



Review Article

Will every child have allergic rhinitis soon?

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ABSTRACT

Objectives: Given the increasing prevalence of AR amongst children, we aimed to review the literature regarding the future of AR in this population.

Methods: We searched the PubMed, Google and Proquest Central databases at Kirikkale University Library. Search terms used were: “allergic rhinitis”, “children”, “paediatric”, “allergy”, “future”, “risk factors”, “treatment”, “pharmacotherapy” and/or “allergen – specific immunotherapy”. With regard to risk factors for allergic rhinitis, the terms “Environmental factors”, “Improved hygiene”, “Increased indoor allergen exposure”, “Farms, villages, worms, and other parasites”, “Environmental toxicants”, “Diet”, “Lifestyle changes”, “Air pollution” and “Climate factors” were searched for. “Prevention of allergic diseases” and “Allergen-specific immunotherapy in the future” were also included in the search.

Results: AR has a high prevalence and causes considerable morbidity, has associated comorbidity and features specific complications. The principal treatments rely on avoiding the allergens responsible, and administering drug treatment or immunotherapy, which targets specific antigens. Genetic drift does not explain the rising prevalence of allergic disorders, but multifactorial environmental factors are likely culprits. Amongst such environmental factors to consider are the rise in caesarean births, decreases in breast feeding, dietary changes resulting in less fresh produce being consumed, the eradication of intestinal worm infestations, alterations in the way homes are aired and heated, children taking less exercise and being outdoors for shorter periods, whilst also having more contact with pollution.

Conclusion: Barring substantial lifestyle alterations, more and more children are likely to develop AR. It may prove feasible to stop allergy developing in the first place through manipulation of the microbiome, but the exact format such a modification should involve remains to be discovered. Molecular allergological techniques do offer the prospect of more precisely targeted immunotherapy, the sole disease modifier at present. However, at present the complexity and cost of such interventions prevents their widespread use and research in this area is still needed. The majority of children with AR are going to be managed using nasal saline sprays, since they are the most straightforward and least risky alternative for first line treatment.

1. Introduction

Within the last few decades, allergic disorders, like autoimmune disorders, have had a rising prevalence. Asthma, allergic rhinitis (AR) and allergic dermatitis have shown increases [1,2], as have anaphylaxis and food allergies [3,4]. These rises were first observed in the West, but developing countries show similar increases as they Westernise, lending support to the so-called Hygiene Hypothesis, according to which a reduction in the variety of the microbiome, especially in the intestines, underlies the problem. Such bacterial changes do not, however, fully account for the rises observed [1,5–7].

Allergic diseases exhibit heterogeneity and are not all found in the

same patient. The sequential development of eczema followed by asthma and finally asthma is seen in a mere 10% of paediatric cases. Indeed, some children initially present with AR and go on to be asthmatic without skin problems occurring [8], a fact which hints at different ways a child may be sensitised and a corresponding variety of (epi-) genetic and environmental events producing the syndrome, including variation in timing, magnitude and manner of exposure as well as underlying predisposition [9,10].

The rate at which the allergic prevalence has risen rules out a purely genetic change, hence the invocation of epigenetic factors (which control genetic expression) to explain the aetiology. It is probable that some aspect(s) of an altered environment either *in utero* or during

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childhood (delivery method, pharmacotherapy, dietary change, number of siblings, school or sporting environment) may play a role. In addition, viral factors are still not fully appreciated and we might expect that advances in virology will lead to the identification of certain allergic problems with viral infection [1,10].

2. Methods

We searched the PubMed, Google and Proquest Central databases at Kırıkkale University Library. Search terms used were: “allergic rhinitis”, “children”, “paediatric”, “allergy”, “future”, “risk factors”, “treatment”, “pharmacotherapy” and/or “allergen – specific immunotherapy”. With regard to risk factors for allergic rhinitis, the terms “Environmental factors”, “Improved hygiene”, “Increased indoor allergen exposure”, “Farms, villages, worms, and other parasites”, “Environmental toxicants”, “Diet”, “Lifestyle changes”, “Air pollution” and “Climate factors” were searched for. “Prevention of allergic diseases” and “Allergen-specific immunotherapy in the future” were also included in the search.

3. Paediatric allergic rhinitis

The definition of AR involves the presence of at least two of the following symptoms: rhinorrhoea, nasal congestion, sneezing or pruritus [11]. These symptoms are produced through the formation of IgE to innocuous allergens in the environment and features both early and late responses [12]. Significant co-morbidity may be seen in AR: asthma, rhinosinusitis, conjunctivitis, sleep disorders, maxillofacial changes, and middle ear infections all occur [11,13]. The majority of asthma cases have co-morbid rhinitis, but if this feature is absent (as it is in 20% of cases), asthma is generally of neutrophilic type. Likewise, 40% of those with AR have co-morbid asthma [14,15].

Whilst AR was once rarely seen and then only in higher socioeconomic groups in England in the 1800's, it has now come to affect more than one in four people living within the UK, the rise especially being seen since the 1950's. At present, the total number of affected individuals in the US is 60 million, representing between 10 and 30% of adults and 40% of children. The International Study of Asthma and Allergies in Childhood (ISAAC) study looked at prevalence across the world, finding the highest rates in Westernised nations. This difference has been steadily eroded as the developing world urbanises [16]. In India, risk factors include lorries passing the home, parents who smoke, paracetamol usage, antibiotic prescribing, woodfires used to cook and watching TV [17]. A global investigation of how fast food affects rates has been undertaken [18] and reveals that consumption of fast food more than three times weekly increases the incidence of rhino-conjunctivitis, severe asthma and allergic dermatitis in both child and adolescent cases. Eating fruit more than three times a week may, conversely, confer some protection. These effects persisted when data were analysed regionally and allowance was made for sex and socioeconomic level and level of prevailing symptoms.

Three out of four AR cases have an onset before the age of twenty, and of those cases, 40% exhibit symptoms before a child is six [19,20]. Nasal symptoms are most often provoked by house dust mites, pollen or pets. Symptoms can also be provoked by non-allergenic factors, such as exercising, inhaling fumes or bad smells and fluctuations in temperature [21].

AR in children is connected to being exposed to infections, polluted air (both inside and outside) and certain dietary factors. It was reported in one study [22] that living on a farm helped protect against developing AR throughout the lifecycle, and if individuals have less contact with microbes (endotoxins included) they have lower rates of allergic disorders linked to Th2 cells. The effect was not universal, however [1].

Recent research indicates that the variety of microbes to which exposure occurs is significant [23–27]. Allergic disease prevalence is linked to diet both *in utero* and postnatally in early childhood [28]. A diet with high lipid levels, deficient in fresh fruit and vegetables and

with low levels of Vitamins A and D has been demonstrated to be linked to asthma and allergic diatheses [20]. What part pre- and probiotics play is being currently researched.

Whilst climatic change could trigger symptoms or worsen them, it is not certain such change would produce more actual cases. Nonetheless, there are reports that do link the prevalence of AR with differing climate conditions [29].

Infants with medically-recognised AR have twice the risk of becoming asthmatic by the age of 11 compared to their peers. One in three cases of childhood asthma go on to become asthmatic and, amongst asthmatics, only 5% do not have comorbid AR [30]. US-based research gave a comparable figure of 39% for paediatric AR cases with comorbid asthma. In many studies, boys are twice as likely as girls to have both AR and asthma [31,32]. The PAA survey gave a rate of 45% asthma in boys with AR and 33% for girls with asthma [21].

Options in the treatment of AR encompass avoiding antigens, taking medication or receiving antigenic-specific immunotherapy [14]. Treating AR ought to also improve the asthma prognosis and immunotherapy for the condition potentially may stop asthma developing at all [33,34].

3.1. Box

3.1.1. Risk factors for AR [35–39]

- A family history of allergic disorders, i.e. genetic predisposition.
- Being male
- Being the first child in a family
- Taking antibiotics at an early age
- Mother who smoked when child was an infant
- Allergenic exposure at home, e.g. house dust mite
- A circulating IgE level exceeding 100 IU/mL recorded at age less than 6
- Antigen-targeting IgE being present

When the results of numerous studies are pooled, the resulting odds ratio for the development of AR when these risk factors were present fell between +3 and +5 [40].

4. Reasons for a likely increase in AR over the next few decades

4.1. Environmental factors

Epigenetic changes linked to the environment have been implicated in the phenotypic development of allergy, affecting gene expression [10]. How genes and the environment interact to produce allergic disorders like AR and asthma is a complicated matter [40–44].

4.2. Improved hygiene

The microbial flora to which we are exposed in early life has a potential effect on our immunological development. According to the Hygiene Hypothesis, a reduced level of exposure to microbes accounts for the rise in atopic disorders [43,44].

Living habits and conditions may also control our exposure to microbial flora, and there are correlations with the prevalence of atopy. One study, for example found that in families where a parent sucked on the child's dummy rather than washing it in water to render it usable by the child had lower rates of asthma, allergic dermatitis and hypersensitivity formation than other families [45].

4.3. Increased exposure to indoor antigens

The following factors have contributed to higher levels of allergenic exposure within homes: insulated homes, warmer homes, in most cases, fitted carpets covering the entire floor (a fashion from the 1930s

onwards, albeit now abating somewhat) and being indoors for longer periods [46].

A habitat which is warm and humid is ideal for house dust mites. In the early 1980s, when testing for mite allergen became practicable, it emerged that the allergen was concentrated in beds, carpets, settees, curtains and clothing in affected homes [47] and that levels of allergen correlated significantly with hypersensitivity to the allergen and subsequent asthma symptoms [48].

Alongside rising levels of allergen inside homes, the degree to which pollen posed a threat decreased in mid-century as air conditioners and filters became more commonplace. Before such developments, being exposed to pollen was more common as windows were more typically open and fans were often situated inside windows. The decrease in pollen exposure may partly account for why AR levels have been rising less steeply from the middle of the 1960s onwards [39].

4.4. Farms and villages, and parasites, such as worms

Children growing up on farms, especially if they drink unpasteurised milk, have less chance of developing atopic disorders [49–53]. A long-cherished theory was that IgE produced in response to parasitic infection was irrelevant to, or, on the contrary blocked allergenic IgE interactions [54]. Of significance, however, is the observation that in individuals who have alpha-gal-specific IgE, high levels of IgE specific to cat and dog allergens are not associated with respiratory problems when cats or dogs are encountered [55]. In African villages, high circulating IgE levels do not necessarily correlate with allergic responses and this may be attributed to IgE being specific to a hapten. Like alpha-gal [41,56,57].

Mazurek and Henneberger [58] calculated a lifetime prevalence of AR in current agricultural workers of 30.8%, from 2.1 million such workers. Farmers with AR, had an odds ratio of 1.38 (95% CI 1.22–1.56) of exposure to pesticides, as compared to farmers without AR. There was a stronger and more statistically significant association between being exposed to pesticide and developing AR plus asthma, or just AR than with the development of asthma alone.

4.5. Environmental toxicants

There is increasing evidence that points to an effect of environmental toxicants on atopy and asthma. Such compounds include endocrine disrupting compounds (EDCs) and phthalates. Amongst the former class are triclosan, parabens and bisphenol A (BPA). Triclosan first appeared in products from the 1970s onwards, having been approved as a pesticide by the US Environmental Protection Agency in 1969 [37].

4.6. Diet

There have also been changes in diet, such as a reduction in eating fresh fruit and vegetables and an increase in snacks, convenience foods and non-alcoholic beverages with additives. Portions have also grown. Despite this general trend, implicating specific dietary modifications in asthma has proven challenging [59]. Whilst one study found that consuming more beta-carotene led to less hypersensitivity to food and inhaled allergen reactions in school children, the level of beta-carotene consumed had a negligible effect on how much wheezing occurred and what type it was [60].

IL-12 levels may be dampened by vitamin D. IL-12 stimulates T-helper 1 (Th1) cells to proliferate. If Th1 levels fall, T-helper 2 (Th2) cells, which are associated with allergy, may increase [61,62]. The offspring of mothers taking vitamin D during pregnancy are less likely to wheeze when growing up [63]. Recently it has been shown that high levels of vitamin D predict better pulmonary function, less hyper-responsivity of the airways and an enhanced response to glucocorticoids [64].

Conversely, allergic asthma and rhinitis have an association with reduced vitamin D levels. The cytokines IL-31 and IL-33, secreted by Th2 cells are found in atopy. If vitamin D in its hydroxylated form is found in low levels, this can act independently of interleukins 31 and 33 and Th2 cells to raise the risk of asthma and AR co-occurring [59]. Administering 1,25-dihydroxyvitamin D lowers levels of the Th1-associated cytokines IL-2 and IFN- γ , whilst elevating levels of IL-4, which is associated with Th2 cells [65].

Vitamin D is synthesised by the action of sunlight on the pre-vitamin, 25 hydroxyvitamin D [66], hence being exposed to sunlight is a necessary step for children to avoid vitamin D deficiency.

4.7. Changes in lifestyle

Lifestyles have also changed in terms of children attending daycare from earlier ages, alterations in the time periods spent playing outside, and the balance of active vs sedentary activities [39].

4.8. Air pollution

It is probable that the changing pattern of air pollution relates to the growth in asthma cases in some localities. A large body of evidence has been gathered to show how traffic pollution from both petrol and diesel vehicles affects allergic disease of the respiratory system [67].

4.9. Climatic factors

Changes in the climate are changing the pattern of antigens children encounter. One such example is that hypersensitivity to ragweed is affecting children in more northerly latitudes. Whilst climate change has been linked to a changing geographical pattern of atopic prevalence, the overall levels of atopy have not been increased by climatic factors [29,39,68].

5. Prevention of allergic diseases

Children whose mothers remained in an area of high microbial concentration, such as living on a farm, whilst pregnant are less prone to becoming atopic [69,70].

Children delivered by caesarean have higher rates of allergy, likely as a result of not being colonised at birth with beneficial maternal vaginal flora. Although there have been efforts to create colonisation by swabbing from the vagina, some reports of infections being passed on has led to abandonment of this procedure [71]. Usage of probiotic bacteria is an area being researched at present.

Gut microbiota is important for immune regulation development. It modulates immune programming, inhibits the development of allergic phenotype [72,73]. Gut microbiota decreases “local inflammation” [74] and “intestinal barrier integrity” is stabilized [75]. It potentially reduces “systemic antigen load” [99]. Probiotics are live micro-organisms. Probiotics affect the plasticity of the gut microbiota and help to prevent from allergic diseases [72]. Probiotics alters gut microbial composition, modulates host's immune system [74,76] and have immune-stimulating effects [77].

Breast feeding, besides its benefits for infant and mother, also confers advantage in terms of reduced antigenic hypersensitivity, thanks to elevated levels of IL-10 and TGF- β in the milk [1,78]. Usage of antibiotics in early life has the opposite effect [79].

Abnormal microbiomes in the intestines may be responsible for atopy and some research has been undertaken with pre-, pro- and syn-biotics, showing that the immune system has responded in such a way as to reduce atopic formation [80].

West et al. [81] describe a variety of RCTs, the results of which were used to draw up the guidelines of the World Allergy Organisation concerning the use of pre- and pro-biotics in preventing atopy in particular situations.

Güvenç et al. [82] performed a meta-analysis revealing that probiotics are of benefit both clinically and immunologically for treating AR, particularly if LP-33 bacteria were used and in seasonal AR.

Children born in dog-owning households have lower rates of atopy, which may be due to the increased microbes in such homes. If an antigen is presented from a young age at high levels, tolerance may develop [83–85]. The LEAP and LEAP-ON studies have shown this to be the case for groundnut allergy [86,87]. Being exposed to antigens in controlled fashion through the skin or mouth, which does not induce hypersensitivity, forms the basis of specific immunotherapy (both subcutaneous (SCIT) and sublingual (SLIT)), and may be a beneficial procedure to prevent allergy occurring in the first place, although more research is required [1].

Keeping children away from both smoke and air pollution in general not only promotes better respiratory health, but might also diminish the risk of becoming asthmatic or atopic [1].

6. The future of allergen-specific immunotherapy

In children with AR, both SCIT and SLIT are beneficial and SLIT is safe overall [88]. Despite this, SLIT is underemployed. Primary health staff need to be more aware of allergen-specific immunotherapy (AIT), especially given that it is the only treatment that actually modifies the disease. Both SCIT and SLIT have proven efficacy in lessening the prevalence and severity of asthma due to grass pollen and AIT is known to decrease antigen hypersensitivity afterward [89,90]. Which children can most benefit needs to be established through phase III studies of good design for registered products, with an emphasis on selecting candidates, the best age for AIT to begin, how high a dose to administer and for how long, and how age affects the efficacy of AIT and its relative safety. We need biomarkers indicative of a good symptomatic response and showing that asthma progression has been halted.

It would be of great benefit if there were harmonisation between trials' end points and measures of safety and efficacy. A plan needs to be in place to ensure patients remain concordant and are followed up regularly by a nurse. The treatment has significant costs and takes up time to the extent that it should only be employed in carefully selected patients.

7. Alternative therapies for AR

There are very few studies for alternative therapies for AR in infants and children [91]. The usage of herbal agents is not common in paediatric group. Some of the herbal agents for AR are [92]:

Butterbur (*Petasites hybridus*): It is an extract of *Petasites hybridus*. It possibly alters the leukotriene pathway [93].

Tinospora cordifolia: It is extract of *Tinospora cordifolia* [94]. It has a possible “immunostimulatory” effect [95,96].

Cinnamon bark, Spanish needle, and acerola: It is an extract of “dehydrated Spanish needle (*Bidens pilosa*)” and “acerola fruit concentrate” [97]. It inhibits production of prostaglandin D₂ affecting late allergic response [98].

Capsaicin (*Capsicum annum*): It is derived from red peppers. It helps to desensitize the nasal nerve fibers and nasal hyper-responsiveness reduces [99].

8. Conclusion

Paediatric AR looks set to keep presenting challenges for the foreseeable future and is probably related to westernization. If lifestyle changes, such as fewer caesarean deliveries and a more natural diet for children, with an emphasis on fruit and vegetables, and more time outdoors can be implemented, we may slowly see the trend in increasing prevalence begin to reverse.

Molecular allergological techniques may provide more precise diagnosis and better targeted specific immunotherapy, but for now,

medication remains the mainstay and saline irrigation the least cost-intensive intervention [100].

Conflicts of interest

Author **CemalCingi** declares that he has no conflict of interest.

Author **Nuray Bayar Muluk** declares that she has no conflict of interest.

Author **Glenis K. Scadding** declares that she has no conflict of interest.

Ethical approval

There is no need to take ethical approval, because this paper is review.

Informed consent

There is no need to take informed consent, because this paper is review.

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Cemal Cingi: Writing – review & editing. **Nuray Bayar Muluk:** Writing – original draft. **Glenis K. Scadding:** Writing – review & editing, Writing – original draft.

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