

Changing World As Principal Reason For Atopy Rising Trend

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Abstract

Allergic respiratory diseases were quite rare at the beginning of last century but their prevalence in industrialized countries has now risen to true epidemic proportions. Much of the increase in asthma prevalence is occurring in subjects without a significant genetic predisposition.

As risk factors are described urban environment, industrialization, air pollution, westernization of life, high hygienic standard, etc.

Therefore, it could be assumed that the above mentioned risk factors act on the human beings or other biologic species relatively for a short time. In this context, such factors might act in this way because of being new environmental constituents and therefore human adaptive mechanisms to them are inadequate yet. However, certain environmental factors may influence genetically some subpopulations even after exposure cessation without directly altering the genome or providing additional survival possibilities, which might induce the deviation of genetic thesaurus for populations into a more frequent allergy-predisposing genotype.

PREVALENCE TREND OF RESPIRATORY ATOPIC DISEASES

Allergic respiratory diseases were quite rare at the beginning of last century but their prevalence in industrialized countries has now risen to true epidemic proportions [1,2]. Also, data from several sources indicate worldwide increases in asthma or allergic rhinitis over the last 30-40 years, especially in English-speaking countries [3,4]. The most affected subjects from this trend are children and young adults [2]. According to a report of ISAAC Steering Committee, prevalence of wheezing or bronchial hyperreactivity in European children aged 13-14 years varied from 32.2% in United Kingdom to only 2.6% in Albania [2,5]. Also ECRHS survey has shown similar variations between European countries among adults aged 20-44 years [6].

Although the presence of affected relatives is associated with an increased risk of atopic diseases, recent data suggest that much of the increase in asthma prevalence is occurring in subjects without a significant genetic predisposition [7]. Thus, described data from MAS cohort study conducted in German children at 5 years of age have shown in a majority of cases that asthmatic subpopulation has originated from

non-atopic parents, indicating for the environmental impact on the atopy rising trend [8].

RISK FACTORS FOR RISING TREND OF ATOPIC DISEASES

In view of rising prevalence are conducted many studies about the risk factors for atopic diseases. Because this prevalence increase happened relatively in a short period of time, the role of populations' genomic transformation is assumed to be limited [2,4]. Moreover, after the 1950s there was a gradient even between East and West Germany regarding the prevalence of atopic diseases, despite the population was genetically the same [2,9]. Therefore, the almost of epidemiologic studies have pointed out the influence of different environmental risk factors on the rising trend of atopic diseases.

Sibship size: The proposal by Strachan that a decrease in family size may reduce the possibility of cross-infections, facilitating the clinical expression of allergic rhinitis had lead to intense interest in this area [10,11]. In addition, number of older, and, to a lesser extent, also number of younger siblings is inversely to the occurrence of hay fever, atopic eczema, skin test reactivity, and the presence of specific IgE antibodies in children, adolescents and adults [12].

Helminths: Despite the induction host-dependent TH2 cytokines profile and hostile IgE antibodies response, helminths can induce a T-cell hypo-responsiveness due to helminth-derived anti-inflammatory molecules [10,13,14,15]. Therefore, the decline of helminthic infestations in industrialized countries is associated with a high sensitization rate toward different respiratory allergens [15,16].

Early life infections and intestinal microbiota: Much attention during last decade has been devoted to the hygiene hypothesis – the apparent inverse relationship between infections in early life and the subsequent development of asthma and atopy – which was once based on epidemiological associations, but has gained strong support also on immunologic grounds [12]. Data from a longitudinal birth cohort study of 1314 German children with a follow up of 7 years suggested that repeated viral infections, particularly common colds ‘runny nose’ and infections of herpes type, in early life may reduce the risk of developing asthma up to school age in a dose-dependent manner [8,12]. Similar effects during early life can induce the exposure to different infectious microorganisms such as hepatitis A, lactobacillus, mycobacterium or exposure to pets, which can favour the development of host TH1 immune profile [2,11,12].

Exposure to antibiotics: The exposure to antibiotics as inducer of atopic response is described from many authors [17,18]. In this respect, it is postulated that antibiotic-induced growth inhibition of enteric flora can suppress the “TH1 education” of children's immunity, leading to the induction of TH2 cytokine profile and allergic inflammatory predisposition [10,11,17,18].

Farming and anthroposophic lifestyle: Evidence suggesting that farming lifestyle is protective against allergic diseases is consistent, and has been reproduced in a number of studies [10,19]. Furthermore, the recently conducted multicentre cross-sectional study (PARSIFAL) has demonstrated that not only living on farms, but also leading anthroposophic lifestyle during early childhood is protective against atopy and allergic disease [10]. Growing up on farms is associated with exposure to endotoxin, helminths, lactobacilli and saprophyte mycobacteria, whilst anthroposophic lifestyle is related to less interference with common childhood infections because of reduced antibiotic use and vaccination, and consumption of naturally fermented vegetables and biodynamic food. In respect of biodynamic food, breast-feeding is a further described protective factor against atopic disease [8,20].

Industrialization and exposure to diesel exhausts: The prevalence of atopic diseases in industrialized countries and especially in urban areas is higher than in developing countries or rural areas [2,12,21,22,23]. Except the increase of socioeconomic level and conducting of an westernized lifestyle (alias avoidance of anthroposophic lifestyle), as an inducer of atopic phenotype in these areas is reported to be the high pollution level, especially due to diesel exhausts [11,12,19,21,22,23]. Beside the direct impact on respiratory mucosa, diesel exhausts act on the increasing of pollen allergenicity [21,22,23,24].

Exposure to tobacco smoking: Passive smoking increases the likelihood of experiencing respiratory symptoms and is associated with increased bronchial responsiveness [25]. The prospective birth cohort study MAS in Germany reported that an increased sensitization risk was found in children whose mothers smoked up to the end of pregnancy and continued to smoke after birth [8]. In addition, experiments in rats, mice, guinea pigs and dogs indicated that sulphur dioxide, ozone, tobacco smoke, or diesel exhausts can induce or amplify a specific IgE-production in these animals [26].

Stressful life: In response to psychological stress, an inflammatory process may occur by release of neuropeptides from a sensory nerve and the activation of mast cells [27]. Moreover, the same neuropeptides such as substance P mediate both stress and allergic inflammation [27]. Experiments in allergised animals have indicated that auditive stress may amplify the immune response and bronchial responsiveness [28,29]. In this context, maternal stress and major depressive disorder could affect the developing immune system, inducing a TH2 cytokines profile, which is a feature of atopic diseases too [12,30]. In addition, the risk of asthma attacks in children is increased after a negative psychological event, especially if this stressful event is chronic [31]. Finally, these mechanisms can explain the fact that depressive disorders are more prevalent in asthmatic patients than for example in subjects with chronic hepatic disease or normal subjects [32].

As previously described, in atopy prevalence investigative studies generally are determined genetic and environmental risk factors as well as the inductive mechanisms of atopic response. However, there is not determined what make these factors as allergy inducers, what their common feature is, or why just these factors predispose the development of atopic diseases. Exactly this will be the purpose of successive

reflections in this review.

HUMANE SUBJECTS ARE NOT NECESSARILY ADAPTED TO CHANGING WORLD EXPOSURE

A principal goal for human beings is the providing of higher prosperity and conducting of better and better life.

Consequently, due to persistent humane efforts the average of actual socioeconomic level is evidently much higher than in past times, and is continuing to increase permanently.

To fulfil this goal, diverse humane populations have undertaken massive enterprises, which lead to decisive transformations for the perspective of future generations. In this context and because of its curious nature, *Homo sapiens sapiens* after its appearance in East Africa migrated subsequently to India and later to Europe or East Asia and finally through Alaska into entire America [33]. The migration in Northern regions is associated with discovery of fire use, which was decisively important not only for surviving in cold climate regions but also as a cornerstone of metal providing, leading to antecedent of successive industrial development [33].

Also, again to conduct a better life, in developed countries many peoples have emigrated from rural areas or from developing countries. Meanwhile, modern lifestyle in industrially developed areas is associated with avoidance of anthroposophic traditions, higher hygienic level, reduced family size, etc [12].

However, in this new environment have arisen many harmful factors such as indoor and outdoor pollution, interfering with health of humane beings [12]. In effect, the influence of these factors originates since prehistoric époques. Also the use of fire as means of coping with harsh temperature variation since the migration in the northern regions of the world, would have led to more time spent in close proximity to smoke – a known air polluter [33]. Consequently, the prevalence of pollution-dependent respiratory diseases such as lung cancer varies in different populations. For instance, independently from individual exposure to accused pollutions such as tobacco smoke, the most affected subjects from this lethal pathology are males, or African-Americans [33]. These data indicate that subjects who experienced during generations a more permanent exposure to smoke are better protected against this pathology. By this Platek et al. mean that in the prehistoric time females were involved principally in camp “household” in close proximity to the fire and fire smoke, whereas males have spent long hours on hunts [33]. In respect of African-

American subjects who originate from equatorial regions, the exposure toward tobacco smoke could be more frequently fatal, because their exposure toward fire and smoke during generations was nearly occasional for climatic reasons and therefore, the adaptation toward this pollution actually is limited [33].

In respect of adaptation inadequacy toward indoor and outdoor smoke, it is reported an increased respiratory allergic prevalence in polluted areas. Also passive smoking increases the likelihood of experiencing of respiratory symptoms and is associated with increased bronchial responsiveness [25,26]. Interestingly, the actual majority of respiratory allergic children originate from non-atopic families [7,8].

The prevalence increase of respiratory allergies after the exposure to air pollution is not at all coincident. According Kovacs, health is conformity to the species design [34]. For example, when a previously unmet virus or bacterium is introduced into a population, 2/3 or 9/10 of population can die from the resulting epidemic, because the individuals were not adapted to the infectious agent [34]. Also novel environmental factors the body is not evolved to cope with [35]. In respect of respiratory diseases we could say that our lungs, immune system, etc. were surely not “planned” to inhale the exhaust-gases of modern cars, so we can be sure that a species typical lung, enzyme system, etc. are not the ones which ensure the best survival in this environment [34]. In summary, the majority of health problems today arise from exposure to novel environments, whereas the design of our body shows how healthy it would have been in the previous environment [34,35].

On the other hand, air pollution influences even the properties of airborne allergens and therefore the inflammatory allergic processes of human airways [24]. In this respect, Molfino et al. found that the mean provocation dose of ragweed necessary to reduce forced expiratory volume at first second by 15% was significantly reduced to about half the dose of allergen when the patients pre-exposed to ozone versus pre-exposure to air [21]. In addition, Behrendt et al. observed that pollen collected from areas with high levels of air pollution (roadsides with heavy traffic, etc.) were covered with airborne microparticulates (5µm or less in size) and postulated that interaction between pollen allergens and these particules is able to alter the allergenicity of pollen antigens [21,22]. Also in studies ongoing on the interrelationship between components of air

pollution and parietaria pollen allergens and using RAST-inhibition, it is found that exhaust emissions from non-catalytic cars increased the allergenic potency of parietaria pollen as compared with exhaust emissions from catalytic cars [21,22].

In particular, pollen-related allergy affecting the nose and the tracheal-bronchial tract has become more frequent in the industrialized world [21]. A classical study in this sense conducted by Ishizaki et al. showed that prevalence of respiratory allergy was higher in subjects living near roads bearing heavy traffic than in subjects living in areas with higher atmospheric concentrations of pollen allergens but with less traffic [21,22].

Similarly to other respiratory smoke-influenced disorders such as lung cancer, the most affected populations from allergic respiratory diseases in air polluted regions originate from immigrants or African-Americans [12,36]. Thus, significant increases in asthma morbidity and mortality in the United States have occurred since 1970s, particularly among the mentioned population [36]. In this respect, for this subjects' group it is postulated that several bio-aerosols and air pollutants have effects that may be clinically significant [36]. Meanwhile, the prevalence of Asthma varies from 0.5-5% in China, and in Africa to 20-25% in English-speaking countries such as Australia and New Zealand, where peoples' ancestors immigrated from distant areas [12,37]. The highest prevalence of asthma symptoms in affluent English-speaking countries may be partly explained by the genetic heterogeneity of these populations; English-speaking communities have a far broader genetic diversity in terms of ethnic backgrounds than those communities with low prevalence of atopic disorders, due to far higher immigration rates [12].

In addition, the atopic predisposition among immigrant populations is reflected in the increased rate of IgE-mediated asthma [37]. Also, immunoglobulin E levels of immigrants in Sweden are higher than those of native Swedes [37]. Similarly, cord blood immunoglobulin E concentrations are more elevated in neonates whose mothers immigrated to Germany from Eastern countries than in those of German native mothers [37].

Remembering once more previously-mentioned environmental risk factors or predisposed populations regarding allergic diseases, it could be suggested that abandonment of former traditional lifestyle, indoor or outdoor environments from diverse human populations and

successive exposure to modern ones is associated with increased allergy prevalence. In this context, being ethnicity a marker for poorer strata or a more traditional lifestyle within industrialized countries, such ethnic populations may serve us for the conduction of diverse studies about the development of atopic diseases in these circumstances [38]. For example, in a study conducted in Berlin the children of Turkish families have been found to be markedly less afflicted with atopic sensitization and asthma than German children [38]. In addition, symptoms of atopic dermatitis were less frequent among Turkish children, and within Turkish population they were higher among those with more frequent use of the German language [38].

The consistent increase of asthma and sensitization prevalences with the increase of German language in Turkish families points towards differences in lifestyle rather than heredity [38]. Thus, the familiar use of German language among this population may be interpreted as conduction of a less traditional life from these families compared to Turkish-speaking ones. However, population density was higher for Turkish families, thus providing a higher chance for infections [38]. In this context, bacterial and viral infections are currently discussed as Th1-inducers that shift the cytokine balance away from atopy [38].

In contrast to German data, epidemiological studies conducted in Turkey suggest that its population is not generally protected from atopic disease [38]. For primary school children, wheeze prevalence varying between 8.4% and 23.3% has been reported [38,39]. Besides strongest associations with personal atopy and atopic heredity, there were significant differences in prevalence rates between children residing in different regions, supporting the role of environment factors [38,39,40,41,42,43,44,45]. Though there were no significant differences among children residing in urban versus rural areas regarding the prevalence of asthma and wheezing, those living in coastal areas had considerably higher current prevalence than those living inland [39,45]. Thus, residence in northern Turkey appeared to be a significant risk factor for wheezing, and children resident in southern Turkey exhibited the highest risk for occurrence of asthma compared with eastern Turkey [39,45]. Moreover, additional risk factors for atopic disease in primary school children of Ankara, beside atopic family history were indoor smoking, keeping pet animals, and male gender, [41,42,43]. Neither age, breast-feeding, nor place of habitation affected the occurrence of allergic disorders [42,43].

The increased atopy prevalence in primary school children at coastal, western and metropolitan Turkey may suggest that life and environment in these regions is largely less traditional than in deep eastern regions. Untraditional habits like indoor smoking or keeping pet animals as well as being male (and therefore as previously-mentioned less adapted toward smoke exposure) act as risk factors, whereas breastfeeding or living in most traditional part of Turkey do not. Meanwhile, the lower atopy prevalence in Turkish-speaking immigrants of Berlin may be explained with rural origin and conserved traditional habits such as consume of home-made food or living in high density families [38].

As previously mentioned, another feature of modern environment is the improvement in hygiene, which generally has been cited to account for the increase of atopy and related disease in Western industrialized countries, particularly over the last 35-40 years of 20th century [2,38]. However anecdotally, the association of allergy with affluence dates back to the 19th century. Charles Blackley, who first demonstrated that hay fever was caused by allergy to grass pollen, described the disease as one of the urban educated classes and was puzzled to find that it was rare among farmers, despite their high exposure to pollen [11].

In this respect, several studies, most performed in the Tropics, have provided further evidence that atopic disorders occur more commonly among individuals living in urban, more affluent and westernized as compared with those living in rural areas with traditional lifestyle [12]. In addition, Gerrard found that the prevalence of asthma and eczema was higher among the white compared with the Saskatchewan Metis population and was contrasted with the increased prevalence of helminth infestation as well as of untreated viral and bacterial infections among the Metis population, whereas a retrospective review of records in an Oxfordshire general practice found a doubling of the risk of hay fever and eczema among children who had received any antibiotics by the age of two years which was independent of the clinical indication for antibiotic treatment [11,12].

Furthermore, it has been suggested that even the increasing prevalence of allergic diseases in Western Europe and the differences between Eastern and Western Europe could be due to less microbial pressure in early childhood as a consequence of improved hygienic conditions [2]. In this respect, Von Mutius et al. showed that in genetically similar individuals, the prevalence of atopic diseases were significantly higher among school children living in the

former West (Munich) as compared with the children in the former East Germany (Leipzig and Halle) [12]. An interesting fact was that mentioned east-west differences were seen only in children and younger adults, and not among Germans born before 1960s, which suggest that a “cohort effect” may be operating with the lifetime allergy risk being influenced by living conditions in early childhood [11,12]. However, during the 1990s, the prevalence of hay fever and atopy in Leipzig appear to have increased, even among generations born before German reunification [11].

Summarizing these data, it could be said that atopic diseases appear, at least in part, to be the price paid for our relative freedom from infections and parasitic diseases in affluent societies [12]. Nevertheless, further hypotheses to clarify increasing allergy prevalence are necessary to be focused in different aspects. It seems undoubtedly that something within “Western lifestyle” contributes to the allergy development. Perhaps we must not forget the fourth dimension, the factor of unstoppable acceleration of our everyday life [46].

In effect, the high allergy prevalence in affluent English-speaking countries may be associated with hygienic improvement, high level of industrialization, air pollution and accelerated life rhythm (accelerated urbanization). For instance, the most characteristic feature of humans is their tendency to transform their environment in a very short period of time, thus they have no fixed and unchanging environment [34]. This period of time is too short to allow biologic or social adaptation to these changes [34]. In the case of humans we can say that the chosen environment is unhealthy, therefore certain individuals cannot adapt [34]. Thus, if somebody cannot adapt to his environment (and in the case of human beings environment means even a social environment, a certain social structure, institutions, moral-, technical-, etc. standards), it can be often said that he is diseased, but in some cases it can just as rightly be said that the environment is unreasonable [34].

In context of accelerated urbanization, the globalization and high tech information had led to the higher life expectations compared to the former period of times when the world was more isolated. Thus, the much higher (sometimes dizzy) life rhythm and disillusion because of non-fulfilment of own expectations may lead more frequently to disappointments and depressive symptoms as well as to induction of allergic disorders. This scenario may be possible because the same neurological or immunologic mechanisms are similarly

regulated in both disorders, which are frequently associated with each other [31,32]. In other words, similarly to allergic subjects, patients who represent major depressive disorder show a Th2 cytokine profile, whereas mediators of neurogenic inflammation such as substance P are shown to be overregulated in allergic inflammatory response, stress and depressive diseases [27,28,30,47,48,49,50,51,52]. Maybe immigrants (adults or children), arrived from rural areas or developing countries during last decades experience this situation relatively late in their lifespan or at least more “violently”, and therefore they are less adapted against these additional challenges. Consequently, their problems can be reflected in the relationships with each other in their own family or social environment, exacerbating worsening their immunologic or neuropsychological situation.

Reflecting about all presented facts, it could be suggested that accelerated transformations of the environment and lifestyle as well as the simultaneous non-fulfilment of life expectations (alias changing world) might be the risk megafactor for the development of atopic diseases. In other words, maybe all risk factors mentioned in this review are not risk factors per se for atopic diseases, rather they act as risk factors because of insufficient adaptation after short-time exposure toward them for certain subpopulations. If the components of modern environment such as improved hygiene, air pollution, and western lifestyle were part of former traditional life, whereas the components of traditional environment such as anthroposophy were part of actual modern life, the anthroposophy were an expected risk factor for atopic diseases. In the circumstances of changing world, the prevalence of allergic diseases might be in correlation with respective transformation rhythms.

Despite the influence for a short period of time, it could be not excluded that certain environmental factors may switch the expression of target genes even after exposure cessation in a heritable manner without directly altering the genome, defined as epigenetic mechanisms [53,54,55,56,57]. In respect of these mechanisms, recent epidemiological studies have shown increased prevalence of diabetes or cardiovascular disease after the cessation of exposure to malnutrition in predecessors of patients [56,57]. In addition, Yehuda et al. reported increased prevalence of posttraumatic stress disorder by babies whose pregnant mothers were exposed to the World Trade Center attacks or in adult offspring of Holocaust survivors [58]. Regarding immune disorders, it is reported that epigenetic mechanisms are involved in gene-environment interactions by innate immunity or asthma

severity, but epidemiological surveys focused on epigenetic mechanisms and their role in the atopy rising trend are limited [59,60,61]. Therefore, to elicit the impact of environmental factors on human genome function even after exposure to a risk factor in a short period of time, actually it might be necessary to conduct approaches about the exposure to environmental indoor and outdoor pollutions such as tobacco smoke or diesel exhausts in newborn experimental animals and successively it should be investigated about the immune response, etc after allergenic exposure in their later lifespan or by their offspring [62,63].

On the other hand, the affluent life and especially the exposure to antibiotics might have provided additional survival possibilities declining the mortality rate after common respiratory and gastroenteric infections in the early life. In other words, maybe the use of broad spectrum antibiotics enables the increase of survival rates in case of serious respiratory and gastroenteric infections for the children who fail to provide adequate natural immune responses. In this category are included subjects who show a production deficiency of specific IgG or IgA against a wide spectrum of pathogenic microorganisms, because the most adequate immune response against almost of mentioned infections is likely to show predominantly a TH1 cytokines profile, similarly to the case of first breast feeding [64,65]. In effect, prior to the antibiotic era, subjects showing a lack of this response had less possibilities to survive and consequently to have their own offspring. In contrast, the massive introduction of broad spectrum antibiotics has promoted parity against these infections. Thus, maybe antibiotics use has enabled the deviation of immune genetic thesaurus for successive adult population to a more frequent allergy-predisposing genotype due to increase of survival rates for subjects who show predominantly TH2 cytokines profile and consequently specific IgE response and atopic diseases.

Therefore, rather than considering a single exposure that may prevent allergic disease, all these indicate that a number of different exposures which differ between modern and traditional lifestyles may act together in impacting on the development of allergic diseases [10]. These facts indicate that epidemiologic perspective of allergic diseases depends on the transformation level of the environment, traditions, life rhythm, etc: the higher the rhythms of these transformations the more prevalent allergic pathologies. That's why, maybe in the long term it will be necessary to deduce the common protective factors from all the published

studies and distil them to interventions that would be acceptable to western lifestyle, but at the same time making sure that such intervention will not exacerbate other disease processes [10].

CONFLICT OF INTEREST STATEMENT

The author has no conflict of interest to declare in relation to his work.

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