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Clinical features and factors of unfavorable outcomes for non-polio enterovirus infection of the central nervous system in northern Taiwan, 1994-2003

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This study investigated the clinical manifestations and outcomes of central nervous system (CNS) infection by enteroviruses. Cases with CNS involvement among all enterovirus-culture-positive cases from January 1995 to June 2003 were retrospectively reviewed. Among 1028 enterovirus-culture-positive cases, there were 333 cases involving the CNS. Of these, the ratio of male to female subjects was 1.78, and the mean (± standard deviation) age was 6.83 ± 5.9 years; 21 were premature neonates, and 10 failed to thrive. Disease entities included 282 cases of aseptic meningitis (84.7%), 44 cases of encephalitis (13.2%), and 7 cases of encephalomyelitis/polio-like syndrome (2.1%). Of these cases, 97.9% (326/333) had fever with peak body temperature at 38.9°C, 85% had headache and vomiting, 70% had meningeal signs, 64% had neck stiffness, 16.6% (55/333) had change of consciousness, 5.4% (18/333) had seizures and 5.2% (17/333) had myoclonic jerks. Mannitol was administered in 77.2% of patients (257/333), along with intravenous immunoglobulin in 6.6% (22/333). Twelve cases received ventilator support. One patient died of hand-foot-and-mouth disease, encephalitis plus cardiopulmonary failure, and 2 premature neonates died of hepatic failure, disseminated intravascular coagulation, sepsis-like syndrome and myocarditis. Eighteen had neurologic sequelae, including 7 with limb weakness, 5 with epilepsy, 2 with sixth cranial nerve palsy, 3 with cerebral palsy, 4 with psychomotor retardation, 2 with spasticity, and 1 with hearing loss. Factors associated with unfavorable outcomes (death or sequelae) included younger age (p=0.0003), higher peak white blood cell count (WBC) [p=0.0009] and skin rash (p=0.005). Younger age and higher peak WBC were poor prognostic factors of severe enterovirus CNS infection. Death was related to neonatal enterovirus infection and enterovirus 71 infection in young children.

Key words: Central nervous system viral infection, enterovirus, pulmonary edema, risk factors, viral encephalitis, viral meningitis

Enteroviruses (EVs) comprise a large group of immunologically distinct serotypes of viruses belonging to the family of *Picornaviridae*. They cause a wide variety of diseases, including nonspecific viral illness, some easily recognized ones such as mild infections of herpangina and hand-foot-and-mouth disease, and potentially serious ones of myopericarditis, meningitis, encephalitis, myelitis and neonatal sepsis [1]. In Taiwan, polioviruses have been eradicated because of generalized vaccinations [2]. However, non-polio EVs (NPEVs) cause epidemic outbreaks annually. Severe EV infection has been reported frequently since the outbreak of the fatal EV71 epidemic in 1998 [3]. Severe diseases were reported in 405 patients, along with fatal diseases in 78 patients, comprising a case fatality rate of 19.3% at that time [3]. This study aimed to investigate the demographics, clinical manifestations, laboratory findings and outcomes of patients with NPEV infection of the central nervous system (CNS) in a medical center in northern Taiwan.

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Materials and Methods

Patients

Inclusion criteria

From September 1994 to July 2003, we reviewed cases with any clinical specimens with positive EV isolation, including cerebrospinal fluid (CSF), throat swabs and

rectal swabs. If patients with positive EV isolation had evidence of CNS involvement, they were included in this study. Evidence of CNS involvement from EV infection was defined as either positive EV isolation from CSF or CNS infection entities plus positive EV isolation from throat swabs and/or rectal swabs. Polioviruses were excluded.

Throat swabs, rectal swabs and CSF were submitted for virus isolation. Samples were inoculated into human embryonic fibroblast (MRC-5), rhesus monkey kidney (LLC-MK2), laryngeal carcinoma (HEp-2) and RD cell cultures. Once the enteroviral cytopathic effect involved more than 50% of the cell monolayer, the cells were scraped, and indirect fluorescent antibody staining with panenteroviral antibody (Chemicon International, Inc., Temecula, CA, USA) was performed to identify the EV.

The EV CNS infection entities included aseptic meningitis, encephalitis, encephalomyelitis, and polio-like syndrome. Aseptic meningitis was defined as CSF pleocytosis (>35 leukocytes/mm^3 in premature, >15 in neonates and >5 in children beyond the neonate stage) [4] plus negative bacterial cultures of CSF or normal CSF cell count with positive viral culture and without distrubed consciousness. Encephalitis was defined as disturbed consciousness or presence of focal neurologic signs with positive electroencephalogram findings or abnormal brain images (magnetic resonance imaging [MRI] or computed tomography [CT] scan). Definition of myelitis or polio-like syndrome was abnormal focal spinal symptom(s)/sign(s) with positive imaging studies of the spinal cord. Encephalomyelitis occurred with both encephalitis and poliomyelitis-like syndrome. EV aseptic meningitis was classified as Group I. Encephalitis, polio-like syndrome and encephalomyelitis were severe EV CNS infections and were classified as Group II.

Data collection

The demographic data, seasonal and age distributions, clinical manifestations, laboratory findings, management and outcomes were analyzed. Prematurity was defined as gestation age below 37 weeks. Failure to survive was defined as body weight below the third percentile of the age group. Unfavorable outcomes were defined as death or neurologic sequelae at discharge. We also investigated the risk factors for severe EV CNS diseases and unfavorable outcomes.

Statistical methods

Continuous variables were analyzed by Student's *t* tests, and categorical data were compared with chi-squared tests. Significance was defined as a p value <0.05.

Results

Demography

The highest monthly frequencies occurred during the summer (May, June and July), as shown in Fig. 1. The male to female ratio was 1.78. Of the 333 patients, 10 (3.2%) failed to thrive, and 21 (8.4%) had a history of prematurity.

Clinical spectrums

1028 patients with positive EV cultures during the study period, 333 patients had EV CNS infections. There were 282 patients with aseptic meningitis alone (84.7%), 44 patients (13.2%) with encephalitis and 7 patients (2.1%) with encephalomyelitis (Table 1). Overall, there were 282 cases in Group I and 51 in Group II. The range of ages was from newborns to 33.6 years, and the mean age was 6.83 years. The majority of cases were of 1 to 6 months old and 4 to 6 years old (Fig. 2). The yield rates of viral culture from throat swabs, rectal swabs

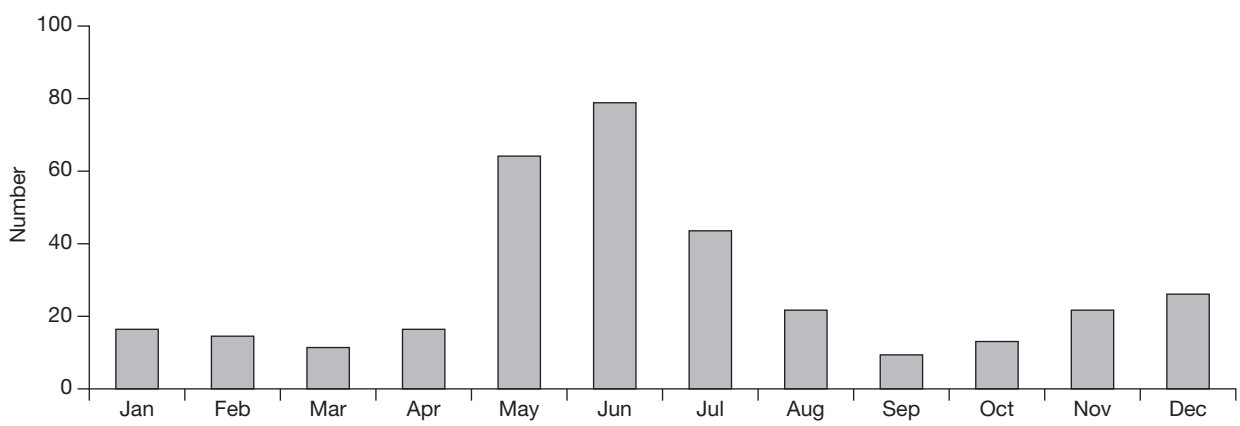

Fig. 1. Seasonal distribution of the 333 patients. The peak occurred in the summer months (May, June and July).

Table 1. Demography and clinical diagnosis of 333 enterovirus central nervous system infections

Demography/diagnosis	Mean ± standard deviation or number (%)
Age (years)	6.83 ± 5.90 (median, 5.67)
Gender	
Male	213
Female	120
Male/female ratio	1.78
Prematurity	21/251[a] (8.4)
Failure to thrive	10/317[a] (3.2)
Clinical diagnosis	
Group I: Meningitis	282 (84.7)
Group II: Severe diseases	51 (15.3)
Encephalitis	44 (13.2)
Encephalomyelitis	7 (2.1)

[a]The denominator is the case number of data available, and the numerator is the case number with the factor.

and CSF were 82% (209/255), 79% (157/199) and 74% (237/320), respectively.

Clinical manifestations and laboratory findings

Of all 333 patients, 97.9% had fever with a peak body temperature of 38.9°C, 85% (252/296) had headaches, 75% experienced vomiting, 70% (189/270) produced meningeal signs (positive Brudezinski or Kernig signs), 64% had neck stiffness, 16.6% presented disturbed consciousness, 5.4% had seizures, and 5.2% had myoclonic jerks (Table 2).

The mean (standard deviation; SD) peak white blood cell (WBC) count was 11,171 (4487) per μL, neutrophil percentage 73 (19), peak C-reactive protein (CRP) 1.90 (2.18) mg/dL, CSF WBC count 214 (355) per μL, neutrophil percentage 59.6 (49.2), CSF protein 58.7 (56.5) mg/dL, and CSF/serum glucose ratio 0.61 (0.14). The mean (SD) aspartate aminotransferase (AST) of 249 patients was 112 (577) IU/L, and alanine aminotransferase (ALT) of 15 cases was 236 (219) IU/L. In addition, disseminated intravascular coagulopathy (DIC) was noted in 10 patients (3%), renal impairment in 7 (2%) and elevated troponin I in 5 (1.5%). Abnormal electroencephalograms were observed in 39 patients (84.8% in Group II), abnormal brain CT in 20 cases and abnormal brain or spinal cord MRIs in 16 cases.

Mannitol was administered in 77.2% of patients (257/333), antibiotics in 41% of patients (135/332), and intravenous immunoglobulin (IVIG) in 6.6% of patients (22/333).

EV meningitis (Group I)

The leukocyte count per μL in the CSF ranged from 0 to 2520. There were 21 patients (7.4%) who had positive CSF culture in the absence of CSF pleocytosis. CSF pleocytosis was noted in 91.7% of patients in Group I. In the patients with CSF pleocytosis, 61.4% had neutrophilic predominance. Thirty one patients (12.2%) had a percentage of neutrophils more than 90%, and 10 cases had a CSF WBC count over 500 per μL. The protein concentration of the CSF ranged from 1 to 494.5 mg/dL. Elevated CSF protein (over 50 mg/dL) was found in 29.4% of the patients.

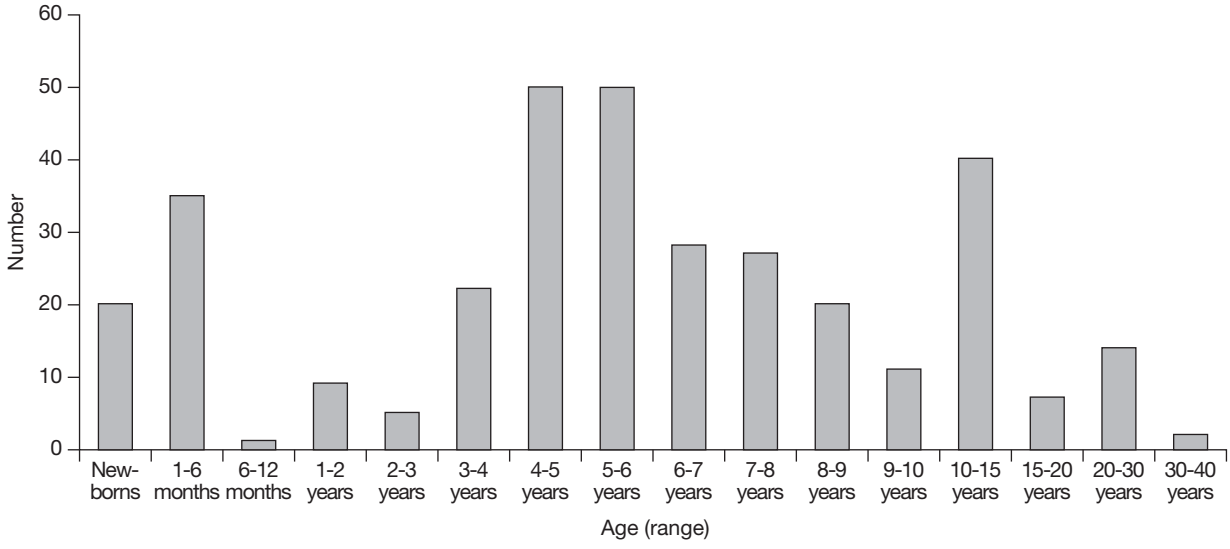

Fig. 2. Age distribution of the 333 patients. Two peaks were found, in those aged <6 months old and in those between 3 and 9 years old (especially 4 to 6 years old).

Table 2. Clinical manifestations of 333 enterovirus (EV) central nervous system (CNS) infections

Manifestation	No. of cases (%) [n = 333]	Group I: EV meningitis (n = 282)	Group II: severe EV CNS disease (n = 51)	*p*
Fever	326 (97.9)	276 (98)	50 (98)	0.94
Peak body temperature (°C) [mean ± SD]	38.9 ± 0.7	38.9 ± 0.6	39 ± 0.8	0.46
Headache	252/296[a] (85)	225/253[a] (89)	27/43[a] (63)	0.001
Vomiting	248 (74)	213 (76)	35 (69)	0.28
Tachycardia	236/319[a] (74)	192/268[a] (72)	44 (86)	0.06
Decreased appetite	85/116[a] (73)	62/92 [a] (67)	23/24[a] (96)	0.005
Decreased activity	83/114[a] (73)	57/85[a] (67)	26/29[a] (90)	0.02
Meningeal signs	189/270[a] (70)	167/233[a] (72)	22/37[a] (59)	0.13
Tachypnea	195/288[a] (68)	151/238[a] (63)	44/50[a] (88)	0.001
Neck stiffness	211/330[a] (64)	184/279[a] (66)	27 (53)	0.05
Photophobia	19/36[a] (53)	16/30[a] (53)	3/6[a] (50)	0.88
Bradycardia	120/318[a] (38)	94/266[a] (35)	26/51[a] (51)	0.05
Hypertension	90/285[a] (32)	63/233[a] (27)	27/51[a] (53)	0.001
Consciousness change	55 (17)	16 (6)	39 (76)	0.001
Myalgia	14/114[a] (12.3)	11/105 (10)	3/9 (33)	0.05
Skin rash	37 (11)	18 (6.4)	19 (37)	0.001
Oral ulcer	36 (11)	18 (6.4)	18 (35)	0.001
Hypotension	31/284[a] (11)	22/232[a] (9.5)	9/51[a] (18)	0.1
Seizure	18 (5.4)	2 (0.7)	16 (31)	0.001
Myoclonic jerk	17 (5.1)	5 (1.8)	12 (24)	0.001
Papilledema	12/231[a] (5.2)	11/209[a] (5.3)	1/22[a] (5)	0.89
Babinski sign	6/158[a] (3.8)	1/132[a] (1)	5/26[a] (19)	0.001
Muscle weakness	11/327 (3.4)	1/277[a] (0.4)	10/50[a] (20)	0.001

Abbreviation: SD = standard deviation

[a]The denominator is the case number of data available, and the numerator is the case number with the symptoms or signs.

Agents that decrease intracranial pressure such as mannitol or glycerol were administered in 77.9% of the patients. Empirical antibiotics were prescribed for 40.5% of patients during the period pending results for bacterial culture or even until an EV was isolated. Most of the patients receiving antibiotics were younger than 4 months of age. None of the patients with EV meningitis had any neurologic sequelae in this study.

Severe EV CNS infections necessitating intensive care

Of the 51 cases of severe EV CNS infection, 12 (10 were under 9 months old) patients received ventilator support. One had hypoxia due to hemothorax. Two were intubated because of intractable seizure. Three patients had apnea due to brainstem encephalitis. The other 6 patients were hypoxemic due to pulmonary edema. EV71 was isolated from the stool of a 5-month-old male, and a high EV71 neutralizing antibody titer was noted in a 4-month-old female. Both of them had hand-foot-and-mouth disease, encephalomyelitis, polio-like syndrome, pulmonary edema and myocarditis. No nosocomial lung infections were found in these 12 patients who received ventilator support.

Twelve patients received inotropic agents (11 of them also needed ventilator support). All of them were under 16 months old, and 7 were male. Ten had elevated cardiac enzymes. Echovirus 30 was isolated from the CSF, throat and rectum of a newborn male, who had neonatal sepsis, encephalitis, hepatitis (AST 544 IU/L, ALT 488 IU/L), myocarditis and pulmonary edema. Two patients (one was a 3-month-old female, and the other was a 4-day-old female) had septic shock with negative bacteriologic etiology. Seven of the 12 patients who received inotropic agents had acute abnormal renal function.

Three patients died. All of them were male, and all had pulmonary edema/hemorrhage, myocarditis and encephalitis. One of them was a 15-month-old male with hand-foot-and-mouth disease, encephalitis and cardiopulmonary failure. He was in a comatose condition 3 days after the onset of disease. The blood WBC count was 21,540/μL, AST 1706 IU/L and ALT 386 IU/L. The initial CSF findings were as follows: WBC 158/μL (30% neutrophils), protein 97.9 mg/dL

and glucose 194 mg/dL. EV71 was isolated from the throat and rectal swabs obtained from the patient. CSF viral isolation was negative. The troponin I level was as high as 16.2 ng/mL on admission, rising to greater than 50 ng/mL on the next day. IVIG (1 g/kg/day) was given immediately after admission. Death ensued despite the patient receiving extracorporeal mechanical oxygenation and other intensive care.

The other 2 fatal cases were premature neonates. One was born at the 35th gestational week, and he became sick on the 3rd day of life, dying of fulminant hepatic failure, DIC and renal failure. EV was isolated from the ascites, throat swab, and rectal swab, but not from CSF. IVIG was used on the first 2 days of hospitalization (1 g/kg/day), but did not seem to work. Because of sepsis-like syndrome and persistent pulmonary edema, he died of respiratory failure and multiorgan dysfunction on the 13th day of life.

The second fatal premature neonate, a twin B, died of fulminant hepatic failure, DIC, sepsis-like syndrome, myocarditis, encephalitis and pulmonary edema. His older sister got hand-foot-and-mouth disease 10 days before his onset of illness. In addition, his mother had low-grade fever 3 days before his birth; the twin A also had fulminant hepatitis, DIC, sepsis-like syndrome, myocarditis, and encephalomyelitis but survived. The CSF, throat and rectal culture were all positive for echovirus 30. He received IVIG 1 g/kg/day for the first 2 days of hospitalization. Eventually, he died of severe myocarditis and pulmonary hemorrhage.

Neurologic sequelae

Eighteen patients had neurologic sequelae, including 7 with limb weakness, 5 with epilepsy, 2 with cranial nerve palsy (CN VI), 3 with cerebral palsy, 4 with psychomotor retardation, 2 with spasticity, and 1 with hearing loss. The range of age was from newborn to 10 years old.

In the 18 patients with neurologic sequelae, brain and/or spinal cord images (CT or MRI) were taken for 13 patients. The most frequent neurologic sequelae was polio-like syndrome in 7 patients, including 5 males. Four patients who received MRI had lesions in the spinal cord. Six of the patients who had polio-like paralysis syndrome also had hand-foot-and-mouth disease. The stool viral culture of one 5-month-old male infant was positive and serotyped as EV71. Three patients had cerebral vascular diseases including ischemia, hemorrhage or venous thrombosis. The 2 patients who had cerebral ischemia had episodes of hypotension, and the one who suffered from cerebral hemorrhage had severe hypertension; their image studies were compatible with the pattern of hypoxic ischemic encephalopathy, and their neurologic sequelae

Table 3. Factors associated with severe enterovirus (EV) central nervous system (CNS) disease

Variable (n or mean ± standard deviation)	Group I: EV meningitis No. of cases (%) [n = 282]	Group II: Severe EV CNS disease No. of cases (%) [n = 51]	*p*
Gender (male/female)	182/100	31/20	0.73
Age (years)	7.4 ± 6.1	3.8 ± 2.8	<0.001
Prematurity	13/200[a] (6.5)	8 (16)	0.05
Failure to thrive	7/269[a] (2.6)	3/48[a] (6.3)	0.23
Fever	276 (98)	50 (98)	0.94
Peak body temperature (°C)	38.9 ± 0.7	39.0 ± 0.8	0.46
Ulcer	18 (6.4)	18 (35)	0.001
Rash	18 (6.4)	19 (37)	0.001
Seizure	2 (0.7)	16 (31)	0.001
Myoclonic jerk	5 (1.8)	12 (24)	0.001
Peak CRP (mg/dL)	1.82 ± 2.16	2.30 ± 2.26	0.16
Peak WBC (/μL)	10,836 ± 4255	13,028 ± 739	0.007
Glucose (mg/dL)	96 ± 21	101 ± 28	0.42
CSF WBC (/μL)	213 ± 339	222 ± 438	0.90
CSF protein (mg/dL)	58.8 ± 49.1	58.0 ± 87.2	0.95
CSF glucose (mg/dL)	59.6 ± 19.8	66.0 ± 26.8	0.11
CSF/serum glucose ratio	0.61 ± 0.13	0.62 ± 0.17	0.81
ALT (IU/L)	48 ± 100	420 ± 1340	0.08
Positive CSF EV isolation	219/270[a] (81)	18/50[a] (36)	0.001

Abbreviations: CRP = C-reactive protein; WBC = white blood cell count; CSF = cerebrospinal fluid; ALT = alanine aminotransferase
[a]The denominator is the case number of data available, and the numerator is the case number with the symptoms or signs.

Table 4. Factors associated with unfavorable outcome among severe enterovirus (EV) central nervous system infections

Variable (n or mean ± SD)	Complete recovery No. of cases (%) [n = 30]	Unfavorable outcome[a] No. of cases (%) [n = 21]	*p*
Gender (male/female)	17/13	14/7	0.62
Age	4.80 ± 2.4	2.0 ± 2.8	0.0003
Prematurity	3/30 (10)	5/21 (23.8)	0.47
FTT	1/30 (3)	2/17[b] (12)	0.22
Fever	29/30 (97)	21/21 (100)	0.32
Peak body temperature (°C)	38.9 ± 0.7	39.1 ± 1.0	0.48
Ulcer	9/30 (30)	9/21 (43)	0.22
Rash	7/30 (23)	12/21 (57)	0.005
Seizure	7/30 (23)	9/21 (43)	0.08
Myoclonic jerk	8/29[b] (28)	4/20[b] (20)	0.70
Peak CRP (mg/dL)	1.95 ± 2.06	2.79 ± 2.47	0.20
Peak WBC (/μL)	10,992 ± 3777	17,451 ± 7132	0.0009
CSF WBC (/μL)	287 ± 534	104 ± 101	0.07
CSF protein (mg/dL)	44 ± 33	84 ± 135	0.23
CSF glucose (mg/dL)	61.9 ± 18.4	71.5 ± 36.3	0.30
CSF/serum glucose ratio	0.57 ± 0.16	0.74 ± 0.16	0.03
ALT (IU/L)	28 ± 6	972 ± 1920	0.05
CSF EV (+)	14/29[b] (48)	4/21 (19)	0.006
Rectal EV (+)	15/23[b] (65)	12/19[b] (63)	0.71
Throat EV (+)	23/26[b] (88)	14/21 (67)	0.04

Abbreviations: FTT = failure to thrive; CRP = C-reactive protein; WBC = white blood cell count; CSF = cerebrospinal fluid; ALT = alanine aminotransferase

[a]Unfavorable outcomes were defined as death or having neurologic sequelae at discharge.

[b]The denominator is the case number of data available, and the numerator is the case number with the factor.

included epilepsy, cerebral palsy or psychomotor retardation.

Factors associated with severe EV CNS infection and unfavorable outcome

To determine factors associated with severe EV CNS infection, we compared Group I patients having EV meningitis with Group II patients (severe CNS diseases). Factors associated with severe CNS diseases included younger age (<4 years old), seizures, myoclonic jerks, higher peak WBC count (>13,000/μL), lower CSF viral yield rate, oral ulcers and skin rash (Table 3).

Unfavorable outcomes in 3 fatal cases and 18 with neurologic sequelae were only found in Group II patients. Among Group II patients, unfavorable outcomes were associated with younger age (<2 years old), higher peak WBC count (>17,000/μL), skin rash and a lower CSF viral yield rate (Table 4).

Discussion

The NPEVs cause a wide spectrum of neurologic syndromes: aseptic meningitis, cerebellar ataxia, encephalomyelitis, and diffuse and focal encephalitis [1]. In this study, we focused on aseptic meningitis, encephalitis and encephalomyelitis. We found that the major NPEV-related CNS disorder was aseptic meningitis (84.1%). The percentages of encephalitis and encephalomyelitis were 13.2% and 2.1%, respectively. The male to female ratio was 1.78 overall, 2.0 (44/22) in patients younger than 2 years old, 2.57 (85/33) in those between 2 and 6, and 1.29 (84/65) in those older than 6. This may be a result of relatively higher physical activity, perhaps due to the higher close contact rate and infection rate for preschool boys than for girls.

Enteroviral meningitis is predominantly a pediatric disease. EVs are the most common cause of viral meningitis, accounting for 80 to 90% of cases [5]. In our study, the age of patients with enteroviral meningitis ranged from newborns to 36.6 years, with a majority in young children, especially in those from 4 to 6 years and those younger than 6 months. Such a phenomenon might be related to kindergarten attendance from 4 to 6 years of age. There were only 14 adult patients (4.2%) [aged ≥18 years] in our study. Nonetheless, NPEV should also be considered in adults with aseptic meningitis. Enteroviral meningitis in adults is not rare: there were 30 adults (17%) in 174 patients with

enteroviral meningitis in one study [6], and 44% in another study [7]. Meningeal signs occur in less than half of such cases [1].

In our study, 71.7% of patients with enteroviral meningitis had positive meningeal signs, 65% had stiff neck and 53.3% had photophobia. Rice et al reported that 80.4% of their cases had stiff neck, and 73.8% had photophobia [7]. In addition to meningeal signs, we found that severe cases tended to have more frequent occurrence of other systemic symptoms or signs such as decreased appetite, decreased activity, hypertension and general weakness (Table 2).

In one study, EVs were isolated in the absence of pleocytosis in 9% of CSF specimens [8]. We also found positive EV isolation in 21 (7.4%) of CSF specimens without pleocytosis. Elevated CSF protein was found in 29.4% of the patients. This is similar to the study of Severien et al [9]. In that study, the mean CSF/blood glucose concentration ratio was 0.62 in 86 patients. Hypoglycorrhachia (CSF/blood glucose concentration ratio ≤0.5) was found in 12 patients (13.9%). However, Roos suggested that only a ratio ≤0.3 is considered highly predictive of bacterial meningitis [10]. The minimum ratio in our patients was 0.35.

Ho et al found that most of those who died of EV71 infection were younger than 5 years of age and had pulmonary edema or pulmonary hemorrhage [11]. There have been various discussions on the possible mechanisms of pathogenesis of pulmonary edema associated with EV71 infection. Most of the evidence suggests a neurogenic origin and systemic cytokine storms, which lead to increased pulmonary vascular permeability [12,13]. In this study, CNS image studies were performed for only 3 patients who had pulmonary edema. According to brain imaging studies, 2qq patients who had brainstem encephalitis did not have evidence of DIC, so their pulmonary edema may have been related to brainstem encephalitis rather than DIC.

There were 8 patients (6 males and 2 females) with pulmonary edema/hemorrhage in the present study. Seven had myocarditis, and 5 were proved to have DIC. In addition to EV71-induced neurogenic pulmonary edema, viral sepsis syndrome, hepatic failure with DIC, or myocarditis can cause fatal pulmonary edema in severe neonatal EV infections [14-17]. Two of our fatal premature neonates contracted EV infection and had hepatic failure, myocarditis and pulmonary edema. This is another important cause of death in severe EV infections. The findings of fatal neonatal EV infection were similar to previous reports [16,17]. Their neurologic sequelae were limb weakness, epilepsy, cerebral palsy or psychomotor retardation. Most sequelae were related to virus invasion to CNS, hemorrhage or venous thrombosis, or hypoxia encephalopathy.

The skin rash as a risk factor of unfavorable outcome in Group II might have been due to the higher possibility of EV71 infection, which was more prone to lead to death or neurologic sequelae. The lower viral yield rate of CSF in Group II patients, especially those with unfavorable outcome, may suggest that direct viral invasion into neurons rather than meninges, causing negative viral isolation of CSF, might be the pathogenesis of severe neurologic diseases caused by NPEV. For example, EV71 was rarely isolated from CSF even in fatal cases or cases with sequelae [18,19].

In conclusion, neurologic diseases of NPEV occur predominantly in children less than 6 months old or those 3 to 9 years old, and in northern Taiwan such cases take place mainly in the summer (May, June and July). Males are predominant. The most common NPEV neurologic disease is aseptic meningitis (84.7%). People who were younger in age and who had higher WBC counts were at increased risk of severe neurologic diseases and unfavorable outcomes. Death was related to neonatal EV infection and EV71 infection in young children.

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