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Viral Infections in Atopic Dermatitis

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In a study of almost 1 000 patients with past or present atopic dermatitis (AD) it was found that histories of recurrent (>5 episodes/year) cold sores and upper respiratory infections, as well as histories of zoster were significantly more common in AD patients than in non-atopic controls. Serological studies revealed that AD patients have clearly elevated titers of antibodies against Epstein-Barr virus. These findings suggest that the increased susceptibility to viral infections in AD is due to immune dysfunction rather than to cutaneous alterations which are associated with the disease. The mechanisms underlying the increased susceptibility to infections may be related to immunological abberrations that are secondary to a basic abnormality in the fatty acid or cyclic AMP metabolism.

It has long been known that patients with atopic dermatitis (AD) are unusually prone to develop severe herpes simplex and vaccinia virus infections and they have also been reported to have increased prevalence of warts and molluscum contagiosum (reviewed in ref. 1). The reason for this increased susceptibility to viral infections is not clear. A common opinion among dermatologists has been that the infections are attributable to the skin abnormalities that are associated with the disease, but more recent data have raised the possibility that the increased susceptibility to viral infections is rather a consequence of defective cell-mediated immunity in the patients (2).

A defective function of cell-mediated immunity should certainly be expected to affect not only the course of cutaneous viral infections but also of infections caused by non-dermatotropic viruses. Furthermore, since maintenance of viral latency is thought to be controlled at least partly by cell-mediated immune mechanisms (3), any disturbance of these mechanisms, such as occurs in AD, should be expected to result in increased rate of recurrencies of latent viral infections. In the investigations to be reported herein, we have approached these questions by studying the history of viral infections in a large number of adult patients who have had AD in childhood. We have also studied the serum levels of antibodies against several viruses in these and other patients with signs or history of atopic disease.

RESULTS

In a follow-up study of 955 adult AD patients, it was found that those patients who had been hospitalised because of severe AD in childhood had a significantly higher incidence of recurrent (>5 episodes per year) cold sores and upper respiratory infections as well as higher incidence of zoster than non-atopic controls (4). Patients with milder AD in childhood (never hospitalized for this disease) had lower incidences of the infections, albeit still higher than those of the controls. There was a remarkable correlation between activity and severity of AD and incidence of recurrent viral infections. Thus, patients with ongoing AD gave histories of recurrent viral infections most frequently, but also patients who had had no clinically overt disease during the past year reported higher frequencies of infections, in the case of cold sores significantly higher than the controls. Patients who had respiratory allergy in addition to AD showed a tendency towards increased frequency of

recurrent infections compared to those with AD only, but this was not statistically significant.

We have interpreted these findings to be in support of the hypothesis that defective cell-mediated immunity rather than cutaneous alterations predisposes for increased susceptibility to viral infections. Further support for this interpretation was obtained in serological studies of AD patients. In concordance with a study of children with various forms of atopic disease (5) we found that AD patients displayed significantly higher serum levels of antibodies (anti-VCA) against Epstein-Barr virus (EBV) than non-atopic controls (6). The raised serum antibody titers were found in AD patients who were healed as well as in those with ongoing dermatitis.

DISCUSSION

Taken together our results have shown that recurrent viral cutaneous infections (herpes simplex and zoster) are more prevalent in AD, but also that the rate of respiratory infections of presumably viral origin is increased. Thus, it seems likely that the increased susceptibility to viral infections is not restricted to viruses affecting the skin, but rather reflects an abnormal host response to viral infections in general.

Although the findings of raised EBV antibody titers in AD probably reflect on abnormal host response to the virus, it cannot be excluded that the cause and effect relationship is the reverse, so that EBV may play a causative role for the development of AD. EBV is a B cell mitogen, which may stimulate IgE antibody formation, and infectious mononucleosis, which is caused by EBV, is associated with raised serum levels of IgE (7). The recent report of a case of AD developing soon after an episode of infectious mononucleosis suggests that EBV may in fact occasionally precipitate atopic disease (8).

The mechanisms underlying increased susceptibility to viral infections in AD can be presumed to be related to an abnormal immune response to the viruses. It is well known that the defence against most viral infections is heavily dependent on cell-mediated immune mechanisms and it is therefore highly relevant that there is abundant clinical and experimental evidence of defective function of cell-mediated immunity in AD (1, 2). In particular the function of T cells has received attention. In our early studies on T cells in AD (9) we found clearly reduced numbers of T cells, correlated to the severity of the disease in much the same way as the frequency of recurrent infections found in the present studies. Not only the numbers but also the function of T cells was reduced as judged by the results of lymphocyte stimulation experiments. Later studies performed by us and others have indicated that the T cell defect is particularly evident in suppressor/cytotoxic T cell subsets (2, 10, 11, 12, 13).

As regards the defence against viral infections, it is of particular interest that cytotoxic T cells thus seem to be deficient in AD. Perhaps equally important are the findings that macrophages (14, 15) and natural killer (NK) cells (16) appear to have an abnormal function in AD. All these various cell types have been shown to be able to produce, or to assist in producing interferons. It is therefore possible that a deficient interferon production may constitute a common denominator, at least partly responsible for the increased susceptibility to viral infections in AD. Studies of interferon production in AD have to our knowledge not been reported, but it may be significant that we have found reduced production of interferon-alfa in children with various atopic diseases (17) as well as subnormal production of interferon-gamma in atopic (but not in non-atopic) patients with food allergy (Bengtson et al., to be published).

Even if an immunologic abnormality might explain many of the features of AD, including increased susceptibility to viral infections (18), the cause of the abnormality has not

been elucidated. The T cell defect appears to be a primary, inherited feature of atopic disease (19). Therefore, it is of interest to study the activity of gene products, in particular enzymes, that affect T cell maturation or function, in AD patients, to obtain information about the genetic basis of AD. Recently, it has been reported that lymphocyte cyclic AMP-phosphodiesterase activity is increased in AD (20). Even if increased activity of this enzyme might be secondary to the release of pharmacological mediators which is associated with active AD, it seems possible that the enzyme abnormality is of a primary nature, which secondarily leads to immunological abnormalities. This possibility is supported by the findings of increased CAMP-phosphodiesterase levels in umbilical cord sera of children with atopic parents (21).

Finally, there is the possibility that an abnormality of enzymes relating to the metabolism of essential fatty acids constitute the genetic basis for the immunological defect in AD. In perfect agreement with earlier results obtained in adult AD patients (22), we have together with Dr L. Svennerholm in Gothenburg, Sweden, found that children with AD display significantly raised serum levels of linoleic acid and decreased levels of arachidonic acid, suggesting defective function of the enzyme delta-6-desaturase. Since arachidonic acid is a precursor of prostaglandins, which affect T cell maturation and function (23) it is entirely possible that an abnormality in the fatty acid metabolism accounts for the immunologic abnormalities and hence the abnormal host response to viral infections that we have found in the AD patients. Work, presently carried out in our laboratories, aims at establishing whether the fatty acid abnormality of AD patients is of a primary nature, or secondary to the manifestations of atopic disease.

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