Risk Factors for Severe Enteroviral Infections in Children

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Objective: *To study the risk factors associated with severe enterovirus infection among hospitalized pediatric patients with hand, foot, and mouth disease (HFMD) at King Narai Hospital, Lopburi, Thailand.*
Material and Method: *We reviewed all of the suspected enterovirus infection cases aged less than 15 years admitted to King Narai Hospital between 2011 and 2013. Cases were classified into mild and severe enterovirus infection. Risk factors for severe enterovirus infection were analyzed using univariate and multivariate logistic regressions.*
Results: *During the study period, 156 patients met the case definition for further analysis. Of those 156 patients, 131 (84.0%) were classified as mild cases, and 25 (16.0%) as severe cases with five (3.2%) deaths. The most common manifestations among the severe cases were seizures, pneumonia, meningoencephalitis, meningitis, and hyperglycemia. Of the 31 identifiable cases, 12 were caused by enterovirus 71 (EV71), 12 by coxsackievirus A16 (CA16), four by both, and three by other enterovirus. The clinical manifestations that were significantly related to severe enterovirus infection in univariate analysis were age of less than one year, highest body temperature greater than 39.0°C, duration of fever greater than three days, absence of skin lesions, diarrhea, dyspnea, and hyperglycemia. The clinical manifestations that were significantly related to severe enterovirus infection by both univariate and multivariate analyses were absence of oral lesions, seizures, and drowsiness/lethargy.*
Conclusion: *The major pathogens of severe disease were EV71 and CA16. High-risk factors significantly related to severe enterovirus infection in both univariate and multivariate analyses were absence of oral lesions, seizures, and drowsiness/lethargy. Early recognition of children at risk and prompt treatment is important to mitigate the deterioration of patients with enterovirus infection.*

Keywords: *Enterovirus infection, Severe*

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Over the last decade, several outbreaks of hand, foot, and mouth disease (HFMD) have been reported in countries of the Western Pacific Region including China, Japan, Taiwan, Malaysia, Vietnam, and Singapore. The disease now presents an increasing threat to public health worldwide[1]. Enterovirus infection may present as HFMD or herpangina (HA), and usually affects young children especially those below five years of age. The common manifestations are fever and vesicular exanthema on the palms, soles, and mouth. Most of the infections are generally mild and self-limited. Severe cases usually present with interstitial pneumonitis, meningitis, encephalitis, pulmonary edema, and myocarditis[2-4]. The factors contributing to severe or fatal HFMD previously documented were young age, absence of mouth ulcers, vomiting, tachycardia, lethargy, hyperglycemia, and leukocytosis[5-7]. However, no reliable markers have been identified. Early recognition of severe cases and timely intervention are crucial to prevent cardiorespiratory failure, increase the ratio of successful outcomes, and reduce mortality[8].

The major pathogens of HFMD are enterovirus 71 (EV71) and coxsackievirus A16 (CA16), both of which are non-enveloped, single-stranded RNA viruses belonging to family *Picornaviridae*[9]. Distinguishing between the possible pathogens in a clinical context is difficult. Some reports suggested that despite the close genetic relationship between EV71 and CA16, only EV71 has the potential to cause neurological disease in acute infection and may result in fatal outcome[10,11].

Although the epidemiology and clinical features of severe HFMD have been widely studied in many countries, limited data are available in Thailand. Clinical information for prediction of severe disease remains insufficient to help physicians detect the severe and fatal cases earlier. Since 2001, HFMD has been one of the notifiable diseases for surveillance in Thailand and HA was added into the surveillance system in 2011[12]. Thailand has reported a high incidence of HFMD cases during the rainy season,

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which is from June to October, with a total of 18,196 to 45,961 cases and two to six deaths per year between 2011 and 2013[13]. Lopburi is one of the provinces in central region with a rising number of cases of HFMD every year with three deaths reported between 2011 and 2013[13]. King Narai Hospital is a referral center for severe HFMD from district and private hospitals in Lopburi province. The authors aimed to describe the epidemiology and clinical features of HFMD, as well as to explore the risk factors associated with severe enterovirus infection among hospitalized patients in King Narai Hospital, Lopburi, Thailand.

Material and Method

The present study was a retrospective study and was approved by the Ethics Committee of King Narai Hospital. We reviewed inpatient medical records of enterovirus infection cases aged less than 15 years admitted to King Narai Hospital between 2011 and 2013 by searching from the ICD-10, laboratory logbook and HFMD investigation system in the hospital. The ICD-10 for enterovirus infections are:

- B08.4 (enteroviral vesicular stomatitis with exanthema; HFMD)
- B08.5 (enteroviral vesicular pharyngitis; herpangina)
- B34.1 (enterovirus infection, unspecified),
- B97.1 (unspecified enterovirus as the cause of diseases classified elsewhere)
- A85.0 (enteroviral encephalitis)
- A87.0 (enteroviral meningitis)

Information on clinical symptoms and signs, duration and severity of illness, length of hospital stay, laboratory results along with treatment outcomes were obtained from medical records.

The patients were classified into three groups as follows:

1. A suspected case was a case with clinical diagnosis of HFMD or HA.

2. A probable case was defined as a suspected case with the presence of viral specific IgG antibodies at least 1:512 in a single serum detected by micro-neutralization method. This criteria was based on the finding that less than 6% of healthy children and less than 1% of adult have had serum titer of 1:512[14,15].

3. A confirmed case was a suspected case with one of the following, the presence of viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR), the presence of enterovirus by viral isolation, or a four-fold increase in IgG antibodies in samples collected at least two weeks apart, and detected by the micro-neutralization method. All laboratory tests were performed at the National Institute of Health, Department of Medical Science, the Ministry of Public Health, Thailand.

All cases were then categorized into mild and severe form as previously described[16,17]. Severe cases were HFMD or HA patients with pneumonia, pulmonary edema, respiratory failure, encephalitis, meningitis, meningoencephalitis, or myocarditis. Mild cases were patients with HFMD or HA who did not meet the criteria of severe case.

Data were entered and analyzed with Epi-Info version 7.1.3 (Center for Disease Control and Prevention, Atlanta, GA, USA) and associated factors for severe enterovirus disease were analyzed. Chi-square test was used to ascertain the differences in signs and symptoms between severe and mild cases. Data were considered statistically significant at a *p*-value below 0.05. We calculated risk ratio (RR) with 95% confidence interval (CI) in univariate analysis for each variable including gender, age, clinical features, underlying disease, duration of fever, duration of admission, laboratory results, and possible risk for severe enterovirus infection. To adjust for potential confounders, we performed a stepwise multivariate logistic regression analysis by adding variables demonstrating significance on univariate analysis and biological plausibility to calculate the adjusted odds ratio.

Results

One hundred seventy two medical records of patients with enterovirus infection were reviewed, and 156 patients met the case definition for further analysis. Of these, 27 were confirmed cases, four were probable cases, and 125 were suspected cases. One hundred thirty one (84.0%) cases were categorized as mild and 25 (16.0%) cases as severe, which include five fatal cases. The male to female ratio was 1.89:1 with median age of one year (ranging from 25 days to 14 years). Most cases were children younger than five years (93.6%). In 2011, 44 cases were identified with the peak of onset of illness from June to October. There were a rising number of cases from 38 cases in 2012 to 74 cases in 2013 due to the prolonged epidemic between October 2012 and March 2013. Moreover, we found an increased number of severe cases from one to two cases between 2011 and 2012 to 22 cases in 2013, which was the year with the highest number of severe HFMD in Lopburi (Fig. 1).

Among the 27 confirmed cases, 12 (44.5%) cases were infected with CA16, eight (29.6%) cases

were infected with EV71, and four (14.8%) cases had dual infections of EV71 and CA16. Three (11.1%) cases tested positive for pan-enterovirus but negative for EV71 and CA16. We also identified two confirmed cases of dual enterovirus and dengue virus co-infection. These two cases had EV71 and CA16 respectively. These two patients stayed in the hospital for six and 18 days respectively.

The majority of mild cases were suspected cases (123 cases) with two probable cases and six confirmed cases. Of the six confirmed cases with mild form, three cases were infected with CA16, two cases were infected with EV71, and one case was infected with other enterovirus. The two probable cases of the mild form were infected with EV71 and presented with acute gastroenteritis and HFMD, respectively. Among 21 confirmed cases with severe form, nine cases were infected with CA16, six were infected with EV71, four had dual infections of EV71 and CA16, and two had other enterovirus (Table 1).

Two probable cases infected with EV71 had severe disease. One was a 12-year-old boy with meningitis and only the blood for serology collected on day 11 after the onset of symptoms showed EV71 titer of 1:512 and CA16 titer of 1:256. The other probable case was a 4-year-old boy with diabetic ketoacidosis (DKA) and encephalitis with fatal outcome. The blood specimen collected on day 4 of illness showed a positive titer for EV71 at 1:8, 192.

The most common clinical symptoms and signs of the 156 cases at the time of admission were history of fever (96%), oral lesions (85%), tachycardia (60%), sore throat (57%), a body temperature of greater than 37.8°C on admission (56%), hand lesions (46%), rhinorrhea (42%), and cough (41%). The clinical features that found significantly higher frequency in mild cases than severe cases were oral lesions, sore throat, and hand and foot lesions. The clinical features that found significantly less were seizures, dyspnea, and drowsiness/lethargy (Table 2). The most common manifestations among the 25 severe cases were seizures (72%), pneumonia (44%), meningoencephalitis (44%) (Fig. 2). The characteristics of all fatal cases were shown in Table 3.

Table 1. Severity of cases and causative agents of enterovirus infection cases in King Narai Hospital between 2011 and 2013 (n = 156)

Severity of cases	Mild	Severe	Total
Confirmed cases	6	21	27
CA16*	3	9	12
EV71**	2	6	8
EV71 & CA16	0	4	4
Other-enterovirus (enterovirus which was neither EV71 nor CA16)	1	2	3
Probable cases			
EV71	2	2	4
Suspected cases	123	2	125
Total	131	25	156

CA16 = coxsackievirus A16; EV71 = enterovirus 71
* One dual infection of CA16 and dengue infection
** One dual infection of EV71 and dengue infection

The clinical manifestations that were significantly related to severe enterovirus infection in univariate analysis were age of less than 1 year, highest body temperature greater than 39.0°C, duration of fever longer than three days, absence of skin lesions, diarrhea, dyspnea, and hyperglycemia. The clinical manifestations that were significantly related to severe enterovirus infection in both univariate and multivariate analyses were absence of oral lesions, seizures, and drowsiness/lethargy (Table 4).

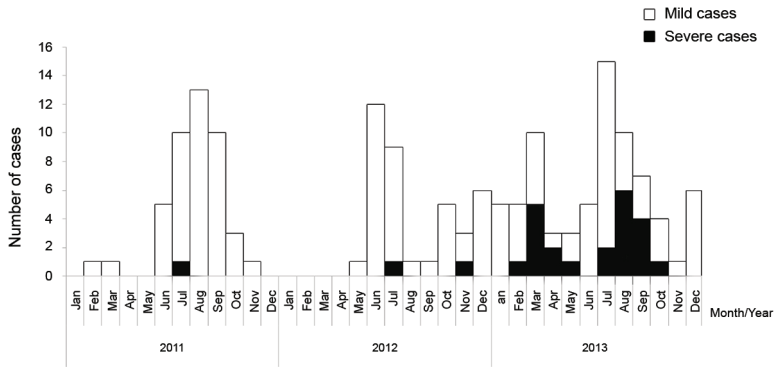

Fig. 1 Distribution of enteroviral infections both mild and severe cases in King Narai Hospital between 2011 and 2013 (n = 156).

Table 2. Percentage of clinical manifestations of enterovirus infection at the time of admission according to severity in King Narai Hospital between 2011 and 2013

	Total cases, n = 156 (%)	Severe cases, n = 25 (%)	Mild cases, n = 131 (%)	*p*-value
History of fever	151 (96)	25 (100)	126 (96)	0.32
Oral lesions	132 (85)	6 (24)	126 (96)	<0.001
Tachycardia	94 (60)	19 (76)	75 (57)	0.08
Sorethroat	89 (57)	4 (16)	85 (65)	<0.001
Admission BT ≥37.8°C	88 (56)	15 (60)	73 (56)	0.69
Hand lesions	72 (46)	2 (8)	70 (53)	<0.001
Rhinorrhea	66 (42)	11 (44)	55 (42)	0.85
Cough	64 (41)	14 (56)	50 (38)	0.97
Nausea/vomiting	53 (34)	6 (24)	47 (36)	0.25
Seizures	31 (20)	18(72)	13 (10)	<0.001
Diarrhea	24 (15)	7 (28)	17(13)	0.05
Foot lesions	17 (11)	1 (4)	16 (12)	<0.001
Fatigue	16 (10)	3 (12)	13 (10)	0.82
Dyspnea	15 (10)	12 (48)	3 (2)	<0.001
Drowsiness/lethargy	14 (9)	12 (48)	2 (2)	<0.001

BT = body temperature

Table 3. Fatal cases and causative agents of enterovirus cases in King Narai Hospital between 2011 and 2013

Sex/age	Diagnosis	Days from onset to death	Days of hospital stay	Type of enterovirus	Case classification
Male/4 years	DKA with encephalitis, brain edema	4	2	EV71	Probable*
Male/3 months	Enterovirus infection, acute respiratory failure, severe sepsis, sudden cardiac arrest	4	1	Other-enterovirus	Confirmed**
Male/2 months	Encephalitis, sudden cardiac arrest, pneumonia, acute respiratory failure	4	4	EV71	Confirmed**
Female/1 month	Encephalitis, pneumonia, respiratory failure	4	1	EV71 & CA16	Confirmed**
Male/25 days	Encephalitis, sepsis, acute respiratory failure	4	1	EV71	Confirmed**

* A probable case was a suspected case with the presence of viral specific IgG antibodies at least 1:512 in a single serum detected by micro-neutralization

** A confirmed case was a suspected case with one of the following: the presence of viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR), the presence of enterovirus by viral isolation, or a four-fold increase in IgG antibodies in samples collected at least two weeks apart and detected by the micro-neutralization method

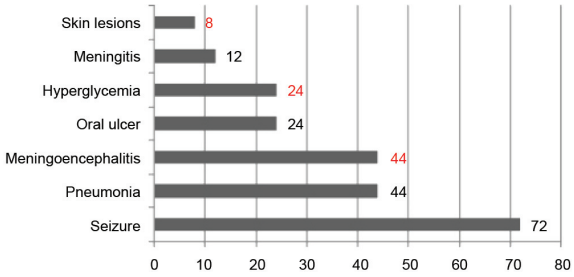

Fig. 2 Percentage of clinical manifestations of severe enterovirus infection in King Narai Hospital, between 2011 and 2013 (n = 25).

Discussion

An increase in the incidence of HFMD with severe and fatal cases was observed in King Narai Hospital, Lopburi province, Thailand between 2011 and 2013. The number of cases was highest in 2013 (74 cases), which was the largest epidemic in Lopburi. This was similar to the overall situation in Thailand[13], which showed an increasing incidence during that time period. The increasing trend of HFMD may have been due to the change in the case definition within the reporting system, which has included herpangina since September 2011. In addition, the raised awareness of

Table 4. Univariate and multivariate analysis of epidemiological and clinical parameters of mild and severe enterovirus infection cases in King Narai Hospital between 2011 and 2013

Variables	Severe cases	Mild cases	Total	RR (95% CI)	Adjusted OR (95% CI)*
Gender					
Male	17	85	102	1.12 (0.51-2.43)	0.31 (0.02-4.12)
Female	8	46	54		
Age					
<1 year	12	17	29	4.04 (2.06-7.92)	8.53 (0.59-121.41)
≥1 year	13	114	127		
Temperature at admission					
≥37.8°C	15	73	88	1.15 (0.55-2.41)	-
<37.8°C	10	58	68		
Highest temperature					
≥39.0°C	18	34	52	5.14 (2.29-11.52)	2.51 (0.21-29.40)
<39.0°C	7	97	104		
Duration of fever					
≥3 days	22	73	95	4.70 (1.47-15.06)	-
<3 days	3	58	61		
Tachycardia**					
Yes	19	75	94	2.08 (0.88-4.93)	-
No	6	56	62		
Skin lesions					
Yes	2	72	74	0.04 (0.01-0.34)	0.06 (0.01-1.45)
No	23	59	82		
Oral lesions					
Yes	6	126	132	0.05 (0.02-0.12)	0.01 (0.0004-0.26)
No	19	5	24		
Vomiting					
Yes	6	47	53	0.61 (0.26-1.44)	-
No	19	84	103		
Diarrhea					
Yes	7	17	24	2.13 (1.01-4.55)	0.09 (0.01-1.76)
No	18	114	132		
Sorethroat					
Yes	4	85	89	0.14 (0.05-0.39)	3.04 (0.24-38.26)
No	21	46	67		
Dyspnea**					
Yes	12	3	15	8.67 (4.87-15.44)	3.38 (0.21-52.21)
No	13	128	141		
Drowsiness/lethargy					
Yes	12	2	14	8.76 (5.01-15.33)	22.54 (1.25-403.94)
No	13	129	142		
Seizures					
Yes	18	13	31	10.36 (4.75-22.60)	43.11 (2.41-770.21)
No	7	118	125		
Hyperglycemia (BS >200 mg%)					
Yes	6	0	6	7.89 (5.18-12.01)	-
No	19	131	150		
Leukocytosis (WBC ≥$10x10^3$/μL)					
Yes	21	105	126	1.25 (0.46-3.37)	-
No	4	26	30		
Stayed in the hospital					
≥3 days	17	40	57	3.69 (1.70-8.00)	-
<3 days	8	91	99		

BS = blood sugar; WBC = white blood cell

* Variables included in the multivariate model were gender, age, highest temperature, skin lesions, oral lesions, sore throat, diarrhea, dyspnea, drowsiness/lethargy, and seizures

** Tachycardia and dyspnea were classified according to age-corrected value

physicians has also been observed in diagnosing and testing for enterovirus. Some patients without skin and oral lesions who had fever and resided in epidemic areas were also tested for enterovirus. These may have been the reasons for the rising number of enterovirus cases in 2013. We also found a prolongation of the epidemic from winter to summer period of 2012 to 2013, which was unusual period for HFMD occurrence in Thailand. Global climate change may play a role in the rising number of cases because increased average temperature and relative humidity have been reported concurrently with the increasing HFMD incidence[18,19].

In the present study, we documented that 16.0% of cases (25/156) were severe disease and most of them (56%) presented with neurological manifestations (meningoencephalitis 44% and meningitis 12%) and respiratory involvement (pneumonia 44%). Although the majority of HFMD cases occur in children aged less than five years, most of the severe cases in the present study were younger than one year, especially the fatal cases, comparable with other reports[20]. The number of male cases was approximately twice the number of female in both severe and mild forms, but it was not a significant factor in univariate analysis, which was consistent with other studies[7,21].

EV71 was the major cause of severe enteroviral infection as shown in our study, which includes four fatal cases. Many studies considered that EV71 plays a major role in causing severe enterovirus disease[22-24]. However, CA16 can also cause severe enterovirus cases[20,21]. We found dual infections of both EV71 and CA16 in four confirmed cases. We considered that EV71 played a major role in causing severe disease. Studies provide evidence that neurons are the main viral targets of EV71 infection resulting in neurogenic pulmonary edema as the primary cause of death[25,26]. Other enteroviruses can also cause HFMD epidemic such as coxsackievirus A6, which was reported in Thailand and other countries as the causative agents of HFMD[27-29].

Clinical manifestations that physicians should be concerned for severe enterovirus infection, which have been found to be significant in univariate analysis, are body temperature hotter than 39.0°C, duration of fever longer than three days, absence of skin lesions or oral ulcer, diarrhea, dyspnea, drowsiness/lethargy, seizures, and hyperglycemia. Those are comparable with other reports[2,7]. Although tachycardia and leukocytosis were reported to be significance in some studies[8,30], there was no statistical difference in the present study. The skin lesions were found to be significant only in univariate analysis. However, the absence of skin lesions or exanthema was found to be related to severe disease in some studies[31].

In multivariate analysis, we found that absence of oral lesions, seizures and drowsiness/ lethargy were the risk factors for severe disease. Chang et al suggested that lethargy might be the useful clinical symptom of neurological involvement during the early stage of illness[2]. Seizures are the main symptom of neurological involvement and many studies found seizures to be related to severe cases (8-28%)[11,32]. We did not find myoclonus as risk factors for a severe case. However, myoclonus was found to be as high as 66% in Vietnam[33].

Oral ulcer was common in mild cases but it was rarely found in severe or fatal cases. A study reported that the absence of mouth ulcer predicted a more complicated or fatal HFMD and have recommended that children without mouth ulcer should be monitored closely[8]. Previous outbreaks also suggested that severe disease is characterized by three clinical pictures including central nervous system involvement, autonomic nervous system dysregulation, and cardiopulmonary failure[16,17]. Therefore, we recommend looking for severe cases in patients with suspected enterovirus infection without oral and skin lesions particularly during an epidemic. Those suspected patients with severe disease will have abnormal neurological signs, symptoms of sympathetic hyperactivity, and cardiopulmonary involvement.

Among the five fatal cases, four of them were aged three months or less. Lack of passive maternal antibody may be a factor for severe disease in these babies. A study in Taiwan found approximately 50 to 60% of pregnant women had antibody for enterovirus that could be passed to the neonate. The antibody level in the neonate declines and disappears at six months of age[15]. Several vaccines for HFMD are currently in development and may play an important role for prevention and control of the disease in the future[34,35]. Until a HFMD vaccine becomes available, control of HFMD is limited to promotion of personal hygiene especially hand washing, isolation of patients, and improved clinical management of enterovirus infection by early recognition of the disease especially the severe cases.

Limitations of the present study were the small sample size of severe cases and retrospective

study. Therefore, prospective surveillance is needed for further clarification of the risk factors for severe enterovirus infection.

Conclusion

EV71 and CA16 were the main causative agents of severe enterovirus infection cases in our study. Factors associated with severe enterovirus infection included age of less than one year, body temperature hotter than 39.0°C, duration of fever longer than three days, absence of skin lesions, diarrhea, dyspnea, hyperglycemia, especially absence of oral lesions, seizures, and drowsiness/lethargy. These results provide evidences to support clinicians to watch out for these risk factors. Early recognition of children at risk and prompt treatment are the keys to mitigate the deterioration of patients with severe enterovirus infection.

What is already known on this topic?

Outbreaks of enterovirus infection have been reported in countries of the Western Pacific Region and it is now an increasing threat to public health worldwide.

Factors contributing to severe infection have been studied in several other countries in order to give early intervention to those patients.

What this study adds?

The clinical manifestations significantly related to severe enterovirus infection in Thai children were studied. These results provide evidences to support clinicians and emphasize the importance of risk factors leading to severe enterovirus infection. Early recognition of children at risk and prompt treatment are the keys to mitigate the deterioration of patients with severe enterovirus infection.

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Potential conflicts of interest

None.

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ปัจจัยเสี่ยงต่อการติดเชื้อเอนเตอโรไวรัสอย่างรุนแรงในผู้ป่วยเด็ก

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วัตถุประสงค์: *เพื่อศึกษาปัจจัยเสี่ยงทางคลินิกต่อการติดเชื้อเอนเตอโรไวรัสอย่างรุนแรงในผู้ป่วยเด็ก*
วัสดุและวิธีการ: *ศึกษาย้อนหลังในผู้ป่วยโรคติดเชื้อเอนเตอโรไวรัสที่มีอายุน้อยกว่า 15 ปี ที่เข้ารับการรักษาในโรงพยาบาลพระนารายณ์มหาราช จังหวัดลพบุรี ระหว่าง พ.ศ. 2554 ถึง พ.ศ. 2556*
ผลการศึกษา: *ผู้ป่วยติดเชื้อเอนเตอโรไวรัสอายุน้อยกว่า 15 ปี ที่รับไว้รักษาเป็นผู้ป่วยใน ทั้งสิ้น 156 ราย เป็นกลุ่มอาการไม่รุนแรง 131 ราย (84%) เป็นกลุ่มอาการรุนแรง 25 ราย (16%) มีผู้ป่วยเสียชีวิต 5 ราย (3.2%) ภาวะแทรกซ้อนในกลุ่มอาการรุนแรงที่พบบ่อย ได้แก่ ชัก ปอดอักเสบ สมองอักเสบ เยื่อหุ้มสมองอักเสบ เชื้อที่ตรวจพบทั้งหมด 31 ราย เป็น enterovirus 71 (EV71) 12 ราย เป็น coxsackievirus A16 (CA16) 12 ราย เป็นเชื้อ EV71 ร่วมกับ CA16 สี่ราย และเป็นเชื้อ enterovirus ชนิดอื่น 3 ราย ลักษณะทางคลินิกที่เป็นปัจจัยเสี่ยงต่อการติดเชื้อเอนเตอโรไวรัสอย่างรุนแรง ได้แก่ อายุน้อยกว่า 1 ปี อุณหภูมิกายสูงกว่า 39 องศาเซลเซียส มีไข้ตั้งแต่ 3 วันขึ้นไป ซึม ชัก ไม่มีผื่นที่ผิวหนัง ไม่มีรอยโรคในช่องปาก ท้องเสีย หายใจลำบาก และภาวะ hyperglycemia ปัจจัยที่มีความเสี่ยงสูง ได้แก่ ไม่มีแผลในปาก ชัก และอาการซึม*
สรุป: *เชื้อที่เป็นสาเหตุหลักของผู้ป่วยที่ติดเชื้อเอนเตอโรไวรัสอย่างรุนแรงคือ EV71 และ CA16 แพทย์และบุคลากรทางการแพทย์ควรให้ความสนใจถึงปัจจัยเสี่ยงต่อการติดเชื้อเอนเตอโรไวรัสอย่างรุนแรงในเด็ก ได้แก่ ไม่มีแผลในปาก ชัก และอาการซึม การวินิจฉัยอย่างรวดเร็วและให้การรักษาทันท่วงที ช่วยลดความรุนแรงของโรคและลดอัตราการเสียชีวิต*