Incidence of Allergy and Atopic Disorders and Hygiene Hypothesis

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Abstract

An important contribution to understanding the causes of the increasing incidence of allergic, atopic and other immunopathological conditions in the pediatric population and, later on increased incidence of non-communicable diseases (eg., Type 2 diabetes, and autoimmune diseases) in adulthood was the hygiene hypothesis. Key risk factors relating to the hypothesis was that children population has inadequate exposure to antigens in the environment, cool chain hypothesis, and infectious agents in the context of antibiotics overuse, urban life-style excessively meticulous daily care of children and high standard of household hygiene. As protective factors were taken such as breastfeeding, family size and sibling relationships, that is life in a larger family. The literature generally states that the reduced exposure to microbial antigens in children probably plays an important role in the growth and incidence of allergies and immunopathological disorders in child and adolescent populations. Strenths of the data supporting data for each of these risk or benefit factors vary considerably. The most promising factors that could be causally associated with the development of allergies include exposure to intestinal microbiome, breastfeeding and sibling factors. However, most studies in this area suffer from serious methodological flaws, particularly the reliance on retrospective recall the requested information, making it difficult to determine the validity of the "hygiene hypothesis". However, the "hygiene hypothesis" as well as follow-up the "old friends hypothesis", are based on knowledge of the critical impact of the intestinal microbiome to the maturation of the immune system of children are an important area of research, which could provide clues to understanding the causes of the current adverse developments in the incidence of allergies, including atopy as well as eg. chronic autoimmune, inflammatory bowel disease not only in children but at a later age also the population of adolescents and adults.

Keywords: Hygiene hypothesis; Exposure to antigenic stimuli; Cold chain hypothesis; Overuse of antibiotics; Old friends hypothesis; Breast feeding

Introduction

Hygiene hypothesis is based on the observation that the increase in the incidence of allergic diseases in both developed and developing countries, coincided with an improvement in the level of hygiene in the 20th century. Factors improving hygiene conditions include access to a safe drinking water, hot water tap in the household, as well as factors such as smaller family size and increasingly stringent supervision over the quality of consumer food basket, especially in economically developed countries, along with the growth in consumption of personal hygiene matters Feeney et al. [1]. However, there are opinions that the increase in the incidence of allergic and autoimmune diseases over the last century, especially in developing countries, may not be accurate because based on data from the World Health Organization, it is clear that there are not availableleven sufficiently accurate even basic demographic information Mathers et al. [2]. In addition, the developing world cannot provide the required public infrastructure necessary for the relevant diagnosis and reporting of these types of diseases or health disorders, which raises doubts about the reliability of the data that the hygiene hypothesis is based. However, [3] was the first to declare hygiene hypothesis by combination increased incidence of allergic diseases with rising hygienic standard of life. He found an inverse relationship between the size of the family and the development of atopic disorders. Hygiene hypothesis is based on the chance that the child may be due semisterile environment in which it growes, protected from desirable exposure to conventional and non-pathogenic infectious agents in the environment in which it grows in the family Bloomfield et al. [4]. If the child then comes into contact with the pathogenic infectious agents or specific antigens of allergenic nature later in life, there is a risk run to suffer undesirable abnormal immunological reactions.

Exposure to Antigenicstimuli of Microbial Nature

Limiting exposure to micro-organisms necessary for programming the immune system maturation of the child and mitigating its future inflammatory response to antigenic stimuli adversely affects maturation of the immune system of a child. The underlying assumption is that common infections in children help create a balance between pro-inflammatory cytokine Th1 and tolerance-inducing regulatory T cells and prevents the development of subsequent adverse reactions to allergens, microbial or other antigenic stimuli [5,6]. There is a rich literature on the key concepts of "hygiene hypothesis", including exposure to Helicobacter pylori, nematodes, cold chain hypothesis, vaccines, antibiotics, breastfeeding, family size and differences between the growing of children in terms of urban and rural environment Koloski et al. [7]. The maturation of the immune system of a child, particularly the natural immunity, is formed on the basis of endogenous factors including the particular genetic disposition. Specific, adaptive immunity is generated mainly due to external factors, including exposure to microbes and external pathogens, microbial colonization of the digestive tract of a child, mainly by exposure to intestinal microbiome, nutritional factors and active immunization [6]. With the increasing level of personal hygiene during the last century in economically developed countries it has also been a dramatic decline in the infestation of child population by geohelmints, particularly helminths and roundworm. Namely by helminths believed to have played an important immunoregulatory role in the intestinal flora Weinstock et al. [8]. Nematodes infestations is associated with a strong Th2 response, which is in contrast to a Th1 responses associated with autoimmune disorders e.g. Crohn's disease (hereinafter referred to as CD [9,10]. Chronic infestations such geohelminty may generate a network of regulatory T (Treg) cells that secrete transforming growth factor (TGF)-B and interleukin (IL)-10 [11]. These cytokines may regulate both Th1 aggressive response, but also "tame" increased Th2 response, which contribute to chronic course of allergic diseases. While there is available a relatively large amount of data from animal models support the immunological role of nematodes, there are limited data to verify these possibilities in the human gut microbiome. Additionally, helminth infections may trigger other mechanisms of anti-inflammatory process in the intestine, including an increase in mucus secretion into the intestinal lumen [12]. This may affect the interaction between enteric bacteria and pathologically altered epithelium, and its effect on intestinal motility. Helminths can affect not only the intestinal microbiome and even perhaps assumed response to helminth infestations in neuroendocrine side Hugot et al. [13]. It is, however, that none of these factors was confirmed by valid clinical study. These are still needed to confirm the potential of these exciting preliminary observations.

Cold Chain Hypothesis

The hypothesis of cold chain refers to the temporal and geographic link between mass expansion of use of refrigerators in households and outbreak of epidemic of infections caused by psychrotrofic microbes, especially *Listeria monocytogenes* Liu et al. [14]. It cannot exclude that the external factors related to cold chain hypothesis, including maintenance of refrigeration equipment, but also the changes in eating habits (increased consumption of soft sausages and cheeses in the imagination of their safe storage in refrigerators) may also explain these trends Walmsley et al. [15].The potential relationship between the mass consumption of chilled food and increasing incidence of idiopathic Inflammatory Bowel Disease (IBD) is mediated by exposure to psychrotroflic bacteria with pathogenic properties such as *Listeria monocytogenes, Yersinia enterocolitica* and *Bacillus cereus* that are able not only to survive but also of growth at low refrigerator temperatures Forbes et al. [16]. Elderly patients afflicted with IBD average age of those who lived in households with a refrigerator was by four years lower than in control patients not owning a refrigerator. The observed difference was statistically significant, voiced suspicions justified, but because of the complex etiology of IBD was causality uncertainin that context Stallmach et al. [17]. While early exposure of the gastrointestinal tract of children to psychrotrofic bacteria in the first years of life, may be a factor that contributes to the development of IBD, is not yet considered to be an independent risk factor in that context.

Infections in Early Childhood

Infectious etiology was originally suspected in patient population afflicted with IBD on the basis of studies describing a significantly higher frequency of infections, e.g. gastroenteritis during the first six months after birth, especially in cases of a CD at a later age. Follow up studies were based on the analysis of questionnaires collected data on the sets of adults and children with IBD in an attempt to identify the link between the incidence of gastroenteritis and diarrhea in infancy and development later on CD in adolescents and adults. However, international multicenter study found no difference in the incidence of gastroenteritis in patients with IBD compared to control group subjects. While a number of infectious agents, such as eg. Paramyxoviruses Montgomery et al. [18] or *Mycobacterium paratuberculosis* Herman-Taylor et al. [19] showed no correlation with the incidence of CD.

Overuse of Antibiotics

Antibiotics may adversely affect meaning microbiome composition and its natural binding of the immune system [20]. In addition, the authors have demonstrated a temporal relationship between the introduction of antibiotics on a large scale after World War II and the significant increase in the incidence of allergies, including atopy and IBD evident in the second half of the last century [21]. In an effort to minimize the impact of confounding factors were analyzed databases General Practice Research (GPRD) in the UK prospectively collected data on CD cases and controls Card et al. [22]. This study evaluated the antibiotic therapy, the use of other medications, if the patient is a smoker, with the focus with respect to the expected development of the latent period of the disease, in particular for a period of 2-5 years before clinical diagnosis. It was found that 71% of 587 patients with CD were prescribed antibiotics 2-5 years before diagnosis, compared with 58% in 1460 controls (adjusted OR 1.32 [1.05 to 1.65], p <0.001). Although the authors avoid the distortion of the results achieved by gender, age, or smoking, a major deficiency was administered antibiotics Not specifying the type of association and other groups of drugs and contraception. This calls into question the causality association with administration of antibiotics. However, a strong association between incident cases of CD and use of tetracyclines, particularly in those individuals with no previous gastrointestinal symptoms, is of interest and may provide some guidance for future studies in this field.

Breastfeeding as a Protective Factor

The role of breastfeeding may play a role in the incidence of atopic eczema and development of chronic idiopatic inflammations

like CD and UC influencing early exposure to food antigens. Some of the important differences between breast milk and infant formula include immunoglobulins (Ig), such as lactoferrin, lysozyme, growth factors, allergic factors, carnitine and DHA ARA. For example, lactoferrin is a protein vázalící iron is found in human breast milk but not in the artificial feeding. This limits the availability of iron for intestinal mikrobion child that can adversely affect the desirable health beneficial bacteria in the intestine. This has a direct impact on the production of natural antibiotics by bacteria, such as *Staphylococcus* spp. and *E.coli* Klement et al. [23]. Most of the evidence supports the protective effect of breastfeeding at UC and CD Corrao et al. [24]. A study based on the Italian populacei 819 IBD patients confirmed the lack of guns and exclusive breastfeeding poses an increased risk for the incidence of CD and UC [25]. These results were supported by the results of studies in Canada and the United States, which found in pediatric patients CDs that were inadequately breastfed. Contrary to the above-cited authors of studies on a range of more than 400 IBD patients whose disease began 20 years ago and who were younger than 25 years old at the time of the study there was no significant difference between patients and control subjects in the frequency of breastfeeding, as well as the consumption of cereals or refined sugar during childhood. The big problem studies in this area is its retrospective design and dependence on patient memory or his mother's response to the questionnaire within the epidemiological investigation. Moreover, none of the cited studies have explored the potential distorting effects on the development of IBD factors, such as maternal effect endocrine modulators (e.g. kontaceptiv) Corao et al. [24]. Further prospective studies using larger sized files examined during an extended range of potential risk factors is urgently needed for strengthening of the power, the validity of these observations in terms of the strength of their evidence.

Family Size and Birth Order Child

Abundance of family members may be used to indicate possible overflow households, which was associated with reduced levels of hygiene and increased potential risk of infection Montgomery et al. [26]. In this context, the term was "crowding index", which refers to the number of rooms in the household divided by the number of residents living in the household Amre et al. [5]. However, no differences were found between the number of people residing in the home environment during infancy (<18 years) patients with IBD compared to controls [27,28]. In a retrospective study Montgomery et al. [26] in children who have older siblings was foud increased risk for UC, even after controlling for multiple births, sex, maternal age, year of birth, region and social status. This may be due to the fact that older siblings pose a risk of exposure to a younger sibling infection at a younger age. If you have a younger sibling, the older sibling found to reduce the risk of CD. This effect was most pronounced when they were younger siblings born within two years after the birth of the patient. This implies the possibility that younger siblings may increase the exposure or re-expose older sibling microorganisms which positively affect the mucosal immunity Ekbom et al. [27]. Birth order as a potential marker for hygienic theory in IBD was investigated in several studies with inconsistent results Bernstein et al. [28]. Theoretically, it was expected that the firstborn are usually exposed to infection later in life compared with younger siblings who come into contact with a viral or bacterial infection from older siblings.

Socioeconomic Status

Studies on socioeconomic status as an important risk factor in the development of autoimmune morbidities (specifically IBD) led to the discovery that higher socioeconomic status was more frequent in patients compared with controls. In the spirit of the hygiene hypothesis has been suggested that higher socioeconomic status families represent usually the lesser number of family members and better standards of household hygiene (hot water, separate bathroom, flush toilet) and associated restrictions on general exposure to micro-organisms [27,28]. Along with the general improvement in household hygiene during the 20th century, socioeconomic status has become less important. However, it would be interesting to identify potential status/problems with the incidence of allergies, autoimmune diseases and atopy in Roma excluded communities in comparison with our general population [29-33].

Conclusion

The incidence of allergies atopic and autoimmune, disease is growing and one of the promising hypotheses referring to the reasons for this is the hygiene hypothesis. Its basic premise is the reduced exposure of the child population to antigenic stimuli during the maturation of the immune system of children brought up in too clean to semisterile environment. Emphasis is placed on the desired effect of natural gut microbiome programming immunological response to new antigenic stimuli from the environment, including infectious agents and letting common childhood viral infections without antibiotic intervention that adversely affect the aforementioned microbiome. Although the strength of the epidemiological evidence supporting this hypothesis fluctuates due to methodological shortages of available individual studies. The impact of microbiome, the overuse of antibiotics, repeated infections, breastfeeding and perhaps even social status of the family are the most promising factors that can promote hygiene hypothesis. They deserve inclusion in a carefully prepared a prospective epidemiologic study of child and adolescent population, to avoid the problems of retrospective studies in particular the memory and selection bias.

Acknowledgement

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