



## Commentary

### Wheezing in children with viral infection & its long-term effects

Both wheezing and viral infections are common in children below five years of age. About 25 per cent of children by nine months of age and 50 per cent of children by six years of age have at least one episode of wheezing<sup>1</sup>. The wheezing in young children had diverse aetiology. It may be caused by an underlying disease such as airway malformation, internal or external narrowing of airways and cystic fibrosis, or it may occur without an underlying disease.

Viral infection is one of the important causes of wheezing in under-five children. However, all viral infections may not result in wheezing. Why only some children get wheezing after viral infections is not well understood. Information available in the literature suggests that variation in clinical manifestations after viral infections may be due to multiple factors such as born with small airways<sup>2</sup>, differential cytokine release leading to airway inflammation and airflow limitation and wheezing<sup>3,4</sup> and possibly type of viral pathogens<sup>5</sup>.

A study from eastern India in this issue<sup>6</sup> evaluated viral infections in 70 hospitalized children with wheezing below five years of age. They found single or mixed viruses in 31.42 per cent (22/70) of cases. Respiratory syncytial virus (RSV) was the most common virus (36%) followed by parainfluenza virus (PIV) 1, 2, 3 (18%), bocavirus (9%) and rhinovirus (RV) (5%). They also noted mixed infection in 32 per cent of cases. Authors tried to identify various clinical phenotype of wheezing and proportion of children with viral infections and their aetiologies. They identified viruses in pneumonia (n=3), bronchiolitis (n=9), episodic wheeze (n=2) and multiple trigger wheeze (n=6). Age and seasonal predilection were also observed in this study<sup>6</sup>. The method of virus isolation used was robust as throat and nasal swabs were evaluated by real-time multiplex polymerase chain reaction assay for 15 common viruses.

The type of virus isolated among children with wheezing may differ among various studies. Takeyama

*et al*<sup>7</sup> from Japan reported that RSV, RV, RSV+RV, influenza, PIV-3 and human metapneumovirus (hMPV) were detected in 33, 14, 8, 8, 5 and 3 per cent of samples, respectively, in children below three years of age who were admitted with wheezing. The isolated viruses in a study by García-García *et al*<sup>8</sup> from Spain were RSV (27%), rhinovirus (24%), adenovirus (17.8%), bocavirus (16%) and hMPV (4.7%); RSV and bocavirus were more common in infants compared to older children<sup>8</sup>.

Mummidu *et al*<sup>6</sup> identified viruses in 31 per cent of children while the same was up to 70 per cent in studies reported from Japan<sup>7</sup> and Spain<sup>8</sup>. However, the study from Japan<sup>7</sup> enrolled children below three years of age and the study from Spain<sup>8</sup> enrolled children below 14 yr of age with wheezing as compared to children below five years of age in the present study<sup>6</sup>.

There may be multiple reasons for not identifying viral infections in all children with wheezing. First and foremost is that wheezing may be due to underlying asthma and precipitated due to other triggers. It is difficult to differentiate between the two groups. Wheezing in children with asthma triggered by other than viral infection can be identified by past history of wheezing, personal or family history of asthma or atopy and predictable good response to bronchodilators. The design of the current study could not provide this information. Wheezing illness may occur due to other microbial agents including *Chlamydia* and *Mycoplasma spp*<sup>9</sup>. Identification of these organisms was not carried out in the enrolled patients. Although authors used a sensitive method for the identification of viruses, viral shedding may decrease with time.

Long-term effect of viral infections during infancy is of much interest and has been studied in detail. It may produce increased incidence of wheezing for the

first few years and possibly may lead to increased incidence of asthma in the later life<sup>7,10,11</sup>. However, mechanism of these long-term effects is not clear<sup>5</sup>. It is important to do a well-planned study on viral infections causing wheezing, aetiological agents, understanding pathogenesis and long-term outcome.

The RSV-induced wheezing early in life is associated with allergic asthma in later childhood and early adulthood<sup>10</sup>. The exact mechanism for this association is not clear. The viral infection may alter the airway function and may produce hyper-responsiveness of airways through various immune-mediated mechanisms, and the severity of such insult may be related to type of virus, host susceptibility and environmental factors. Recently, elevated levels of interleukin-3 (IL-3) and IL-12p40 in the bronchoalveolar fluid of infants with RSV-induced bronchiolitis have been correlated with recurrent wheezing and asthma late in life<sup>3</sup>. Sugai *et al*<sup>4</sup> reported that elevated level of macrophage inflammatory protein-1 $\alpha$  in nasopharyngeal aspirate in infants with RSV infection was a strong risk factor for the development of recurrent wheezing between two and five years of age. Rhinovirus infection in young children has also been found to have an association with recurrent wheezing and asthma in the later life independent from atopy<sup>7</sup>. Takeyama *et al*<sup>7</sup> followed the children with virus-induced wheezing for three years and found that children having rhinovirus were more likely to develop recurrent wheezing in follow up<sup>7</sup>. In another study, an outpatient wheezing illness caused by rhinovirus in children below three years of age was associated with asthma even in adolescents<sup>11</sup>.

To conclude, wheezing is common in preschool children and viruses are important cause of wheezing among them, but why all viral infections do not produce wheeze is still an area of further research. Similarly, the underlying mechanisms for association between viral infections early in life and development of recurrent wheezing and asthma later in life including adulthood are not understood well and need further research. Suggested mechanisms may be multiple and include host factors (born with smaller airways) or agent factors (virus type and strains). To identify virus aetiology of wheezing in young children is only initial step; there is a long way to go to prove the association between viral infection and wheezing and asthma in children and adults.

**Kana Ram Jat & Sushil Kumar Kabra\***

Department of Pediatrics, Division of Pediatric Pulmonology, All India Institute of Medical Sciences, New Delhi 110 029, India

\*For correspondence:  
skkabra@hotmail.com

Received September 2, 2016

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