

Atopy and immunodeficiencies: an intriguing overlap

Mini Review

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SUMMARY

A few years after the identification of serum IgEs and their biological function, Burgio et al. published a paper entitled "Atopy as Minimal Immunodeficiency". The authors wondered whether immunodeficiencies, "experimentum naturae" which had allowed basic progress in the knowledge of the functioning of the immune system, could also help in understanding the pathogenetic mechanisms that lead to the development of allergic diseases. A quick excursus on the allergic diseases that characterize many immunodeficiencies, or rather many inborn errors of immunity (IEI), demonstrate there are many points of convergence and overlap between atopy and immunological defects. Atopy itself is a more or less expressed form of immune system dysregulation and knowing which are the defective genes of the IEI in which atopic stigma are expressed will clarify how the allergic disease develops and, consequently, what the therapeutic measures can be targeted.

KEYWORDS: atopy, immunodeficiency, Inborn error of Immunity

INTRODUCTION

The clinical picture of immunodeficiencies and allergic diseases can be to some extent confusing as the symptoms of both can contribute to each other's development and be confused with each other. For example, it is known that allergic inflammation of the nasal or bronchial mucosa in cases of rhinitis and asthma favors viral colonization and proliferation with prolonged secondary infections¹. Atopic dermatitis caused by primary defects of the skin barrier (e.g. Filaggrin deficiency), predisposes to infections by *molluscum contagiosum*⁸; in other forms of eczema, the increased production of IL-13 counteracts the protective action of the natural antimicrobial peptides of the mucosal surface, increasing the probability of skin infections². Allergic diseases can therefore often be associated with severe and chronic infections which can mislead the diagnosis: this is not surprising.

Less linear is explaining the onset of allergic symptoms in primary immunodeficiencies because one must imagine an immunological damage so serious as to destroy the ability of the immune system to orchestrate an effective response to pathogens (with susceptibility to infections), but also such as to increase the capacity to mount an allergic inflammatory response to ubiquitous and harmless antigens.

It is therefore rightful to ask whether atopy and immunodeficiencies are different and casually combined diseases or whether allergy in its various manifestations (gut, skin, lungs and nose) is in itself an immunodeficiency, with a wide range of severity albeit with a clear prevalence of particularly mild and benign forms.

ATOPY AS MINIMAL IMMUNODEFICIENCY

The first, historic classification of primary immunodeficiencies, published in 1971, includes a small number of immunodeficiencies and only two of them also present atopic symptoms

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³. Job's syndrome was first described by Davis et al. (1966) in two sisters with eczema, cold boils, and bacterial pneumonias ⁴. The second, Wiskott-Aldrich Syndrome, was described as characterized by eczematous lesions, but above all by serious bacterial and viral infections and hemorrhages caused by thrombocytopenia. In those years, Kim and Teruko Ishizaka identified serum IgE for the first time ⁵. The existence of serum antibodies responsible for allergic reactions had been hypothesized in 1921 when Prausnitz and Kustner, by intradermally injecting the serum from an allergic patient into a healthy subject, found that the serum carried substances responsible for allergic reactivity. At that time the classes of immunoglobulins had not yet been identified, so they called these substances "reagins".

As is known, the first identification of IgG took place in the 1950s, quickly followed by that of IgM and IgA, but only at the end of the 1960s were IgE recognized and their crucial role in allergic diseases was confirmed ⁵.

In those years, there were also the first reports that patients with selective IgA deficiency had allergic symptoms more frequently than the general population, a characteristic which has also been confirmed in the latest case studies ⁶⁻⁸.

Starting from this suggestion, Soothill hypothesized that the primary cause of allergy and atopic march was due to the defect of the secretory IgA normally present on all mucosal surfaces (respiratory and intestinal, etc.). Secretory IgA are absent in the first months of life and begin to appear in the secretions in a detectable amount, after the 3rd-6th month of life to reach adult levels at 2-6 year of life ⁹.

Soothill therefore hypothesized in 1974 that allergic sensitization – which he imaginatively called "allergenic original sin" – occurred in the first months of life when secretory IgA had not yet physiologically appeared. The lack of immunological exclusion and of protective barrier by IgA would have allowed the passage of potentially allergenic molecules through the intestinal mucosa, which are capable of stimulating the production of specific IgE with sensitization in genetically predisposed subjects ¹⁰. Sensitization can elicit symptoms immediately or in the following months or years, or even never. Specific IgE can be biologically active and therefore cause authentic allergic diseases or be only present and constitute only an atopic state, without actual disease. Original sin generally occurred with food allergens: in the very first days or months of life in newborns/infants fed even only occasionally with cow's milk or at 4-6 months of life during weaning. It is therefore not surprising that dietary rules such as delaying the introduction of milk, eggs and potentially allergenic foods such as peanuts persisted obstinately until a few years ago, despite the fact that the hypothesis of allergenic original sin had been proven wrong. On the contrary, the LEAP study has shown that introducing peanuts during weaning (therefore in the 4-6 month time frame) decreases the probability of developing allergy to peanuts ¹¹. The current recommendations are to introduce peanuts (later it was demonstrated for the egg too) starting from 4 -6 months of life or in any case before the ninth month in infants at atopic risk ¹².

In any case, the identification of IgE also changed the name of many immunodeficiencies. Job's syndrome was redefined by Buckley et al.

(Buckley syndrome) who described the extremely high serum levels of IgE ¹³. Finally, it was more correctly called Hyper IgE Syndrome (HIES), denoting not only the high or very high levels of IgE but also the extreme clinical variability ¹⁴. HIES is characterized by multiple symptoms in various combinations: not only eczema and skin and lung infections, but also osteopenia with bone fragility, scoliosis, typical facial appearance, alterations of the vessels (aneurysms) and malformations of the central nervous system.

Wiskott-Aldrich syndrome (WAS), already known for having atopic stigmata, did not change the name but was enriched with new and important details: in addition to eczema, the presence of high levels of IgE and intestinal disorders often associated with anti-milk antibodies was recognized.

On the basis of this exciting story, in 1979 Burgio et al. stigmatized the question of whether atopy itself could also be considered an immunodeficiency, laying the bases for research on the immunological genesis of atopic sensitization and allergic diseases ¹⁵. The time was ripe for such a question since on the one hand the identification of IgE as "reagins" had opened the door to an in-depth study of the molecular mechanisms responsible for allergy and to the strengthening of the immunological scientific bases in the field of allergology, which was still largely empirical at that time. On the other hand, the authors underlined how primary immunodeficiencies were phenomenal "experiments of nature" which had allowed – or suggested – the identification of precise functions of the immune system. New knowledge has made it possible to better understand not only immunodeficiencies, but also many other immune-mediated diseases. From then on, the primary immunodeficiencies with atopic stigmata have been studied in depth, also to better understand the allergy, test hypotheses, or formulate new ones on the complex pathogenesis of atopy.

At the same time, as diagnostic techniques were refined, the number of primary immunodeficiencies with atopic symptoms increased; among these, some were also reported with very serious manifestations, such as Omenn's syndrome, a SCID described by Omenn for the first time in 1985 as a familial reticuloendotheliosis with eosinophilia and characterized by erythrodermia, hepatosplenomegaly, lymphadenopathy, alopecia, and marked eosinophilia ¹⁶. Currently, primary immunodeficiencies are more correctly defined as Inborn Errors of Immunity (IEI) and include a large number - around 500 - diseases for which the genetic defect is known ¹⁵.

Following the research logic suggested by Burgio et al, an interesting study was recently published on 1409 patients with IEI registered in the USIDNET national registry, a registry funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH) (17). The authors want to identify which IEIs are frequently associated with signs and symptoms of allergy because they consider it fundamental to guide the differential diagnosis of patients presenting with an allergic disease. Furthermore, since the gene(s) responsible for or associated with the various IEIs with atopic stigma are also known for the majority of IEIs, studies can be focused on particular genes and obtain in-depth information on the possible mechanisms

involved in determining allergic immune dysregulation. The study analyzed patients with available laboratory data indicative of Th2 inflammation (eosinophils and IgE) before the start of any therapy and related them to the defective genes and atopic symptoms presented, finding that the spectrum of IEI with atopy was larger than anyone knew. Eosinophilia was present in 183 subjects among the 975 eligible patients (18.8%) and was cumulatively associated with 29 genes. High IgE values were present in 135 among 645 eligible patients (20.9%) and were associated with 13 genes. Eosinophilia together with hyper IgE was a condition associated with 10 genes: *ADA*, *CARD9*, *CYBB*, *DOCK8*, *FOXP3*, *IKBKG*, *NCF1*, *SPINK5*, *STAT3*, and *WAS*.

As expected, the categories of IEI most frequently associated with atopy were the immunodeficiency disease due to immunodysregulation, those due to a combined defect of cellular and humoral immunity, both severe and less severe or associated with syndromic features, of which HIES is an exemplary part. Even many forms of predominantly antibody defects presented atopic stigma and in cases of recessive X agammaglobulinemia even the presence of IgE, high specific IgE level, and asthma or allergic rhinitis marked a particular phenotype (leaky XLA) supported by a hypomorphic variant of BTK¹⁸. Finally, at least one allergic clinical symptom (eczema, asthma, allergic rhinitis, or food allergy) was present in 10% or more of patients and this percentage was maintained in every category of immunological defect, including antibody defects¹⁷.

In conclusion, the description of the multiple genotype/phenotype relationships will be able to guide more detailed study on the function of these genes and their role in the orchestration of the mechanisms underlying all atopic diseases, even the mildest ones, and thus provide valid therapeutic tools.

A second study on case series of patients with IEI appeared almost simultaneously in the literature with similar, but almost complementary, aims. This is a study by the World Allergy Organization (WAO) Inborn Errors of Immunity Committee that evaluated patients from 61 centers in 41 countries around the world to establish the frequency of atopic stigmata and whether their presence caused a delay in diagnosis¹⁹. Allergic manifestations constituted the presenting symptom(s) of IEI in 5-25% of patients (median 8%) and had delayed diagnosis with a frequency of 0 to 50% with possible negative impact on the morbidity and mortality of the IEI. Regarding individual allergic diseases, bronchial asthma was the most frequent allergy in antibody defects, atopic dermatitis was extremely frequent and even the first symptom in a third of cases of hyper IgE syndrome, while food allergy was very rare and reported only in patients with HIES and IPEX.

CONCLUSIONS

We have now an increasing amount of data that contribute to better defining the pathogenesis of atopic diseases, the type of underlying immunodysregulation, and the genetic bases that, in various combinations, trigger the entire cascade of downstream events. All this, once again, is due to the in-depth study of those exemplary "*experimentum naturae*" which are the primary immunodeficiency

diseases. The hope is that new knowledge can lead to a truly targeted and effective therapy, even if there is still a long way to go.

Happell et al. evaluated a series of 12 patients with HIES and food allergy who underwent stem cell transplantation (HSCT)²⁰. After transplantation they observed that although the total IgE level fell in all patients, and in almost half IgE remained above normal levels. Food-specific IgE also persisted for many months and in some patients at very high levels even though 8 of the 10 patients who had performed the challenge had become tolerant. Therefore, the dysregulation does not resolve in all patients, even after a radical therapy such as HSCT and even more so, only the understanding of why these alterations can persist may lead us to develop effective prevention and treatment strategies. It's true, there is still a long way to go.

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Conflicts of interest statement

The authors declare no conflict of interest

Ethical considerations

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Author's contribution

Both authors contributed equally to the paper and approve its publication

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