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Prognostic implications of myoclonic jerk in children with enterovirus infection

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To determine the prognostic value of myoclonic jerk in children with enterovirus 71 (EV71) infection, a retrospective study was conducted on 665 enterovirus culture-confirmed patients admitted to Chang Gung Children's Hospital from January 2000 to September 2001. The mean age was 35.0 months ± 32.2 months, ranging from 1 day to 15 years and 416 (62.6%) of them were male. Among these patients, 140 (21.1%) had EV71 isolated, and 150 (22.6%) had myoclonic jerk. Fifty one percent (72/140) of EV71 cases and only 15% (78/525) of non-EV71 cases had myoclonic jerk (p<0.001). The age of enterovirus patients with myoclonic jerk was younger than that of patients without myoclonic jerk (23.2 ± 17.6 vs 38.4 ± 34.6 months, p=0.005). The hospitalization and fever durations were significantly longer in the EV71 group than in the non-EV71 group (8.3 ± 13 vs 4.2 ± 2.7 days, p<0.001; 5.9 ± 4.8 vs 4.2 ± 3.0 days, p=0.009, respectively). Patients with myoclonic jerk also had higher percentages of severe illness, and neurologic sequelae (20% and 9%, respectively) than those without myoclonic jerk (5% and 1%, respectively) [p<0.001]. The positive predictive values of myoclonic jerk for EV71 infection, severe cases, and neurologic sequelae were 0.48, 0.20, and 0.09, respectively; the negative predictive values for severe cases and neurologic sequelae were 0.95 and 0.99, respectively. This study demonstrated that myoclonic jerk and EV71 infection are both independently associated with more severe disease and higher incidence of neurologic sequelae.

Key words: Enterovirus, myoclonic jerk, prognosis, risk factors

Enteroviruses can cause a wide spectrum of infectious illness in infants and children [1]. Most cases of enterovirus infection are mild illness without complications. The neurovirulent enterovirus 71 (EV71) was first recognized in 1969 in California and several outbreaks of EV71 have been reported worldwide thereafter [2-6]. During the past 4 years, severe outbreaks of EV71 have occurred in Taiwan, with 79 deaths in 1998, 25 deaths in 2000, and 26 deaths in 2001 [7].

Myoclonus, which ranged in severity from occasional myoclonic jerk during sleep to very frequent myoclonus, was a very frequent manifestation with unclear prognostic implications in children with central nervous system (CNS) involvement during the 1998 EV71 epidemic of Taiwan [6,8]. Enterovirus infection associated with this manifestation has rarely been reported, although its frequency could be underestimated [9,10]. Since the 1998 outbreak, myoclonic jerk has become one of the most important clinical manifestations pediatricians use to screen for and to monitor the severity of enteroviral infection in Taiwan. However, whether myoclonic jerk only implies enterovirus CNS involvement or also predicts the prognosis of disease remains unclear. This study investigated the prognostic value of myoclonic jerk in EV71 infection in children.

Patients and Methods

Patients

We retrospectively reviewed 665 hospitalized patients with culture-confirmed enterovirus infection at Chang Gung Children's Hospital from January 2000 to September 2001. Patients were divided into 3 groups as follows: 1) uncomplicated cases with herpangina or

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hand, foot, and mouth disease (HFMD); 2) aseptic meningitis cases; and 3) severe cases, including encephalitis, encephalomyelitis, poliomyelitis-like syndrome, and cardiopulmonary failure.

Herpangina included oral ulceration on anterior tonsillar pillars, soft palate, buccal mucosa, or uvula. HFMD patients had mouth ulcers plus vesicular rash on the hands, feet, knees, or buttocks. Aseptic meningitis was defined as an illness clinically compatible with cerebrospinal fluid (CSF) pleocytosis (leukocytes >5/μL if the patient was older than 1 month, >25/μL if the patient was a newborn) plus negative bacterial culture or isolation of enteroviruses from CSF. Encephalitis was defined as an altered level of consciousness, and poliomyelitis-like syndrome was defined as acute limb weakness and decreased reflex and muscle power. Encephalomyelitis included both encephalitis and poliomyelitis-like syndrome.

Sequelae were defined as residual neurologic deficits, tracheostomy with or without ventilator support, naso-gastric tube or other disability at 6 months' follow-up.

Myoclonic jerk records and data collection

Myoclonic jerk was defined as sudden contractions of muscle which may occur singly or twice or thrice in rapid succession, usually but not invariably affecting the flexors of the upper limbs and the extensors of the lower limbs; these contractions vary in degree and may range from a contraction insufficient to move a joint to one so violent as to throw the patient to the ground or to cause sudden waking during their sleep. We reviewed the medical records of patients, and searched and recorded available data on myoclonic jerk. Myoclonic jerk was detected and confirmed by a pediatrician if it occurred during hospitalization. In cases where it occurred before the patient was hospitalized, the patient's family were carefully interviewed about the presentation of myoclonic jerk to verify its occurrence. Other data collected included age, gender, fever and hospitalization duration.

Viral isolation

Throat swabs, rectal swabs, and CSF were submitted for virus isolation. Samples were inoculated into human embryonic fibroblast (MRC-5), LLC-MK2, and rhabdomyosarcoma (RD) cell cultures. When the enteroviral cytopathic effect involved more than 50% of the cell monolayer, cells were scraped and indirect fluorescent-antibody staining with panenteroviral antibody (Chemicon International, Temecula, CA, USA) was done to identify the enterovirus.

EV71 infections were defined as the isolation and typing of virus from at least 1 specimen mentioned above, in addition to a negative bacterial culture. EV71 was subsequently identified using 2 EV71 serotype-specific monoclonal antibodies, mAb 3323 and 3324 (Chemicon International) with immunofluorescence stains.

Statistical analysis

Student's *t* test was used to analyze the demographic and clinical data. Pearson's chi-squared test and Fisher's exact test were used to analyze the data of clinical diagnosis and outcomes, and the correlations of myoclonic jerk with EV71 infection and outcome. A *p* value of less than 0.05 was considered statistically significant.

Results

Demographic and clinical data

A total of 693 children had specimens that yielded enterovirus. Twenty eight patients with poliovirus isolates were excluded. The 665 remaining children included 416 boys and 249 girls with a male-to-female ratio of 1.67. Their ages ranged from 1 day to 180 months (mean ± SD, 35.0 ± 32.2 months). The duration of hospitalization ranged between 0 and 90 days (5.0 ± 6.6 days) and the fever duration varied from 1 to 41 days (4.5 ± 3.5 days). Of these 665 cases, 140 (21.1%) had EV71 isolated and 150 (22.6%) had myoclonic jerk (Tables 1 and 2).

Rate of EV71 and other enterovirus infection

Of the total cases, 462 (69.5%) were uncomplicated cases including 251 (54.3%) with HFMD and 211 (45.7%) with herpangina. Aseptic meningitis accounted for 149 (22.4%) cases (Tables 1 and 2). There were 54 severe cases, including 19 with encephalitis, 3 with encephalomyelitis, 14 with poliomyelitis-like syndrome, 16 with encephalitis/encephalomyelitis plus cardiopulmonary failure, and 2 with neonatal hepatic necrosis. Among them, 11 (1.7%) patients died, including 9 (1.4%) EV71 cases with cardiopulmonary failure and 2 (0.3%) non-EV71 cases with neonatal hepatic necrosis. Sequelae were noted in 18 (2.7%) EV71 cases.

Among the 140 EV71 cases, 94 (67.1%) were uncomplicated, including 88 (63%) with HFMD and 6 (4%) with herpangina (Table 1). Among the 39 severe cases, 9 were fatal cases and 18 had neurologic sequelae. These sequelae were as follows: limbs weakness with muscle atrophy in 11, and dysphagia with nasogastric tube feeding, diaphragmatic paralysis or central

Table 1. Demographic and clinical data in children with enterovirus 71 (EV71) and non-EV71 enterovirus infection

	Enterovirus 71 n = 140 (%)	Non-enterovirus 71 n = 525 (%)	*p*
Age (months)	26.4 ± 20.1 (2.4-104)	37.3 ± 34.4 (0-180)	0.064
Male/female (ratio)	91/49 (1.86)	325/200 (1.63)	0.566
Hospitalization duration (days)	8.3 ± 13.0 (0-90)	4.2 ± 2.7 (0-34)	<0.001
Fever duration (days)	5.9 ± 4.8 (1-41)	4.2 ± 3.0 (1-32)	0.009
Myoclonic jerk	72 (51)	78 (15)	<0.001
Clinical syndrome			
Uncomplicated cases[a]	94 (67)	368 (70)	<0.001[c]
Aseptic meningitis	7 (5)	142 (27)	
Severe cases[b]	39 (28)	15 (3)	
Outcome			
Sequelae cases	18 (13)	0 (0)	<0.001
Fatal cases	9 (6)	2 (0.4)	<0.001

[a]Uncomplicated cases were cases of hand, foot, and mouth disease or herpangina.

[b]Severe cases were cases of encephalitis, encephalomyelitis, polio-like syndrome, or cardiopulmonary failure.

[c]*p* value was measured with chi-squared test to test the difference of percentages of uncomplicated cases, aseptic meningitis, and severe cases between the EV71 group and non-EV71 group.

hypoventilation with tracheostomy plus ventilator support and also limb weakness in 7.

Among the 525 cases with non-EV71 infection, 13 were severe non-fatal cases and 2 were fatal cases (Table 1). None of the 21 newborns (3%) had EV71 isolates. The non-EV71 isolates from these 13 severe non-fatal cases included 6 panenteroviruses (untypable enterovirus), 1 coxsackievirus A9, 3 coxsackievirus A16, 1 echovirus, 2 coxsackievirus B3. The 2 fatal cases occurred in patients aged 6 and 7 days old, respectively, who died of neonatal hepatic necrosis and coagulopathy. One of them had echovirus 4 isolated from rectal swab and from throat swab, and the other had coxsackievirus B3 isolated from throat swab and CSF.

Overall, EV71 infection was associated with higher incidences of severe, neurologic sequelae resulting physical handicap, and fatal cases in comparison with non-EV71 enterovirus infection (Table 1).

Frequency of myoclonic jerk

Children with myoclonic jerk were younger and had a higher incidence of EV71 infection ($p<0.001$). Children with myoclonic jerk were also more likely to have severe illness ($p<0.001$) [Table 2].

Table 2. Demographic and clinical data in children with or without myoclonic jerk

	Myoclonic jerk n = 150 (%)	No myoclonic jerk n = 515 (%)	*p*
Age (months)	23.2 ± 17.6 (1.4-111)	38.4 ± 34.6 (0 -180)	0.005
Male/female (ratio)	87/63 (1.37)	330/185 (1.78)	0.208
Enterovirus 71	72 (48)	68 (13)	<0.001
Hospitalization duration (days)	6.5 ± 10.8 (1-90)	4.6 ± 4.8 (0-66)	0.096
Fever duration (days)	5.0 ± 2.9 (1-21)	4.4 ± 3.6 (1-41)	0.312
Clinical syndrome			
Uncomplicated cases[a]	113 (75)	349 (68)	<0.001[c]
Aseptic meningitis	7 (5)	142 (28)	
Severe cases[b]	30 (20)	24 (5)	
Outcome			
Sequelae cases	13 (9)	5 (1)	<0.001
Fatal cases	2 (1)	9 (2)	0.99

[a]Uncomplicated cases were cases of hand, foot, and mouth disease or herpangina.

[b]Severe cases were cases of encephalitis, encephalomyelitis, polio-like syndrome, or cardiopulmonary failure.

[c]*p* value was measured with chi-squared test of the difference of percentages of uncomplicated cases, aseptic meningitis, and severe cases between the myoclonic-jerk group and no-myoclonic-jerk group.

Table 3. Enterovirus 71 (EV71) and non-EV71 status according the presence or absence of myoclonic jerk in patients with different clinical syndromes

Syndrome	Enterovirus serotype	Myoclonic jerk n = 150 (%)	No myoclonic jerk n = 515 (%)	*p*
Uncomplicated cases[a]	EV71	42 (45)	52 (55)	<0.001
	Non-EV71	71 (19)	297 (81)	
Complicated cases[b]	EV71	31 (67)	15 (33)	<0.001
	Non-EV71	6 (4)	151 (96)	
Severe cases[c]	EV71	25 (64)	14 (36)	0.083
	Non-EV71	5 (33)	10 (67)	
Aseptic meningitis	EV71	6 (86)	1 (14)	<0.001
	Non-EV71	1 (1)	141 (99)	
Total cases	EV71	72 (51)	68 (49)	<0.001
	Non-EV71	78 (15)	447 (85)	

[a]Uncomplicated cases were cases of hand, foot, and mouth disease and herpangina.

[b]Complicated cases were cases of both aseptic meningitis and severe cases.

[c]Severe cases were cases of encephalitis, encephalomyelitis, polio-like syndrome, and cardiopulmonary failure.

Table 4. Predictive values of myoclonic jerk for enterovirus 71 infection, severe cases, and sequelae

	Positive predictive value	Negative predictive value
Enterovirus 71	0.48 (72/150)	0.87 (447/515)
Severe cases[a]	0.20 (30/150)	0.95 (491/515)
Sequelae	0.09 (13/150)	0.99 (510/515)

[a]Severe cases were cases of encephalitis, encephalomyelitis, polio-like syndrome, and cardiopulmonary failure.

Relationship between EV71 or non-EV71 and myoclonic jerk

A significantly higher percentage of EV71 cases had myoclonic jerk (72/140, 51%) than non-EV71 cases (78/525, 15%; $p<0.001$). About two-thirds (31/46, 67%) of complicated EV71 cases (severe and aseptic meningitis cases) had myoclonoic jerk. Interestingly, 45% (42/94) of uncomplicated EV71 cases also had myoclonic jerk (Table 3). The most likely reason for this may be lack of complete CSF study and EEG (electroencephalogram) examination in these cases with myoclonic jerk, which did not allow CNS involvement to be confirmed or excluded. Out of 42 EV71 cases with myoclonic jerk without other complications, only 5 had CSF exam. The CSF findings in these cases were normal: white blood cell range 1 to 5/μL with 100% lymphocytes, glucose range 57 to 70 mg/dL, and protein 35.1 to 68.6 mg/dL. Since all of the 42 cases with myoclonic jerk alone recovered completely, only 4 out of 42 EV71 cases with myoclonic jerk had EEG exam, and all of these exams were negative.

Predictive values of myoclonic jerk

The positive and negative predictive values of myoclonic jerk for predicting EV71 infection, severe cases, and sequelae are listed in Table 4. Although the positive predictive values of myoclonic jerk for severe cases and cases with sequelae were not high (0.2 and 0.09, respectively), the negative predictive values for severe cases and cases with sequelae were very high (0.95 and 0.99, respectively).

Discussion

Outbreaks of EV71 infection with a high incidence of CNS involvement have been reported with presentation varying from acute severe neurological diseases to devastating long-term neurological sequelae and even death [2-6]. In this study, EV71 infection resulted in higher incidences of severe cases, sequelae, and fatality than non-EV71 infection (28% vs 3%, 12.8% vs 0%, and 6% vs 0.4%, respectively, $p<0.001$). In contrast, almost all children (99.6%) with non-EV71 infection recovered completely. The majority (95%) of aseptic meningitis cases in this study were caused by non-71 enteroviruses, similar to a previous report [11].

Myoclonic jerk is defined as sudden contractions of muscles and may occur singly or twice or thrice in rapid succession. It may be provoked by touching or by sudden noise. The most common form occurs just as a person falls to sleep [12]. In addition, normal startle response, startle disease, sudden bodily jerk on falling

asleep, and nocturnal myoclonus, including periodic limb movement disorders in sleep, hypnotic jerk, and sleep starts, should be differentiated from myoclonic jerk with enterovirus infection [13-15].

Marsden et al divided myoclonus into 4 major etiologic categories, with CNS infection being one cause of myoclonic jerk [12]. There were several reports of myoclonic jerk induced by CNS infections, including subacute sclerosing panencephalitis, varicella-zoster virus, herpes simplex virus, rubella virus, human immunodeficiency virus [16] and opsoclonus-myoclonus syndrome induced by coxsackievirus B3 and Epstein-Barr virus [9,17]. Although the presentation of opsoclonus-myoclonus differs from myoclonic jerk in that opsoclonus-myoclonus has initial presentation of general tonic posture, the etiology and mechanism may be partly similar [12,18]. However, the detailed mechanism of these 2 syndromes remains unknown.

The trigger of myoclonus and myoclonic jerk may be from the cerebral cortex, brain stem, cerebellum, and spinal cord [19]. It should not be surprising that many anatomic sites in the CNS appear to be implicated in different types of myoclonus [12]. Particularly, Lai and Siegel reported that myoclonic jerk could be induced by microinjection of some neural substrates or pharmacologic substances into the brainstem of cats [19]. CNS infections of EV71 were usually associated with encephalitis, rhombencephalitis, encephalomyelitis, and polio-like syndrome [2-8]. Huang et al divided brainstem encephalitis into 3 grades as follows: grade I brainstem encephalitis with myoclonic jerk and tremor, ataxia or both; grade II brainstem encephalitis with myoclonus plus focal neurologic signs or cranial nerve palsy; and grade III with transient myoclonus plus cardiopulmonary failure [6].

This study found that patients with enterovirus infection who had myoclonic jerk appeared more likely to have severe presentations (20% vs 5%) and neurological sequelae resulting in handicap (9% vs 1%) [$p< 0.001$]. Nevertheless, we found that myoclonic jerk alone was not diagnostic for brainstem encephalitis and poorer prognosis in this study, because not all cases with myoclonic jerk had evidence of brainstem encephalitis or even evidence of CNS involvement. Although the majority of our patients with myoclonic jerk alone did not receive CSF or EEG study, and CNS involvement could therefore not be excluded, all of them recovered without neurological sequelae. Similarly, there have been reports of spontaneous recovery from opsoclonus-myoclonus syndrome caused by enterovirus infection [9] and rapid recovery from severe enteroviral encephalitis [10,20].

Interestingly, this study revealed that myoclonic jerk occurred more frequently in younger children. Perhaps that is because the younger the children are, the more limb reflex takes place [21], resulting in easier induction of myoclonic jerk whenever the CNS is infected in younger children.

Among 149 cases of aseptic meningitis in this study, most (142/149, 95%) were induced by non-EV71 enteroviruses and only 5% (7/149) had myoclonic jerk. The very low frequency of myoclonic jerk in aseptic meningitis may be due to non-EV71 infection or low association of meningitis with myoclonic jerk, but more investigations have to be done to test these hypotheses.

With regard to the predictive value of myoclonic jerk, there were low positive predictive values for severe or sequelae cases, but high negative predictive values for severe cases. Therefore, enterovirus-infected children without myoclonic jerk had a lower incidence of severe disease or sequelae.

There may have been some bias and other limitations in this study. First, this study used a retrospective review of chart records to collect data, with some records of myoclonic jerk based on the statements from the patients' family that might not have been entirely objective. Second, the real incidence of myoclonic jerk might have been underestimated in severe cases if we failed to observe or record the sign of myoclonus in patients who showed systemic manifestations of rapid deterioration or fatality. Third, we could not define the exact frequency of myoclonic jerk and the relationship between this frequency and clinical severity. Future prospective studies may be the only way to address these limitations.

In conclusion, this is the first report of the predictive value of myoclonic jerk on enterovirus infection. We found that although not all cases of enterovirus infection with myoclonic jerk were EV71 infection or brainstem encephalitis, EV71 patients and severe cases had a higher rate of myoclonic jerk. Importantly, patients with myoclonic jerk had probabilities of 48%, 20%, and 9%, respectively, for EV71 infection, and severe and devastating long-term neurological sequelae.

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