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Review article

Preschool wheeze: pathogenetic factors

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Content

- Definition and causes of recurrent early life wheeze
- The role of airway infections in preschool wheeze
- Anatomic features of the airways of infants and young children
- Functional features of the airways of recurrent wheezers

Definition and causes of wheeze

Prevalence studies of recurrent wheeze in children under five have reported that one third of children in the US and Europe are affected, and rates and severity appear to be higher in developing countries.[1,2]

Episodic cough and wheezing is common in non-asthmatic children. Young children with multiple-trigger wheeze are more likely to have asthma compared to those with episodic (viral) wheeze. Atopic features, family history, and association between wheeze and colds or other triggers such as cigarette smoke, allergens, and exercise help predicting asthma.[3]

Table 1. Definition of wheezing disorders in preschool children.

Term	Definition
Temporal pattern of wheeze	
Episodic (viral) wheeze	Wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes
Multiple-trigger wheeze	Wheezing that shows discrete exacerbations, but also symptoms between episodes
Duration of wheeze	
Transient wheeze	Symptoms that commenced before the age of 3 yrs and are found (retrospectively) to have disappeared by the age of 6 yrs; transient wheeze may be episodic or multiple-trigger wheeze
Persistent wheeze	Symptoms that are found (retrospectively) to have continued until the age of ≥6 yrs; persistent wheeze may be episodic or multiple-trigger wheeze
Late-onset wheeze	Symptoms that start after the age of 3 yrs; late-onset wheeze may be episodic or multiple-trigger wheeze

Adapted from Brand, et al. Eur Respir J 2008;32:1096-110.[4]

The role of airway infections

Upper respiratory tract infections account for more than 80% of wheezing episodes in young children. Most children wheeze only when they have respiratory tract infections, are usually non-atopic, and outgrow symptoms by 6 years of age. Yet, since preschool-age children have 6 to 10 upper respiratory tract infections each year, recurrent virus-induced wheezing is associated with considerable distress and use of health care services.[5]

Many infants with severe bronchiolitis experience recurrent wheezing in later childhood.[6] Acute bronchiolitis is usually caused by:

- Respiratory syncytial virus (RSV) which infects most children worldwide by the age of two years
- Rhinovirus
- Human metapneumovirus (hMPV)
- Parainfluenza virus
- Influenza virus
- Adenovirus

Rhinoviruses (RVs) and recurrent wheeze
The mean age at the first symptomatic RV infection is 4 - 6 months compared with more than 6 months for other viruses, such as RSV. Re-infections occur regularly and are usually caused by different viral strains. RVs are frequently associated with wheeze in infants aged from 2–6 months. Whether RV infections are directly involved in the development of wheeze or whether they unveil obstructive lung diseases, is subject to debate. As RVs have the ability to invade lower airways and escape immunity, they may promote exaggerated inflammatory responses towards further stimuli, such as allergens, and lead to enhanced airway responsiveness. Infancy is a period of profound growth and development for the pulmonary and immune systems, and recurrent RV infections and associated inflammatory and remodeling processes may thus disrupt normal processes of lung growth.[7]

Human Metapneumovirus (hMPV) and recurrent wheeze
hMPV has a worldwide distribution and affects all age groups but predominantly affects young, elderly and immunocompromised patients, with children younger than five years of age being most susceptible to infection. Infection with hMPV occurs throughout the year but seasonal prevalence in late winter and spring has been observed and coincides with the peak of RSV infection.[8] In a large, prospective study of children with lower respiratory tract illness, human metapneumovirus was identified in 49 of 248 specimens (20 percent) that were negative for other pathogenic viruses The mean age of the infected children was 11.6 months, and 59 percent had symptoms of bronchiolitis.[9]

The role of bacterial colonization
Colonization of the airways with S. pneumoniae, H. influenzae, M. catarrhalis, or more than one of these organisms in asymptomatic neonates at one month of age was associated with increases by a factor of two to four in the risk of a first wheezy episode, persistent wheeze, acute severe exacerbation of wheeze, and hospitalization for wheeze, as well as increased blood eosinophil counts and total IgE and, eventually, increased reversibility of airway resistance and development of asthma by the age of 5 years. These associations are compatible with the observation of a predominantly neutrophilic inflammation in young children with severe recurrent wheeze.[10]

Early life Anatomic Features of the Airways
Until approximately 18 months of age, infants are virtually obligatory nose breathers. The airway caliber is considerably smaller than in older children and adults. If the radius of an airway is reduced, resistance will increase. As a consequence, factors that limit ventilation may be magnified in infants compared with older children and adults. The infant larynx is situated much higher in the upper respiratory tract (URT), close to the base of the tongue, and the epiglottis, which is relatively narrow and floppy, is located closer to the palate. The infant pharynx and supraglottic tissues are less rigid than those of adults and thus more susceptible to collapse and obstruction of the URT, particularly during inspiration. These anatomic differences could partially explain the infant preference for nose breathing and the difficulty of delivery of therapeutic aerosols to the lower respiratory tract (LRT).[11]

Gender differences in lung growth and development
Although girls tend to have smaller lungs and fewer bronchioles than boys in early childhood, they have higher size-corrected flow rates and specific airway conductance, probably due to a higher ratio of large to small airways. In addition, surfactant production, which begins at about 30 weeks' gestation, is delayed in males, possibly because of androgen production. Enhanced surfactant production in females might lead to increased patency of the small airways, and this could reduce the risk of respiratory distress in the neonatal period and possibly reduce the risk for virus-induced wheeze in early infancy.[12]

Functional features of the airways of recurrent wheezers
Compared with healthy controls, airway function is reduced in young children with recurrent wheeze, particularly those at risk for subsequent asthma. After adjustment for sex, age, body length and maternal smoking, significant reductions in expiratory flows and volumes were observed in steroid naïve young children with three or more episodes of physician confirmed wheeze.[13]

Disturbed lung functions in young wheezers

It was hypothesized that younger children may have relatively small airways caliber, significantly limiting airflow, and thus impairing secretion clearance and predisposing to lower airway infection. Elevated functional reserve capacity (FRC) was associated with anatomical lower airway abnormalities. The forced vital capacity (FVC) was higher in subjects with neutrophilic inflammation.[14]

Airway remodeling in preschool children with severe recurrent wheeze

In a study using flexible endoscopy, reticular basement membrane thickness was lower in preschool recurrent wheezers than in school children with asthma and was lowest below three years of age. Airway smooth muscle area was lower in preschoolers than in school children and was highest in preschoolers with atopy. Vascularity was higher in wheezy children under three years than in those 3-5 years old or school aged asthmatics. Mucus gland area was higher in preschoolers than in school children. Inflammatory cell counts in biopsies did not correlate with airway wall structure.[15]

The malfunction of alveolar macrophages in young infants

In the mature lung, alveolar macrophages (AM) prevent inappropriate immune activation by removing inhaled antigen via phagocytosis, and by directly suppressing pulmonary T cell proliferation. AM suppression of T cell proliferation is attenuated during the critical period for the development of immune tolerance, i.e. the first few months of life. Compared with the older child, there is attenuation of suppression of peripheral blood mononuclear cells (PBMC) proliferation in the infant at the higher AM:PBMC ratios.[16]

Vitamin D Status and Recurrent Wheeze

Vitamin D may modulate the risk of wheezing exacerbations being inversely associated with adverse asthma-related outcomes in older children and adolescents. The situation in infants and young children is less clear. A higher rate of exacerbation requiring oral corticosteroids (OCS) was observed in preschool children with severe intermittent wheezing who had serum 25-OH-VitD levels <20 ng/ml.[17]

The observed inverse associations between 25(OH)D levels and specific types of viral infection raise the question of whether vitamin D could moderate the frequency or severity of acute respiratory tract infections.[18] A strong inverse association between maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age was reported. Pregnant and lactating women are known to be at higher risk of vitamin D deficiency, and this observation provides additional support to the recommendations of maternal intake of >400 IU/d during pregnancy.[19]

However, a more recent study revealed that the use of 2800 IU/d of vitamin D3 during the third trimester of pregnancy compared with 400 IU/d did not result in a statistically significant reduced risk of persistent wheeze in the offspring through age 3 years.[20] Also, the 2017 Global Initiative for Asthma (GINA) guidelines stated that there is no good quality evidence to date that vitamin D supplementation leads to improved asthma control or fewer exacerbations.[21]

Key Notes

- Viral respiratory infection is the leading cause wheezing episodes in infants and young children
- Bacterial colonization of the airway in early infancy may increase the risk of recurrent wheeze
- Upper and lower airway anatomic peculiarities in infants and young children contribute to airway resistance
- Airway remodeling can start in young children
- The relation between nutritional status and the risk of wheezing exacerbations needs extensive evaluation

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