Influenza A and B Virus Infections in Children

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To obtain data on the clinical manifestations of infection, the age distribution, and the underlying conditions of children with influenza severe enough to lead to hospital referral, we performed a retrospective study of children treated at Turku University Hospital (Turku, Finland) in 1980–1999. Influenza A or B antigen was detected in the nasopharyngeal aspirates of 683 of the 15,420 children studied. The median age of children with influenza A was 2.0 years (n = 544), and that of children with influenza B was 4.2 years (n = 139) (P < .001). One-fourth of the children had an underlying medical condition. High fever, cough, and rhinorrhea were the most frequently recorded symptoms. Acute otitis media developed in 24% of the children, and pneumonia developed in 9% of the children. The study shows that the majority of patient hospitalizations for pediatric influenza involve previously healthy infants and young children. Laboratory confirmation of influenza is particularly important for children because the clinical presentation of the infection is less characteristic than that seen in adults.

Influenza in children ranges from subclinical illness to complicated disease that affects multiple organs. In addition to its typical manifestation as respiratory tract and systemic signs and symptoms, influenza can present as croup, bronchiolitis, pneumonia, febrile disease mimicking bacterial sepsis, or, on occasion, CNS, cardiac, muscle, or renal complications [1–6]. Influenza predisposes the infected patient to bacterial superinfections, of which otitis media [7, 8] and pneumonia [9, 10] are the most common. It is difficult to diagnose influenza in young children on the basis of clinical grounds, because no specific signs or symptoms exist, and because other viral respiratory infections that present with fever also occur frequently during an influenza season [11]. Therefore, the influenza-associated morbidity among infants and young children may have been underestimated.

Recently developed vaccines and antiviral drugs offer new approaches to the prevention and treatment of influenza. Live, attenuated, intranasally administered vaccine is safe and effective for use in children [12]. The neuraminidase inhibitors zanamivir [13] and oseltamivir [14] have been shown to be effective in the treatment of influenza. Because the use of extensive vaccination against influenza among children is under discussion [15], more data are needed regarding the risk factors for severe disease and hospitalization for influenza. Awareness of the different clinical manifestations of influenza in children is particularly necessary when effective antiviral agents are available. We report the clinical presentation of laboratory-confirmed influenza A or B virus infection in 683 children treated at a referral hospital.

PATIENTS AND METHODS

Patients. This retrospective study involved children treated as inpatients or outpatients at the Department of Pediatrics, Turku University Hospital (Turku, Finland), during the 20-year period from 1980 through 1999. Turku University Hospital, the only tertiary-care
hospital in southwestern Finland, serves a population of 750,000 individuals, including ∼150,000 children and adolescents <17 years of age. Most children are referred to the hospital by primary care givers. Children who had influenza A or B antigen detected in nasopharyngeal aspirates were identified by a review of the files of the Department of Virology, University of Turku (Turku, Finland). The medical records of these children were reviewed to collect clinical data. The following underlying conditions were recorded: asthma, major neurologic defects, malignancies for which treatment was being received, other immunosuppressive states, premature birth (i.e., birth at <37 weeks’ gestation), cardiovascular disease, and other significant chronic illnesses. Only radiologically verified pneumonias were recorded. The influenza vaccination status of the study children could not be recognized, but, during the study period, influenza vaccines were rarely used for children in Finland.

Virologic analysis. Detection of antigens in nasopharyngeal aspirates was used for rapid diagnosis of respiratory viral infections. Viral antigens were detected by indirect immunofluorescence in 1980–1981, by indirect EIA in 1982–1986, and by time-resolved fluoroimmunoassay from 1987 through 1999 [16]. In our laboratory, these methods of antigen detection have been found to have good sensitivity and specificity for the diagnosis of influenza, compared with serologic analysis [17] and immunoperoxidase staining of cell cultures [18]. A total of 15,420 nasopharyngeal aspirates were tested during the study period. Influenza A was detected in 544 children, and influenza B was detected in 139 children.

Statistical analysis. For continuous data, comparisons of the groups were performed by use of the $t$ test or the Mann-Whitney test in the case of failed normality tests, and, for categorical data, comparisons were performed by use of the $\chi^2$ test after Yate’s correction.

RESULTS

Diagnosis and patient characteristics. Influenza A diagnoses were made during outbreaks of varying intensity that occurred in winter. The month of peak activity varied between December and May. When data on full outbreak periods in 1980–1999 were compiled, it could be calculated that 90% of the influenza A diagnoses were made during a 60-day period around the peak of the annual outbreak (figure 1). Influenza B outbreaks occurred on a more irregular basis than did influenza A outbreaks. Although the total number of children with influenza B was only 20% of all influenza-positive children, diagnoses of influenza B predominated in 5 of 20 influenza seasons during the study period.

The median age of the children with influenza A was 2.0 years, and that of the children with influenza B was 4.2 years ($P<.001$; table 1). Figure 2 shows the age distribution of the children. Infants <1 year of age accounted for 27% of the children with influenza A and for 24% of those with influenza B. Influenza A clearly occurred more frequently among children <7 years of age and, especially, among those <4 years of age, than in older children. The frequency of influenza B also was high in infants. However, in children ≥1 year of age, the age-related decrease in the frequency of influenza B was not as exteensive as was that in the frequency of influenza A. Boys were overrepresented in both groups of children (those with influenza A and those with influenza B). One-fourth of the children had a chronic illness or another underlying condition (table 1). When hospitalized patients were analyzed separately (312 of those with influenza A were hospitalized, and 77 of those with influenza B were hospitalized), underlying conditions were detected in 26% of the children with influenza A and in 34% of those with influenza B. Children with influenza A or B presented at the Department of Pediatrics after having had fever for a median of 1 day or 2 days, respectively ($P=.048$).

Clinical findings. Table 2 shows the signs and symptoms of influenza in the children at presentation. Most children had a high fever, and febrile convulsions occurred in 12% of the children with influenza A and in 9% of the children with influenza B. Rhinorrhea occurred as frequently as did cough, and it occurred more frequently among children with influenza A than among those with influenza B ($P=.04$). Vomiting or diarrhea was documented in 24% of the children. Ill appearance was recorded more frequently for children with influenza A than for those with influenza B ($P=.02$). The presence of localized pain was assessed in children ≥3 years of age: cephalalgia was present in every fourth child in both groups, whereas
myalgia was present in 6% of the children with influenza A and in 15% of those with influenza B ($P = .02$).

Hospitalized patients accounted for 57% of all the study children and for an even higher proportion of the youngest children in the study. The rate of hospitalization was similar for children with influenza A or B infection. The median duration of hospitalization was 2.0 days for children with influenza A and 3.0 days for those with influenza B (difference not statistically significant). The median duration of fever (temperature, $\geq 38^\circ C$) during hospitalization was 1.0 days (no difference between patients with influenza A and those with influenza B). The incidence of febrile convulsions was 16% in inpatients with influenza A, compared with 6% in outpatients.

Acute otitis media occurred in 26% of the study children with influenza A and in 19% of those with influenza B (difference not statistically significant). Pneumonia was diagnosed in 9% and 8% of the children with influenza A or influenza B, respectively, and croup was diagnosed in 5% and 4% of the children with influenza A or influenza B, respectively. The frequencies of these influenza-related diagnoses were higher among hospitalized children than among nonhospitalized children; for example, acute otitis media occurred in 30% and 22%, pneumonia occurred in 12% and 10%, and croup occurred in 7% and 5% of the inpatients with influenza A infection or influenza B infection, respectively.

**CNS manifestations.** Encephalitis was diagnosed in 5 children, of whom 3 children with influenza A infection and 1 child with influenza B infection had an uneventful recovery. Encephalitis with multiviral etiology (parainfluenza 3, influenza B, and influenza A) followed by Guillain-Barré type polyradiculopathy resulted in major neurologic defects in a 6-year-old boy. Influenza A possibly caused CNS infection in both a boy with a diagnosis of viral meningitis and a girl with seizures, confusion, and abnormal findings of electroencephalography. Four children with influenza A infection had status epilepticus.
Table 2. Clinical findings, at presentation, for 683 children with influenza.

<table>
<thead>
<tr>
<th>Finding</th>
<th>Percentage of children with influenza A (n = 544)</th>
<th>Percentage of children with influenza B (n = 139)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>94</td>
<td>89</td>
<td>.10</td>
</tr>
<tr>
<td>Cough</td>
<td>67</td>
<td>60</td>
<td>.14</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>66</td>
<td>56</td>
<td>.043</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>17</td>
<td>.71</td>
</tr>
<tr>
<td>Febrile convulsions</td>
<td>12</td>
<td>9</td>
<td>.48</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>10</td>
<td>4</td>
<td>.021</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>8</td>
<td>.71</td>
</tr>
<tr>
<td>Conjunctivitis or photophobia</td>
<td>7</td>
<td>7</td>
<td>.98</td>
</tr>
<tr>
<td>Wheezing</td>
<td>6</td>
<td>6</td>
<td>.95</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>6</td>
<td>.95</td>
</tr>
<tr>
<td>Cephalalgia a</td>
<td>24</td>
<td>23</td>
<td>.99</td>
</tr>
<tr>
<td>Abdominal pain a</td>
<td>10</td>
<td>15</td>
<td>.29</td>
</tr>
<tr>
<td>Myalgia a</td>
<td>6</td>
<td>15</td>
<td>.023</td>
</tr>
</tbody>
</table>

* These symptoms were assessed only in children ≥3 years of age (i.e., in 203 of those with influenza A and in 79 of those with influenza B).

Of these 4 children, 2 had an uneventful recovery after undergoing short treatment with a ventilator, a 2-year-old previously healthy boy needed treatment with the ventilator for 7 days and then recovered with mild neurologic defects, and a 3-year-old girl with tuberous sclerosis died of status epilepticus without responding to treatment.

Other severe or uncommon manifestations. A 3-year-old girl with Down syndrome and myeloid leukemia was given a diagnosis of myocarditis and cardiac failure associated with influenza A infection. Two other female infants with Down syndrome, who were aged 5 months and 1 year, needed ventilator treatment for severe influenza A pneumonia, as did a 2-week-old female infant born with multiple anomalies. A 6-year-old girl had *Staphylococcus aureus* laryngotracheitis as a complication of influenza A infection. Myositis was diagnosed in 3 boys with influenza B, who were 6, 8, and 11 years of age. A 3-year-old girl with acute lymphoblastic leukemia died of progressive pneumonia of polymicrobial etiology 5 weeks after influenza A virus was detected. A male infant who had a severe neurologic defect caused by birth asphyxia died of bronchiolitis due to concomitant influenza A and respiratory syncytial viral infections.

Laboratory findings. A decreased WBC count (<4.0 × 10⁹ cells/L) was seen in 8% of the children with influenza A, compared with 19% of those with influenza B (P = .001), excluding children with malignancy or other immunosuppression (table 3). The WBC count was elevated to >15.0 × 10⁹ cells/L in 8% of all children in the study. Serum C-reactive protein (CRP) concentrations were normal or only slightly increased in most children (table 3). CRP values of >20 mg/L were more frequently found among children with influenza A infection than among those with influenza B infection (P = .004). However, CRP values of >40 mg/L were measured in only 12% of the children with influenza A and in 8% of those with influenza A without acute otitis media or pneumonia. Blood for culture was obtained from 160 children. One culture yielded *Stenotrophomonas maltophilia* interpreted as a pathogen. The results of cultures of spinal fluid samples obtained from 45 children were negative.

Antimicrobial therapy. Every fifth child received antibiotic treatment or prophylaxis before referral to the Department of Pediatrics. During hospitalization or at discharge, 50% of the children hospitalized with influenza A and 45% of those hospitalized with influenza B infection received antibiotics, usually for the treatment of otitis media or pneumonia. Antiviral drugs were not used for the treatment of influenza during the study.

DISCUSSION

In the present study, 78% of the children hospitalized with influenza A infection were <4 years of age. This finding is in agreement with the findings of other studies that showed that infants and young children have an increased risk for hospitalization for influenza [19–26]. Neuzil et al. [22] estimated that the rate of hospitalization attributable to influenza is as high in healthy infants <1 year of age as it is in adults with high-risk conditions. As with influenza A, the highest frequency of influenza B infections was observed in infants <1 year of age; however, thereafter, the age distribution of influenza B was
more even. School-aged children have been found to be primary disseminators of influenza B at the community level [27], although infants are the majority of hospitalized patients [28, 29]. In all age-distribution studies, a detection bias favoring infants is possible because infants shed the virus in larger amounts and for longer periods than do older children or adults. However, we do not consider detection bias to play any major role in the 10–20-fold decrease in the incidence of influenza noted in a comparison of infants and school-aged children in this study.

Underlying medical conditions—usually, asthma, neurologic deficits, or malignancies—were documented in one-fourth of the children with influenza A or B. This finding is consistent with the reported excess number of hospitalizations of children with chronic medical conditions during influenza seasons [19, 30]. In Finland, influenza vaccine is offered free of charge to children with chronic pulmonary, cardiac, or renal disease, diabetes mellitus, or immunosuppression, or to those receiving long-term salicylate treatment. However, vaccination coverage in the country is probably similar to that in the United States, where the majority of children are at risk with conditions such as asthma do not receive the vaccine annually [31, 32]. Although achieving higher vaccination coverage among high-risk children is important, the present study shows that the vast majority of patient referrals and admittances to hospitals involve previously healthy children and cannot be prevented with vaccination programs targeted to children with underlying conditions.

The predominant clinical features of influenza vary with age [1, 4]. The younger the child, the more difficult it is to distinguish influenza from other febrile illnesses on the basis of clinical grounds alone. The most common signs and symptoms of influenza recorded in the present study—fever, cough, and rhinorrhea—do not help in differentiating influenza from other viral infections. When the symptoms and signs of influenza A were compared with those of influenza B, ill appearance and rhinorrhea were found to be associated more often with influenza A. It should be noted, however, that the difference between the median age of children with influenza A and that of children with influenza B may interfere in this comparison. Influenza typically presents with an abrupt onset of high fever, provoking febrile convulsions in some children. Influenza has been found to cause febrile convulsions and, also, repeated seizures more often than do adenoviruses or parainfluenza viruses [33]. Although muscle ache and headache may be characteristic of influenza in adults, these symptoms are reported by a minor proportion of children and cannot be communicated reliably by children <3 years of age.

Frequent gastrointestinal manifestations have been previously reported in children with influenza [34]. Vomiting or diarrhea was seen in 24% of the children in the present study, but they usually were not the predominant symptoms. The nonspecific clinical presentation of influenza in children stresses the importance of laboratory diagnosis. Rapid detection of influenza A in the emergency department has been shown to decrease the need for other diagnostic testing and antibiotic use [35, 36]. Obviously, the population studied markedly affects the presentation of influenza seen. In a hospital-based study like the present study, more-severe presentations of influenza are typical. At the primary care level, the age distribution and presentation of children with influenza probably are different, and severe manifestations are rare.

Acute otitis media was diagnosed in 26% of the children with influenza A, which is slightly less than the 35% frequency of diagnosis of acute otitis media reported from a previous study of hospitalized children [37]. Nevertheless, the results support the concept of influenza viruses frequently predisposing to acute otitis media [7, 8, 26]. Whether some of the children treated as outpatients developed otitis media later in the course of their disease is not known. Inactivated [11, 38], live attenuated [12], and virosomal [39] vaccines have been shown to protect against influenza-associated otitis media. Treatment of children with influenza with oseltamivir also reduces the risk of acute otitis media [14].

Croup was the presenting diagnosis for 5% of the children with influenza. Fewer cases of croup are caused by influenza viruses than by parainfluenza viruses [28]. However, croup may be clinically more severe in children with influenza infection than in those with parainfluenza virus infection [40]. Influenza A virus also has been recognized as an important agent that predisposes patients to bacterial tracheitis [41]. Pneumonia occurred in 9% of our patients; whether these cases represent primary viral or secondary bacterial infections cannot be established. Juven et al. [10] detected influenza viruses in 4% of 254 children with community-acquired pneumonia. They demonstrated mixed infection with influenza and Streptococcus pneumoniae in one-half of these patients. In the case-control study of O’Brien et al. [42], severe pneumococcal pneumonia was associated with a preceding influenza A infection in children. It should be noted that in our analysis of influenza-positive children, later bacterial complications occurring when the virus is no longer secreted remain undetected. Determinations of WBC counts and serum CRP level may be helpful in the detection of bacterial coinfections because these values are low in patients with uncomplicated influenza. Leukopenia observed in association with influenza infection should not prompt any further evaluation, because influenza is known to cause lymphopenia. In our study, influenza B was more clearly associated with leukopenia than was influenza A.

PCR analyses of CSF suggest that influenza A [43] and influenza B [44, 45] may directly cause CNS infections. Recently, Morishima et al. [46] reported a high incidence of influenza-associated encephalitis and encephalopathy in Japan. They con-
sider, however, that direct invasion of the CNS by influenza virus is unlikely in most of their cases. We identified 11 children with encephalitis, encephalopathy, or status epilepticus associated with influenza infection. To further elucidate the pathogenesis of CNS disease during influenza infection, direct methods for detection of the virus in CSF should be used more widely.

The main advantages of neuraminidase inhibitors, compared with amantadine and rimantadine, are fewer adverse effects, activity against both influenza A and B, and rare resistance [47]. Reduction in the duration of symptoms of laboratory-confirmed influenza has been demonstrated in children 5–12 years of age who were receiving inhaled zanamivir [13] and in children 1–12 years of age who were receiving orally administered oseltamivir [14]. In field trials, the greatest benefit from anti-influenza drugs is gained if therapy is started early, within 48 h after onset of symptoms [48]. Studies of the use of neuraminidase inhibitors for the treatment of children hospitalized with influenza or infants <1 year of age are not yet available. Antigen-positive children hospitalized for severe influenza would probably benefit from antiviral therapy, regardless of duration of symptoms, which, in the present study, however, was short in the majority of children.

Our opinion is that the use of antiviral therapy for influenza generally should be based on detection of the virus. Although we support the use of specific antiviral therapy for children treated at the hospital, decisions about treatment of influenza at the primary care level cannot be based on data from hospitalized patients. In addition to treatment, antiviral drugs can be used prophylactically in specific situations when vaccination is not possible or effective [48]. In our study, the duration of the influenza A outbreak usually was 8 weeks. Because of the annual variations in influenza epidemics, the timing and duration of chemoprophylaxis should be based on local surveillance.

Recently, the US Advisory Committee on Immunization Practices recommended influenza vaccination for healthy 6–23-month-old children when feasible, in addition to strongly recommending vaccination of children with certain medical conditions [48]. This recommendation is in accordance with findings of the present study and of previous studies showing that previously healthy young children account for most patient hospitalizations for pediatric influenza [20, 21, 23, 25]. Calculations suggest that, for healthy children, vaccination against influenza would be cost-effective [49, 50]. It is noteworthy that immunization of children may also decrease influenza-associated morbidity and mortality in the adult population because of the important role of children in the dissemination of influenza [51].

Acknowledgment

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References
