ABSTRACT

The explosive rise in the incidence of atopic diseases in the Western developed countries can be explained on the basis of the so-called “hygiene hypothesis”. In short, it attributes the rising incidence of atopic dermatitis to reduced exposure to various childhood infections and bacterial endotoxins. Reduced exposure to dirt in the clean environment results in a skewed development of the immune system which results in an abnormal allergic response to various environmental allergens which are otherwise innocuous. This article reviews the historical aspects, epidemiological and immunological basis of the hygiene hypothesis and implications for Indian conditions.

Key Words: Atopic dermatitis, Hygiene hypothesis

INTRODUCTION

A substantial rise in the cumulative incidence of atopic dermatitis in children has been documented in cross-sectional studies from several North European countries. The incidence was less than 3% in children born before 1960, 4-8% if born between 1960 and 1970, 8-12% for those born after 1970 and over 15% in the recently born. Thus there has been a true and significant rise in the prevalence of atopic dermatitis over the past three decades in the Western industrialized society. What later came to be known as the ‘hygiene hypothesis’ had its origin in a small report published by Strachan in 1989. He studied a national sample of 17414 British children born during one week in March 1958 and followed them up for 23 years. His observations revealed that hay fever incidence was inversely related to the number of children in the household and eczema in the first year of life was related to the number of older children in the household. He concluded that over the past century declining family size, improvement in household amenities and higher standard of personal cleanliness have reduced the opportunities for cross-infections in young families. This may have resulted in more widespread clinical expression of atopic diseases emerging earlier in wealthier people. Another study involving 812 twin pairs in Denmark revealed that the cumulative incidence rate of atopic dermatitis (up to seven years) increased from 0.06 for birth cohort 1965-1969 to 0.12 for the birth cohort 1975-1979. In this study, the concordance rate in monozygotic twins was 0.72 and in dizygotic twins was 0.23. This twin study provided a convincing evidence of a rapidly increasing disease frequency due to the influence of exogenous factors. These authors also concluded that trends in infant feeding and exposure to house dust mites cannot explain the rising incidence of the disease.

Also, the incidence of atopic disease is shown to be related to the age of entry into the nursery in a large study conducted by Kamer et al. in Germany. Those children from small families who enter the nursery at a later age (and are less exposed to infections from other children) have a higher chance of getting atopic disorder than those who enter the nursery at a younger age. This effect is not seen in children from larger families as they are exposed to other children in the house itself.
THE IMMUNOLOGICAL BASIS

The helper T cells are divided into various groups (Th0, Th1, Th2, Th3) according to the type of lymphokines they produce. Th0 cells are the naive T cells whose polarization to either Th1 or Th2 cells occurs through the release of cytokines from the cells of the innate system like macrophages, basophils, eosinophils, mast cells and natural killer cells. Th1 cells produce lymphokines [Interleukin 1 (IL-1), Interferon γ (INF-γ), tumor necrosis factor (TNF)] which stimulate macrophages and cytotoxic T cells. Th2 cells produce lymphokines that stimulate B cells to proliferate and produce antibody. These lymphokines are IL-4, IL-5, IL-6, IL-10 and IL-13. The regulatory or Th3 type of cells are now recognized to be important in regulating or switching off the immune response by production of IL-10 and transforming growth factor β (TGF-β). The cytokines produced by these various cells and their interactions are important in understanding the immune basis of the hygiene hypothesis.

In the 1990s, the hygiene hypothesis was explained by the fact that there is a cross-regulation between the two subsets of T helper cells. This refers to the down-regulation of Th2 cells by Th1 cytokines and vice versa. This means that increased incidence of atopy was explained by the lack of infections leading to reduced stimulation of Th1 cells resulting in increased activity of Th2 cells leading to allergic manifestations. This proposition had several supporting observations. A study in Japan by Shirakawa et al. showed that in children who were positive tuberculin responders, the rate of current atopic symptoms was one-third the rate in negative responders. The positive tuberculin responders had significantly higher levels of Th1 cytokine IFN-γ and lower levels of Th2 cytokines IL-4, IL-10 and IL-13. However, this proposition of Th1/Th2 imbalance fails to explain some observations. For example, parasitic infections shift the immunological balance towards Th2 responses but there is no increase in atopic disorders although IgE levels may be higher in these cases. In a study conducted in Gabon by Van de Biggelaar et al., it was found that children with urinary schistosomiasis had a lower prevalence of a positive skin test reaction to house dust mites than those free of this infestation. It was also found that this could be explained by the high levels of anti-inflammatory cytokine, interleukin-10 produced in chronic schistosomiasis, which depresses atopy in African children.

Thus it is found that both bacterial and parasitic infections reduce the incidence of atopy in children. Yazdanbakhsh et al. have concluded that the induction of a robust anti-inflammatory regulatory network by persistent immune challenge offers a unifying explanation for the inverse association of many infections with allergic disorders.

Besides these explanations, some other additional mechanisms may be at work. One of these is antigenic competition, in which the immune response to an antigen is decreased by a concomitant immune response against an unrelated antigen. Lack of antigenic competition in the absence of childhood infections may explain the increased incidence of allergic phenomena seen in atopy.

Toll-like receptors (TLRs), after binding to bacterial ligands stimulate mononuclear cells to produce some cytokines, which may down-regulate some allergic responses. Similarly, superantigens which are components of some bacterial products or of viral proteins, may induce deletion or activation of T cells. These roles of TLRs and superantigens need to be understood in a better way to explain the observed facts. Thus there are several possible mechanisms by which childhood exposure to infections in a ‘dirty’ environment may protect against atopy.

CLINICAL RELEVANCE

It is now possible to expose the children in a clean and hygienic environment to dirt by feeding them with probiotics, which are cultures of potentially beneficial bacteria of healthy gut microflora. In biological terms, dirt consists of microbes found in feces and feces-contaminated soil. One such microbe found in healthy gut microflora is Lactobacillus rhamnosus (Lactobacillus GG). If the hypothesis is true, it should be possible to reduce the incidence of atopy in children by exposing them to dirt. Kalliomaki et al. conducted a trial in Finland which was double-blind, randomized and placebo-controlled. Mothers with family history of atopy were enrolled in the study (n=159). They were given either two capsules of placebo or 1×10^10 colony-forming units of Lactobacillus rhamnosus daily for two to four weeks before delivery. After delivery, breastfeeding mothers were given the capsules or the children received the agents orally for six months. The children were followed up for two years after birth and it was found that the frequency of atopic eczema in the probiotics group was half that of the placebo group. Thus it was shown that exposure to bacterial products in early life reduces the incidence of atopy.

What relevance does the hygiene hypothesis have for us in India? Personal communications with colleagues who have also worked abroad and some publications reveal an impression that atopic dermatitis is less common and mild in India
compared to the West. Are we likely to have an increase in incidence of this condition like the increase in the incidence of diabetes and ischemic heart disease? Not likely if the hygiene hypothesis is true. With lack of toilet and drainage facilities in most parts of the country and presence of cattle and cattle-sheds even in urban areas, we are still exposed to a lot of dirt which will keep on protecting us from atopic diseases.

REFERENCES


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