A Summer Outbreak of Influenza A Virus Infection among Young Children

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In the summer of 2003 in Jerusalem, Israel, 23 children were hospitalized with influenza A virus (A/Fujian/411/02-like virus) infection. The majority were neonates and infants. Clinical manifestations included neonatal fever, bronchitis, bronchiolitis, and pneumonia, and outcomes were favorable. Continued surveillance between epidemic seasons could allow early recognition of influenza strains that will appear in the following influenza season.

Influenza epidemics typically occur in the winter months in temperate climate zones. During seasonal outbreaks, attack rates are highest among preschool- and school-aged children, and excess hospitalization and mortality occur among young children and the elderly population [1–3].

Summer outbreaks of influenza are rare in the Northern Hemisphere and have been mostly described in cruise ships and in crowded institutional conditions, such as occur in nursing homes [4,5]. Recognition of influenza A infection may be delayed when an outbreak occurs at an unusual time of the year or in an atypical clinical setting. We report on the occurrence of an unusual summer outbreak of influenza A virus among young children from Jerusalem, Israel, with predominant involvement of neonates and infants.

Patients and methods. All children hospitalized at the Hadassah University Hospital (Jerusalem) with acute respiratory tract infections were prospectively examined throughout the year for the presence of respiratory viruses by direct immunofluorescence assay (IFA) analysis and culture of nasopharyngeal aspirate specimens.

IFA was performed using commercial monoclonal antibodies (Chemicon International) directed against respiratory syncytial virus, influenza A and B viruses, parainfluenza viruses, and adenovirus. For direct typing and subtyping of influenza virus in respiratory specimens, RNA was extracted from nasopharyngeal aspirate specimens by use of QIAamp Viral RNA Minikit (Qiagen) and analyzed by multiplex RT-PCR as described elsewhere [6]. Influenza virus was isolated on Madin Darby Canine Kidney (MDCK) cells. Antigenic typing and subtyping of influenza virus isolates was performed by hemagglutination inhibition.

Nucleotide sequences of the hemagglutinin gene (HA) and the neuraminidase (NA) gene of influenza isolates were determined by direct PCR sequencing and analyzed as described elsewhere [7]. Serological tests for influenza antibodies were performed using standard hemagglutination inhibition assay. The presence of IgM antibodies was determined following 2-mercaptoethanol treatment.

Results. From December 2002 through April 2003, low influenza activity was recorded, and it was almost exclusively due to influenza B. During this period, no circulation of influenza A virus was documented in Israel, and the few cases of influenza A reported all occurred in travelers [8]. Between 27 May and 16 July 2003, there were 23 children with influenza A infection hospitalized in the Hadassah University Hospital in Jerusalem. Twenty-one of the patients were epidemiologically unrelated Arab children from East Jerusalem. These children came from different neighborhoods, and a careful epidemiological survey revealed no relation between their families and no identifiable common source of infection. Twenty-one children had community-acquired infection, and nosocomial acquisition was suspected for 2 of them: a 1-year-old patient who contracted the infection on hospital day 12 and a 1-week-old neonate who was readmitted with influenza infection 2 days after his discharge from the hospital.

Patients’ ages ranged from 1 week to 6 years (median, 6 months). Ten of the 23 patients were full-term, previously healthy neonates <3 months of age, and 15 of the 23 were younger than 1 year of age. Of the 8 children who were 1 year of age and older, 5 had other risk factors, such as asthma (2 children), congenital heart disease (1), failure to thrive (1), and cerebral palsy (1).

The onset of illness was acute, and fever was present in all the children. Clinical manifestations included neonatal fever, upper respiratory tract infection, otitis media, bronchitis, bronchiolitis, pneumonia, and gastroenteritis. Respiratory compli-
cations requiring intensive care occurred in 2 children. However, the outcome was eventually favorable for all children.

Influenza A was identified by IFA in nasopharyngeal aspirate specimens from all 23 children, and PCR revealed the presence of the H3N2 subtype. Influenza A viruses isolated in MDCK cells from 13 children were shown by hemagglutination inhibition tests with postinfection ferret antisera to be antigenically similar to A/Fujian/411/02-like viruses. A/Fujian/411/02-like viruses, distinguishable from A/Panama/2007/99-like viruses by hemagglutination inhibition testing, emerged during late 2002 and became increasingly prevalent worldwide during 2003 [9]. Sequences of the HA genes of selected viruses revealed 11 amino acid changes, relative to the HA of A/Panama/2007/99, that are characteristic of the HA genes of A/Fujian/411/02-like viruses. Furthermore, comparisons of partial sequences of the NA gene from the isolates showed that they fell within the other phylogenetic group, represented by the NA gene of A/New York/55/01, and therefore that the viruses were more closely related to many of the A/Fujian/411/02-like viruses circulating during the latter half of 2003.

Family history of recent upper respiratory tract infection was reported for at least 9 of the children. In addition, serological testing for influenza IgM antibodies identified subclinical infections among siblings and adults from 2 of 4 households available for testing.

Discussion. Reports of influenza in neonates are rare and have been limited to involvement of this age group in widespread winter outbreaks or as a result of nosocomial transmission in neonatal intensive care units [10, 11]. The predominance of neonates and infants in the out-of-season influenza outbreak we describe is highly unusual and suggests the presence of unique circumstances. In this regard, it is noteworthy that influenza A was not circulating in Israel during the preceding winter and a new antigenic variant, represented by A/Fujian/411/02, had emerged. Under these circumstances, neonates could have been more susceptible to influenza infection during the spring and summer of 2003 because of their low levels of protective maternal antibodies. Recently, it has been shown that a substantial proportion of children hospitalized for influenza during epidemic seasons are younger than 6 months of age [12]. In view of the mechanism suggested herein, one might predict increased activity and morbidity of influenza among neonates and infants following introduction of a new variant into the population.

The virus may have been introduced to Israel via international travel. It is interesting that the HA/NA combination of the Israel isolates was typical of A/Fujian/411/02-like viruses isolated during the second half of 2003 in Australia and New Zealand (A. Hampson, personal communication) and later in other European countries. In relation to recent reports and increasing concern regarding mortality among children with influenza in the United Kingdom and the United States, possibly due to infection with a similar H3N2 virus, most of the infections reported here were not particularly severe, and only 2 of the 23 children required intensive care.

Although symptomatic disease occurred among the very young and susceptible and among older children with underlying diseases, there was evidence of more widespread subclinical and low-grade infection among older children and adults. Furthermore, our investigation led to early recognition of a subsequent small outbreak of influenza A (data not shown) in 2 nursing homes whose staff workers resided in East Jerusalem, and it allowed for rapid application of control measures.

This report illustrates that influenza A infection can occur in the community throughout the year and underscores the need for continued active surveillance between epidemic seasons. This could contribute to early recognition of influenza strains that will appear in the following influenza season and could enhance preparedness for new variants.

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