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Influenza A virus infection in infants

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Influenza A virus causes a variety of respiratory and nonrespiratory illness in children. The symptomatology varies with different age groups. The purpose of this retrospective study was to define the clinical characteristics of influenza A infection in Taiwanese infants. During the period from December 1997 to February 1998, 37 febrile patients younger than 1 year of age, including five newborns, were admitted to our hospital due to suspicion of sepsis or meningitis. The medical records of these patients were retrospectively evaluated. Influenza A virus was isolated from the specimens of the throat swabs in all patients, whereas no bacterial pathogen was detected. The most common clinical manifestations of these infants were lower respiratory tract infections, including pneumonia, bronchiolitis, and croup. There was no significant difference between the clinical characteristics of infants younger than 3 months and those aged from 3 months to 1 year. The mean duration of fever, peak of body temperature, and duration of hospitalization were 3.41 (±1.86) versus 4.4 (±2.02) days, 39.0 (±0.57) versus 39.9 (±0.63) oC, 4.9 (±1.49) versus 6.3 (±3.7) days in infants younger than 3 months and infants aged from 3 months to 1 year, respectively. The older infants aged from 3 months to 1 year had a significantly higher peak body temperature than the infants younger than 3 months ($p < 0.05$). Two patients with croup had a more severe clinical course, however, the outcomes were good in all patients. During an influenza A virus outbreak, influenza A infection should be included in the differential diagnosis of infants with lower respiratory tract infection.

Key words: Infant, influenza A virus, lower respiratory tract infection

Influenza A infection may cause a wide spectrum of clinical manifestations in infants, ranging from subclinical infection, upper respiratory tract infection, lower respiratory tract infection, neurological disorders with varying severity, to fatal pneumonitis [1-6]. Disease caused by influenza A virus has different clinical manifestations in different age groups. In Taiwan, influenza A virus infection occurs throughout the year, but is especially prevalent in cold months and rainy seasons. About 10% of Taiwanese patients are children younger than 1 year of age [7]. Several reports of the severity of influenza A infection in young infants have found various results [1,2,5,6]. However, no data has been reported in this population in Taiwan. During the period from December 1997 to February 1998, an outbreak of influenza A virus occurred in Taiwan. Two hundred and twenty strains of influenza A virus were isolated from the pediatric patients at the Diagnostic Virology Laboratory of Chang-Gung Children's Hospital. Of these patients, 37 (18.3%) patients were younger than 1 year of age. The purpose of this retrospective study was to define the clinical characteristics of influenza A infection in these infants and to compare the clinical manifestations of infants younger than 3 months of age with those infants aged 3 months to 1 year old.

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Materials and Methods

Subjects

We retrospectively reviewed the medical records of children younger than 1 year of age who were admitted to Chang-Gung Children's Hospital from December 1997 to February 1998, and had influenza A virus identified from throat swabs. We collected and analyzed data including age, gender, clinical symptoms and signs, diagnosis, and disease course of these children.

Viral isolation

Procedures for viral isolation were performed in all children at the time of admission. The specimens were obtained from the throat swab and inoculated to the cell culture as soon as possible. Human epidermoid carcinoma (Hep-2), canine kidney (MDCK), human embryonal lung (MRC-5), Rhesus monkey kidney (MK-2) cell cultures were used. Cultures were incubated

at 33 °C, rotated at 12 round per hour and maintained in minimal essential media containing antibiotics. All cultures were observed daily for cytopathogenic effect.

MK-2 cultures were tested for hemadsorption with 0.5% guinea pig erythrocytes at 4 °C at 3-day intervals. Suspected influenza virus isolates were identified by immunofluorescent assay using specific monoclonal antibody.

Statistics

Differences in categorical data between groups were analyzed with the Chi-square test. Continuous variables were analyzed with the Student's t-test. A p value less than 0.05 was considered statistically significant.

Results

Thirty-seven patients were included in this retrospective study. Fourteen patients were younger than 3 months of age. Twelve patients were male. According to their medical charts, 17 (45.9%) of the 37 patients had family members who had flu-like illness recently. Three patients had underlying conditions, including bronchiolitis obliterans, floppy infant, and atrial septal defect, respectively. However, only the patient with bronchiolitis obliterans had a more complicated disease course.

The most common clinical diagnoses among infants younger than 3 months were pneumonia/bronchiolitis (71.4%), and upper respiratory tract infection (28.6%) (Table 1). Mixed infections were found in two neonates. One neonate had upper respiratory tract infection and concomitant aseptic meningitis, with influenza A virus isolated from the throat swab, and enterovirus isolated from the cerebrospinal fluid, throat swab, and rectal swab. Another neonate with bronchiolitis was coinfected with *Chlamydia* sp. One 53-day-old infant had bronchiolitis and hepatitis. Liver function returned normal rapidly in this infant. In the patients aged 3 months to 1 year, the most common presentations included pneumonia/bronchiolitis (95.7%), otitis media (26.0%), and croup (13.0%). One 6-month-old boy had lobar pneumonia over the right middle lung but no bacterial pathogen was found on blood culture. Mixed infections occurred in two patients, including one with *Mycoplasma pneumoniae* infection and one with parainfluenza virus type 3 infection. Two of the three patients with croup had unusually severe courses. Due to respiratory failure, endotracheal intubation was required for one patient and intensive care for the other.

Table 1. Diagnosis in 37 infants with influenza A infection

Diagnosis	≤ 3 months n = 14 (%)	> 3 months-1 year n = 23 (%)
Pneumonia/bronchiolitis	10 (71.4)	22 (95.7)
URI[a]	4 (28.6)	0
Otitis media	0	6 (26)
Croup	0	3 (13)
Conjunctivitis	0	1 (4.3)
Meningitis	1 (7.1)	0
Hepatitis	1 (7.1)	0

[a] URI = upper respiratory tract infection

Table 2. Symptoms and signs in 37 infants with influenza A infection

Symptom/sign	≤ 3 months n = 14 (%)	> 3 months-1 year n = 23 (%)
Fever	14 (100)	23 (100)
Cough	11 (78.6)	23 (100)
Rhinorrhea	9 (64.3)	21 (91.3)
Crackle	8 (57.1)	18 (78.3)
Poor appetite	9 (64.3)	16 (69.6)
Poor activity	8 (57.1)	12 (52.7)
Rhonchi	6 (42.8)	10 (43.5)
Wheezing	3 (21.4)	10 (43.5)
Vomiting	2 (14.3)	9 (39.1)
Diarrhea	2 (14.3)	7 (30.1)
Cutis marmorata	2 (14.3)	0
Maculopapular rash	0	1 (4.3)

The most common symptoms and signs in infants younger than 3 months were fever (100%), cough (78.6%), rhinorrhea (64.3%), poor activity (64.3%), poor appetite (57.1%), and crackle (57.1%) (Table 2). These signs and symptoms were similar to those observed in patients aged 3 months to 1 year. Abdominal symptoms were more common in patients aged 3 months to 1 year. However, this difference was not statistically significant between these two age groups. Four patients had skin rashes; of these, three patients had cutis marmorata, and one patient had maculopapular rash.

The laboratory findings were unremarkable among these patients. Most of them had normal leukocyte count. Five (35.7%) of the 14 patients younger than 3 months and three (13%) of the 23 patients aged 3 months to 1 year had leukopenia (WBC < 5,000/mm^3). Only three (13%) of the patients aged 3 months to 1 year had a leukocyte count greater than 15,000/mm^3. The C-reactive protein level was normal or mildly elevated in most patients. Only one (7.1%) patient younger than 3 months and five (21.7%) patients aged 3 months to 1 year had C-reactive protein level greater than 40 mg/L. Abnormal liver function was demonstrated in one young infant, whose aspartate aminotransferase (AST) was 1248U/L (normal range: 15-55 U/L), and alanine

aminotransferase (ALT) was 886U/L (normal range: 5-45 U/L). However, both values returned to normal range 2 weeks later.

The mean duration of fever, peak of body temperature, and duration of hospitalization were 3.4 (±1.86) versus 4.4 (±2.02) days, 39 (±0.57) versus 39.9 (±0.63) °C, 4.9 (±1.49) versus 6.3 (±3.7) days in infants younger than 3 months and infants aged 3 months to 1 year, respectively. The older infants had a significantly higher peak body temperature than those younger than 3 months ($p < 0.05$). In general, infants with influenza A infection were characterized by abrupt onset of high fever which lasted for about 3.4 (±1.86) to 4.4 (±2.02) days, prominent symptoms involving the respiratory tract and occasionally involving the gastrointestinal tract, toxic appearance in nearly half of the patients, and were presumed to have a bacterial infection. Antibiotics were prescribed for all patients for at least 3 days. The clinical outcome was good in all patients.

Discussion

Unlike the "classic influenza" in older children and adolescents, influenza A infection in infants has its distinctive clinical features [8]. In older children and adolescents, it presents with an abrupt onset of fever, and is associated with flushed face, chills, headache, myalgia, and malaise. Cough and coryza are also present, however, the severity of these symptoms is generally far less than the severity of the systemic manifestations. Approximately 10% of older children and adolescents have evidence of pulmonary involvement [8]. However, among the infants younger than 1 year in this study, influenza A infection was characterized by high fever accompanied by lower respiratory tract infections, including pneumonia/bronchiolitis (86.5%), and croup (8%). There was no significant difference in the incidence of lower respiratory tract infection between infants younger than 3 months and those aged 3 months to 1 year. The high rate of lower respiratory tract infections in the present series is different from previous reports. This difference may be attributable to the different populations studied. In our study, all of the enrolled patients were in-patients with moderate to severe febrile illness. Hall and Douglas [1] reported that 12 children younger than 2 years of age in the pediatric ward with influenza A infection had a nosocomial acquisition, and seven (58.3%) of these 12 patients developed lower respiratory tract infections which were demonstrated by evidence of pulmonary infiltrates on the chest x-ray. In the series of Meibalance *et al* [2], five premature infants younger than 70 days old who contracted nosocomial influenza A infection developed symptoms and signs mimicking bacterial sepsis, i.e., lethargy, poor feeding, poor peripheral circulation and apnea. Three (60%) of the five patients had interstitial pneumonitis. In another report of influenza A infection imitating bacterial sepsis in early infancy, one (8.3%) of 12 infants younger than 3 months of age developed pneumonia [5]. A recent study by Glezen *et al* [6] of the clinical spectrum of influenza A infection showed that 11 (16%) of 69 episodes of influenza A infections in children younger than 1 year were lower respiratory tract infections. The remaining patients manifested either upper respiratory tract infections, otitis media, or subclinical infections. Patients from their study had less severe disease than patients from our study group, probably because of that all of their patients were from out-patient clinics.

The clinical outcomes were excellent in all of our patients. However, two of three patients with croup had a severe clinical course. The most common pathogen responsible for croup was parainfluenza virus, followed by influenza virus [9,10]. From our experience, croup caused by influenza A virus seemed to be more severe than that caused by parainfluenza virus. This is consistent with the result of Howard *et al* [11]. In their report, eight of 10 patients with croup who received tracheostomy had been caused by influenza A virus.

In the seasons during which influenza A virus infection is common as well as during a known outbreak, influenza A infection should be included in the differential diagnosis of infants with lower respiratory tract infection.

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