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Clinical features of echovirus 6 and 9 infections in children

Hao-Yuan Lee[a,b,f], Chih-Jung Chen[a,c], Yhu-Chering Huang[a,c,*], Wen-Chen Li[a], Cheng-Hsun Chiu[a,b], Chung-Guei Huang[c,d,e], Kuo-Chien Tsao[c,d,e], Chang-Teng Wu[a], Tzou-Yien Lin[a,c]

[a] Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[b] Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[c] Research Center for Emerging Viral Infections, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[d] Department of Medical Biotechnology and Laboratory Science, College of Medicine, Chang Gung University, Taoyuan, Taiwan
[e] Department of Laboratory Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[f] Department of Pediatrics, Nan Men General Hospital, Hsinchu City, Taiwan

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ABSTRACT

Background: Clinical features of echovirus 6 and 9 infections in children have not been comprehensively evaluated, particularly for sporadic cases.
Objective: To describe the clinical features of children with echovirus 6 or 9 infections.
Study designs: From 2000 to 2008, 199 children with culture-proven echovirus 6 or 9 infections identified in a university-affiliated hospital were included. Data extracted from 174 inpatients were further analyzed.
Results: Age ranged from 4 days to 15 years with a mean of 4.7 years. 123 (62%) were male. The disease spectrums were similar for echovirus 6 ($n = 100$) and 9 ($n = 74$) infections, with aseptic meningitis (49% and 51%, respectively) being the most common syndrome, followed by meningismus, upper respiratory tract infection, pneumonia, and herpangina. All 174 inpatients had fever but the duration of fever was significantly longer in patient with echovirus 9 infection than those with echovirus 6 infections (6.0 days vs. 3.8 days, $p < 0.001$). The rate of leukocytosis (leukocyte count > 15,000/μL) were significantly higher in patients with echovirus 6 infections than those with echovirus 9 infection ($p < 0.001$). One neonate with echovirus 6 infection died from hepatic necrosis with coagulopathy, and one infant with echovirus 6 infection and one child with echovirus 9 infection died from brain involvement. Two children had long-term sequelae of seizure disorder. The remaining 169 children (97%) recovered uneventfully.
Conclusion: For children with echovirus 6 or 9 infections requiring hospitalization, aseptic meningitis was the most common manifestation and fatal outcome or long-term sequel, though rare, might occur.
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1. Background

Echoviruses are single strand RNA viruses with 34 serotypes and are belonged to the genus *Enterovirus* of *Picornaviridae* family. The clinical syndromes associated with echoviruses are diverse, ranging from non-specific febrile illness, mild skin or mucosa lesions to overwhelming diseases such as sepsis-like syndrome, hepatic necrosis and disseminated intravascular coagulopathy.[1–3] In the United States from 1970 to 2005, echovirus 9 was the most prevalent enterovirus serotype and usually associated with aseptic meningitis outbreak.[4] Echovirus 6 was also a common serotype and contributed to 6.2% of all known serotypes in the US surveillance.[4] Similar to echovirus 9, echovirus 6 was also frequently associated with central nervous system infection. Both serotypes can occasionally cause severe diseases such as pneumonitis, hepatitis and death in neonates. However, the clinical features of echovirus 6 and 9 infections have not been comprehensively evaluated, particularly for non-outbreak cases.

Virologic database from Chang Gung Memorial Hospital (CGMH) between 2000 and 2008 indicated that echoviruses 6 and 9 were the two most prevalent serotypes and together contributed to 65.2% of all echoviruses isolates identified (unpublished data). Although being considered as a self-limited disease, echoviruses 6 and 9 have been found to cause deaths in children, especially in neonates.[5–13]

2. Objectives

In order to better characterize the clinical features of echovirus 6 and 9 infections in children, we conducted this study.

* Corresponding author at: Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Children's Hospital, No. 5, Fu-Shin Street, Kweishan 333, Taoyuan, Taiwan. Tel.: +886 3 3281200; fax: +886 3 3288957.
E-mail addresses: ychuang@cgmh.org.tw, ychuang@adm.cgmh.org.tw (Y.-C. Huang).

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3. Study designs

3.1. Isolation and identification of echoviruses 6 and 9

Chang Gung Memorial Hospital (CGMH) is a 4000-bed university-affiliated medical centre located in northern Taiwan. Virus isolation from clinical specimens was routinely carried out by the department of laboratory medicine with a previously described method.[14] Briefly, specimens were inoculated into human epidermoid carcinoma cells, canine kidney cells, human embryonic lung fibroblasts, and rhesus monkey kidney cells, and then observed daily for cytopathic effects (CPE) for at least 2 weeks. When the cell culture presented at least 25% of CPE, the cells were spotted and fixed on slides. When enteroviral cytopathic effect involves more than 50% of the cell monolayer, indirect fluorescent antibody staining with panenteroviral antibody was done in order to identify enterovirus (Chemicon International, Temecula, CA, USA), and then identified by immunofluorescent staining with echovirus blend monoclonal antibodies and echovirus-specific monoclonal antibody. All positive specimens were further confirmed by neutralization with type-specific pools of immune sera.

3.2. Case enrollment and data collection

From January 2000 to December 2008, a total of 118 children with echovirus 6 isolates and 81 children with echovirus 9 isolates were identified via an electronic database of virologic laboratory. After being approved by the institutional review board of CGMH, medical charts of these cases were reviewed. Demographics from both inpatients and outpatients were collected and analyzed. Only inpatients without concomitant bacterial or viral infection were included for further analyses of clinical diagnosis, clinical manifestations, laboratory findings, treatments, and outcomes.

3.3. Definitions

Aseptic meningitis was defined as pleocytosis (a white blood cell (WBC) count in the cerebrospinal fluid (CSF) >30 cells/mm^3 in neonates and >5 cells/mm^3 beyond the neonatal age) with a negative bacterial culture in CSF, and/or a positive result of virus isolation from CSF.[15] Meningismus is defined as patients had symptoms and signs of meningeal irritation, such as meningeal signs, headache, nausea, vomiting and fever, but without CSF obtained for analysis or negative results for CSF studies. Pneumonia was defined as patients had respiratory symptoms/signs and a compatible chest radiological finding. The diagnosis of encephalitis was based on altered consciousness lasting more than 24 h and/or focal neurological signs with abnormal electroencephalogram (EEG) or neurological image studies. Poliomyelitis-like syndrome was defined as acute limb weakness plus decreased reflux and muscle power. Myocarditis was defined as evidence of focal or diffuse depressed left ventricular function identified by an echocardiography or an elevation of cardiac fraction of creatinine kinase.[16] Hepatic necrosis with coagulopathy[15] was defined as aspartate aminotransferase more than three times the upper limit of normal value and platelet count less than 10^5/mm^3.

3.4. Statistical analysis

The descriptive statistics was performed with SPSS 16.0. The categoric variables were compared by ANOVA, chi-square test or Fisher's exact test where appropriate differences in means were assessed by the Student *t*-test. Statistical significance was determined at $p < 0.05$.

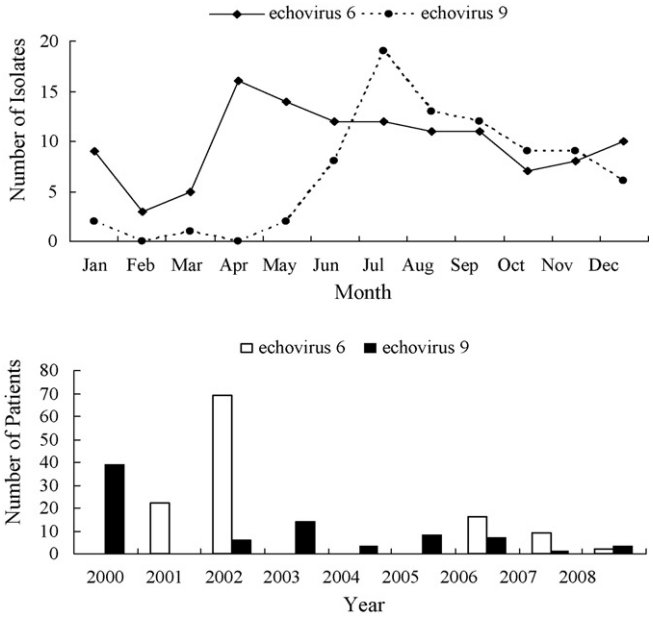

Fig. 1. Monthly incidence and yearly distributions of children with echovirus 6 and echovirus 9 isolates in Chang Gung Memorial Hospital from 2000 to 2008.

4. Results

Distributions of echoviruses 6 and 9 isolates during the study period are displayed in Fig. 1. Echovirus 6 isolates were identified in 2001–2002 and 2006–2008. Echovirus 9 isolates were distributed throughout the study period except for 2001. Seventy-one percent of echovirus 6 and 79.2% of echovirus 9 were identified during warm season from April to October.

Among the 199 children with echoviruses 6 or 9 isolates, throat swab or CSF were the two most common sources of specimens (Table 1). The proportion of isolates from rectal swab was significantly higher for echovirus 6 than for echovirus 9 (28.4% vs. 5.1%, $p < 0.001$). Echovirus 6 was also more commonly identified from multiple sites than echovirus 9 (18.4% vs. 6.4%, $p = 0.018$) (Table 1). The isolation rate of throat swab was 62% (73/118) for echovirus 6 and 75% (61/81) for echovirus 9. For CSF specimen, the isolation rate was 53% (33/62) for echovirus 6 and 44% (17/39) for echovirus 9.

Of the 118 children with echovirus 6 infection, 105 (89%) children were hospitalized; 93% of 81 children with echovirus 9 infection were hospitalized. Five patients with echovirus 6 infections were co-infected with other pathogens, including respiratory synovial virus in two cases, adenovirus, *Acinetobacter baumannii* and *Haemophilus influenzae* in one each. Two patients with echovirus 9 infections were co-infected with *Mycoplasma pneumoniae* and adenovirus, respectively. These seven patients were excluded for further analysis except demographics. Totally, 100 children with echovirus 6 infection and 74 children with echovirus 9 infection were included for further analysis.

Table 1
The source of specimens positive for echovirus 6 and echovirus 9 identified from 199 children.

Source of specimens collected	No. (%)	
	Echovirus 6 ($n = 118$)	Echovirus 9 ($n = 81$)
Throat	73 (61.9)	61 (75.3)
Cerebrospinal fluid	33 (28.0)	17 (21.9)
Rectum	33 (28.0)	5 (6.2)
Blood	3 (2.5)	0 (0)
Urine	1 (0.9)	4 (4.9)
Multiple sites (≥2 sites)	21 (17.8)	5 (6.2)

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