

## **Wheezing During the First Year of Life: Is it Asthma?**

### **Definition of Infantile Asthma**

Bronchial asthma, the most common chronic disease of childhood, is defined as a chronic inflammatory disease of the lower airways, leading to symptoms of recurrent wheezing and cough. Hence, asthma should be considered as a syndrome, made up by a number of different types and occurring at all ages, with symptoms that can start during infancy or childhood and even can persist up to adulthood(1). Most definitions of asthma do not include duration of the disease nor frequency of the symptoms. However, most researchers accept a duration of at least 6 months and a frequency of at least 3 attacks. Therefore, if asthma is defined as being the equivalent of 'recurrent wheeze', then logically, recurrent wheezing of infancy can be defined as asthma (at least after having excluded specific airway diseases such as cystic fibrosis, immune deficiencies, structural airway abnormalities, and others). On the other hand, asthma should be considered as a chronic disease, which holds in that chronicity was shown, or at least, can be expected. In other words, it is expected that the asthmatic infant will develop persistent episodes of wheezing during subsequent childhood, even during adulthood. In view of this, the main definition of asthma in infants should be based on the prediction of persistence of symptoms beyond infancy. Infantile asthma can, therefore, be defined as recurrent wheezing of which it is expected to persist, leading to the question: how to

predict persistence of recurrent infantile wheezing?

### **Infantile wheezing**

Wheezing is a symptom that is not always easily recognized. Other symptoms such as snoring and rattles, are often labelled as wheezing. In studies by Cane and Elphick it was shown that there is an important degree of inaccuracy in the use of the term 'wheeze' by parents and clinicians, which may lead to overdiagnosis(2,3). Moreover, imprecise use of this term has potentially important implications for clinical trial selection and for assessment of therapy.

In our studies on Singaporean infants, we found that one-fourth had wheezed before the age of 2 years(4). Similar results were found in other studies, such as the Tucson Children's Respiratory Study, a cohort study on 1246 subjects, in which the prevalence of infantile wheezing was more than 30%(5).

Infantile wheezing is a heterogeneous disease, in which, among others, two major types of wheezing can be distinguished: viral-induced wheezing and wheezing that is associated with allergy. The first group consists of two-thirds of all wheezy infants, is a transient form of recurrent airway obstruction, and is associated with low premorbid lung function. As these wheezy infants have a favorable prognosis, they only need minimal supportive treatment. However, severe attacks of wheezing, induced by RSV and clinically diagnosed as bronchiolitis, can be associated subsequently with an increased risk of recurrent wheezing and allergic reactions during early childhood(6). More recently, human metapneumovirus (HMPV)

has been identified as a new respiratory virus that can induce wheezing and lower respiratory tract infections in otherwise healthy infants (mean age 11.6 months)(7). Long term effects of HMPV and its impact on severity and persistence of asthma need to be established.

The second type of infantile wheezing is associated with allergy (or atopy) and is not very frequent in early life, but becomes preponderant during school years. However, this form is more persistent and is associated with significant deficits in lung function growth up to age 11 years(8). Most of the children who will go on to develop persistent wheezing beyond infancy and early childhood usually have a family history of asthma and allergies and present with allergic symptoms very early in life.

#### **Atopy and other risk factors**

Atopy has been associated with persistence of asthmatic symptoms beyond infancy and seems to be the major risk factor for an unfavorable prognosis. In the MAs study, a large cohort study performed in Germany, it was demonstrated that any allergic sensitization early in life increases significantly the risk of becoming asthmatic at an older age(9). However, at the moment a lot of discussion is still ongoing regarding the role of early exposure to allergens and the subsequent risk of sensitization. For house dust, mite and pollen, it is generally accepted that an increased exposure early in life increases the risk for subsequent sensitization and subsequent allergic disease. The role of early exposure to pets is less clear; more and more data are showing that early pet exposure induces tolerance, instead of sensitization, especially in children from allergic families and especially in those exposed to dogs(10,11).

Assessment of underlying atopy is advocated in infants suffering from recurrent wheeze, especially in those infants from atopic families or in those who show other allergic symptoms, such as eczema or rhinoconjunctivitis. The Tucson group, proposed the usage of an allergy index, based on family history and atopic features, to predict persistence of asthma(12). They were able to show that 95% of young wheezy children with a negative index, never developed asthma between the ages 6-13 years. In other studies, the presence of food allergy during the first three years of life, was also a risk factor to develop persistence of asthma until school age. Besides allergy, other risk factors for persistence of asthmatic symptoms beyond infancy seem to be male gender, severe attacks, and severe RSV bronchiolitis(1).

#### **Treatment - Prevention**

The treatment of wheezing infants is largely ignored in the different asthma guidelines, including the Global Initiative for Asthma (GINA) and the guidelines of the British Thoracic Society (BTS). Furthermore, there are no international guidelines for the management of acute bronchiolitis(13). The majority of wheezy infants will grow out of their symptoms, and, therefore, only need minimal relief treatment, such as administration of beta-agonists or ipratropium bromide or, in case of severe attacks, short courses of systemic corticosteroids. The general trend nowadays, however, is to prescribe inhaled corticosteroids to young wheezy children, although the majority do not need that kind of treatment. On the other hand, prevention of allergic reactions (allergen avoidance procedures, especially avoidance of house dust mites) and anti-inflammatory treatment, including inhaled corticosteroids, should be considered in asthmatic infants with

### Key Messages

- Not all wheezy infants have asthma.
- Diagnosis of infantile asthma should be considered in those wheezing infants who are at risk to develop persistent symptoms beyond infancy.

an unfavorable prognosis, *i.e.*, in those infants who wheeze in association with underlying allergic reactions or who suffer from severe post-RSV-induced attacks. Randomised, controlled studies on the long term effect of inhaled corticosteroids in those wheezy infants with an unfavorable prognosis are urgently needed. However, in a number of studies the effectiveness of inhaled corticosteroids in young asthmatic children was shown, although not all studies showed clinical beneficial effects(14-16).

### Conclusion

If asthma is considered to be a chronic disease, then, certainly, not all wheezing during infancy is asthma, as most infants will grow out of their symptoms. Therefore, it is suggested to consider the diagnosis of infantile asthma in those wheezing infants who are at risk to develop persistent symptoms beyond infancy (example: a male infant with an underlying atopic constitution, and severe attacks after a RSV bronchiolitis). These infants need a careful evaluation and are candidates for preventive treatments. The beneficial effect of long term inhaled corticosteroids and other anti-inflammatory treatments have not been established in these asthmatic infants. Nevertheless, most pediatricians prescribe inhaled corticosteroids for wheezing infants. Further studies should be set up to answer the questions whether or not inhaled corti-costeroids can help asthmatic infants to grow out of their symptoms.

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