Human Metapneumovirus Infection in the Paediatric Population

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G lobally, respiratory infections in childhood are a leading cause of morbidity, contributing to significant absenteeism and economic burden through utilization of healthcare resources. In the developing world, respiratory infections are also a major cause of childhood mortality, although the extent to which viruses contribute to such mortality is still unclear. Respiratory syncytial virus (RSV) and influenza are recognized as important contributors to hospitalization. However, despite the availability of sensitive diagnostic methods, an aetiological agent still cannot be identified in a proportion of children and adults with acute respiratory infection. For example, while paediatricians have known for a long time that the majority of acute bronchiolitis is caused by RSV, there remains a significant proportion of acute bronchiolitis that test negative for RSV. In June 2001, van den Hoogen et al[1] from the Netherlands reported the discovery of a respiratory virus in 28 nasopharyngeal aspirate (NPA) samples of children with respiratory tract infections. The new virus was named human metapneumovirus (hMPV).

VIROLOGICAL FEATURES

hMPV is an enveloped RNA virus of the Paramyxovirdae family.[1,2] This virus family includes human pathogens such as parainfluenza, mumps, measles and RSV. hMPV is classified in the

pneumovirus subfamily along with the human pathogen RSV and an avian virus that causes upper respiratory tract disease in turkeys, the avian pneumovirus. Although first recognized in 2001, hMPV is not a novel human pathogen that has recently crossed the species barrier from avian species to humans. There is serological evidence of human infection dating back at least to 1958 in the Netherlands, and in the past 10 to 25 years in Europe, Canada and the US.[1,3,4] This is probably a virus that has been well established in the human population for centuries and had not been previously detected because it is not easy to grow in the conventional cell lines that are routinely used for virus culture in the laboratory.

Two distinct types of hMPV (type A and B) have been delineated on the basis of genetic and antigenic analysis.[5] Both types appear to cause essentially similar clinical syndromes and have a widespread geographical distribution.[6] Since the virus is relatively difficult to culture in vitro, molecular methods such as reverse transcription-polymerase chain reaction (RT-PCR) are more sensitive and feasible options for routine clinical diagnosis. However, it is important to ensure that the primers used for RT-PCR diagnosis are sensitive in detecting both types of hMPV. Otherwise, there is a possibility of one type being under-represented.

EPIDEMIOLOGY

Serologic data from the Netherlands showed that 70% of Dutch children are infected by the age of 5 years, and all children are infected between 5 and 10 years of age. In the original report, 27 of 28 patients were below 5 years of age and 13 of them were infants between ages of 0 and 12 months. Subsequent studies have confirmed such findings. Our study of Hong Kong children and adolescents under the age of 18 years with respiratory tract infection hospitalized over a 13-month period found hMPV infection in children ranging from 3 months to 5 years of age, with a mean age of 32 months.[6] Another Dutch study in hospitalized children aged over 17 months also demonstrated that most hMPV infections occurred in children younger than 2 years, with a peak in children between 4 and 6 months of age.[7] While primary hMPV infection usually occurs at a young age, available data suggest that, like RSV infection, hMPV does not seem to induce persistent immunity, and reinfection may happen. The higher range of antibody titres for individuals older than 2 years suggests boosting of antibody responses as a consequence of reinfection. In addition, documented infection in adults, the elderly and recurrent infections in an immunocompromised child as well as immuno-competent children all support the notion that repeated infection with hMPV can happen throughout life.[4,8]

Distribution
Since the initial discovery of hMPV, reports from all over the world showed that it has a global distribution and affects all age groups. Places that have documented hMPV infection include Canada, the UK, Australia, France, Finland, Hong Kong, United States, China, Thailand, Japan, Italy, Israel, Argentina, Norway, Brazil and South Africa.[6,9-23]

Prevalence
The disease prevalence of hMPV largely depends on the study population. Studies limited to hospitalized children under the age of 2 years showed a prevalence of hMPV as high as 25%.[19] We found that hMPV accounted for 5.5% of the acute respiratory infections in 587 hospitalized children under 18 years in Hong Kong. Since it was a systematic sampling of hospitalized children, and the public hospital system in Hong Kong cares for 90% of the population, we estimated that hMPV contributed to 441.6 hospital admissions per 100,000 population ≤6 years of age in Hong Kong. Most studies of hospitalized children under 5 years of age showed that hMPV accounts for 5% to

7% of all respiratory infections. Studies that included adults and the elderly in addition to children reported a lower prevalence of 2.2% to 4.5%.[3,10,24] On the other hand, two studies that included only children with samples negative for other respiratory viruses found a prevalence of hMPV of about 10% and one study found a prevalence as high as 20%.[1,4,25] However, studies that examined only those tested NPA-negative for other common respiratory viruses may have underestimated the prevalence of hMPV infection since coinfection of hMPV with another virus has been documented not infrequently.

Seasonality

Initial studies of hMPV seasonality in temperate regions were limited to the winter months. Subsequent year-round studies confirmed that the peak season of hMPV is similar to that of RSV in temperate regions, mainly in the winter months from December to February. Our 13-month study in Hong Kong showed that hMPV had a spring-summer circulation during the study period, similar but not identical to that of RSV circulation. In addition, there may be a marked difference in the incidence of hMPV infections from year to year. A study from Italy found hMPV in 7% of children aged under 2 years in 2001 but 37% in such children the year before.[19] Similarly, a US study showed a significant difference in the rates of hMPV illnesses between two consecutive winters, at 1.5% during the winter in 1999-2000 and 7% in 2000-2001.[24] A more recent 5-year study from Argentina in children aged under 5 years found no hMPV in one year but detected hMPV in up to 16.6% in another.[20] All these observations suggest a variable intensity of annual hMPV outbreaks with absence of outbreaks in some years. Whether this reflects that hMPV circulates more like parainfluenza virus (with cycles >1 year) whereas influenza or RSV viruses have an annual peak circulation, needs to be determined in long-term studies.

Wheezing and asthma exacerbation are common in hMPV-infected children.

CLINICAL MANIFESTATIONS

Clinical Manifestations in Children

While asymptomatic infection documented by serologic responses in pre- and postseason blood samples has been noted in 4.1% of young adults in a prospective study in the US, asymptomatic infection has not been reported in children.[24] Clinical manifestations of hMPV in the initial report included symptoms ranging from mild respiratory problems to severe cough, bronchiolitis and pneumonia, accompanied by high fever, myalgia and vomiting. A wide spectrum of disease manifestations has been described since. Feeding difficulties, conjunctivitis and otitis media have also been reported.[14,26] We observed diarrhoea, hoarseness of voice, rash and febrile seizures in some of our series of children, which had not been previously reported.[6] The rash was a transient, nonpruritic maculopapular of truncal distribution. A significant proportion of children had febrile seizures, and two children had three seizures each during the same febrile episode. We also documented high fever with a mean temperature of 39.2°C in hospitalized children with hMPV, which has lasted for a mean duration of 4.5 ± 2.2 days.

While one study showed that asthma exacerbation was not associated with hMPV in children, most studies found wheezing to be one of the more prominent manifestations of hMPV in children.[6,13,26-28] Wheezing was found in 83% of 12 hospitalized hMPV-infected children with a mean age of 9 months, more frequent than those in the comparison groups with RSV or influenza A.[26] Wheezing was also found in 50% of another series of 54 hMPV-infected children with a mean age of 7.5 months.[28] In younger children, bronchiolitis rather than asthma exacerbation was more common. In a French study in which 88% of the 26 hMPV-infected children were between 3 and 12 months of age, 62% had bronchiolitis and 15% had

The newly discovered hMPV.

asthma exacerbations.[12] In a US study of hMPV-infected children with a mean age of 11.6 months, 59% of the 49 children had bronchiolitis and 14% had asthma exacerbations.[4] However, asthma exacerbation was more frequently diagnosed in hMPV-infected children when compared with children infected with RSV or influenza, despite the fact that children with RSV and influenza infection are older, with a mean age of 13 and 20 months, respectively.

In older children infected with hMPV, asthma exacerbation was more commonly diagnosed. In a Japanese study, 47% of children aged 2.5 years, on average, had wheezing; asthma exacerbation was diagnosed in 8.8% and wheezing bronchitis in 36.8%; none was diagnosed with acute bronchiolitis.[16] We noticed wheezing in 28% of children with a mean age of 31.7 months, with a diagnosis of asthma exacerbation in 23% and acute bronchiolitis in 10%. When compared with RSV-infected children, we found that children with hMPV infection were older and wheezing was more likely to represent asthma exacerbation rather than acute bronchiolitis. Asthma exacerbations accounted for 66.7% of wheezing cases among hMPV-infected children, compared with 16.7% in RSV-infected children.

Conversely, a study of 132 hospitalized children (mean age, 7 months) with acute wheezing found hMPV in 8% of them.[13] The authors also found that the chemokine profiles of interleukin-8 (IL-8), a chemotactic factor for neutrophils, and regulated on activation, normal T cell expressed and secreted (RANTES) chemotactic factor for eosinophils, in nasal secretions of hMPV-infected children who wheezed were different from those in RSV-infected children. Children with RSV infection had high levels of RANTES and varying concentrations of IL-8, whereas children infected with hMPV had low concentrations of RANTES and high concentrations of IL-8. Whether this finding suggests a different role of hMPV compared with RSV in asthma exacerbation warrants further investigation.

Clinical presentations of hMPV infection in children are largely felt to be similar to those of RSV. van den Hoogen[7] could not discriminate between clinical symptoms caused by RSV and hMPV when 25 hMPV-infected children were age-matched to RSV-infected children, although dyspnoea, hypoxaemia
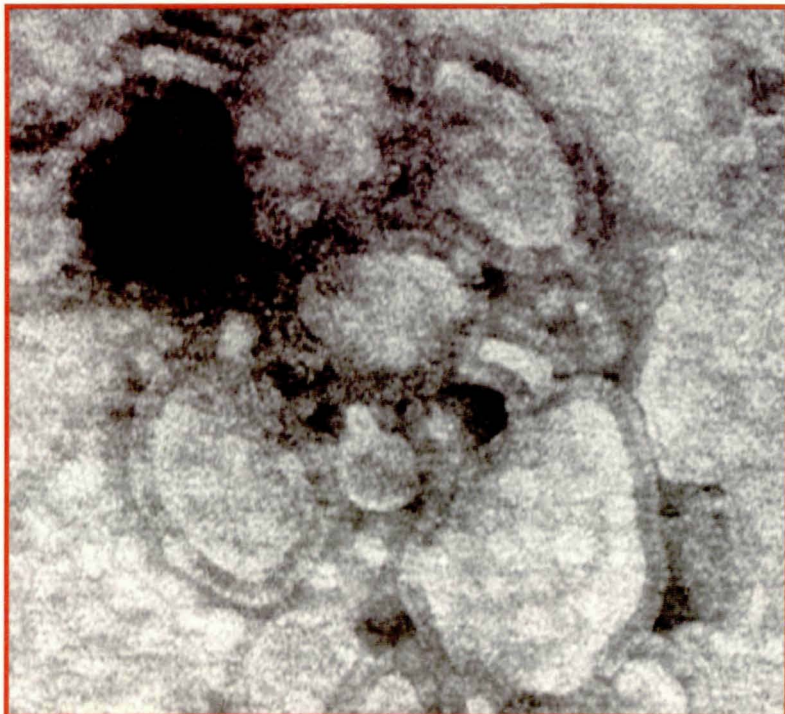
and feeding difficulties were found more often in RSV-infected children, suggesting hMPV infection to be a milder disease than RSV. However, when we compared 32 hMPV-infected children with age-matched controls infected with influenza A or RSV, hMPV was more frequently associated with lower respiratory tract involvement, in accordance with two other studies that observed that hMPV was more frequently diagnosed in children with lower respiratory tract infection than in those with upper respiratory tract infection.[3,19] An Argentina study also found that children with hMPV infection were hospitalized for significantly longer than those infected with RSV, with a mean duration of 11.5 days in the hMPV group vs. 5 days in the RSV-infected group.[20]

Clinical Manifestations in the Immunocompromised

Fatal pneumonia has been reported in at least one 7-month-old child with acute lymphoblastic leukaemia (ALL).[8] She had hMPV infections in two consecutive seasons by two genetically distinct strains. This incident also demonstrated that infection with one strain does not induce immunity against another. There had also been documentation of death in a child with ALL in an earlier report from the same series; detailed descriptions were lacking and this might represent the same patient.[3]

In our series, hMPV infection was also found in one child with ALL. The illness was nevertheless very mild, presumably because the infection occurred at the time of diagnosis of ALL and no immunosuppressive therapy had been initiated yet. hMPV infection has been documented in only three HIV-infected children.[23] One 6-month-old infant had very mild disease manifested as wheezing without hypoxia, and was hospitalized for only 1 day. One 6.6-month-old infant who was expremature had rales on examination, was hypoxic and was hospitalized for 9 days. The third child was a 5.7-month-old who also had pulmonary tuberculosis;

Practice Points

- Both type A and B hMPV appear to cause similar clinical symptoms and have widespread geographical distribution.

- Current data suggest that hMPV does not induce persistent immunity, and reinfection with hMPV happens.

- The peak season of hMPV is mainly in the winter months from December to February. Incidence may vary from year to year, suggesting that hMPV may circulate with cycles >1 year.

- hMPV infection has a wide spectrum of disease manifestations resembling those of RSV infection.

- Bronchiolitis is more common in younger children infected with hMPV, whereas wheezing and asthma exacerbations are more common in older children.

hypoxia and both wheezing and rales were noted on physical examination. She was hospitalized for 13 days.

CONCLUSION

It is exciting that a virus infecting humans for at least over 46 years was recently discovered. hMPV has since been shown to have global distribution and is a common cause of respiratory infections in children as well as adults. While preliminary data show that the general epidemiology and clinical features of hMPV infection appear to be similar to those of RSV, there are differences. Much needs to be learned of the full spectrum of hMPV disease, its impact on the immunocompromised, its seasonal and year-to-year circulation and its role in asthma exacerbation and perhaps even genesis.

About the Authors

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PICTORIAL MEDICINE

DACRYOCYSTOCELE

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Dacryocystocele is a relatively uncommon presentation of a nonpatent nasolacrimal system. Management is conservative (including gentle massage) avoiding the need for probing of the nasolacrimal system as the condition usually resolves within a week (on day 8 after birth in this case).

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Dr Sandhu is Clinical Research Fellow, Dr Robinson is Consultant Ophthalmologist (Oculoplastic), and Dr Aclimandos is Consultant Paediatric Ophthalmologist. All are from King's College Hospital, London, United Kingdom.

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A 2-day-old infant was referred by the neonatology department with a swelling (arrow) in the region of the nasolacrimal sac noted at birth. This was bluish in appearance, cystic and transilluminant, measuring 10 to 12 mm in diameter and consistent with a diagnosis of dacryocystocele (also termed amniotocele, mucocele).