

Bronchial hyperresponsiveness from infancy to adulthood: epidemiological aspects

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Responsiveness to challenges may be “direct”, with pharmacologic agents such as histamine or methacholine, which have a specific receptor-mediated action on bronchial smooth muscle causing contraction, or “indirect”, such as exercise, hyperventilation of cold dry air, inhalation of hypertonic saline or distilled water, and allergen challenges, which stimulate release of endogenous substances that cause the airways to narrow. These endogenous substances are present in increased amounts as a result of airway inflammation. Thus, the airway response to these indirect challenges is thought to provide evidence of inflammation.

Significance of bronchial responsiveness

There has been continuing argument as to the significance of an increased response to direct challenge tests with histamine or methacholine. Not all children with asthma or asthma symptoms are responsive to histamine, while more than 30% without a history of asthma will respond to this agent (1, 2). Longitudinal follow-up of children show that symptoms and severity of asthma are independent of response to mediator (3). It is also argued that they are unable to distinguish between asthma and other obstructive airway diseases (4).

Severity of bronchial responsiveness to histamine and methacholine may be difficult to interpret due to confounding by airway obstruction, difficulty defining the delivered dose of aerosol with changing patterns of breathing and growth (3) and uncertainty regarding the cut-off dose for abnormality (5). In spite of these limitations, these tests have proved useful in differentiating subgroups within the population for asthma and non-asthma symptoms.

The indirect challenges with exercise or hypertonic saline have proved particularly useful in identifying those with current symptoms or predisposition to symptoms. Although more specific for those with the risk of asthma symptoms, they are less sensitive in identifying those with a predisposition but no current symptoms. Unlike the direct challenges, there have been very few longitudinal studies of indirect challenges through childhood to adult life.

The airways of infants have been shown to respond to methacholine (6), cold dry air (7) and histamine (8). These studies have demonstrated a response to a mean dose of mediator lower than that required in older children and a range of responsiveness similar to that seen in older children. At least two thirds of infants respond to relatively low doses of mediator, while less than one third are relatively unresponsive. Understanding the mechanisms responsible for this range in responsiveness and its natural history will be important to understanding the physiological basis of asthma.

Airway responsiveness in infancy is not related to baseline function or other parameters of airway size (6, 9). Airway narrowing induced by methacholine can be reversed by inhalation of beta-agonists (6) or blocked if given before the challenge (10).

Epidemiologic aspects

Although inconsistent, there is evidence that a family history of asthma and maternal smoking are both associated with increased airway responsiveness measured in the early weeks of life (9). Yet, wheezy infants have not been shown to consistently have increased airway responsiveness (11, 12). Although infants with bronchiolitis have evidence of airway

narrowing before the episode of bronchiolitis that persists following the infection, airway responsiveness is only transiently increased around the time of infection (13). Some studies did suggest an association with increased airway responsiveness in later life, but this observation appears to be related to selection bias of hospitalised bronchiolitis patients with a greater predisposition to asthma.

Recently, children followed from infancy who have asthma and increased airway responsiveness at 6 years of age have been found to have increased responsiveness at 1 month of age (14). There is increasing evidence that hyper-responsiveness in the early months of life is not necessarily associated with wheezing illnesses during infancy. Wheezing at this age appears to be more likely to be due to abnormal airway function, which improves during the early years of life. On the other hand, increased airway responsiveness in early life appears more predictive of later onset atopy and wheezing illnesses typical of asthma. This very important observation highlights the significance of this critical period for the evolution of the inflammatory process characteristic of asthma.

The median dose or concentration of mediator to which response occurs from infancy through adolescence appears to increase (15–17). This might suggest that children are more sensitive than adults to bronchial challenge agents and that airway responsiveness declines from infancy through to adult life. Unfortunately, there are many factors that confound comparisons between response at different ages and in spite of attempts to correct for these, the situation is not yet clear. Reduced response may be due to decreased dose reaching the airway or decreased deposition of mediator with growth. The absolute size of the airways may influence the potential for narrowing. Changing baseline airway calibre and elastic recoil with growth may be important. Infants may indeed have increased airway responsiveness due to the early development of inflammation, which persists into adult life in those with the predisposition to asthma. Tepper et al (18) compared female adolescents with female adults of the same size and found increased airway responsiveness in the adolescents which could not be explained on baseline lung size, airway calibre or delivered methacholine dose.

Persistence of airway hyper-responsiveness from childhood through adolescence has been found to be associated with the presence of atopy (19). Genetic studies have found linkage between clinical asthma and atopy with markers on chromosome 11 and in other cases on chromosome 5. Linkage between the marker on chromosome 11 and bronchial hyperresponsiveness has been reported (20).

Studies of bronchial responsiveness in males and females in the general population have produced

conflicting results but most show a trend to an increased airway responsiveness in males. Males have smaller airways than females before puberty (21), they have increased muscle tone (22), and bronchial reactivity has been shown to be increased in Turner's syndrome with a return to female levels with initiation of oestrogen treatment (23).

The relationship between wheezing and airway responsiveness varies in different ethnic groups. In New Zealand, approximately 20% of all children have documented wheezing episodes. European children demonstrate approximately 20% bronchial hyper-responsiveness, whereas Maori children show this in only 13% and the Pacific Islanders in 9% (24). Clearly the relationship between bronchial hyperresponsiveness and wheezing will vary in groups with different social circumstances, and this needs to be taken into account when interpreting the significance of the airway responsiveness.

As children grow into adolescence, repeated studies have shown a significant association between the presence of atopy and continued bronchial hyperresponsiveness (18). This supports the argument that many young children have increased airway responsiveness, some due to airway pathology that will resolve through the early years of life and others due to asthma which will continue. Atopy at present is one of the better markers of those with underlying asthma.

Those with marked and persistent airway hyper-responsiveness demonstrate a decrease in baseline pulmonary function with growth from adolescence to early adult life (25). Persistence of airway hyper-responsiveness correlates better with continuing asthma (26) and indicates those at risk of deteriorating lung function with growth. With ageing from early adult life to old age, airway responsiveness once again starts to increase, and it has been suggested that this is associated with continuing inflammatory mechanisms (27). This may have important implications for anti-inflammatory agents in adults with continuing symptoms.

Conclusion

Airway hyperresponsiveness is present from early infancy and persistence is associated with atopy and asthma. Cross-sectional analyses at any point in time will show varied associations which are probably dependent on environmental influences. Hence, the test is not particularly valuable as a clinical diagnostic procedure. On the other hand, the presence of airway hyperresponsiveness in early infancy and its persistence throughout childhood is significantly associated with the inflammatory process due to asthma. Bronchial hyperresponsiveness has proved to be a most valuable tool for epidemiological studies of

the prevalence of asthma in the community, for clues to mechanisms and as an indication for response to treatment in an attempt to avoid impairment of lung function and quality of life.

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