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Relationship between atopy, allergic diseases and total serum IgE levels among HIV-infected children

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Key words

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Summary

In recent years there has been increasing prevalence of allergic diseases globally, especially in children. Many IgE-dependent allergic manifestations have been described in HIV-infected individuals. However, it seems to be controversial whether immunological changes, such as IgE elevation, results from the infection or is related to the presence of allergy in these subjects. The aim of this study was to survey the literature of articles focused on the pediatric population with HIV infection, total serum IgE and / or allergic diseases and atopy. We conducted a narrative review, from articles found in Medline and LILACS published in the last 20 years using the key words: children, allergic disease, HIV, IgE. After eliminating duplicates in databases, 33 international articles were considered. We selected seven articles that addressed the proposed aim of study to perform a complete reading and discussing. Conclusion: this review showed that high IgE levels can be found for other reasons than atopy or allergic disease in children with HIV. Specific IgE against the antigens of the HIV virus and higher levels of total serum IgE can be seen in children with or without aggravation of AIDS. Finally, we reiterate the call made by the authors of some studies for more studies on the subject, especially with larger samples in pediatric population.

Introduction

Despite of the important role in protection against pathogens and tumor cells, the immune system is able to cause injuries by hypersensitivity reactions. The type I hypersensitivity, also known as the immediate hypersensitivity reaction, is present in allergic diseases and is related to atopy, which is the genetic predisposition to increased production of immunoglobulin E (IgE) (1). The elevated level of IgE found in allergic disease is resulted of an imbalance in cytokine production, with a predominance of T helper (Th)-2 profile. The release of IL-4, IL-5 and IL-13 especially from Th-2 cells, eosinophils and mast cells promote activation and/or recruitment of B cells and more production of IgE (2).

Different studies have shown the increase in the prevalence of allergic diseases in patients infected with Human Immunodeficiency Virus (HIV), which paradoxically, progress into immunosuppression (3,4). This contradictory effect has been assigned to quantitative and functional alterations in the regulators of T cells (5,6). Other observations suggest that secondary immunological changes to HIV infection, such as the polyclonal activation of B cells and the consequent increased production of IgE may also interfere in the development of allergic diseases in patients with HIV (7). However, there is *in vitro* demonstration of IgE antibodies inhibiting the replication of HIV in the culture of lymphocytes, suggesting a role in anti-HIV IgE-mediated inhibition of virus, justifying the elevated production of IgE in some patients with HIV (8).

Nevertheless, a high frequency of clinical manifestations suggestive of IgE-mediated allergic diseases have been described in HIV-infected patients, such as nasal congestion, sinusitis, consistent cutaneous eruptions with atopic dermatitis, asthma, symptoms of hypersensitivity to drugs and pruriginous cutaneous alterations (3). Aspects related to the pathophysiology of atopy in these patients have been studied preferably in the adult population, in transversal evaluations (4,9,10).

With the increase in the prevalence of allergic diseases observed globally, mainly in the children (11), an unsettling question arises: What are the evidences in literature on the relationship between atopy and / or allergic diseases, high level of total serum IgE and HIV in children infected by this virus?

Thus, the purpose of this study was to make a survey on the literature of articles searching relation between HIV-infected children, total serum IgE and/or allergic diseases and atopy.

Methods

To carry out this review, articles were selected from publications indexed in the following electronic databases: Latin American Literature on Health Sciences (LILACS) and International Literature on Health Sciences (MEDLINE).

The descriptors used were: children, allergic diseases, HIV, IgE, allergy and atopy. Filters were used in the advanced search with combinations such as allergic disease + HIV + children + IgE or atopic disease + HIV+ IgE + children or atopy + HIV + IgE + children or allergy + HIV + IgE. Additionally, references of the selected articles, which were not mentioned in the databases but were related to the topic, were also sought eventually.

It were verified all abstracts available in journals found in the above-cited databases, published in English language since 1990 until to 2013.

Articles were initially selected after reading the abstracts, being subsequently searched and analyzed as a whole when the abstract had a direct relation to the research question. Repeated publications in both databases, and those, which did not have direct relation to the formulated question, and reviews on the proposed topic, were all excluded.

Results and discussion

Thirty-three articles were found, of which 26 articles were excluded for not addressing the issue directly, such that seven articles were selected, which were read entirely and used for the discussion.

The characteristics of the seven selected articles are shown in Table 1.

In general, elevated level of total serum IgE (excluded: corroborate) is related to atopic or parasitic diseases. In HIV infection, the interpretation of this laboratory finding is complex because the cell stimulating IgE production by B-lymphocytes, the CD4+ T-lymphocyte, or T-helper (Th) cell is impaired in quantity and function. Moreover, data from studies on adults indicate that there is a change in the pattern of cytokine release from Th1 to Th2 in the progression of HIV infection (19). Since for IgE synthesis the Th2 cytokines, such as IL-4 and IL-13, are needed, it is speculated that the regulation of IgE synthesis is impaired in HIV-infected patients (7).

In the reading of the selected articles, the first study investigated children with HIV and the relationship between the presence of IgE levels and disease progression. It was observed an abnormal IgE synthesis and an increase in serum immunoglobulin correlated to the disease progression, similar to literature data in adults (12).

It was also found that the persistent overproduction of IgE appeared to be associated with events related to Aids, such as severe decline in CD4+ cell count and increased susceptibility to opportunistic infections. The authors suggested that the elevated IgE level could serve as a marker for disease progression and that it would be an indirect indication of the deviation of cytokine production from Th1 to Th2 (12).

In another study involving 29 children with HIV, successive measurements of total serum IgE, CD4+ and CD8+ cell count and Radioallergoabsorbent Test (RAST) for six aeroallergens were performed. The results showed that 29.8% of children had elevated level of total IgE, but no correlation was found between total IgE levels and CD4+ cell count, or CD4+:CD8+ (13).

Moreover, in a range from 0 to 6, all results of RAST were of class 0, that is, there were no specific IgE to allergens considered. The authors concluded that, although there was a high frequency of HIV-infected children with high IgE levels, this does not seem to reveal a particular immune response. They attributed this findings to polyclonal activation and the altered production of cytokines, associated with HIV infection and / or its effect on the immune system (13).

The next article tried to extract characteristics from clinically healthy children with HIV in relation to serum IgE level. It was demonstrated that out of the 30 children who

were studied, 26% had high IgE levels (14).
The authors analyzed the children dividing them into high IgE and normal to low IgE level. Among those with high IgE level, 70% had low CD4+ cell count (5/7), of which 1/7 children fell in the standards of the classification of the Centers for Disease Control and Prevention (CDC), due to recurrent bacterial infection. In contrast, among children with normal to low IgE, 26% had opportunistic infections, 35% had other serious infections and 30% met criteria for failure to thrive. There was no difference in the incidence of allergic symptoms between the groups (14).
Another finding was the demonstration of specific IgE against HIV proteins (anti-IgE anti-p24 and p17) in three of the seven children with high IgE level. Curiously, all three were Puerto Ricans. Nevertheless, in the group of normal to low IgE level, only one in 24 children had specific IgE against HIV proteins. This was an African American child and had opportunistic infections and demonstrated failure to thrive (14).
From these results, the authors speculated that the elevated IgE, particularly the HIV-specific IgE, was a contributor to the prolonged health of the children with HIV infection, and they suggested prospective studies to test this hypothesis (14).
In the overall of these first studies, elevated IgE levels may be related or not to the progression of HIV disease in children. Previous adult studies found correlation between IgE elevation and HIV infection or IgE elevations markedly increase during progression of the disease from the asymptomatic stages to the Aids stage (20,21). An Immune dysregulation with a shift to the Th2 pattern of production cytokine, proposed as a mechanism for clinical deterioration in adult, may be also the response in children with HIV. On the other hand, it is possible to find specific IgE against virus proteins and this may perhaps portray a response to attempt to control the infection in those children in which IgE elevated levels did not relate to the progress of disease.
The relationship between total serum IgE and atopy and/or allergic diseases was not observed in these studies or it was not their main focus. Other researchers have sought this relationship in children with HIV, which is presented in the following articles.
In the evaluation of 43 children with HIV, authors searched the incidence of allergy, IgE levels, eosinophilia and CD4+ cell count. These children were more than three years old. Out of the 43 infants, two died during the survey, 28% of the survivors had a positive immediate hypersensitivity skin test (IHST) to common aeroallergens and 40% had elevated serum IgE levels. There was no eosinophilia greater than 470/mm3 and 40% had immunodeficiency characterized by CD4+ cell count, which was less than 200/mm^3 and did not change significantly over a year. There was no significant correlation between serum IgE levels and CD4+ cell count. A comparison between children with positive and negative skin tests failed to show significant difference in CD4+ cell count as well as eosinophils and IgE levels (15).
Therefore, the authors propose that the high IgE levels found could be reflecting the presence of specific IgE against HIV antigens or a nonspecific polyclonal activation of B-cell typical of the HIV infection. They concluded by saying that if the IgE levels are high, this can neither be assigned to immunodeficiency nor allergy and ended suggesting new studies to clarify this issue (15).

Another cohort study conducted in the USA investigated the prevalence of atopy and sensitization by aeroallergens in children with perinatal HIV infection. These were compared with HIV-negative children. An evaluation was also done to assess whether high IgE levels were associated with the clinical progression of the disease (16).
In results, 42% of HIV-infected children had some sort of allergic disease giving a prevalence of allergy of 52% (16/31 HIV+ children), nevertheless hypersensitivity to aeroallergens was 29%, which was similar to the general population. There was no correlation between serum IgE levels and CD4+ cell count and the immunological classification CDC. However, when the non-atopic HIV+ children were separated, there was correlation between high IgE levels and disease progression in accordance with the clinical classification CDC [16]. Moreover, there was no correlation between levels of serum IgE with the prevalence of atopy, CD4 + cell count, immunologic classification CDC, duration of infection and serum levels of IgG, IgM or IgA (16).
The authors commented that the lack of correlation between IgE levels, CD4+ cell count and CDC immunological classification may be due to the characteristics of the population. All patients were using antiretroviral therapy and few were symptomatic, unlike other studies that showed this type of correlation. With regards to the correlation between IgE levels and clinical classification, but not CDC immunological classification in non-atopic children with HIV, the authors suggest that serum IgE was not exclusively related to allergy. They also indicate that elevated levels of IgE, is not a consequence of poly-

clonal activation, but for fighting pathogens, including HIV. Limitation of the study was the small number of patients, then, authors suggested that further studies be conducted, especially in the advanced state of the disease (16).

In a case-control study evaluating 100 South African children, 50 with HIV and 50 seronegative, the presence of atopy was investigated through skin tests and questionnaires to identify personal and family allergic diseases. Only 10% of children with HIV had positive skin test and 24% had a positive family history of allergic diseases. However, there was no significant association between atopy and HIV. The authors noted that their study should be considered as a pilot study due to its limitations. For example, there was no attempt to prove whether rhinitis as reported by patients were due to allergy and the RAST test to verify allergy to foods or inhalants was not requested. However, emphasis was laid on the fact that previous studies showed a high frequency of allergic diseases in children with African HIV (17).

A longitudinal study in Brazil with 68 HIV-infected children, aged between one to 13 years, underwent evaluations on two different occasions in an average time of 10 months of research (18).

The objective was to determine whether immunological changes influenced the development and prevalence of atopic diseases in those children. The results showed a frequency of atopy diagnosed by IHST in 21% of the children in the first trial and 30% in the second. Atopic children seen on two occasions had total serum IgE levels greater than non-atopic children. Those atopic children had association between personal history of atopy and greater proportion of elevated serum IgE in the first and second evaluation (18).

In the second phase, a logistic regression analysis also showed an association between serum IgE levels and higher absolute count and percentage of eosinophils in atopic children only. This study verified that six patients changed the condition of the skin test from negative in the first assessment to positive in the second assessment and, among the positive, one patient changed to negative IHST on the second occasion. This was one of the patients who had progressive disease with worsened immune response (18).

The authors commented that those patients with a change in response of IHST to positive showed indication of improvement or maintenance of their immune state, as compared to earlier levels of CD4+ cell count. These changes suggest that the immune profile change is perhaps the main reason for the positive or negative skin test [18]. In this study there was a high prevalence of atopy in children with HIV, which is demonstrated by positive IHST, history of allergic disease and elevated serum IgE levels. Authors postulated that the development of atopy might have been influenced by genetic and environmental factors as well as the immune status of children (18).

From this review, it can be observed that the literature on the subject is still scarce. Moreover, studies are sometimes inaccurate due to primarily, the small number of cases in the pediatric population or the presentation of controversial results. Regardless of the criteria employed for allergy diagnosis, in general, high IgE levels were verified for other reasons than allergic or atopic diseases in children with HIV. The presence of specific IgE against HIV antigens and high total serum IgE levels was shown in children with and without disease progression. Hence, corroborating what some authors have reported, we reinforces the need for more research to answer or to explain the relationship between IgE levels and HIV infection in children, and specially, studies that justify the increased frequency of allergic diseases, diagnosed by more rigorous criteria (e.g. food oral challenge, clear correlation between IgE sensitization and rhinitis) in children with HIV. In view of the apparent difficulty, wherever possible, studies involving larger samples are suggested.

Conclusion

High IgE levels can be found in HIV-infected children with or without allergic diseases, and it may be a feature of the infection per se. More studies are needed, preferably with larger sample size to clarify the role of IgE in HIV infection and whether it is related to prevalence of allergic diseases in the pediatric population with HIV.

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