of myocarditis was detected. Sections of the lungs revealed congestion, diffuse alveolar damage with oedema and occasional hyaline membranes and scanty inflammatory infiltrates. The liver, adrenals and kidneys were essentially normal except for passive congestion.

Virological findings

Enterovirus 71 was isolated either by culture in Vero cell lines (after incubation for 5 days) or identified by the polymerase chain reaction (PCR) (CDC EV71 primers) in 10 of 11 case-patients; 7 of 10 isolates (culture/PCR) were from sterile tissue sites while three other isolates (culture/PCR) were from throat and rectal swabs. Five of 7 sterile-tissue site isolates were from central nervous tissues; one each was isolated from the heart and lung tissues.

No other viruses were isolated by culture or identified by PCR in various specimens submitted for virologic studies.

Table I: Symptoms of the 11 case-patients at presentation to hospital

Symptoms	No. of patients (%)
Fever	11 (100)
Oral ulcers	8 (72)
Extremity rashes	5 (45)
Vomiting	6 (55)
Cough or 'colds'	3 (27)
Limb weakness or paralysis	1 (9)
Diarrhea	1 (9)
Seizures	Nil

Table II: Findings on physical examination in the 11 case-patients at time of admission

Sign	No. with data	No. (%) of patients	Median (range)
Temperature (≥ 37°C)	6	6 (100)	38 (37.3 - 38.3)
Skin mottling	5	4 (80)	-
Weak peripheral pulses	6	4 (67)	-
Oral ulcers	11	7 (63)	-
Capillary refill > 2 seconds	10	6 (60)	-
Heart rate ≥ 180 beats per minute	10	6 (60)	170 (120 - 224)
Respiratory rate ≥ 40 /minute	4	2 (50)	50 (20 - 60)
Lung crackles/rales	9	4 (44)	-
Extremity rashes	11	4 (36)	-
Weakness of one or more limbs	11	1 (9)	-
Mean arterial pressure (mm Hg)	7	-	65 (0 - 86.5)

Table III: Results of laboratory studies of the 11 case-patients during hospitalisation

Sign	No. with data	No. (%) of patients	Median (range)
Hematological			
White cells- x 10^3/ mm^3	7	20.6	10.9 - 35.1
Polymorphonuclear cells--%	6	61	52 - 88
Hematocrit-- %	8	38	29 - 44
Platelets -- x 10^3/ mm^3	7	40.5	20.8 - 64.0
Prothrombin time – seconds	2	14.0	...
Partial thromboplastin time – sec	2	37	...
Electrolytes and serum chemistry			
Sodium – mmol/ L	9	134	128 - 140
Potassium – mmol / L	9	4.6	3.8- 6.6
Chloride – mmol / L	1	99	...
Calcium – mmol /L	2	2.7	...
Glucose – mmol /L	3	10.8	9.04 - 13.6
Blood Urea – mmol /L	9	6.25	2.7 - 11.3
Creatinine – micromol /L	3	77.3	43 - 106
Creatine kinase --- IU /L	8	226	81 - 562
Lactate dehydrogenase – IU/ L	6	541	326 - 860
Liver function			
Alanine aminotransferase – IU/L	5	22.8	8 - 41
Aspartate aminotransferase – IU/ L	8	74.8	43 - 33
Alkaline phosphatase – IU / L	2	143	...
Albumin – g /L	2	40	...
Total bilirubin – mmol/ L	2	16	...
Cerebrospinal fluid			
White cells -- / mm^3	4	42	0 - 113
Lymphocytes -- %	4	45	0 - 90
Protein – g/L	4	0.76	0.08 - 1.1
Glucose – mmol/L	4	5.8	4.7 - 7.8

Discussion

The reported fatalities in Peninsular Malaysia, of children less than 4 years of age, with a constellation of unique clinical features suggesting acute severe progressive refractory myocardial failure following a brief febrile illness, temporally associated with an increased observation of hand, foot and mouth disease, closely parallels the experience in Sarawak and Taiwan[1,2, 17-22].

The overwhelming myocardial failure masked the more subtle neurological manifestations as represented by aseptic meningitis, acute flaccid paralysis and marked emesis. Significantly, a clinicopathologic discordance of acute myocardial failure in the face of an essentially normal myocardial histology was observed. Autopsy examinations however, demonstrated a remarkably uniform pattern of necrotizing inflammation of the brain-stem. This was coupled with a significant, consistent and sole isolation/identification of EV 71 from various sterile tissue sites, especially from central nervous system tissues.

Cumulatively, the weight of evidence favours the hypothesis of an acute primary EV 71 necrotizing brain-stem encephalitis, in the background of an outbreak of HFMD, as responsible for the deaths[9,10]. The observed acute myocardial failure and fatalities were probably mediated through mechanisms akin to neurogenic

pulmonary oedema [24-34]. Though this mechanism has not been entirely elucidated, neurogenic pulmonary oedema has been implicated in deaths following bulbar poliomyelitis, wherein lesions in the dorsal vagal nuclei and vasomotor centers of the brain-stem were observed [38-41]. Pulmonary oedema in these cases was believed to probably result from massive increases in pulmonary vascular pressures following intense sympathetic stimulation or through alterations in pulmonary vascular endothelial permeability.

Disturbing questions therefore arise regarding HFMD, hitherto considered a benign seasonal childhood disease. While outbreaks of EV71 HFMD and non-lethal and fatal central nervous system infections have been reported [3-14], a fulminant fatal EV71 encephalitis of this magnitude has been observed elsewhere only in Sarawak and Taiwan [1,2, 17-23], similarly in the background of concurrent HFMD outbreaks. The genotype strain from a non-fatal case in Peninsular Malaysia was genotype C, which was the main circulating genotype in Taiwan in 1998; while the genotype strain isolated from fatal and non-fatal cases in Sarawak was genotype B [16,*]. This suggests the possibility that many strains of EV71 can cause severe disease.

Of more immediate clinical and practical value however, would be to examine our ability to reliably identify children who may potentially deteriorate to shock, from among those children with typical hand, foot and mouth lesions in future HFMD outbreaks. One consistent observation of potential benefit is the nature of the palmo-plantar lesions in our case-children. In contrast to the florid vesiculopustular lesions of typical non-fatal HFMD, fatal case-children often had scanty, papular (some with a suggestion of vesiculation) lesions that needed to be actively sought for. Acute flaccid paralysis/paresis, often with associated aseptic meningitis, appears to be another alerting presentation. While children with atypical rashes and/or limb paresis, presenting with protracted vomiting and associated mild dehydration, and appearing unwell with sustained moderate tachycardia, were a subset that often deteriorated acutely to shock, no reliable early indicators emerged that could consistently predict deterioration. Ironically however, even if such indicators were determined, no therapeutic intervention was identified that could consistently forestall imminent deterioration to death.

Acknowledgements

We thank the following for providing the data on the case-patients: G L Dan, K K Tan, G L Kuan, K E Lim, L Lum, R Elangkovan, Bhupinder Singh, Zubaidah Abd Wahab, Joshua Daniel and all other paediatricians and pathologists who were involved in the management and investigation of these case-patients. Pediatricians: Dr Dan Giap Liang, Island Hospital, Penang, Dr Tan Kah Kee, Hospital Sultanah Aminah, JB, Dr Kuan Geok Lan, Hospital Melaka, Dr Lim Kok Ewe, Metro Specialist Hospital, Sg Petani, Kedah, Dr Lucy Lum, University Hospital, Dr Yu, Hospital Sg Petani, Dr Elangkovan Ramakrishnan, Hospital Alor Setar, Kedah. Pathologists: Lam Sai Kit, University Malaya Medical Centre, Dr Bhupinder Singh, Penang Hospital, Dr Zubaidah Abd Wahab, Hospital Kuala Lumpur, Dr Joshua Daniel, Hospital Melaka.

References

1. Chan LG, Parashar UD, Lye MS et al. Deaths in children during an outbreak of Hand, Foot and Mouth Disease in Sarawak, Malaysia: Clinical and pathological characteristics of the disease. Clin Infect 2000; 31: 678-83.
2. Cardosa MJ, Krishnan S, Tio PH, Perera D, Wong SC. Isolation of subgenus B adenovirus during a fatal outbreak of enterovirus 71-associated hand, foot, and mouth disease in Sibu, Sarawak. Lancet 1999; 354: 987-91.
3. Centers for Disease Control and Prevention. Deaths among children during an outbreak of hand, foot, and mouth disease — Taiwan, Republic of China, April-July, 1998. MMWR 1998; 47: 629-32.

4. Wu TN, Tsai SF, Li SF, et al. Sentinel surveillance for enterovirus 71, Taiwan, 1998. Emerg Infect 1999; 5: 458-60.

5. Wang SM, Liu CC, Tseng HW, et al. Clinical spectrum of enterovirus 71 infection in children in southern Taiwan, with an emphasis on neurological complications. Clin Infect 1999; 29: 184-90.

6. Ho M, Chen ER, Hsu KH, et al. An epidemic of enterovirus 71 infection in Taiwan. Taiwan Enterovirus Epidemic Working Group. N Engl J Med 1999; 341: 929-35.

7. Huang CC, Liu CC, Chang YC, Chen CY, Wang ST, Yeh TF. Neurologic complications in children with enterovirus 71 infection. N Engl J Med 1999; 341: 936-42.

8. Chang LY, Lin TY, Hsu KH, et al. Clinical features and risk factors of pulmonary oedema after enterovirus-71-related hand, foot, and mouth disease. Lancet 1999; 354: 1682-6.

9. AbuBakar S, Chee HY, Al-Kobaisi MF, Xiaoshan J, Chua KB, Lam SK. Identification of enterovirus 71 isolates from an outbreak of hand, foot, and mouth disease (HFMD) with fatal cases of encephalomyelitis in Malaysia. Virus Res 1999; 61: 1-9.

10. Lum LCS, Wong KT, Lam SK, et al. Fatal enterovirus 71 encephalomyelitis. J Pediatr 1998; 133: 795-8.

11. Ell SR. Neurogenic pulmonary oedema: a review of the literature and a perspective. Invest Radiol 1991; 26: 499-506.

12. Simon RP. Neurogenic pulmonary oedema. Neurol Clin 1993; 11: 309-23.

13. Smith WS, Matthay MA. Evidence for a hydrostatic mechanism in human neurogenic pulmonary oedema. Chest 1997; 111: 1326-33.

14. Colice GL, Matthay MA, Bass E, et al. Neurogenic pulmonary oedema. Am Rev Respir 1984; 130: 941-48.

15. Wray NP, Nicotra MB. Pathogenesis of neurogenic pulmonary oedema. Am Rev Respir 1978; 118: 783-86.

16. Dettbarn CL, Davidson LJ. Pulmonary complications in the patient with acute head injury: neurogenic pulmonary oedema. Heart Lung 1989; 18: 583-9.

17. Loughnan PM, Brown TCK, Klug GL. Neurogenic pulmonary oedema in man: etiology and management with vasodilators based on hemodynamic studies. Anaesth Intensive Care 1980; 8: 65-71.

18. Colice GL. Neurogenic pulmonary oedema. Clin Chest Med 1985; 6: 473-89.

19. Fein IA, Rackow EC. Neurogenic pulmonary oedema. Chest 1982; 81: 318-20.

20. Malik AB. Mechanisms of neurogenic pulmonary oedema. Circ Res 1985; 57: 1-18.

21. Minnear FL. Malik AB. Mechanisms of neurogenic pulmonary oedema. Ann NY Acad Sci 1982; 384: 169-90.

22. Lum LC, Wong KT, Lam SK, Chua KB, Goh AY. Neurogenic pulmonary oedema and enterovirus 71 encephalomyelitis [Letter]. Lancet 1998; 352: 1391.

23. Chang LY, Huang YC, Lin TY. Fulminant neurogenic pulmonary oedema with hand, foot, and mouth disease [Letter]. Lancet 1998; 352: 367.

24. Baker AB. Poliomyelitis: a study of pulmonary oedema. Neurology 1957; 7: 743-51.

25. Baker AB. Bulbar poliomyelitis: its mechanism and treatment. Am J Med 1949; 6: 614-9.

26. Baker AB, Matzke HA, Brown JR. Bulbar poliomyelitis: a study of medullary function. Arch Neurol Psychiatr 1950; 63: 257-81.

27. Smith E, Fineberg HI. Bulbar poliomyelitis and its treatment. J Pediatr 1934; 4: 590-4.

28. Blomberg J, Lycke E, Ahlfors K, Johnsson T, Wolontis S, Zeipel G von. New enterovirus type associated with epidemic of aseptic meningitis and/or hand, foot, and mouth disease [Letter]. Lancet 1974; 2: 112.

29. Tagaya I, Takayama R, Hagiwara A. A large-scale epidemic of hand, foot and mouth disease associated with enterovirus 71 infections in Japan in 1978. Jpn J Med Sci Biol 1981; 34: 191-6.

30. Hagiwara A, Tagaya I, Yoneyama T. Epidemic of hand, foot and mouth disease associated with enterovirus 71 infection. Intervirology 1978; 9: 60-3.

31. Miwa C, Ohtani M, Watanabe H, Fujimoto J, Kinbara K, Tanaka H. Epidemic of hand, foot and mouth disease in Gifu prefecture in 1978. Jpn J Med Sci Biol 1980; 33: 167-80.

32. Ishimaru Y, Nakano S, Yamaoka K, Takami S. Outbreaks of hand, foot and mouth disease by enterovirus 71. High incidence of complication disorders of central nervous system. Arch Dis Child 1980; 55: 583-8.

33. Chonmaitree T, Menegus MA, Schervish-Swierkosz EM, Schwalenstocker E. Enterovirus 71 infection: report of an outbreak with two cases of paralysis and a review of the literature. Pediatrics 1981; 67: 489-93.

34. Nagy G, Takatsy S, Kukan E, Mihaly I, Domok I. Virological diagnosis of enterovirus type 71 infections: experiences gained during an epidemic of acute CNS diseases in Hungary in 1978. Arch Virol 1982; 71: 217-27.

35. Samuda GM, Chang WK, Cheung CY, Tang PS. Monoplegia caused by enterovirus 71: an outbreak in Hong Kong. Pediatr Infect J 1987; 6: 206-8.

36. Gilbert GL, Dickson KE, Waters MJ, Kennett ML, Land SA, Sneddon M. Outbreak of enterovirus 71 infection in Victoria, Australia, with a high incidence of neurologic involvement. Pediatr Infect J 1988; 7: 484-8.

37. Alexander JP, Baden L, Pallansch MA, Anderson LJ. Enterovirus infection and neurologic disease – United States, 1977-1991. J Infect 1994; 169: 905-8.

38. Komatsu H, Shimizu Y, Takeuchi Y, Ishiko H, Takada H. Outbreak of severe neurologic involvement associated with Enterovirus 71 infection. Pediatr Neurol 1999; 20: 17-23.

39. McMinn P, Stratov I, Dowse G. Enterovirus 71 outbreak in Western Australia associated with acute flaccid paralysis. Commun Dis Intell 1999; 23(7): 199.

40. Chao CH, Huang MD, Liu CC et al. Neurologic complications in children with Enterovirus 71 infection. N Engl J Med 1999; 341: 936-42

41. Brown B, Oberste MS, Alexander JP et al. Molecular epidemiology and evolution of Enterovirus 71 strains isolated form 1970 to 1998. J Virol 1999; 73: 9969-75.

* Personal communication J. Alexander, CDC Atlanta.