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Eczema in Primary Immune-deficiencies

Clues to the Pathogenesis of Atopic Dermatitis with Special Reference to the Wiskott-Aldrich Syndrome

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Eczema is one of the cutaneous manifestations of primary immune deficiencies. It may therefore serve as a model for the understanding of atopic dermatitis (AD) provided the eczema in the immune deficiency under consideration is a constant feature and is similar to AD. In the Wiskott-Aldrich syndrome the eczematous eruption is (i) a constant feature of the syndrome, (ii) indistinguishable from AD when diagnostic criteria for AD are used, and (iii) clears dramatically after a successful bone marrow graft, which suggests that immune dysfunction is directly involved in the pathogenesis of the eczema. *Key words: Atopic dermatitis; Immunodeficiency; Wiskott-Aldrich syndrome.*

ECZEMA AND PRIMARY IMMUNE-DEFICIENCIES

"Eczema" is a characteristic skin manifestation of many primary immune deficiencies (Table I). This observation is of special interest in the understanding of atopic dermatitis because a subtle defect of cellular immunity is thought to play a role in this common disease. We have recently reviewed the literature on the skin manifestations of primary immune-deficiencies (PID) in childhood (9) and came to the conlusion that the eczematous eruptions in each PID could not be considered a similar to those of AD. A list of PID in which an eczematous eruption may be a feature is given in Table II. In this table we have used the terms atopic dermatitis or "seborrheic dermatitis" because, from descriptions in the literature and/or from our own experience with such children, it seems that the dermatitis may share features with these entities. This table is however only illustrative. For instance, it is generally accepted that the dermatitis of the hyper IgE syndrome may be very similar to AD or alternatively quite different (9).

In order to obtain relevant clues as to whether or not the eczematous eruptions of PID might serve as a model for AD, we proposed that the following three questions should be considered if (i) the eczematous eruption is a constant feature of the particular PID, (ii) the eczematous eruption fulfils the diagnostic criteria for AD, and (iii) how the evolution of eczema relates to the PID; this latter is a most interesting issue arising in a period of increasing use of bone marrow transplantation for the correction of PID. When running the Pediatric Dermatology Unit, at the Hôpital des Enfants Malades, in Paris, we had the opportunity to see many children with PID in the immunology unit headed by Prof. C. Griscelli. It seemed that the Wiskott-Aldrich syndrome might be a good candidate for commencing a study of this relationship.

THE WISKOTT-ALDRICH SYNDROME (W.A.S.) AS A MODEL

This X-linked recessive syndrome is characterized clinically by the triad of eczema, purpura and bleeding, and susceptibility to infections. Symptoms may begin at birth with a hemorrhagic syndrome due to thrombocytopenia which is always found in WAS. This hemorrhagic tendency sometimes follows a viral infection, but, in general, becomes less severe as the child grows older. The platelets in W.A.S. are of diminished size. Recurrent infections do not usually appear until after 6 months because until then, the child is

protected by placentally transmitted maternal antibodies. Pulmonary infections, meningitis, and otitis due to pneumococci, meningococci, *Haemophilus influenzae* and *E. coli* are frequently seen. Later, as cellular immune function wanes, infections with agents such as *Pneumocystic carinii* and herpesviruses become more frequent. These children are at risk of developing lymphoreticular malignancies, often within the central nervous system. These risks justify bone marrow transplantation.

The cutaneous signs include purpura, eczema and skin infections: the purpuric lesions are diffuse and not limited to areas of high orthostatic pressure (even the face may be involved). Purpuric lesions can precede the eczema, and be aggravated by intercurrent infections which increase the thrombocytopenia. When the eczema first appears, the purpura may be induced by the patient's scratching causing linear purpuric streaks. In boys, the presence of purpura within eczematous lesions should always alert the clinician to the possibility of W.A.S. Eczematous lesions usually begin very early within the second month after birth. It is usually a severe recurrent intractable pruritic eczematous dermatitis that may be considered as very similar to infantile AD although this possibility has never been carefully analysed (see later).

The clinical picture is also dominated by secondary infected eczematous lesions that most commonly harbor gram-positive cocci. Vaccination with BCG (given before the diagnosis is known) does not usually provoke major complications, nor are chicken pox infections particularly severe. In contrast, chronic and extensive viral warts have been observed, as well as severe herpes simplex infections.

The diagnosis of WAS is made by the three associated clinical signs noted above, in addition to the following immune anomalies: normal IgG with elevated IgA and IgE, decreased IgM and absent or low levels of isohaemagglutinins. There is no antibody

Table I. *Cutaneous manifestations of primary immunodeficiencies*

1. Chronic and recurrent infections
2. Eczemas
3. Graft versus host reactions
4. Collgen–vascular syndromes
5. Independent cutaneous markers
6. Other skin symptoms associated with P.I.D.

Table II. *"Eczema" in primary immunodeficiencies (PID)*[a]

Type PID	"Type" of eczema[b]
1. Wiskott-Aldrich syndrome	AD
2. Hyper IgE syndromes	AD
3. Ataxia telangiectasia	AD
4. Chronic granulomatous disease	SD and AD
5. X-linked hypogammaglobulinemia	AD
6. X-linked ID with hyper IgM	AD
7. Selective IgA deficiency	AD
8. Severe combined ID	SD
9. C5 dysfunction	SD
10. Tuftsin-deficiency	SD
11. Shwachman's syndrome	AD

[a] See ref. 9 for details.
[b] AD = atopic dermatitis, SD = seborrheic dermatitis, see text for comments.

response to immunization with polysaccharide antigens. Furthermore, there is a monocyte chemotactic defect due to a lymphocyte product that renders the monocyte unresponsive to chemotactic stimuli in vitro. The number of T cells is normal, as is their proliferative response to mitogens. Nevertheless, the initially normal T and B cell functions progressively deteriorate. Abnormalities of glycoproteins normally present on the surface of lymphocytes and platelets have been found which could be a direct reflection of the primary defect in WAS (8).

From this brief description of the features of WAS, it seems *that eczema is an almost constant feature of the syndrome.*

The next question to be considered is whether or not the eczema fulfills the criteria of AD. Presently, the only available criteria for the diagnosis of AD are the guide lines proposed by Hanifin and Rajka after the first symposium on AD in 1979 (4). These include 4 basic features (AD patients must have 3 or more) and 24 minor features (AD patients must have 3 or more). In cooperation with F. Cambazard we analysed the occurrence of these features in 5 boys with well established WAS and compared the resulting score to five age and severity matched boys with typical AD. All the WAS patients fulfilled more than 3 major criteria and more than 3 minor criteria (9). Therefore, from the available criteria for the diagnosis of AD it appears that *the eczema of WAS should not be considered as different from AD.*

As eczema was a constant feature of the WAS and was undistinguishable from AD, it was important to consider its course and development after complete immune reconstitution by bone marrow graft. Bone marrow graft is now frequently used for the treatment of several PID.

As far as WAS is concerned, there are now 10 cases in the literature that have been successfully grafted (1, 2, 3, 5, 6, 7). In all cases where the immune function was reestablished, the intractable eczema dramatically cleared. We have had the opportunity to care for the eczema of one of these children (3). It was very similar to AD, had started by one month of age and was a permanent feature until the age of 3 years when the bone marrow graft was performed. The eczema dramatically cleared immediately following the graft and has never recurred, within a follow up period of 5 years. Interestingly, the xerotic skin also disappeared and the child has since had a normal smooth skin.

Clearing of the eczema seen in such cases might be due to several possible factors: (i) the pre- and posttransplant conditioning regimens, which include cytostatic drugs, antilymphocyte serum, total body irradiation and prednisolone, might act directly on the skin. It is however unlikely that their effect would persist after 5 years; (ii) the graft-versus-host-reaction; however, several children in which the eczema cleared had had no such reaction (3); (iii) the correction of some enzymatic defect not necessarily related to the immune anomaly; this cannot be excluded but seems unlikely; and (iv) the establishment of normal T lymphocyte function replacing the abnormal one. The last possibility is considered as most likely by R. Parkman (7) who suggests that abnormal T lymphocyte function is the basis of the eczema.

This phenomenon may be of paramount importance to the understanding of the pathogenesis of AD. Such an experiment of nature implies that AD may be a reflection of a primary immunological defect. In this respect, precise analysis of eczematous eruptions in children with PID would be most informative to dermatologists with an interest in AD.

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