

Clinical characteristics of children with influenza A virus infection requiring hospitalization

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From September 1997 to March 2002, a total of 84 children were admitted to Chang Gung Children's Hospital due to influenza A virus infection. Influenza A virus infection was documented in 61 cases by viral isolation from throat and in 23 cases by serologic studies. The mean age of patients was 43.8 months, ranging from 20 days to 16 years. Forty-one (49%) patients were male. Lower respiratory tract infection (53 of 84 cases) was the most common clinical manifestation, occurring predominantly in children younger than 5 years (49 of 53 cases). The types of lower respiratory tract infection included bronchiolitis/bronchopneumonia in 33 cases, pneumonia in 17, and croup in 3. Central nervous system dysfunction was noted in 26 patients, predominantly in older children (18 of 26 cases). This included encephalopathy in 11 cases, encephalitis in 10, aseptic meningitis in 2, psychosis in 1, febrile convulsions in 1, and acute disseminated encephalomyelitis in 1. Gastrointestinal symptoms were mild in most patients. Diarrhea occurred in 18.4% of the children younger than 5 years, compared with only 8.4% of the older children. By contrast, abdominal pain was more common in older children (16.7%) than in younger children (6.7%). Ten children had leukocytosis (white blood cell ≥ 15000 / μ L) and 9 of them were younger than 5 years. Eleven children had a C-reactive protein level greater than 100 mg/L and 10 of them were younger than 5 years. The mean duration of fever and hospitalization were 4.6 ± 2.8 days and 7.4 ± 5.7 days, respectively. The clinical outcomes were excellent in all but 1 patient who died from intractable pulmonary hemorrhage. The frequency and duration of hospitalization due to influenza A virus is much greater than generally thought in Taiwan, suggesting an urgent need for educational programs to increase awareness of the characteristics and risks for this illness.

Key words: Child, hospitalization, influenza A virus

Influenza A virus causes diseases in all age groups. The clinical spectrum of influenza A virus infection is extremely broad, ranging from asymptomatic, respiratory tract infection with systemic features, multisystem complications affecting the heart, brain, liver, kidney and muscle, to even death [1]. Influenza A virus causes a variety of diseases which are partially influenced by the nature of virus but to a greater extent modulated by the age of patients [2,3]. Children have an important role in the spread of influenza, because school-age children are the main channel through which influenza is introduced into households [4]. Hospitalization and death occur primarily in infants and in the elderly [5].

Influenza virus infection frequently remains undiagnosed, even in hospitalized patients. It can precipitate secondary complications, including bacterial

infections and exacerbation of chronic conditions that lead to hospitalization. The association between influenza virus and pediatric hospitalization rates has not been fully explored. Glezen [6,7] found that although most influenza virus infections in children appear to be self-limited and without complications, more than 1% of the infections result in serious disease requiring hospitalization. However, there have been few studies of influenza A virus infection among children in Taiwan [8]. The purpose of this retrospective study was to define the clinical characteristics of influenza A virus infection in children requiring hospitalization and to compare the differences in clinical manifestations of children younger than 5 years with those of children aged 6 to 18 years.

Materials and Methods

Study period and population

A total of 84 children with a diagnosis of influenza A virus infection were treated in Chang Gung Children's

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Hospital from September 1997 to March 2002. The diagnosis of influenza A virus infection was based on a positive throat culture in 61 (72.6%) and on serologic evidence of influenza A virus infection in 23 (27.4%). Patients in whom viral isolation was done over 48 h after admission were considered nosocomially infected and were excluded from this study.

Definitions of illnesses

Pneumonia and bronchopneumonia were defined as respiratory tract infections with evidence on physical examination and chest film. The chest films were categorized according to the classification of Kantor [9]. Encephalopathy was defined as a depressed or altered level of consciousness, including lethargy, extreme irritability, or a significant change in personality or behavior that persisted for ≥ 24 h. Encephalitis was defined as the presence of encephalopathy plus ≥ 2 of the following criteria: fever (body temperature $\geq 38^{\circ}\text{C}$), seizure, focal neurologic findings, pleocytosis of cerebrospinal fluid (CSF) (white blood cell count >5 cells/ μL), electroencephalographic (EEG) findings compatible with encephalitis, and abnormal neuroimaging. Aseptic meningitis was defined as an inflammatory process of the meninges. The CSF in patients with aseptic meningitis is characterized by pleocytosis, increased protein, and the absence of microorganisms on gram stain and on routine culture [10].

Viral isolation

Human epidermoid carcinoma (Hep-2), canine kidney (MDCK), human embryonal lung (MRC-5), and rhesus monkey kidney (MK-2) cell cultures were available. Cultures were maintained in minimal essential media containing antibiotics and incubated at 33°C , rotated at 12 revolutions per hour. All cultures were observed

daily for cytopathic effects. MK-2 cultures were tested for hemadsorption with 0.5% guinea pig erythrocytes at 4°C at 3-day intervals. Immunofluorescent assay using specific monoclonal antibody (Trinity Biotech plc, Wicklow, Ireland) was used for identification of influenza virus.

Serologic study

Complement fixation antibodies were determined by standard microtiter techniques. A 4-fold or greater rise in paired serum antibody titer is considered a significant increase.

Statistical analysis

Analysis of variance was used to analyze the differences among subgroups. Correlations between two parameters were analyzed by Pearson's chi square test. A p value of less than 0.05 was considered statistically significant.

Results

Eighty-four patients were included in this retrospective study. None of them had received influenza vaccine prior to the development of infection. Forty-one (48.8%) patients were male, and 60 were younger than 5 years. The mean age was 43.8 months, ranging from 20 days to 16 years 2 months. Six children had underlying conditions including one each of bronchiolitis obliterans, floppy infant, atrial septal defect, epilepsy, thalassemia, and Down syndrome. Three patients had additional viruses isolated from specimens. One 20-day-old neonate with aseptic meningitis had enterovirus isolated from throat and rectal swabs. Another 76-day-old boy with bronchiolitis had enterovirus isolated from throat swab. A third patient was an 8-month-old boy who was admitted due to bronchiolitis and had parainfluenza virus type III isolated from throat swab. Concomitant bacterial

Table 1. Diagnosis in children with influenza A virus infection

| Category | No. of cases (%) | | p |
|--------------------------------|------------------------------------|--------------------------------|-------|
| | Age ≤ 5 years ($n = 60$) | Age 6-18 years ($n = 24$) | |
| Bronchiolitis/bronchopneumonia | 32 (53.3) | 1 (4.2) | 0.001 |
| CNS dysfunction | 8 (13.3) | 18 (73.3) | 0.001 |
| Pneumonia | 14 (23.3) | 3 (12.5) | 0.264 |
| Otitis media | 8 (13.3) | 1 (4.2) | 0.220 |
| Liver function impairment | 6 (10.0) | 0 | 0.108 |
| URI | 5 (8.3) | 0 | 0.145 |
| Croup | 3 (5.0) | 0 | 0.265 |
| Myocarditis | 0 (0) | 2 (8.3) | 0.024 |
| Conjunctivitis | 1 (1.7) | 0 | 0.525 |

Abbreviations: CNS = central nervous system; URI = upper respiratory tract infection

infections were identified in 8 patients, including *Mycoplasma pneumoniae* infection (serologic evidence) in 5 patients, pneumococcal antigen positive result from urine in 2, and sputum positive for *Chlamydia* antigen in 1.

Of the 84 children, 53 (63.1%) had lower respiratory tract infection (LRI), including bronchiolitis/bronchopneumonia in 33 cases, pneumonia in 17, and croup in 3 (Table 1). Twenty-six patients (31%) had central nervous system (CNS) dysfunction, including encephalopathy in 11 cases, encephalitis in 10, aseptic meningitis in 2, psychosis in 1, febrile convulsions in 1, and acute disseminated encephalomyelitis in 1.

Among the 26 patients with CNS dysfunction, 13 had lumbar puncture performed, and only the two patients with aseptic meningitis had pleocytosis in CSF (leukocyte count 55 and 34). Twenty-two patients underwent electroencephalography and 10 had abnormal EEG findings, including diffuse cortical dysfunction in 8 and focal epileptiform discharge over the temporal lobes in 2. Six brain computed tomographies and 2 brain magnetic resonance imaging (MRI) studies were performed and revealed brain edema in 2 cases and white matter lesions in 1. All but one of the patients with CNS dysfunction recovered fully at the time of discharge. One of the patients, a 1-year-4-month-old boy, was admitted to the intensive care unit after a short generalized convulsion from which he had not regained full consciousness. Nuchal rigidity was found but CSF analysis showed 1 leukocyte, protein 33.7 mg/dL, glucose 89 mg/dL, and a negative gram-stain smear. Laboratory studies including white blood cell count and C-reactive protein (CRP) were normal. No significant abnormality was found on EEG, but brain MRI scan revealed white matter lesion and thalamus

involvement. Under the impression of acute disseminated encephalomyelitis, steroid was given, and the patient's neurologic condition gradually improved over the following days. Influenza A virus was isolated from throat swab collected in admission. No neurologic sequelae or relapse of convulsion were noted during 2 years' follow up.

Of 13 patients available for alanine aminotransferase (ALT) determination, 6 had liver function impairment (at least 2-fold increase) that was mild and transient.

Two patients had acute myocarditis that presented with fever, lethargy, and arrhythmia. Regional myocardial dysfunction was revealed by multi-directional echocardiography, and cardio-specific creatine phosphokinase was elevated in both patients.

The clinical manifestations by age group are shown in Table 2. Lethargy was more frequent in younger children (56.7%) than in older children (12.5%) ($p < 0.05$). Neurologic symptoms were noted predominantly in older children and were characterized by confusional state (62.5%), visual hallucination (33.3%), or seizure (12.5%). Gastrointestinal symptoms were generally mild. Diarrhea occurred in 18.3% of the children younger than 5 years, compared with only 8.3% of the older children. By contrast, abdominal pain was noted less often in younger children (6.7%) versus older children (16.7%).

Complete blood cell counts and CRP level were measured in all patients either on admission or when symptoms appeared (Table 3). Ten children had leukocytosis (white blood cell count $\geq 15000/\mu\text{L}$) and 9 of them were younger than 5 years. In addition, 11 children had a CRP level greater than 100 mg/L and 10 of them were younger than 5 years.

Table 2. Clinical manifestations in children with influenza A virus infection

| Symptom/sign | No. of cases (%) | | <i>p</i> |
|----------------------|--|------------------------------------|----------|
| | Age ≤ 5 years (<i>n</i> = 60) | Age 6-18 years (<i>n</i> = 24) | |
| Fever | 57 (95.0) | 19 (79.2) | 0.026 |
| Cough | 52 (86.7) | 16 (66.7) | 0.035 |
| Coryza | 44 (73.3) | 16 (66.7) | 0.541 |
| Lethargy | 34 (56.7) | 3 (12.5) | 0.001 |
| Vomiting | 21 (35.0) | 8 (33.3) | 0.885 |
| Confusional state | 3 (5.0) | 15 (62.5) | 0.001 |
| Diarrhea | 11 (18.3) | 2 (8.3) | 0.252 |
| Visual hallucination | 1 (1.7) | 8 (33.3) | 0.001 |
| Abdominal pain | 4 (6.7) | 4 (16.7) | 0.158 |
| Tachypnea | 7 (11.7) | 1 (4.2) | 0.290 |
| Headache | 1 (1.7) | 6 (25.0) | 0.001 |
| Seizure | 1 (1.7) | 3 (12.5) | 0.035 |
| Myalgia | 1 (1.7) | 1 (4.2) | 0.497 |

Table 3. Laboratory data of children with influenza A virus infection

| Category | No. of cases (%) | | Mean | | p |
|------------------|--------------------------|----------------------------|--------------------------|----------------------------|-------|
| | Age ≤5 years (n = 60) | Age 6-18 years (n = 24) | Age ≤5 years (n = 60) | Age 6-18 years (n = 24) | |
| WBC (/μL) | | | 9675 ± 6702 | 7308 ± 3362 | 0.035 |
| ≥15 000 | 9 (15.0) | 1 (4.2) | | | 0.166 |
| ≤5000 | 13 (21.7) | 7 (29.2) | | | 0.466 |
| Hemoglobin, g/dL | | | 10.9 ± 1.2 | 12.6 ± 1.1 | 0.001 |
| Platelet (K/μL) | | | 297 ± 122 | 243 ± 118 | 0.068 |
| <100 | 3 (5.0) | 1 (4.2) | | | 0.871 |
| CRP (mg/L) | | | 60.7 ± 115.6 | 22.9 ± 34.5 | 0.025 |
| <10 | 32 (53.3) | 14 (58.3) | | | 0.677 |
| 10-40 | 11 (18.3) | 4 (16.7) | | | 0.857 |
| 41-100 | 7 (11.7) | 5 (20.8) | | | 0.278 |
| >100 | 10 (16.7) | 1 (4.2) | | | 0.125 |

Abbreviations: WBC = white blood cell; CRP = C-reactive protein

In this study, the mean duration of fever and hospitalization were 4.6 ± 2.8 days and 7.4 ± 5.7 days, respectively. There was no significant difference in these durations between children younger than 5 years and those aged 6 to 18 years.

The clinical outcomes were excellent in all but one previously healthy 12-month-old girl, who developed severe bronchopneumonia with respiratory failure 3 days after a febrile illness. Heart failure was also found on admission. She died 1 day after hospitalization due to intractable pulmonary hemorrhage. Influenza A virus was isolated from a nasopharyngeal swab. Autopsy was not performed.

Discussion

Although influenza virus is classified as a respiratory virus, LRI is thought to account for only about half of the influenza infections that result in hospitalization of children [7]. The remaining half reportedly have nonrespiratory illnesses including unexplained fever that rules out sepsis, febrile convulsions, acute gastroenteritis, and myositis of the calf muscles. Therefore, to clarify the prevalence of influenza A virus infection among pediatric patients requiring hospitalization, it is essential to perform virological studies in patients with involvement of major organ systems other than the respiratory tract.

Most of the nonrespiratory syndromes associated with influenza virus infection have been described in adults or older children. However, few studies of these nonrespiratory illnesses have been conducted in children [2,4]. Based on the data obtained in this study, LRI (53/84) was the most common clinical manifestation, occurring predominantly in children under 5 years of age (49/53). Central nervous system dysfunction was noted in 26 cases, predominantly in older children (18/

26). These findings show that influenza A virus may cause a wide spectrum of respiratory and neurologic illness in children in Taiwan.

A wide range of LRI rate was found in previous studies [11,12]. This difference may be attributable to difference in the populations studied. Approximately 10% of older children (age >5 years) and adolescents with influenza virus infection developed LRI [13]. The high rate of LRI (53/84, 63.1%) in this study does not conform to previous reports. Since the study population was restricted to hospitalized children, interpretations of the data should take into consideration that very ill or very young children were more likely to be hospitalized. Sugaya *et al* [3] reported that among 53 children hospitalized with influenza virus infection, 14 (26.4%) had bronchiolitis, 10 (18.7%) had pneumonia, and 4 (7.5%) had croup.

Influenza infection is a common risk factor for secondary bacterial pneumonia among adults and children [14]. Pneumococcal pneumonia is preceded by influenza A virus infection in many cases [15,16]. In this study, we identified 5 children co-infected with *M. pneumoniae* and one with pneumococcus. This may be attributed to the retrospective design of this study, because virus culture is usually not done when bacterial LRI is suspected, while viral culture and paired serum for *Mycoplasma* are done when LRI is suspected. A prospective study would have included virus culture in all cases.

An encephalitis-like picture is not uncommon among children hospitalized with influenza virus infection [17]. True encephalitis is comparatively rare in cases of influenza A infection, while benign confusional states and minor neurologic signs are more often observed [18]. Acute psychosis following influenza A has also been reported [19].

The frequency of CNS complications in influenza is hard to document accurately. The major difficulty in establishing the etiologic link between influenza and encephalitis is the infrequent isolation of virus from the CSF. Nevertheless, virus has been demonstrated in fatal cases in the brain [20,21] or in CSF in a few cases. Virologic evidence for systemic influenza A infection in 6 children with nonfatal encephalopathy was reported by Delorme and Middleton [22]. These 6 children had symptoms ranging from abnormal behavior to coma, which developed 2 to 5 days after fever or evidence of an upper respiratory tract infection, and all of them completely recovered. In this study, CNS dysfunction developed within 7 days of the respiratory symptoms in all patients. All 10 encephalitis were diagnosed based on clinical manifestations in addition to EEG or imaging study. But definitive causal association was not substantiated in these cases. Lethargy was more frequent in younger children, while a confusional state was predominant in older children. The retrospective nature of this study brings into question the accuracy of data on the consciousness level in younger children.

Based on the findings of electrocardiogram, echocardiography, and cardio-enzyme studies, a prospective study indicated that myocarditis is not uncommon in influenza infection, but is mostly asymptomatic [23]. In this series, 2 patients had acute myocarditis and both presented with arrhythmia.

Symptoms referable to the gastrointestinal tract such as anorexia, nausea, vomiting, and diarrhea can be found in as many as 40% to 50% of children with influenza virus infection, with an inverse relation to age [24]. Vomiting tends to be a more significant finding than diarrhea [25]. The present results are in agreement with previous reports. In this study, vomiting (35%) and diarrhea (18.3%) were an important component of the presenting symptom complex in children less than 5 years of age. By contrast, abdominal pain was more common in older children (16.7%) than in younger children (6.7%). This may be explained by their ability to describe the symptoms.

Among children hospitalized with influenza A infection, marked leukocytosis and a high CRP level are frequently observed in infants [10]. Putto *et al* [26] reported that the mean duration of fever was 5.1 days among children with influenza A virus infection. The findings of this study were similar to their report.

Although safe and effective influenza vaccines are available, influenza immunization has not been recommended for healthy young children, mainly because the importance of influenza virus infection as a cause of pediatric hospitalization has not been fully

understood. Many people have the misconception that influenza constitutes an illness that occurs in the vast majority of the population and only leads to hospitalization in a few debilitated persons with underlying conditions. However, most of our patients with influenza virus infection were healthy young children and not in the high-risk category. The results of this study indicate that the impact of influenza A virus on pediatric hospitalization is much greater than is generally thought and should receive increased attention in educational programs for health care workers and the general population in Taiwan.

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