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Review Article

Environmental Influence on the Increased Prevalence of Allergic and Autoimmune Diseases, Modifications through Epigenetic Mechanisms

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Abstract

Epidemiologic research has detected an astonishing increase of the appearance of many multifactorial diseases such as allergic and autoimmune diseases, including diabetes mellitus type I. However, studies using advanced molecular techniques could not establish genes responsible for these diseases in the majority of the population. Instead, genes related frequently to inflammation were detected in fewer of 10% of the patients. Thus, it is possible that environmental factors influence the expression of the genome through epigenetic modifications. These conclusions are of major importance since they demonstrate that lifestyle, eating habits and the pollution of the environment contribute to our health.

Keywords: *Allergic and Autoimmune Diseases; Epigenetic Mechanisms*

Introduction

Multifactorial diseases are concerned with the involvement of multiple genes more or less significant in the development of the phenotype. Molecular research of those diseases in based on GWAS (Genome-wide association studies) of a wide population and the investigation of genes in monozygotic twins. Regarding allergic and autoimmune diseases, research revealed that the predominance of some genes is linked to the population examined and they show a geographic distribution. It is interesting that none of the responsible genes accounts for more than 10% of the cases. Moreover, recent data demonstrate that there is a strong environmental influence starting from the early childhood.

Increase of allergic and autoimmune diseases

Epidemiological data suggest that there is a tremendous increase of allergic diseases (Figure 1) [1], diabetes mellitus (Figure 2) [2], inflammatory bowel disease (Figure 3) [3] as well as neurological diseases including autism (Figure 4) [4] the previous 50 years reaching the numbers of an epidemic. In addition, the genetic background remains highly unchanged. Is this increase a myth due to appropriate diagnosis methods or is this an unpleasant reality.

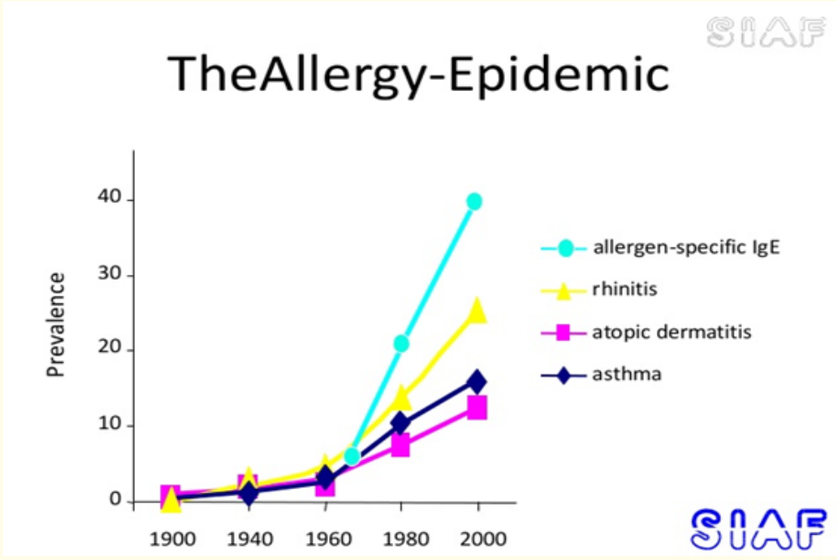

Figure 1: *The increasing prevalence of allergic disease the previous century.*

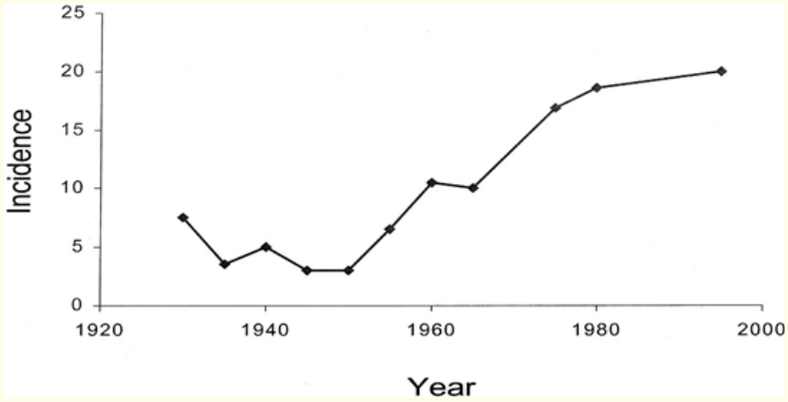

Figure 2: *The increasing incidence of diabetes mellitus the last 50 years (www. Data360. org).*

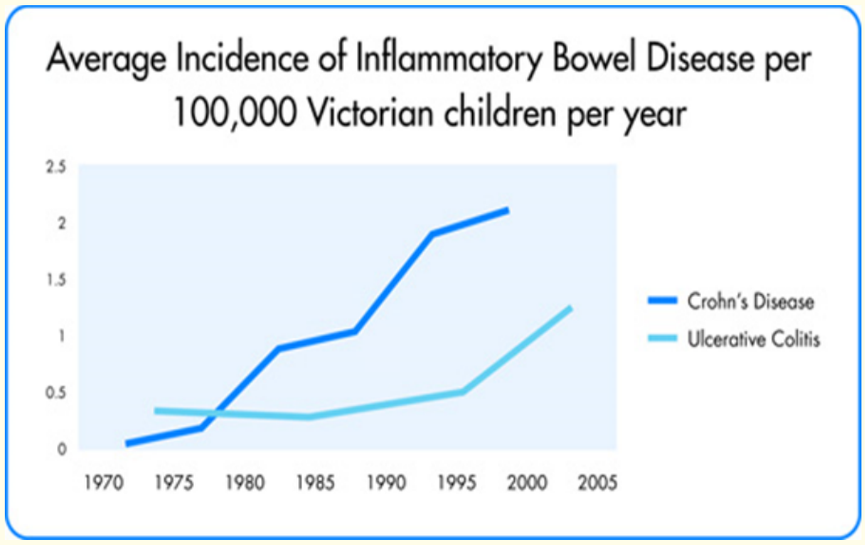

Figure 3: *Inflammatory bowel disease (The Gutsy Group).*

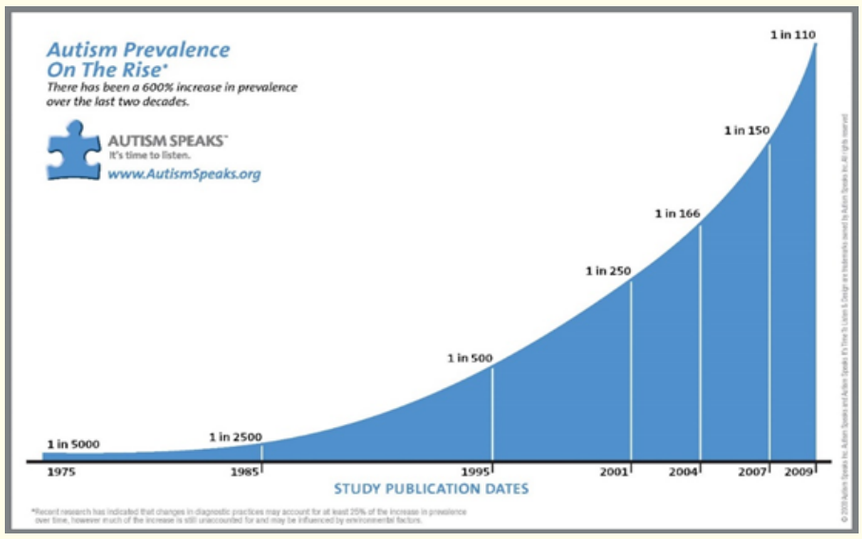

Figure 4: *Autism, an environmental or genetic disease?*

Hygiene hypothesis

In 1989 David Strachan introduced the scientific view that children growing in extended families suffered from hay fever in lower percentages than children growing in nuclear families. His research demonstrated that there was an increase of 1 - 5% of asthma in the UK and New Zeeland from 1961 to 1991 and the percentage of the incidence of the disease was 4% more in nuclear families. He was the first scientist to observe the protective role of the environment in the development of asthma. His research has become the ground for the development of hygiene hypothesis [5].

Regarding the remarkable features of this assumption, it has been suggested that infections during early life educate the immature immune system to acquire a balanced response to different antigens. Particularly, infections contribute to the balance of T helper response towards the TH1 phenotype (promoting cytotoxic reactions) or TH2 (promoting antibody and allergic reactions). A dysregulation of this balance contributes to the development of allergic diseases when the response turns in favor of TH2 and autoimmune diseases when there is predominant TH1 response and scarcity of immunoregulation mechanisms.

However, this hypothesis was an oversimplified view to explain further data. In 1999 a study in Finland published on Lancet showed increased incidence of asthma among children going to nursery due to increased frequency of infections [6]. There were a number of further publications concluding that frequent infections as well as socioeconomic background are not always connected with the appearance of allergies. Endotoxin thought to protect children growing in a rural environment does not protect children living in the disadvantaged areas of the cities [7]. Moreover, the infections at the early life due to syncytial respiratory virus could be a contributing factor in the development asthma and the infection with rhinovirus is connected with the exacerbations of the disease in a significant proportion of adult and children with asthma. It was interesting to find out that the distribution of allergic and autoimmune diseases was a mirror of the distribution of hepatitis A and infections with helminths [8]. Considering the above, it seems that the reality is that infections either contribute to protection or they promote disease. Furthermore, what has happened in patients suffering from allergies and autoimmune diseases together?

Microbiome

As microbiome is characterized the symbiotic antigenic burden of the body and it includes non-pathogenic bacteria colonizing the mucous membranes of the respiratory and intestinal track as well as the epidermis. It is suggested to include 10 - 100 trillions of cells. Today, it is known that the complex interaction of the immune system with PRRs patterns of the bacteria not only infective, but also symbiotic are important for the development and function of immunity. Apart from microbiome, the denominated biome including the viruses incorporated in the DNA, provide the basis for the homeostasis of the immune system and the development of immune tolerance. Thus, TH1/TH2 balance is achieved, there is a polarization of antigen presenting cells and mechanisms of tolerance are developed. This huge number of cells and patterns are frequently called 'a super-organism' [9].

Microbiome is influenced by lifestyle and environmental factors. The so-called 'Western type of lifestyle' is characterized by nuclear families, pollution of the atmosphere and soil and water by toxic substances from commuting and industry and industrial and chemical compounds such as pesticides and deterrents used in everyday life. Convenient meals containing high salt and unsaturated lipids, the lack of sunlight and reduced time for physical activities contribute to the construction of microbiome.

The Hygiene hypothesis broadens to the so-called biodiversity hypothesis that suggests that the multilevel interaction of the body with the environment is beneficial for good health. It is important that it starts from the embryo and continues through life. A simplified form of the above is depicted by Hippocrates in his book 'regarding air, water and soil' written long ago who first suggested the impact of climate and environmental issues to health.

Epigenetic mechanisms

The term epigenetics is used to describe the inherited modifications of the expression of the genes contributing to changes in the phenotype without alterations of the DNA sequencing. Epigenetics is the bridge between genotype and phenotype and it is thought to behave as a form of imprinting of environmental factors to the genome. Those changes contribute to the developmental transformation of the genome in order to adapt to the alterations of the environmental conditions and it is inherited for three generations [10].

The epigenome can be modified during the life span, but the major changes happen during some 'windows' such as gametogenesis, fertilization, embryogenesis and the early years of life. The influence is imprinted by chemical changes of the histones capping the DNA. Thus, the genes become available or not to transcription. Methylation of cytosine by the enzyme methyltransferase Dnmt 1 is the major mechanism of those modifications. The pattern remains unchangeable through cell division [10].

How important are those alterations is obvious from the fact that 2 - 5% of the genome has methylated cytosine. This methylation takes place into the so-called 'GpG islands' with increased constitution with cytosine and guanine bases. Those islands locate mainly in the promoters of genes that are in a different pattern methylated depending on the tissue. Generally speaking, over-methylation means low expression and vice versa. Hypo-methylation contributes to genome instability. The increased methylation pattern in Alu and LINE-1 (long interspersed nuclear element-1) transposons is of unknown etiology [10].

Methylation is the basis of normal cell function in different tissues producing differentiation and of genetic imprinting of large areas of the DNA connected with development and central nervous system maturation as well as ageing of the cells.

In 1992 Barker., *et al.* suggested the fetal basis of the diseases in adulthood. That is to say that epigenetic reprogramming during fetal period predetermines the appearance of disease in adulthood such as obesity, cardiovascular disease and diabetes type II, cancer, osteoporosis and even psychiatric disease [11]. Different environmental factors such as diet, pollution, pesticides, trihalomethanes, PAH and cigarette smoking can be harmful [12].

Endocrine disruptors are compounds affecting the reprogramming. Diethylstilbestrol alters the expression of many genes including catechol-O-methyltransferase (COMT) which suppresses methylation. Bisphenol A used for the packaging of everyday products causes over methylation and has estrogenic properties and the myriad of compounds is continuously increasing [13].

Discussion

As can be supported from the above our genetic background is our personal fingertip differentiating us from the other people. However, under certain conditions make us vulnerable and susceptible to different diseases or on the other hand more resistant. The genome is not static and determined, but it shows the ability to adapt having amazing plasticity due to epigenetic modifications.

Modern developed societies have combated the life threatening infectious diseases burden responsible for thousands of deaths, but new diseases have emerged. Research is ongoing to analyze the data in order to prevent those new epidemics such as allergic and autoimmune diseases. New medications are also developed such as biologic factors implicated in the genomic modifications through methyltransferase and methylase of histones for the treatment of rheumatoid arthritis or lupus erythematosus [14].

Finally, our knowledge can contribute to raise our awareness about environmental issues and personal or social interventions. Pediatricians have an important role since they educate the family during the early years of life and they have to be aware of the new data.

Conclusion

The increasing prevalence of allergic and autoimmune diseases the last 50 years is based on epidemiological data. This increase was associated with the Hygiene hypothesis at first. Ongoing research expanded the theory to the theory of biodiversity and the microbiome which modulates immunity and introduces epigenetic modifications in order to adapt to environmental changes. These maladaptive changes are the basis of the increase of allergic and autoimmune phenomena in modern society.

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