

Food allergen sensitization as a determinant of disturbed airway function in young infants: First step on the path to persistent asthma?

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Increasing evidence supports the broad hypothesis that derangements in airway function early in life precede the full phenotypic expression of childhood asthma. In this issue of the Journal, Tepper et al¹ present the results of a novel study that examines the association between early-life sensitization to milk and egg allergens with abnormal airway function and expired nitric oxide concentration (FeNO) in a sample of infants with eczema but no respiratory symptoms. They found that infants sensitized to egg or milk allergens had relatively lower forced expiratory flows and heightened airway responsiveness to methacholine compared with age-similar controls without demonstrable food sensitization. Interestingly, the magnitude of FeNO correlated with the serum total IgE concentration, but not as well with variables of airway function. This study is important in that it links atopic sensitization in the first year of life with aberrant airway function, and supports the potential importance of early-life sensitization to foods as a “priming event” leading to established asthma. Furthermore, the study uniquely explores the relationship between atopic status, as determined by serum total IgE and a panel of RAST tests, with FeNO, lung function, and airway responsiveness in young, asymptomatic infants.

The results of Tepper et al,¹ while original, must be interpreted with caution because the determinants of lung function early in life are subject to a complex interaction of genomic, sociocultural, and environmental factors. For example, infants of atopic parents studied before 6 months of age have abnormal lower airway function.² Tepper et al¹ did control their analysis for parental atopy, and the association between food sensitization and disturbed airway function remained significant. Other risk factors, including gastroesophageal reflux, exposure to respiratory viruses, antibiotic treatment,³ and urban air pollution, are also likely determinants of lung development and function. Certainly the entity nonatopic asthma can be recognized in school-age children, with an inception phase not readily attributed to atopic mechanisms.⁴ Nonetheless, this and other studies of similar design suggest that various

early-life events, including sensitization to food allergens, constitute a stimulus that affects the functional properties of the airways. If modified or amplified by later exposures, including viral respiratory infections, this early stimulus may result in permanent alterations and thereby establish a foundation for lifelong asthma.⁵

Nitric oxide is a reactive molecule formed from arginine by the activation of inducible nitric oxide synthase in the respiratory epithelium in response to inflammatory cytokines.⁶ The level of nitric oxide in expired breath has been widely touted as a useful biomarker of inflammation in the diagnosis and management of asthma.⁷ In young infants, FeNO is influenced by several factors, including sex, maternal caffeine consumption, and prenatal and postnatal tobacco smoke exposure, and is strongly modified by maternal atopy.⁸⁻¹⁰ In recent studies, FeNO levels distinguished asthma phenotypes in preschool children with respiratory symptoms,¹¹ and in children of comparable age with asthma, FeNO levels decreased from baseline in response to treatment with either fluticasone or montelukast.^{12,13} In the current study, FeNO correlated significantly with serum total IgE concentration but not forced expiratory flows or airway responsiveness. This result suggests that mechanisms driving atopic sensitization may be unique from those affecting the functional properties of the airways. A more likely explanation is that many processes, including but apart from atopic sensitization, may affect early-life airway function. A relatively strong relationship between FeNO and expiratory flows as well as airway responsiveness to methacholine has been established in adults and children with known asthma.

The study by Tepper et al¹ uses an observational cross-sectional design. Therefore, the results, although important, support associative relationships and not definite causality. The latter would require a controlled clinical trial with an intervention to impede the onset of food sensitization in at-risk infants and would also involve longitudinal measurements of asthma symptoms, atopy, FeNO, and airway function. Because measurements of lung function and FeNO are relatively difficult in young infants, repeated measurements may not be feasible. The sample in the current study was restricted to infants with eczema and thus may not be applicable to infants without eczema. Additional long-term clinical studies controlled for genomic factors as well as a wide range of exposures will be necessary to understand further the relationship between prenatal and postnatal atopic sensitization and the establishment of the asthma phenotype in young children.

Although the study by Tepper et al¹ addresses a theoretical hypothesis, it also has practical implications for the care of wheezy infants. The wheezing infant continues to be a difficult yet common challenge to clinicians. A major conundrum is whether to subject the stable wheezy infant who presents for general evaluation to treatment with corticosteroids. On the basis of the results of Tepper et al,¹ it is reasonable for clinicians to at least consider

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atopic mechanisms in wheezy infants while also considering the plethora of other factors associated with wheezing in the very young. This assumes that the decrease in expiratory flows and increase in airway responsiveness described by Tepper et al¹ in food-sensitized infants lead to symptomatic wheezing. Certainly in wheezy infants with measureable atopic sensitization who present in clinical practice, treatment with not only bronchodilators but also a carefully monitored therapeutic trial of an anti-inflammatory medication such as a corticosteroid or montelukast is reasonable. Ideally future studies will clarify the value of exhaled nitric oxide testing in this setting as well, thereby improving both diagnosis and treatment of asthma early in life.

REFERENCES

1. Tepper RS, Liapur CJ, Jones MH, Tiller C, Coates C, Kimmel R, et al. Exhaled nitric oxide and airway reactivity in infants at risk for asthma. *J Allergy Clin Immunol* 2008;122:760-5.
2. Young S, Lesouef PN, Geelhoed GC, Stick S, Turner DJ, Landau LI. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991;324:1168-73.
3. Kummeling I, Stelma FF, Dagnelie PC, Snijders BE, Penders J, Huber M, et al. Early life exposure to antibiotics and subsequent development of eczema, wheeze, and allergic sensitization in the first 2 years of life: the KOALA Birth Cohort Study. *Pediatrics* 2007;119:e225-31.
4. Kurukulaaratchy RJ, Fenn M, Matthews S, Arshad SH. Characterisation of atopic and non-atopic wheeze in 10 year old children. *Thorax* 2004;59:563-8.
5. Gern JE, Rosenthal LA, Sorkness RL, Lemanske RF. Effects of viral respiratory infections on lung development and childhood asthma. *J Allergy Clin Immunol* 2005;115:668-74.
6. Gaston B, Drazen J, Loscalzo J, Stamler JS. The biology of nitrogen oxides in the airways. *Am J Respir Crit Care Med* 1994;149:538-51.
7. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med* 2005;352:2163-73.
8. Wildhaber JH, Hall GL, Stick SM. Measurements of exhaled nitric oxide with the single breath technique and positive expiratory pressure in infants. *Am J Respir Crit Care Med* 1999;159:74-8.
9. Hall GL, Reinmann B, Wildhaber JH, Frey U. Tidal exhaled nitric oxide in healthy, unsedated newborn infants with prenatal tobacco exposure. *J Appl Physiol* 2002;92:59-66.
10. Frey U, Kuehni C, Roiha H, Cerneic M, Reinmann B, Wildhaber JH, et al. Maternal atopic disease modifies effects of prenatal risk factors on exhaled nitric oxide in infants. *Am J Respir Crit Care Med* 2004;170:260-5.
11. Moeller A, Diefenbacher C, Lehmann A, Rochat M, Brooks-Wildhaber J, Hall GL, et al. Exhaled nitric oxide distinguishes between subgroups of preschool children with respiratory symptoms. *J Allergy Clin Immunol* 2008;121:705-9.
12. Moeller A, Franklin P, Hall GL, Turner S, Straub D, Wildhaber JH, et al. Inhaled fluticasone dipropionate decreases levels of nitric oxide in recurrently wheezy infants. *Pediatr Pulmonol* 2004;38:250-5.
13. Straub DA, Moeller A, Minocchieri S, Hamacher J, Sennhauser FH, Hall GL, et al. The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma. *Eur Respir J* 2005;25:289-94.