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Childhood asthma inception and progression: role of microbial exposures, susceptibility to viruses and early allergic sensitization

Fernando D. Martinez, M.D

Asthma and Airway Disease Research Center, The University of Arizona, 1501 N. Campbell, room 2350, Tucson, AZ 85724

Synopsis

Inappropriate responses to respiratory viruses, especially rhinovirus, and early allergic sensitization are the strongest contributors to the inception and persistence of early onset asthma. The *ORMDL3* asthma locus in chromosome 17q seems to exert its effects by increasing susceptibility to HRV in early life. Being raised on animal farms is highly protective against the development of asthma, and this protective effect is mediated by exposure to microbes. Two trials in high risk young children, one to prevent wheezing lower respiratory tract illness using bacterial lyophilizates and another using anti-IgE to prevent asthma progression, are already under way.

Keywords

asthma; allergy; rhinovirus; prevention; microbiome; genetics

New concepts have emerged in the last decade regarding the incidence, risk factors, and progression of asthma and asthma-like symptoms during childhood. These issues have been addressed in dozens of longitudinally followed cohorts, and their results have considerably enriched our understanding of childhood asthma. The goal of this review is to focus on the most recent developments and novel ideas, especially those that point to new strategies for the primary and secondary prevention of the disease.

Incidence of childhood asthma

Many of the birth cohorts from which information on asthma incidence could be derived were enriched for children with a family history of asthma and allergies. It is fair to surmise that these studies would bias findings of the age distribution of asthma onset towards an earlier age. Long-term follow up data from longitudinal studies may also be biased by preferential retention of participants at increased risk for the disease. The most reliable

Corresponding Author: Fernando D. Martinez, M.D. Asthma and Airway Disease Research Center The University of Arizona, 1501 N. Campbell, room 2350, Tucson, AZ 85724, fdmartin@email.arizona.edu.

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information comes from large population samples in which assessment of incidence was based on use of asthma medication or other health-care utilization-based indices. The National Asthma Program undertaken in Finland from 1994 to 2004 provided the most recent comprehensive data¹: its results indicate that asthma can start at any age, but the highest incidence occurs during the first four years of life, with a steady decrease thereafter, at least until the sixth decade of life. These findings confirmed older information from Rochester, Minnesota² and particularly from the 1958 British Birth Cohort³, which followed 7,000 persons born in England, Scotland and Wales in a single week in 1958. It is thus unlikely that the marked peak in asthma incidence during the first years of life observed in the Finnish data may be due to the influence of a significant number of transient wheezers⁴, whose symptoms will remit before they reach the school years.

The fact that new symptoms of asthma can start at any time during the lifetime and that inception most often occurs in early life suggests two major conclusions. On the one hand, the disease is fundamentally heterogeneous, and the umbrella of “asthma” may shelter many distinct illnesses starting at different ages, and all characterized by recurrent airway obstruction. On the other hand, the most frequent expression of the disease, early onset asthma, must be caused or triggered by factors that are active very early postnatally or even intrauterine.

Genetics of early onset asthma

The results of two recent genome-wide association studies (GWAS) have provided strong support for the contention that early onset asthma may be a specific asthma phenotype, in which interactions between asthma loci and both viral respiratory illnesses and microbial exposures play a major role. By far the largest and most recent of these GWAS comprised more than 20,000 cases and over 100,000 controls from a multiethnic sample collected in a large number of countries⁵. This study confirmed that a score of loci distributed in the genome show strong association with asthma. The definition of asthma was based on physician diagnosis or standardized questionnaires, and it thus most likely included many of the different sub-illnesses that the diagnosis is likely to comprise. The study clearly suggested that asthma is a polygenic disease, because it was powered to detect quite small signals and still, could only explain a small fraction of the total genetic variance of the disease. As suggested by a previous, smaller GWAS⁶, the great majority of loci identified were close to genes not known to be related to modulation of IgE- or Th2-mediated responses. By far the strongest signal detected was located at and around chromosome 17q21, a locus that has been consistently replicated in most of the largest asthma GWAS published to date. Of particular importance was the fact that Demenais et al⁵ identified two separate sub-loci within this single 17q locus: one near the *ORMDL3* gene and a second one close to the *PGAP3* gene. Of note, the first of these signals was more strongly associated with childhood asthma whereas the signal closer to *PGAP3* was stronger among adults. This finding thus replicated previous reports showing that the *ORMDL3* locus identifies a form of asthma that starts in early life.

A second asthma-related locus identified by GWAS, but not replicated by Demenais et al, was identified in the *CDHR3* gene⁷. The fact that a very specific phenotype, namely,

development of severe wheezing illnesses during the preschool years, was used in this study may explain the mismatch between the two GWAS result. Of importance, however, was the fact that recent functional studies demonstrated that *CDHR3* is a major component of the receptor system for rhinovirus type C⁸, an important etiologic factor for asthma exacerbations, especially in young children. Moreover, the *CDHR3* at-risk allele was found to specifically alter in-vitro responses to rhinovirus C⁸, suggesting a mechanism through which the genetic variant could increase the risk for severe wheezing illnesses⁹.

Rhinoviruses and the inception of early onset asthma

The finding that a protein involved in the response to human rhinoviruses (HRV) could be a component of the genetics of early onset asthma supported the contention that HRV could play a significant role inception of the disease. Birth cohort studies in Madison, Wisconsin, and Perth, Australia^{10,11} had shown that children in whom HRV was isolated from the upper airway during wheezing illnesses in early were more likely to develop early onset asthma by the age of 6 years than those who did not have HRV-related wheezing. Moreover, in the Madison cohort, children who had HRV-related wheezing illnesses in early life showed significant delays in lung function growth by the school years¹². It remained unclear, however, what caused this increased susceptibility to HRV, and in which way it was connected to the subsequent development of early onset asthma.

Important new insights came from combining genetic and virologic data from the two separate birth cohorts. Caliskan et al¹³ studied the Madison birth cohort and a second one from Copenhagen and reported that the children with the highest risk for early onset asthma were those who had HRV-related wheezing illnesses in early life and were carriers of the at-risk allele in the *ORMDL3* locus. These findings suggested the possibility that this locus could explain at least in part the connection between early HRV illnesses and subsequent early onset asthma. The biological mechanism explaining the HRV-*ORMDL3* interaction remains unexplained, but tantalizing insights come from studies of the *ORMDL3* locus in animal farming communities.

Animal farming and early onset asthma

For decades, the predominant paradigm explaining early onset asthma causation postulated that excessive exposures to allergens strongly associated with early onset asthma such as house dust mites were the main etiologic factors for the disease¹⁴. This idea inspired a handful of primary prevention trials^{15,16} comparing incidence of early onset asthma in children raised from birth in homes extensively treated to decrease exposure to mites with respect to those raised in control homes. These trials yielded mostly negative findings. These results were perplexing, because early sensitization to aeroallergens, and especially to house dust mites in many locales, is one of the strongest risk factors for the development of early onset asthma¹⁷.

The subsequent finding that children raised from birth on animal farms in the Alpine region were protected against the development of early onset asthma and early allergic sensitization¹⁸ revolutionized our understanding of the factors that determine the inception

of the disease. A large cross-sectional study of children living in several countries across Europe confirmed this finding¹⁹, and suggested that environmental microbial burden could explain the protection, because a major correlate of the association between early onset asthma and animal farming was exposure to environmental bacteria and fungi²⁰. It was also shown that children raised on an animal farm had decreased incidence of both transient wheezing and persistent, atopic wheezing as compared with those not exposed to farm animals¹⁹. Moreover, the trans-European study replicated in a completely different context the finding by Caliskan et al¹³ of an interaction between early wheezing illnesses and at-risk variants in the *ORMDL3* locus as determinants of early onset asthma in the early school years²¹. Of greater importance, however, was the fact that the same 17q alleles that conferred asthma risk in children with wheezing illnesses in early life granted strong protection against early onset asthma in children raised on animal farms²¹.

When combined, these findings contribute to our understanding of the role of the *ORMDL3* locus in the inception of early onset asthma. This locus comprises a large number of genetic variants that, in populations of European ancestry, are in very high linkage disequilibrium (i.e., travel together from parents to their offspring) within a very extensive genomic region of chromosome 17q21. The risk alleles for early onset asthma are present in approximately half of all chromosomes in populations of European origins, suggesting that unidentified interactive factors mediated its expression in early onset asthma. The fact that among children raised on animal farms the early onset asthma risk alleles at the *ORMDL3* locus are associated with protection against the development of early onset asthma strongly suggests that a major mechanism that explains the decreased incidence of asthma in these children is protection against potential ill effects of viral respiratory infection in early life. The hypothesis emerging from these data is that, in the absence of high levels of microbial exposure in early life, *ORMDL3* enhances the clinical expression and the disruption of airway architecture associated with viral infection in early life. On the contrary, in the presence of microbial exposure, carriers of the *ORMDL3* risk alleles are protected against these ill effects. Since this hypothesis is based on still limited data, further functional and mechanistic studies are needed to confirm it.

Human microbiome and the inception of early onset asthma

In parallel to studies of the environmental microbiome, assessment of the microbial content of both the upper airway and the stools in early life have provided new insights into the role of mucosae and microbes in determining asthma risk. Data from the Copenhagen birth cohort first showed that infants carrying three major pathogenic bacteria in their nasopharynx (i.e., *Streptococcus pneumoniae*, *Moraxella catharralis* and *Hemophilus influenzae*) were more likely to develop asthma by the age of 6 years than those not carrying these microbes²². In a more comprehensive analysis of the full microbiome, Teo et al²³ confirmed that presence of these three species conferred increased risk for the subsequent development of asthma. These studies left unclear, however, if these bacterial pathogens could somehow trigger the mechanisms that lead to the inception of asthma or vice versa if their ability to colonize the upper airway of young infants at risk for asthma is a marker of alterations in the host's immune response at the mucosal level²⁴. Of interest, Jartti et al²⁵ studied 52 children aged 3 or less who were hospitalized with their first episode of severe

wheezing and reported that 60% had a positive nasopharyngeal culture for at least one of the three above mentioned pathogens. In a different study, Isolation of these same microbes was associated with a similar risk of having wheezing episodes as the isolation of respiratory viruses from the upper airways of preschool children²⁶. These results suggested that bacteria may be as likely as viruses to trigger episodes of airway obstruction, but still did not help clarify the causative role of bacteria in the inception of early onset asthma.

Cogent new data has emerged from studies of fecal microbiome of young children who would go on to develop asthma or asthma-related phenotypes in the first years of life. Arrieta et al²⁷ first showed that infants whose stools contained four species of bacteria (*Faecalibacterium*, *Lachnospira*, *Veillonella*, and *Rothia*) during the first months of life, but not at age 1, were protected against the development of atopic wheeze by the end of the first year of life. These same species, when administered orally to germ-free mice, who transmitted them to their offspring, protected the offspring against the development of allergic inflammation and bronchial hyperreactivity after sensitization with ovalbumin²⁷. In a subsequent comprehensive assessment of the fecal microbiome during the first months of life, Fujimura et al²⁸ identified three different microbial community patterns, dubbed NGM1, NGM2, and NGM3. Carriers of the NGM3 pattern, which showed lower relative abundance of certain bacteria (e.g., *Bifidobacterium*, *Akkermansia* and *Faecalibacterium*), were significantly more likely to develop physician-diagnosed asthma by age 4 years and allergic sensitization by age 2 years than carriers of the NGM1 pattern. The NGM3 pattern also showed a distinct fecal metabolome, enriched for pro-inflammatory metabolites. Taken together, these results suggest that the type of microbial communities that colonize the intestine during early infancy may influence immune responses in a distal organ such as the airways. This may occur either through direct effects of their metabolic products on somatic function or through the activation of protective immune mechanisms mediated through the intestinal mucosa. Support for the latter mechanism was provided by experiments using lyophilized bacterial products used empirically to prevent respiratory infections. Navarro et al²⁹ showed that oral administration of these products blocked eosinophilic responses and the development bronchial hyperreactivity in mice sensitized and re-exposed to aeroallergens. They also showed that the lyophilizates interacted with dendritic cells in the gut mucosa, which in turn activated T-regulatory cells that migrated to the airway mucosa and were responsible for the protective effects attributable to the medicines.

Why bacteria that confer risk or protection against early onset asthma are able to colonize the airways and gut of different children is unknown. Since mucosal colonization is not a passive process but involves active interfaces between bacteria and the local immune system, it is likely that three factors are at play: genetic background of the individual, degree of maturation of the local immune response and the timing of the exposure to microbes and their products during the first months of life. A cogent hypothesis, still to be tested, is that inadequate exposure to protective bacteria due to environmental sterilization and excessive antibiotic use may delay the development of the normal microbial-mucosal interface³⁰ and allow colonization of the airway and gut by pathogenic and asthma-inducing bacteria.

Progression of early onset asthma into chronic disease: the role of aeroallergen sensitization

Longitudinal studies have shown that not all subjects who develop early onset asthma will go on to have symptoms that persist during the school years and into adult life. Stein et al³¹ showed that children who wheezed at age six and were sensitized to aeroallergens, and especially to the mold *Alternaria* in Tucson's desert environment, were much more likely to have persistent asthma at age 11 than non-atopic wheezers. Of interest, the diameter of the wheal elicited by the *Alternaria* antigen in the skin strongly correlated with the number of aeroallergens to which the child was sensitized³², suggesting that sensitivity to *Alternaria* was a marker for a global increased propensity to develop IgE responses to environmental stimuli. This hypothesis was supported by studies among children enrolled in the Dunedin cohort³³, in which sensitization to house dust mites predicted which 9-year-old children would go on to have wheezing that persisted into adult life. Extending these findings, Illi and coworkers³⁴ reported that in the MAAS birth cohort in Germany, sensitization and exposure to perennial aeroallergens (house dust mites, dogs, and cats) during the first 3 years of life was strongly associated with the likelihood of having asthma that persisted beyond the early school years. They also showed that children who wheezed and were sensitized to perennial aeroallergens had significantly lower FEV1/FVC ratio than those who were not sensitized. These results suggest that in early onset asthma, after the "first hit" associated with inappropriate responses to viruses, a "second hit", aeroallergen sensitization, may be necessary to trigger airway remodeling and chronic airflow limitation, the hallmarks of persistent early onset asthma. This conclusion is supported by the finding that early allergic sensitization^{35,36}, that is, during the first 3 years of life, is much more strongly associated with early onset asthma than late allergic sensitization.

The fact that the type of aeroallergen most strongly associated with this second hit differs so markedly by locale (e.g., house dust mites in more humid areas, *Alternaria* in dry deserts) strongly suggests that it is not any specific allergen but, more likely, a general propensity to become sensitized to locally dominant aeroallergens that is responsible for the second hit. Moreover, in the Manchester, UK birth cohort, the factor most strongly associated with severe early onset asthma was early sensitization to multiple aeroallergens³⁵.

The molecular mechanisms that determine the tendency to develop multiple early allergic sensitization and associated early onset asthma are the matter of intense research. Custovic et al³⁷ recently assessed multiple cytokine responses by peripheral blood mononuclear cells (PBMC) to HRV stimulation in over 300 11-year-old children enrolled in the Manchester birth cohort. They used machine-learning technologies and identified six cytokine response clusters. Children from one of the clusters, which had the lowest interferon induction and high induction of pro-inflammatory cytokines, showed all the characteristics associated with early onset asthma. Indeed, they were significantly more likely to be sensitized to aeroallergens by age 1 year, to have "bronchiolitis" in early life, to have persistent asthma symptoms up to age 16, and to have more severe symptoms between birth and adolescence³⁷. This observation suggests the possibility that the susceptibility to respiratory viruses described earlier for early onset asthma and the tendency to develop early allergic

sensitization may be mechanistically linked or have common origins. An objection to these observations in the Manchester cohort could be, however, that responses to HRV were assessed at age 11 and not in early life and therefore, that asthma and allergic sensitization may cause the subsequent patterns of HRV response. Against this latter interpretation is the observation from the Tucson birth cohort that diminished interferon gamma responses by PBMC to mitogenic stimuli at age 9 months were associated with increased subsequent risk for both allergic sensitization to *Alternaria*³⁸ and for wheezing persisting up to 11 years of age³⁹. Moreover, Bosco et al⁴⁰ showed that school age children with more severe asthma (i.e., associated with chronic airflow limitation) had diminished expression of interferon genes in sputum obtained during acute exacerbations as compared with asthmatic children with normal baseline lung function. Similarly, Johnston and his coworkers have published several studies showing diminished interferon responses by bronchial epithelial cells in subjects with severe adult asthma⁴¹. Recent studies with ORMDL3 deficient mice further highlight the intertwined nature of the respiratory virus/allergic sensitization complex⁴². These mice were unable to mount an airway allergic response to *Alternaria*, the main aeroallergen associated with asthma in the desert Southwest. These animals showed no bronchial hyperresponsiveness or eosinophilia in response to *Alternaria*, but restoration of ORMDL3 expression using an adeno-associated virus vector fully reinstated these responses to the allergen. Thus, although ORMDL3 does not increase the risk of allergic sensitization⁴³, it may increase susceptibility to an inflammatory response against aeroallergens in the airways.

Taken together, these results suggest the hypothesis that children with genetically mediated alterations of immune regulatory mechanisms that affect responses to both respiratory viruses and to aeroallergens and who are not exposed to protective mechanisms such as early microbial exposures may be at the highest risk of developing the most severe and persistent early onset asthma phenotypes.

The existence of a potential common mechanism for the development of both early allergic sensitization and susceptibility to viral respiratory infection may also help resolve the question as to which of these two risk factors comes first⁴⁴. Complex statistical assessments using data from the Madison birth cohort suggested that allergic sensitization precedes wheezing due to HRV in early life⁴⁵. The investigators argued that this sequential relationship supported a causal role for allergic sensitization, which would increase susceptibility to viruses and, by this mechanism, determine the inception of asthma. This interpretation, however, is not compatible with the finding that HRV interacts with the ORMDL3/17q locus to determine asthma susceptibility and that this interaction is independent of allergic sensitization¹³. In fact, several studies have failed to find any association between this locus and allergic sensitization⁴³. It is important to stress that the Madison cohort was enriched for children with a family history of allergies. If a common pathogenic mechanism determines at least in part both early allergic sensitization and susceptibility to HRV, it is plausible to surmise that the timing of the expression of these two phenotypes may depend of the genetic background of the individual. Therefore, in children with a family history of allergies, skin test reactivity may come before HRV wheezing, and the opposite may be true in those without such family history²³, without any implication as to which one is the cause of the other.

Conclusions

Strong epidemiological observations from birth cohorts suggest that both inappropriate responses to respiratory viruses, especially HRV, and early allergic sensitization are the strongest contributors to the inception and persistence of early onset asthma. The most highly replicated GWAS hit for asthma is the so-called *ORMDL3* locus in chromosome 17q, and this locus seems to exert its effects by increasing susceptibility to HRV in early life. However, being raised on animal farms, which is highly protective against the development of asthma, blocks the increased susceptibility to early onset asthma associated with the *ORMDL3* locus and decreases the incidence of both atopic and non-atopic wheezing in early life. Most available evidence indicates that the protective effect of animal farms is mediated by exposure to microbes, and this has suggested the tantalizing prospect that pharmaceutical products containing protective bacteria, or their products could prevent early onset asthma. A primary wheezing lower respiratory tract illness prevention study using bacterial lyophilisates in high risk infants and young children is already under way (trial number: NCT02148796). In addition to susceptibility to respiratory viruses, early sensitization to multiple aeroallergens appears to be essential for persistence of asthma beyond the preschool years and into adult life. A secondary prevention trial will soon test the hypothesis that anti-IgE therapy might decrease the risk for subsequent persistent asthma in aeroallergen-sensitized children with early onset asthma (trial number: NCT02570984).

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Key points:

- Inappropriate responses to respiratory viruses, especially rhinovirus, and early allergic sensitization are the strongest contributors to the inception and persistence of early onset asthma.
- Children with genetically mediated alterations of immune regulatory mechanisms and who are insufficiently exposed to environmental microbes may be at the highest risk for early onset asthma.
- Mucosal colonization is not a passive process but involves active interfaces between bacteria and the local immune system.