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Study of Circulating Immune Complexes in Atopic Dermatitis

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The authors examined sera from 92 patients (78 adults, 14 children) with atopic dermatitis (AD), for the presence of circulating immune complexes (CIC). Using the PEG precipitation technique they found an increase in *CIC total protein*. In the quantity of precipitated proteins, elevated IgA and IgG levels and decreased C3 in CIC were measured. Neither the acute nor the subacute stage of the disease, nor skin involvement, correlated with CIC. In increased content of CIC was found in patients who had AD with associated disease recurrent infections, recurrent conjunctivitis, asthma, allergic rhinitis) and especially with pustulosis varicelliformis Kaposi, i.e. eczema herpeticatum. The T lymphocytes, together with other surface complement receptor-positive cells, are able to induce CIC production and keep them in solution. *Key words: Pathogenesis of AD; Associated diseases; Pustulosis varicelliformis Kaposi (eczema herpeticatum).*

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Atopy, a word of Greek derivation, was introduced by Cooke in 1923 (1) to connote a strange disease. The constitutional stigmata which distinguish atopic skin disease from other eczemas were summarized by Rost & Marchionini (2), while atopic dermatitis was introduced by Sulzberger in 1933 (3).

The incidence of atopy in the general population is about 30%; of those affected 10% develop atopic dermatitis (AD). The incidence of the disease in infancy is over 10% (4, 5). Its distribution is worldwide.

To avoid errors in the diagnosis af AD, uniform criteria were established by Hanifin & Rajka in 1980 (6, 7) and were adopted in America and Europe. These criteria can be divided into major and minor features, and are determined mostly according to the clinical picture.

The pathogenesis of AD is complex. In the development of the disease, numerous factors are involved: in the circulation, a pathogenic functioning of T lymphocytes, while in the skin, IgE-positive Langerhans cells (8) seem to play the main role. The eczematous skin reactions are caused by antigen presentation and immunomodulation of these Langerhans cells.

In the development of inflammatory skin reactions, as in the degranulation of the mast cells, the circulating immune complexes (CIC) could play an important role. The high level of CIC can also depress B cell function and T cell activation, both important in the pathogenesis of AD (8, 9).

MATERIAL AND METHODS

We examined 92 patients (78 adults and 14 children) at our clinic according to the Hanifin-Rajka guidelines for the diagnosis. 32% of the patients had an individual and 29% a familial atopic history.

For detection of CIC, a PEG-precipitation laser nephelometer technique (*ad modum* Kraft (10)) was used. The serum samples were precipitated with PEG (polyethyleneglycol) 6000 and EDTA – VBS (veronal buffer coat).

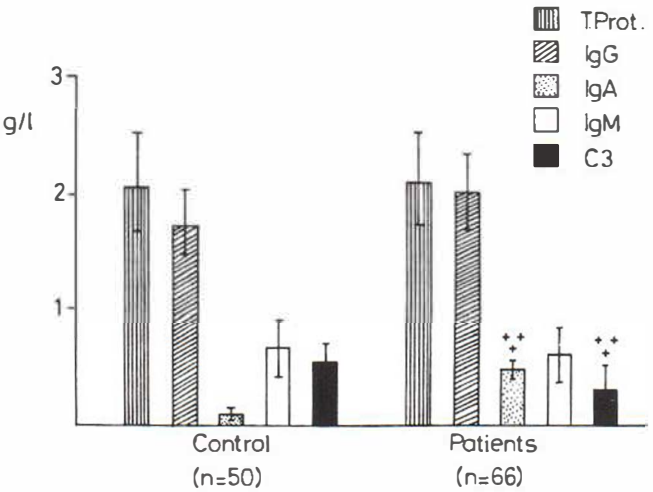
After 24 h of incubation they were centrifuged for 20 min at 12.000 revolutions per minute at +4°C. After removal of the debris, the samples were centrifuged once more with PEG. For the quantitative analysis, Biuret reagent was used and the total CIC protein content of the samples was investigated with a Milton photometer operated at 540 nm wavelength. For detection of IgA, IgM, IgG, C3 CIC, the Hyland laser nephelometer was used, with certain anti-human sera (by Human). The samples were measured after 1 h of incubation.

RESULTS

We divided our patients into three groups who had no differences between their acute and subacute clinical sypmtoms. Table I shows the results of sera from 66 patients, who had AD but no associated diseases. It was found that, compared with the controls, there was a slight increase in total CIC protein (2,118 + 0,914: normal values (n.v.): 2,072 ± 0,829) and CIC-IgG (2,050 ± 1,122: n.v.: 1,775 ± 0,374) and a significant increase in CIC-IgA (0,488 ± 0,386: n.v. 0,088 ± 0,114)) was detected. CIC-IgM was also slightly decreased (0,590 ± 0,414: n.v. 0,629 ± 0,395).

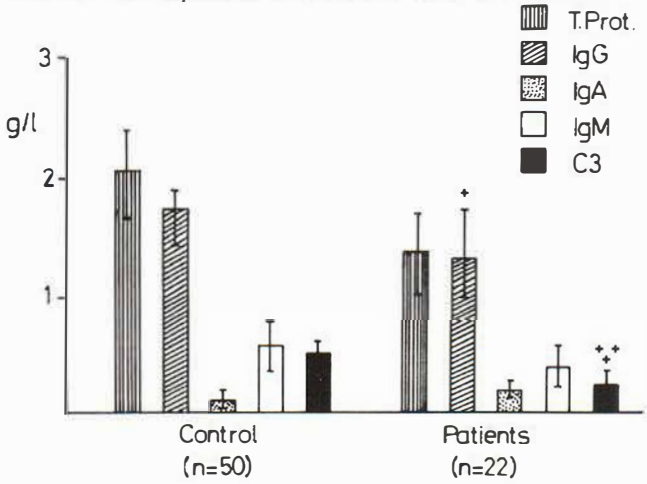
Table II shows the results of patients who had asthma, rhinitis, food intolerance, dyshidrosis associated with AD. The CIC-IgA level here was also increased though not significantly. (0,189 ± 0,197: n.v.: 0,088 ± 0,114) and there was a significant decrease in the CIC-C3 level (0,194 ± 0,112: n.v.: 0,561 ± 0,885). It is of some interest, that, compared with the 'pure' AD patients, a decreased level of total CIC-protein (1,374 ± 0,483: n.v.: 2,072 ± 0,829) and CIC-IgG (1,338 ±

Table I. *CIC in patients with atopic dermatitis*



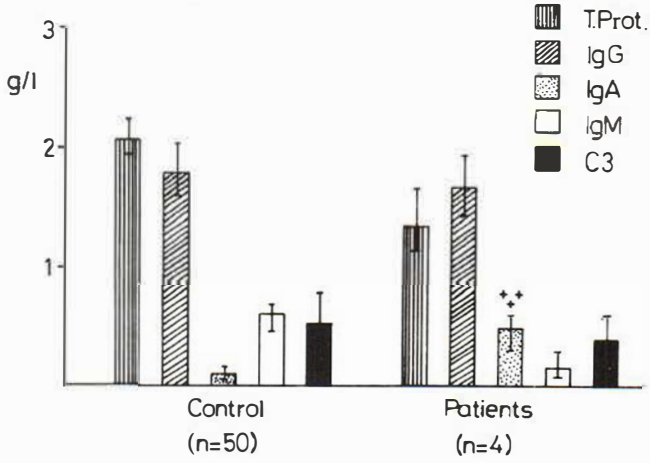
CIC = circulating immune complexes
T.Prot. = total protein
* = significance (± SD at the top)

Table II. *CIC in patients with AD and associated diseases*



CIC = circulating immune complexes
AD = atopic dermatitis
T.Prot. = total protein
* = significance (± SD at the top)

Table III. *CIC in patients with AD associated with PV Kaposi*



CIC = circulating immune complexes
AD = atopic dermatitis
PV = pustulosis varicelliformis
T.Prot. = total protein
* = significance (± SD at the top)

0,483: n.v.: 1,776 ± 0,829) was found, possibly caused by the higher consumption of the associated disease in these patients. CIC-IgM (0,434 ± 0,256: n.v.: 0,629 ± 0,395) was also slightly decreased.

In Table III, the CIC serum levels of 4 patients who had pustulosis varicelliformis Kaposi associated with AD are shown. The CIC-IgA level was also significantly higher (0,486 ± 0,014: n.v.: 0,088 ± 0,114), than the previous findings. Furthermore, a low total CIC-protein level (1,339 ± 0,016: n.v.: 2,072 ± 0,829) and CIC-IgG-level were found (1,656 ± 0,465: n.v.: 1,776 ± 0,374). The CIC-C3 level was considerably (though not significantly) decreased (0,357 ± 0,004: n.v.: 0,561 ± 0,885) and a considerable decrease in CIC-IgM level was also found (0,165 ± 0,004: n.v.: 0,561 ± 0,885).

DISCUSSION

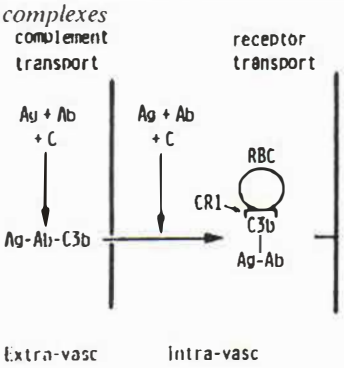
In the literature, CIC examinations in AD patients were only performed by a few authors and with fewer patients. CIC-IgG was found in AD patients with milk allergy by Paganelli and Kapp (11, 12).

Similarly to other authors we could not find any correlation between the CIC-Ig levels and the severity of AD, but the differences between the AD and the group of patients with associated diseases are of interest. Patients with associated diseases had more intensive immune reactions than those who had only atopic skin problems, and they could have a higher consumption of immune complexes. This tendency was observed mostly in those cases who had pustulosis varicelliformis Kaposi associated with AD, i.e. a serious condition, with severe systemic symptoms and skin involvement. We have not found data in the available literature about CIC level in this connection.

The mechanism of the immunological reactions – and particularly the formation of CIC in AD – is very complex. For the normal processing of soluble immune complexes, the binding of C3b complement factor (Table IV) (13, 14) is the first step. These soluble complexes can then be transported intravascularly and cellular receptors are necessary to bind the complex through its complement protein.

These complement receptors are found not only in the erythrocytes (as noted in the table) but, for other complement factors, on neutrophils, eosinophil granulocytes, B and T lymphocytes and monocytes. With the solubilization of the immune complexes, phlogistic pragments (C3a, C5a) can be released. With the binding of CIC-complement complexes to the various complement receptors, the function of the respective cell is affected, i.e. depressed or activated. We have also found a decreased function of granulocytes, natural killer cells and T lymphocytes in our AD patients. In addition to the classical

Table IV. *The mechanism of complement-mediated formation of immune complexes*



Ag=denotes antigen
Ab=antibody
C=complement
RBC=red cell

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pathway, the complement system could be activated by the alternative way as well, when the antigen is bound to IgA immunoglobulin. On the other hand, IgA, IgE and IgG4 may form CIC by direct cellular binding as well.

We are continuing with our studies, as we wish to investigate IgE-CIC levels and IgG subpopulation-CIC levels (15, 16), and the immune complexes in the skin in order to answer the question, whether there is any correlation between the immune complexes in the skin and the CIC in the serum of patients with atopic dermatitis.

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