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The changing epidemiology of paediatric childhood asthma and allergy in different regions of the world

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Allergic disorders encompass a variety of conditions including asthma, atopic dermatitis, food allergy, allergic rhinitis, and eosinophilic esophagitis. These atopic disorders are connected via an abnormal host immune response to the environment. A series of longitudinal cross-sectional studies conducted over the past 3 decades have reported on the epidemiological trends that contribute towards the development of pediatric asthma and allergic disease. Infant birth cohort studies assessing the microbiome have offered clues as to the underlying biological mechanisms and basis for allergic disease. Why this abnormal immune response is occurring is the basis of decades of research and the reasons for this chapter. Our understanding of the biology of the immune system has increased exponentially with the advances in genomic testing, providing further opportunity for targeted treatments and more importantly, primary prevention of atopic disease.

KEYWORDS

asthma, allergy, epidemiology, inborn error immunity, primary atopic disorders

Introduction

Asthma and allergic diseases are the most common chronic pediatric conditions and are leading healthcare costs. In 2013, direct costs of pediatric asthma were US$5.92 billion, with the average annual costs per child ranging from US$3,076 to US$13,612 (1). Allergic disorders encompass a variety of conditions including asthma, atopic dermatitis, food allergy, allergic rhinitis, and eosinophilic esophagitis. Allergic disease develops in a time-based sequence, often referred to as the 'atopic march': beginning with atopic dermatitis and food allergy in infancy, to the development of asthma and allergic rhinitis in later childhood or beyond (2, 3). Severe forms of atopic diseases are a manifestation of immune dysregulation and reflect a new category of inborn errors of immunity collectively defined as primary atopic disorders (4). These allergic conditions are connected via an abnormal host immune response to the environment. For reasons that are currently unknown, exposure to common environmental factors like animal dander, certain foods, inhaled molds or pollens are not tolerated but instead generate a T Helper type 2 (T_H2)-like immune response driven by proinflammatory cytokines such as interleukin (IL)-4, IL-5 and IL-13 which activate effectors cells such as mast cells and eosinophils, thus driving inflammation. Classically, the diagnosis of allergic disease is established clinically based on the presence of effector cells like eosinophils or

immunoglobulin E (IgE)-mediated activation of mast cells and/or basophils. These immune cells promote an allergic response leading to symptoms of asthma such as paroxysmal cough, dyspnea, and wheezing; for allergic rhinoconjunctivitis symptoms of rhinorrhea, angioedema and conjunctivitis, and urticaria, flushing and possibly hypotension in the setting of anaphylaxis (5).

Understanding the biology driving inflammation is a key goal for research and prevention

Environmental exposures vary in an urban vs. rural setting, which seems to factor into the development of allergic disease. The term 'hygiene hypothesis' was coined in 1989 by Strachnan reflecting an observational theory that children with fewer viral infections in early life were more likely to develop allergic rhinitis (6). Stiemsma et al. summarized the evolution of the immune dysregulation associated with the hygiene hypothesis including the early report of low incidence of rheumatoid arthritis in Western Nigeria where malaria exposure is frequent (7) and how experimental theories have expanded the hygiene hypothesis to also include commensal and symbiotic intestinal microbes (8). One of the earliest studies assessing the role of farm exposures was described by Martinez and Holt by comparing two cross-sectional studies in Europe and concluded that children who lived on farms are exposed to a more diverse range of microbial agents and develop less allergic disease as demonstrated by reduced prevalence of asthma and atopy (9). Stein et al. demonstrated that even among genetically similar populations such as the Amish and Hutterite communities in the United States, environmental exposures as it relates to differing farming practices elicits varying innate immune responses. Amish farmers use a traditional practice with exposure to environments rich in microbes, whereas Hutterites apply industrialised technology. None of the Amish children studied had asthma in contrast to 20% of Hutterite children (10). However, the impact of rural exposures on asthma is complex and in some cases under-diagnosis of asthma may be occurring in these rural/remote communities (11). New research assessing the modality or route of exposure (inhaled, ingested) and effect on the varying tissue microbiomes (respiratory, intestinal, cutaneous) are emerging as a key question in our understanding of causal mechanisms (12). Early life exposures to inflammation generate innate immune responses that vary within and across populations (13). The discovery of T regulatory cells and innate lymphoid cells add to our understanding of the complexities of the immune system in atopic disease development beyond Th1 vs. Th2 imbalances (14). The increased prevalence of allergic disease has been attributed in part to epigenetic mechanisms such as DNA methylation, whereby environmental effects create biochemical changes of transcriptionally relevant genetic information without altering the nucleotide sequence of the genome (15). Evolutionary life history theory considers the relative cost and effectiveness of different immune responses: innate immune responses are lower cost up front however are

imperative for novel infections; acquired immune responses are most effective against secondary infections due to antigen-specific antibodies however require nutritional abundance (16). Socioeconomic factors, including access to healthcare, complicate the relationship of location and allergy.

Nutrition also plays a role in homeostasis between the balance of Th_1 and Th_2 immune responses. Micronutrient deficiencies may contribute to atopic diseases: iron, zinc, vitamins A and D deficiencies are drivers of atopic diseases. Children with allergic diseases in the US and China are up to 8 times more likely to be anemic compared to children without allergic disease. Dietary restrictions due to food allergy can also lead to micronutrient deficiencies (17). Gut microbiome studies of semi-nomadic gatherer/hunter people of the Yanomami has been found to be distinctly more diverse when compared to westernized counterparts. Indigenous diets contain high-fiber plant products rich in inulin, which has been shown to stabilize gut homeostasis via short chain fatty acids that inhibit pro-inflammatory cytokines when absorbed by gut epithelial cells (18).

Epidemiological trends of asthma and atopic disease among children and youth

Asthma is one of the most common chronic respiratory conditions of childhood worldwide, but regional differences exist. Several large population-based and cohort studies have shaped our understanding of asthma and allergic disease worldwide, providing early clues into the factors impacting the epidemiology of allergic disease and asthma worldwide including climate change, pollution, nutrition, birthing patterns, use of antibiotics early in life, and environmental exposures including viral infections.

In North America, data from the Center for Disease Control in the United States in 2019–2021 reported the prevalence of asthma among children less than 18 years was 6.5%. Prevalence was higher among youth 15–17 years (9.5%), in Black/African American children (11.6%), in Puerto Rican children (17%), and in those with the lowest household incomes (10.2%). Data from the National Institute of Health reported the prevalence of childhood asthma was 8.4% in 2017 declining to 5.8% in 2020, however the authors caution that a newer data collection strategy, coupled with the COVID19 pandemic reducing the number of viral respiratory tract infections, may be contributing factors to the declining prevalence (19).

The International Study of Asthma and Allergies in Childhood (ISAAC) is the largest study examining the prevalence and severity of asthma symptoms, allergic rhinitis and eczema among children in different parts of the world. The ISAAC studies advanced our understanding of the epidemiology of pediatric asthma, and led to the exploration of environmental factors that might contribute to the asthma and the atopic march at a population level. This cross-sectional study consisted of three phases. ISAAC Phase I (1994–1995) involved the assessment of prevalence and severity of asthma and allergic disease and included 700,000 school-age children from 56 countries using simple core questionnaires that

were easy to implement regardless of health care resources. Phase II investigated possible etiological factors as suggested by Phase I; and Phase III (2011–2003) was a repetition of Phase I to assess trends in prevalence over time. There were two age groups of children studied: 6–7- and 13–14-year-olds. The Phase I study found significant differences in the prevalence of asthma between countries: In the 13–14-year-old age group, the prevalence of wheeze in the preceding 12 months ranged from 2.1 in Indonesia to 31.2% in the United Kingdom (UK) and 4.1 in Indonesia to 32.1% in Costa Rica in the younger age group. Prevalence was higher in countries that were English speaking or Latin America. This study had three countries with 14–15 study sites each, however the prevalence of asthma varied from low in India, moderate in Italy and high in the UK, suggesting discrepancies were most consistent between countries compared to within countries (20).

ISAAC also reported prevalence results for allergic rhinitis and atopic dermatitis. Allergic rhinitis symptom prevalence was reported between 0.8% and 14.9% in the 6–7-year-olds and from 1.4% to 39.7% in the 13–14-year-olds. This variation in reporting of allergic rhinoconjunctivitis symptoms highlighted differences in how allergic disease symptoms are labelled and reported at a population level (21). For atopic eczema, the ISAAC study reported that the highest prevalence rates were seen in countries where asthma rates were not similarly elevated including Scandinavia and African countries (22). The discordance in prevalence for atopic diseases within a country reflects a need for further research as to why some countries seemingly follow an 'atopic march' and others may not.

ISAAC Phase III study included approximately 1,200,000 children from 233 centers in 98 countries. Results found that the global prevalence of current asthma, rhinoconjunctivitis and eczema in the 13–14-year age group was 14.1%, 14.6% and 7.3%, respectively. Consistent with results from the Phase I study, The Phase III study demonstrated a wide variability in the prevalence and severity of asthma, rhinoconjunctivitis and eczema depending on the regions. Additionally, the Phase III study further established that the prevalence of allergic disease is high in non-affluent centres with low socioeconomic conditions. This suggests local environment characteristics play a key role in determining the differences in prevalence between one place and another (23).

To improve our understanding of asthma symptoms in younger children, the International Study of Wheezing Infants (EISL) was performed as a multicenter, cross-sectional study assessing the prevalence of recurrent wheezing and related risk factors in infants during the first year of life. This study revised the ISAAC questionnaire and validated it for infants less than 12 months of age and administered the survey between 12 and 15 m of age. In 2005, 30,093 children participated from 17 centers [25,030 in Latin American (LA) countries in 12 sites; and 5063 from 5 European (EU) sites]. Of the results reported, symptoms of a viral infection in the first 3 months of life were the most consistent factor associated with a shorter time to first episode of wheeze (24).

More recently the Global Asthma Network (GAN) Phase 1 study published results from a cross-sectional study striving to report on global surveillance of asthma prevalence, severity, management and risk factors. This was the first study since ISAAC that aimed to assess global asthma prevalence over a 27-year period among school age children. Results include a decrease in prevalence for severe asthma symptoms in adolescents however there was an overall increased report of ever having asthma symptoms and night cough in both adolescents and school age children. Key findings of the GAN study indicates that the overall prevalence of asthma remains stable, however 1 in 20 children worldwide has severe asthma (25).

Lastly, the Environmental Influences on Child Health Outcomes (ECHO) study assessed 5,809 children from 10 of the 12 cohorts from the Children's Respiratory and Environmental Workgroup (CREW) birth cohort consortium. This study assigned census-derived tract-level data for socioeconomic, demographic, and housing variables. Study findings included Black and Hispanic children had higher rates of asthma and asthma morbidity compared to White children; Black and Hispanic children in this study resided in communities with economic deprivation at a disproportionate rate compared to White children. Applying census data to the CREW cohorts, the authors reported environmental characteristics at birth relating to population density and poverty were associated with an elevated risk of asthma incidence. Black and Hispanic children were at higher risk than White children for developing asthma regardless of neighbourhood, further linking race, ethnicity and neighbourhood factors with onset of asthma (26).

The role of viruses in the development of asthma

Viruses are important factors in the environment which the host must respond to. This response can be important in the development of asthma and the diagnosis of asthma (27). Numerous studies have shown that infants (<2-year-olds) with a more severe response [i.e., hospitalized with Respiratory Syncytial Virus (RSV) bronchiolitis] are at increased risk of developing later asthma and in some cases even allergic disease (28–32). In addition, there are data that other viruses which cause hospitalization at this young age (i.e., human metapneumovirus) can also increase the risk of later asthma and allergic disease (33). It is also well described that common cold viruses like Rhinovirus are a key trigger for an asthma exacerbation in all ages. People that present to urgent care with Rhinovirus are much more likely to have a diagnosis of asthma (34). The host response to these common viruses is critical to our understanding of allergic disease and asthma (35). For example, there is excellent data *in vivo* and *in vitro* that typically allergic effector cells like eosinophils can be triggered by viral infection to release mediators and induce airway hyperresponsiveness (36, 37). RSV has unique characteristics that could attract allergic effector cells to the airway (38). Overall, the reason why people with allergic inflammation respond so poorly to common colds is an important factor in our understanding of allergic airway disorders.

The role of the microbiome: expanding understanding of genes and environment on development of allergic disease

The Canadian Healthy Infant Longitudinal Development (CHILD) Study is a longitudinal birth cohort study that aims to advance knowledge about the genetic and environmental determinants of atopic diseases including asthma, allergy, allergic rhinitis and eczema. This study recruited 3,500 pregnant women who gave birth between 2009 and 2012 from 4 provinces and followed the infants prospectively. One of the first published reports from this cohort study reported on the gut microbiome of 24 healthy infants and correlated with mode of delivery and feeding status (breastfed or formula fed). Infants born by elective caesarean section had low bacterial diversity and richness. This study advanced understanding of infant gut microbiota and offered new evidence correlating to mode of delivery (39). Another key finding from the CHILD study is the impact of the timing of systemic antibiotics administered within the first year of life are associated with risk of atopic dermatitis [adjusted odds ratio (aOR) = 1.81; 95% CI: 1.28–2.57; $P < 0.001$]. Additionally, antibiotics in the first year of life were linked to infant gut microbiome disruption and elevated atopic dermatitis risk. This study also identified key gut microbiome components that could potentially be used to predict and possibly prevent the onset of atopic dermatitis (40). Antibiotic stewardship programs have successfully reduced the use of antibiotic prescriptions in infants and children: a systematic review of 113 studies assessing antimicrobial stewardship programs in children 0–18 years, 79.6% of the studies showed a significant reduction in inappropriate antibiotic prescriptions (41). A Canadian population level study coupled with a prospective cohort analysis found that declining rates of asthma diagnosis at age 1–4 years was associated with decreased antibiotic use in infancy (age < 1 year). Asthma incidence increased by 24% with each 10% increase in antibiotic prescribing (adjusted incidence rate ratio 1·24 [95% CI: 1·20–1·28]; $p < 0.0001$) (42). Birth cohorts from around the world continue to collect key information and data, providing clues on mechanisms of disease for the development of asthma and atopic disease, and offer strategies towards primary prevention at an individual and population level.

Severe atopy: the tip of the iceberg for uncovering inborn errors of immunity (IEI)

While the environment is important, family history and a genetic basis for disease is well-described. Inborn errors of immunity are a group of disorders caused by damaging germline variants in single genes. The International Union of Immunological Societies (IUIS) has curated and maintained an updated list of inborn errors of immunity since the 1970s. In the United States the incidence of IEIs is 6 per 10,000 individuals (43). Although once considered a rare group of diseases, more recently our understanding has shifted to recognize that collectively these disorders are more common and

important for allergic diseases. In the 2024 summary, the IUIS listed 555 IEI's and 17 phenocopies due to genetic variants in 504 different genes (44). Severe atopy including atopic dermatitis, allergic asthma and food allergy are a well described presentation for a group of IEIs categorized as primary atopic disorders (PADs), a term first coined in 2018 to delineate this distinct group. PADs are a group of heritable monogenic allergic disorders, often characterized by severe, early-onset, and co-existent allergic conditions such as atopic dermatitis, food allergy and allergic asthma (45). One of the challenges of PADs is that environmental and host factors can contribute to the heterogeneity of the clinical presentation and severity of disease, requiring clinicians to have a high index of suspicion for IEI, particularly in the absence of infections (46). Our understanding of the biology of these conditions has laid the groundwork for therapies for some of the most common allergic disorders affecting large portions of the population.

Conclusion

Allergic disorders affect a significant proportion of the global population. Abnormal host immune responses towards common antigens in the environment, coupled with genetic predisposition, form the matrix of atopic disease. Epidemiologic data arising from birth cohorts and cross-sectional studies around the world have significantly altered our understanding of the gene-environment interaction as it relates to allergic conditions and factors influencing the risk of developing disease. Our understanding of the biologic and immunologic mechanisms underpinning monogenic forms of the primary atopic disorders characterized by immune dysregulation has contributed towards targeted therapies. Ongoing research and applications of genomic testing to further characterize biological pathways may help pave the transition towards precision medicine for atopic disorders.

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