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Original Article

Decreased leukocytes and other characteristics of laboratory findings of influenza virus infections in children

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Background and Purpose: An outbreak of influenza A and influenza B appeared at the beginning and end of 2006 in southern Taiwan. We conducted this study to test whether laboratory findings could differentiate influenza A from influenza B infection.

Methods: All children aged 16 years or less, who had nasal and/or throat swabs sent from inpatient or outpatient settings at National Cheng Kung University Hospital for the diagnosis of influenza infection from January 2005 to February 2007, were considered eligible subjects. Retrospective chart review of clinical and laboratory data was performed.

Results: 274 patients were enrolled, 151 with influenza A and 123 with influenza B, of whom 127 (46.4%) received laboratory examinations. The peak month of influenza A and influenza B infections was January 2006 and January 2007, respectively. Children with influenza B infections were older than those with influenza A infections ($p<0.001$). Influenza B-infected patients were more likely to have myalgia ($p=0.004$) than those with influenza A infections. Furthermore, children with influenza B infections tended to have lower leukocyte counts (6383 ± 3970/mm^3 vs 7639 ± 3476/mm^3, $p=0.004$), and higher serum creatine kinase level ($p=0.002$) than those with influenza A infections. The clinical outcomes were usually favorable.

Conclusions: The clinical features of influenza B and influenza A infections are similar. However, decreased leukocytes and increased serum creatine kinase can be used as adjunctive criteria for diagnosis of influenza B infection before viral culture results are available.

Key words: Child; Differential diagnosis; Influenza A virus; Influenza B virus; Leukopenia

Introduction

Acute respiratory tract infection (RTI) is not only the most common disease, but also the major cause of morbidity and mortality among children worldwide [1]. With the development of more sensitive diagnostic methods, several respiratory viruses have been found to cause acute RTIs. Among these, influenza infections remain the leading cause of RTIs and are responsible for substantial health burden in children [2-4]. Influenza virus infection has been associated with a spectrum of clinical manifestations, ranging from self-limited febrile illness to bronchiolitis and pneumonia.

The clinical manifestations in young children are generally similar to other respiratory viral infections, such as adenovirus, respiratory syncytial virus and human metapneumovirus [5]. Until now, no clinical features have proven useful for differentiating influenza infections from other respiratory viral infections. Although hematological abnormalities, such as isolated leukopenia or pancytopenia have been observed in influenza infection [6], related laboratory findings did not differ significantly among respiratory viral infections [7].

In general, clinical findings alone cannot differentiate between infection by different influenza species, with the exception of influenza B infection, which has

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a tendency to invade skeletal muscles more frequently than influenza A virus [8]. No comparative data on laboratory findings are available for different influenza viral infections in children. In 2006, we observed outbreaks of influenza A and B infections at the beginning and the end of the year in southern Taiwan. The objective of this study was to compare clinical findings and laboratory parameters in these two outbreaks in 2006 in order to identify possible markers to differentiate influenza A and B infections.

Methods

Patients

Children aged 16 years or less who presented with RTI or febrile illness who were suspected to have influenza infections by the pediatricians in the National Cheng Kung University Hospital were enrolled from January 2005 to February 2007. Data on demographics, past medical history, clinical and laboratory findings, hospital course, and outcome were obtained from medical records.

Laboratory study

All blood samples were analyzed at the central laboratory at our hospital after collection. The biochemistry profile, including aspartate aminotransferase, alanine aminotransferase, creatine kinase (CK) and C-reactive protein were generated via the VITROS 5,1 FS Chemistry System (Ortho-Clinical Diagnostics, Inc., Raritan, NJ, USA) after centrifugation. Complete blood cell counts and white cell differential counts were obtained by automatic analysis (Beckman Coulter® LH 750 hematology analyzer; Beckman Coulter, Miami, FL, USA) first and then checked by manual calculation under light microscope.

Viral culture

All of these specimens were collected in 2 mL of a viral transport medium containing 0.5% gelatin, Eagle's minimal essential medium, 200 U/mL penicillin-streptomycin, 0.05 mg/mL gentamicin, and 1.25 μg/mL amphotericin B. Refrigerated samples were inoculated within 24 h into tubes containing Madin-Darby canine kidney cells, Vero, A549 and rhabdomyosarcoma cells. The cultures were incubated at 37°C and inspected daily for a minimum of 14 days for viral cytopathic effect. Immunofluorescent assay was used for final confirmation of influenza virus infection by specific monoclonal antibody for influenza A and B viruses (Millipore, Temecula, CA, USA).

Statistical analysis

Continuous variables were summarized with mean and standard deviation and compared by Student's *t* test. The Mann-Whitney *U* test was used for non-parametric data. Categorical variables were compared by Pearson chi-squared test. A p value <0.05 was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS, Chicago, IL, USA) software package.

Results

Demographic data

There were 151 children with influenza A infections and 123 children with influenza B infections (Table 1). Children with influenza A infections were younger than those with influenza B infections (mean age, 5.7 ± 3.7 years vs 7.3 ± 3.6 years, $p<0.05$). There was no gender difference between influenza A and influenza B infections. Thirty patients (10.9%) had underlying conditions, including epilepsy, cerebral palsy, congenital heart disease, nephrotic syndrome, chromosome anomaly, leukemia, aplastic anemia and other malignancies under chemotherapy. Sixty nine patients (25.2%) required hospitalization, but none of them received intensive care. There was no significant difference in hospitalization days or febrile days between these two groups. Antiviral agents were not routinely used since the clinical symptoms usually improved after viral culture results were available. However, one case suspected to have nosocomial influenza infection had received oseltamivir treatment.

Outbreak descriptions

There were 47, 142 and 85 influenza infections in 2005, 2006, and from January to February 2007, respectively. The two major clusters were at the beginning of 2006 and at the end of 2006, the latter extending to February 2007 (Fig. 1). In 2005, there were only sporadic cases throughout the year and the predominant influenza subtypes were A/Wisconsin/67/05(H3N2)-like A/New Caledonia/20/99(H1N1)-like and a reassortant influenza B virus. In 2006, influenza A predominated in the first outbreak from January to April, while influenza B was responsible for the second outbreak from October 2006 to February 2007. A/Wisconsin/67/05(H3N2)-like, A/Solomon Islands/3/06(H1N1)-like and a reassortant influenza B strain were the major strains circulating during 2006-2007.

Table 1. Demographic data and clinical features of influenza A and influenza B infection in children

Variable	Influenza A (n = 151) No. (%)	Influenza B (n = 123) No. (%)	*p*
Age (years; mean ± SD)	5.7 ± 3.7	7.3 ± 3.6	<0.001
Male gender	98 (64.9)	86 (69.9)	0.379
Hospitalization	44 (29.1)	25 (20.3)	0.095
Underlying disease	15 (9.9)	15 (12.2)	0.551
Duration of hospitalization (days; mean ± SD)	4.8 ± 1.3	5.6 ± 1.8	0.057
Febrile (days; mean ± SD)	4.8 ± 2.4	4.9 ± 1.6	0.568[a]
Clinical presentation			
Fever	148 (98.0)	121 (98.4)	0.824
Maximum body temperature >39ºC	73 (48.3)	65 (52.8)	1.000
Cough	140 (92.7)	109 (88.6)	0.241
Coryza	116 (76.8)	84 (68.3)	0.114
Sore throat	37 (24.5)	43 (35.0)	0.058
Hoarseness	5 (3.3)	10 (8.1)	0.081
Nausea/vomiting	44 (29.1)	32 (26.0)	0.566
Diarrhea	19 (12.6)	18 (14.6)	0.621
Abdominal pain	24 (15.9)	18 (14.6)	0.773
Headache	16 (10.6)	19 (15.4)	0.231
Seizure	5 (3.3)	4 (3.3)	1.000
Myalgia	17 (11.3)	30 (24.4)	0.004
Ataxia	1 (0.7)	2 (1.6)	0.119
Conjunctivitis	9 (6.0)	2 (1.6)	0.119
Rash	7 (4.6)	2 (1.6)	0.095

Abbreviation: SD = standard deviation

[a]Available data in 56 patients in influenza A group and 29 patients in influenza B group.

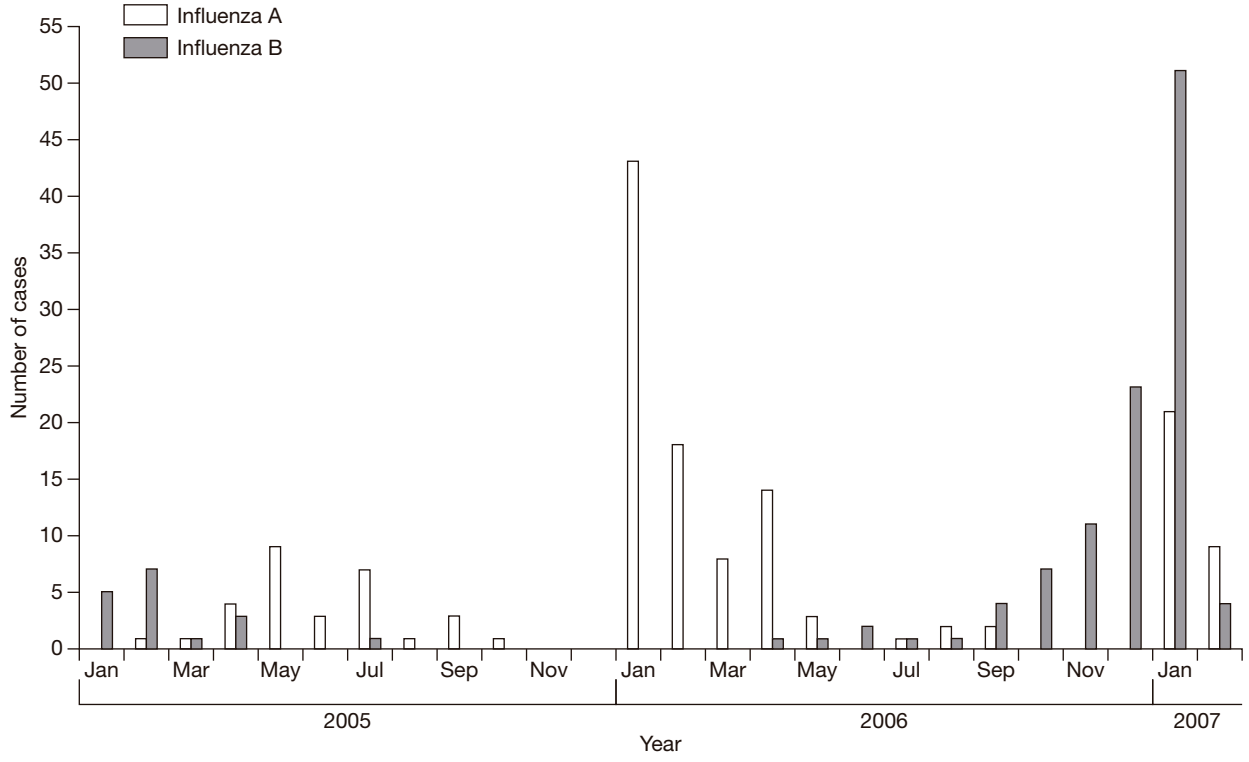

Fig. 1. Monthly distribution of influenza A and influenza B cases, from January 2005 to February 2007.

Clinical manifestations

The most common symptoms and signs were fever (98.2%), cough (90.9%), coryza (73.0%), sore throat (29.2%), nausea/vomiting (27.7%), myalgia (17.2%), abdominal pain (15.3%), diarrhea (13.5%) and headache (12.8%). These signs and symptoms were similar between influenza A- and influenza B-infected children, except myalgia (Table 1). Myalgia was more frequently seen in children with influenza B infections than influenza A infections (24.4% vs 11.3%, p=0.004). However, the mean duration of fever was not significantly different between the two groups (4.8 ± 2.4 days vs 4.9 ± 1.6 days). The clinical outcome was usually favorable.

Laboratory findings

Seventy four children (49.0%) with influenza A infections and fifty three children (43.1%) with influenza B infections had received laboratory examinations. The laboratory findings are summarized in Table 2. Mean white blood cell counts were lower in children with influenza B infections than influenza A infections (7639 ± 3476 cells/mm^3 vs 6383 ± 3970 cells/mm^3, p=0.004). Six (8.1%) of the 74 influenza A-infected children and seventeen (32.1%) of the 53 influenza B-infected children had leukopenia (white blood cell count <4000/mm^3). Leukopenia was more frequently detected in influenza B infections (p=0.001). Patients with influenza B infection had lower absolute neutrophil counts (p=0.018), absolute segment counts (p=0.019) and absolute monocyte counts (p=0.006) than those with influenza A infection. The mean hemoglobin level was higher in influenza B infections (12.4 ± 1.2 g/L) than in influenza A infections (12.9 ± 1.2 g/L, p=0.024). The mean platelet count was also lower in influenza B infections (223 ± 97 × 10^3 cells/mm^3) than influenza A infections (258 ± 92 × 10^3 cells/mm^3, p=0.01).

Elevated liver enzymes were found in 7 children with influenza A infections (30.4%; 7 of 23 children tested) and in 9 children with influenza B infections (45.0%; 9 of 20 children tested). CK was evaluated in 8 children in the influenza A group and 22 children in the influenza B group who complained of myalgia — two of 8 influenza A-infected children and eight of 22 influenza B-infected children had elevated CK. Children with influenza B infections had higher CK level than those with influenza A infections (131.8 ± 96.9 mg/L vs 1079 ± 2107.6 mg/L, p=0.002; Fig. 2). C-reactive protein was normal or mildly elevated in most patients, but was significantly higher in influenza A infections than in influenza B infections (36.5 ± 51.2 mg/L vs 18.3 ± 31.6 mg/L, p=0.003).

Clinical diagnosis

The most common clinical diagnosis in influenza A and B infections was upper RTI (Table 3). Children with influenza A infections had higher incidences of lower RTIs (including acute bronchiolitis, acute bronchitis, bronchopneumonia and pneumonia), than

Table 2. Peripheral blood cells and biochemical measurements in children with influenza A and influenza B infection

	Influenza A (n = 74)[a]	Influenza B (n = 53)[a]	p
WBC count (cells/mm^3)	7639 ± 3476	6383 ± 3970	0.004
WBC count (<4000 cells/mm^3; no. [%])	6 (8.1)	17 (32.1)	0.001
Hemoglobin (g/dL)	12.4 ± 1.2	12.9 ± 1.2	0.024
Platelet (× 10^3 cells/mm^3)	258 ± 92	223 ± 97	0.010
Platelet (<150 × 10^3 cells/mm^3; no. [%])	3 (4.1)	7 (13.2)	0.092
ANC (cells/mm^3)	5264 ± 3232	4016 ± 2566	0.018
ABC (cells/mm^3)	931 ± 1045	723 ± 690	0.803
ASC (cells/mm^3)	4333 ± 2843	3293 ± 2270	0.019
AMC (cells/mm^3)	704 ± 411	538 ± 399	0.006
ALC (cells/mm^3)	1560 ± 1535	1722 ± 1786	0.444
AST (U/L)[b]	50.4 ± 20.5	81.2 ± 97.1	0.869
ALT (U/L)[b]	22.3 ± 19.0	40.9 ± 48.7	0.140
CK (U/L)[c]	131.8 ± 96.9	1079.0 ± 2107.6	0.002
CRP (mg/L)	36.5 ± 51.2	18.3 ± 31.6	0.003

Abbreviations: WBC = white blood cell; ANC = absolute neutrophil count; ABC = absolute band form count; ASC = absolute segment count; AMC = absolute monocyte count; ALC = absolute lymphocyte count; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CK = creatine kinase; CRP = C-reactive protein

[a]Data are mean ± standard deviation unless otherwise indicated.

[b]Twenty three children were tested in the influenza A group; 20 children were tested in the influenza B group.

[c]Eight children were tested in the influenza A group; 22 children were tested in the influenza B group.

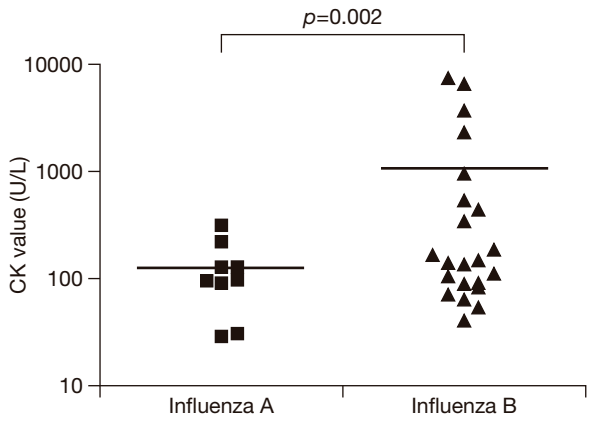

Fig. 2. Serum creatine kinase (CK) in children with influenza A and influenza B infections.

those with influenza B infections (28.5% vs 17.1%, p=0.031). About 10% of influenza-infected children had the principle diagnosis of gastroenterocolitis. Gastroenteritis was equally likely to be caused by influenza A and influenza B viruses in this study. Myositis was more frequently associated with influenza B infections than influenza A infections (13.0% vs 4.0%, p=0.006). Neurological complications, including febrile seizure, aseptic meningitis and cerebellar ataxia, were noted in five children with influenza A infections (3.3%) and six children with influenza B infections (4.9%). All of these patients recovered well without sequelae.

Discussion

In Taiwan, influenza outbreaks can occur either throughout the year with no distinct seasonality or with peak activity during winter seasons [9,10]. The present study demonstrated these two different patterns of disease activity in 2005 and 2006, respectively. Influenza viruses usually cause epidemics or pandemics by antigenic shift or drift of their hemagglutinin and neuraminidase genes. However, influenza B has never shifted to cause a pandemic, because it evolves by the accumulation of mutations and reassortment between different genes. From previous laboratory-based surveillance, the predominant strains circulating in Taiwan during 2003-2004 were A/New Caledonia/20/99(H1N1)-like, A/Fujian/411/2002(H3N2)-like, A/Panama/2007/99(H3N2)-like, and B/HongKong/330/2001-like[10]. From 2002 to 2005, there were increasing numbers of laboratory-confirmed cases caused by influenza B virus. The phylogenetic analysis revealed that the reassortment strain of the B/Victoria and B/Yamagata lineage contributed to the genetic diversity, providing the explanation for the observed epidemiology [11,12]. The increasing appearance of reassortant influenza B virus might also explain the unusual outbreak during 2006-2007 seasons. However, influenza vaccination may provide degrees of protection, since these influenza B reassortant isolates are antigenically similar to the WHO-recommended vaccine strain, B/Malaysia/2506/2004. In addition to influenza B virus, A/Solomon Islands/3/2006 (H1N1)-like strain influenza subtype circulated in 2006, and was subsequently chosen as the recommended influenza vaccine strain in 2007-2008 influenza season.

In both influenza A and influenza B infections, the most common clinical presentations are fever, cough, coryza and sore throat. In addition to respiratory symptoms, these patients sometimes present with

Table 3. Clinical diagnosis of children with influenza A and influenza B infection

	Influenza A (n = 151) No. (%)	Influenza B (n = 123) No. (%)	p
Upper RTI	106 (70.2)	94 (76.4)	0.275
Pharyngitis	78 (51.7)	82 (66.7)	0.012
Tonsillitis	18 (11.9)	9 (7.3)	0.203
AOM	10 (6.6)	3 (2.4)	0.153
Lower RTI	43 (28.5)	21 (17.1)	0.031
Bronchitis	7 (4.6)	5 (4.1)	0.818
Bronchiolitis	1 (0.7)	1 (0.8)	1.000
Bronchopneumonia	32 (21.2)	14 (11.4)	0.031
Pneumonia	3 (2.0)	1 (0.8)	0.630
Gastroenterocolitis	15 (9.9)	12 (9.8)	0.961
Myositis	6 (4.0)	16 (13.0)	0.006
Neurological complications[a]	5 (3.3)	6 (4.9)	0.511

Abbreviations: RTI = respiratory tract infection; AOM = acute otitis media

[a]Neurological complications include cerebritis, aseptic meningitis, and seizure.

extrapulmonary symptoms. Practically, it is still very difficult to differentiate these two viral infections from each other or from other respiratory viral infections by clinical symptoms alone. However, myalgia is more common in children with influenza B infections and may be the only clinical feature able to differentiate these two influenza infections. The relationship between acute myositis and influenza B infection has been reported previously [8,13,14]. Symptoms of myositis may vary from mild calf tenderness to severe impairment in walking. CK is an enzyme found primarily in skeletal muscles, and increases when there is significant injury to muscle, including myositis. Here, we not only demonstrated the correlation between symptoms of myositis and infection type, but also predictive value of laboratory findings of serum CK. Therefore, CK can be used as a biomarker to differentiate influenza B infection from influenza A infection.

RTI remains the most common diagnosis in both influenza A and B infections. However, influenza A infection is more often associated with lower RTIs in comparison with influenza B infection. There are two possible contributing explanations. First, children with influenza A infection are much younger than those with influenza B infection. Younger children more easily develop lower RTI in comparison with older children [15]. Second, the influenza A virus enters the host cell by recognition of alpha-2,6-linked sialic acid receptor via viral hemagglutinin protein. Because these receptors are mainly expressed in ciliated respiratory epithelium and goblets cells, such infections could result in significant impairment of the respiratory mucociliary apparatus [16]. Subsequently, influenza A infection would cause more severe lower respiratory tract damage.

Influenza infection is known to be associated with hematological abnormalities, such as pancytopenia or isolated leucopenia [6,17]. In recent years, the newly emerging avian influenza virus infection has also been commonly associated with pancytopenia induced by hemophagocytosis [18]. We found that leukopenia is not an uncommon finding in influenza infection, especially influenza B virus. In most circumstances, leukopenia is self-limited and usually resolves spontaneously soon after fever subsidence. It has been proposed that transient leukopenia induced by influenza A virus infection is through Fas-FasL-mediated apoptosis in peripheral blood lymphocytes [19]. In another way, influenza infections would impair hematopoeisis through induction of bone marrow B-cell apoptosis and subsequently lead to leukopenia and thrombocytopenia [20]. However, the influence of hematological manifestation between distinct influenza virus infections has not been addressed yet. This clinical observation can be used as an adjunctive criteria for diagnosis of influenza B infection in epidemic seasons, before viral culture results are available. In addition, many other viral infections, including enterovirus 71 [21], Epstein-Barr virus [22,23] or dengue virus [24] could cause leukopenia.

Because this was a retrospective study, the clinical presentation and laboratory data were collected from chart review. The medical records or laboratory examinations were done before the availability of viral culture results. As a result, there were some limitations, such as incomplete information and sensitivity of viral culture. Since not every patient had received laboratory tests, there might be selection bias in the interpretation of these results.

In summary, influenza infections remain one of the leading RTIs among children. The clinical presentations of influenza A and B infections are nearly indistinguishable, except that myalgia is more common in influenza B infection. Regarding laboratory findings, influenza B infections in children are more frequently associated with leukopenia and elevated CK level than influenza A infections. These typical features may provide useful diagnostic information for influenza B infection before viral culture results are available.

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