

## Unclassified endogenous eczema

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Patients with intractable eczema are often referred for patch testing to exclude contact dermatitis. If this is excluded, then a diagnosis of endogenous eczema is made. At our clinic, we find a sizeable proportion of these patients do not fit any of the known patterns of endogenous eczema. These patients are given the diagnosis of unclassified endogenous eczema and make up 8% of the patients seen at our Occupational and Contact Dermatitis Clinic. There is little information available on this group of patients, with no mention of this problem in the recent dermatological literature. Since March 1996, we have further investigated these patients, to develop some understanding of this category. 12 of 34 patients reviewed over this period had an elevated IgE level above 100 IU/ml. Thus, despite no past history or family history of eczema, asthma or hayfever, at least 1/3 of these patients are probably suffering from atypical, late onset atopic dermatitis. Patients were later contacted by telephone (average 2 years) to assess the natural history of this condition. In 20 of the 31 patients contacted, their eczema had either improved or resolved. We think that this important category of eczema needs to be recognized and further investigated.

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The term 'eczema' or 'dermatitis' signifies a particular type of inflammatory response of the skin. It is characterized histologically by the presence of spongiosis in the epidermis with varying degrees of acanthosis and a predominantly lymphohistiocytic infiltrate around the upper dermal blood vessels. The clinical features of eczema include itching, redness, scaling, papules and vesicles. Eczema accounts for a large proportion of all skin disease and is caused by a wide range of external and internal factors acting singly or in combination. It is customary to divide the eczematous disorders into 2 major subgroups: exogenous and endogenous. The exogenous eczemas are caused by external factors, i.e., contact dermatitis (allergic and irritant). The endogenous eczemas include atopic eczema, seborrhoeic eczema, discoid eczema, asteatotic eczema, stasis/varicose eczema, and endogenous hand and foot eczema (also known as pompholyx or dyshidrotic eczema).

Patients who develop severe intractable eczema are often referred for patch testing to exclude exogenous causes. If exogenous causes are excluded, patients usually have an endogenous eczema of one of the accepted categories (Table 1). However, at our clinic we find a significant number of these pa-

tients do not fit into one of the known categories of endogenous eczema. These patients are given the diagnosis of 'unclassified endogenous eczema'. This classification was developed at St John's Hospital for Diseases of the Skin, London, and has been used at the Skin & Cancer Foundation Australia for 16 years. Since computerization of data in 1991, 193 of the 2398 patients seen have received this diagnosis. This accounts for 8.0% of the patients seen in our Contact and Occupational Dermatitis Clinic.

These patients are very puzzling. They develop widespread or localized dermatitis which does not fit into one of the above known patterns, with no contact factors detectable. This subgroup of eczema is not widely recognized and consequently there is little information available on the natural history or pathogenesis. Both patient and physician find this an unsatisfactory diagnosis.

Since March 1996, all patients diagnosed as having unclassified endogenous eczema were offered further investigation in order to develop some understanding of this condition. This included a questionnaire, a biopsy, prick tests and a serum IgE.

The objective of this paper was to draw atten-

Table 1. Classification of eczema

| Endogenous   | Exogenous |
|--------------|-----------|
| atopic       | allergic  |
| seborrhoeic  | irritant  |
| discoïd      |           |
| hand         |           |
| foot         |           |
| asteatotic   |           |
| stasis       |           |
| unclassified |           |

tion to the existence of this group of patients and to determine their demographics, natural history and possibly underlying cause.

### Patients and Methods

The Skin & Cancer Foundation is a tertiary referral centre in Sydney. The majority of patients seen at the Contact and Occupational Dermatitis Clinic have already been assessed by 1 or more dermatologists. There are about 117 practising dermatologists in the state of New South Wales, Australia. About 1/3 of these dermatologists refer patients for patch testing at the Skin & Cancer Foundation in Sydney. These tend to be difficult cases, with eczema that is not responding to treatment.

All patients referred to this clinic are patch tested with our standard series (European standard plus extras) and any other relevant allergens. Patch testing is carried out using Trolab allergens applied in Finn Chambers on Scanpor (Epitest). Patches are applied for 3 days and evaluated at 3 and 7 days. Since 1998 patches have been removed after 2 days and read at 3 and 7 days.

Patients with negative patch tests or no relevant positives are then assessed for endogenous causes. A diagnosis of unclassified endogenous eczema is only made if the dermatitis does not fit a known pattern of eczema (Table 1). In this study, patients diagnosed as unclassified endogenous eczema were offered further investigation, including prick tests, serum IgE and a biopsy. They were also asked to fill in a simple questionnaire.

The prick tests were performed using the Dome/Hollister-Stier allergy diagnostic mini-kit (Bayer, Australia). This consisted of introducing 23 allergens plus a positive and negative control intradermally into the flexor aspect of the patient's forearm by pricking with a lancet. A positive response was defined as a wheal at least 50% the diameter of the positive control (histamine).

Serum IgE was assessed by the Quanticlone Total IgE Kit (Kallestad Diagnostics, MN, USA). Results are expressed in IU/ml. Levels over 100 IU/ml are regarded as highly suggestive of atopic disease.

A 4-mm punch biopsy was performed on 26 patients. 8 patients refused to have a biopsy or did not have any existing dermatitis at the time.

Questionnaires investigated the extent of the disease, present and past treatments, exacerbating factors and stress.

Patients were later contacted by telephone to assess their progress. They were questioned as to the presence and severity of their eczema. The severity of eczema was graded as follows.

1. Resolved – no residual eczema.
2. Greatly improved – minimal amounts of intermittent eczema, requiring only intermittent topical therapy.
3. Improved – patient perceived that eczema had improved since their patch testing was performed.
4. Unchanged – patient perceived that eczema had not improved or worsened since their patch testing was performed.
5. Worse – patient perceived that eczema had worsened since their patch testing was performed.

### Results

Over a 22-month period, 45 patients were diagnosed as having unclassified endogenous eczema. These patients made up 7.7% of the 583 patients reviewed at the Contact and Occupational Clinic over this period. Of these 45 patients, 28 (62%) were female and 17 (38%) were male, with an average age of 50.6 years (range 19.2 to 82.7 years).

34 patients agreed to undergo further investigation. Of these, 19 (55.9%) were female and 15 (44.1%) were male. The average age of the patients was 53.0 years (range 19.2 to 74.5 years). At the initial review the patient's dermatitis had been present on average for 35.7 months (range 2 to 240). 24 patients had a continuous dermatitis and 10 had an intermittent dermatitis. 19 patients felt their rash was made worse by stress.

12 patients had IgE levels greater than 100 IU/ml. These ranged from 103 to 3186, with an average of 974 and a median of 655 (Fig. 1). 5 patients had 3 or more +ve prick tests; all of these patients had an IgE >100 IU/ml.

26 biopsies were done. 24 showed chronic or subacute dermatitis, and 2 showed urticarial dermatitis. The 34 patients who had agreed to undergo further investigation were later telephoned for follow-up. Of the 34 patients, 31 were contacted. The average time from original visit to follow-up was 24.0 months (range 9.4–31.3 months). Presence and extent of eczema on follow-up is summarised in Table 2. In 20/31 (65%) patients their eczema had either resolved or improved. 9/11 (82%) pa-

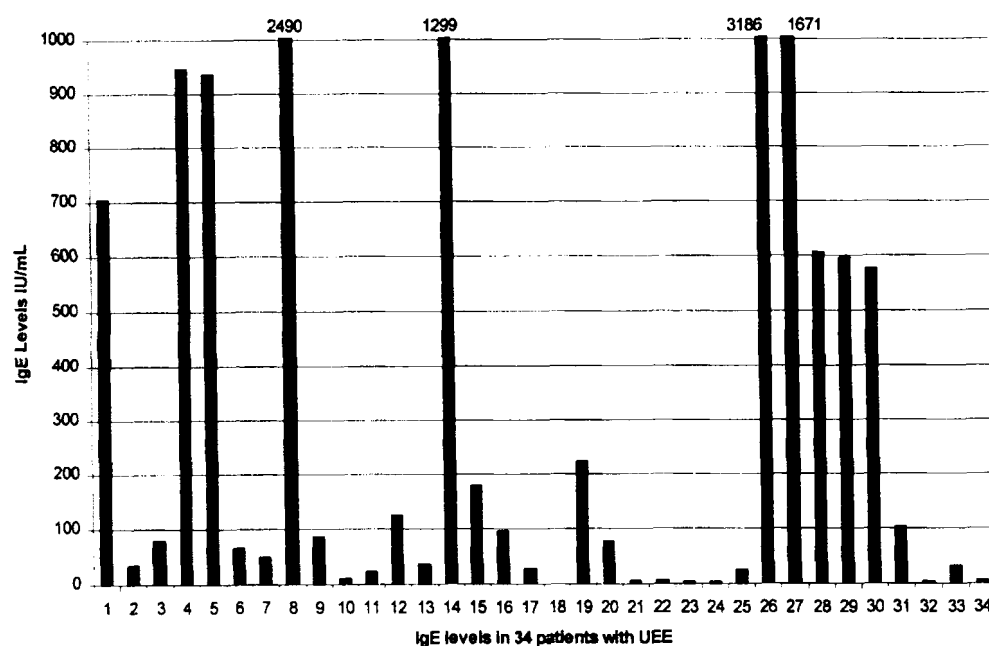


Fig. 1. IgE levels (IU/ml) in the 34 patients with unclassified endogenous eczema (UEE).

tients with IgE >100 had either resolved or improved.

### Discussion

Unclassified endogenous eczema, although commonly seen in our clinic, is ignored by the literature, with no mention of this problem in the major dermatology texts or journals. Charles Calnan, of St Johns Hospital for Diseases of the Skin, London, refers to unclassified eczema in a 1968 article (1). He thought that 20–30% of the eczema cases that he saw had this diagnosis. He suggested that degenerative factors in the skin could be important in determining the onset of unclassified eczema (1), as he had noted a predominance in old age or late middle life. Our work has defined 2 interesting features of this group. Firstly, at least 1/3 of these patients, despite no past history or family history of eczema, asthma or hayfever, are probably suffering from atypical, late onset atopic dermatitis. This conclusion is drawn from the fact that over 1/3 had elevated IgE levels over 100 IU/ml, which

is highly suggestive of atopic disease (2). Elevated IgE is associated with atopic dermatitis, with or without associated asthma or allergic rhinitis, in 43% to 82% of patients (3–5). IgE can also be elevated in parasitic infection, some immunological diseases (e.g., Job's syndrome) and chronic photosensitivity dermatitis with actinic reticuloid (7). However, with these exceptions, the IgE level is usually not elevated in non-atopics (2, 4, 6). It is also generally not elevated in patients with other forms of dermatitis, such as discoid eczema and contact dermatitis (5).

In the 22 patients with IgE values less than 100 IU/ml, a diagnosis of atopic eczema cannot be excluded. Up to 63% of patients with pure atopic eczema (i.e., with no personal or family history of respiratory atopy) can have IgE levels less than 100 IU/ml (8).

Prick tests were also performed, as patients with atopic dermatitis have been reported to have a higher incidence of positive prick test reactions than healthy controls (9, 10). 5 patients had 3 or more positive prick tests. All these patients had IgE levels above 100.

Other markers of atopy were looked for, such as keratosis pilaris, flexural eczema, and dry skin. Patients were also questioned about wool intolerance and itch when sweating. However, these minor atopic features were not helpful when analysing these patients and did not discriminate between patients with normal or elevated IgE levels.

The 2nd interesting finding from our study concerns the natural history of these patients. In the

Table 2. Course of eczema on follow-up

| Course           | No. |
|------------------|-----|
| resolved         | 8   |
| greatly improved | 7   |
| improved         | 5   |
| unchanged        | 8   |
| worse            | 3   |
| total            | 31  |

majority of patients (2/3) their eczema improved or resolved over the follow-up period (average 2 years). In approximately 1/4 of the patients the eczema had totally resolved, and in another 1/4 only minimal intermittent eczema, requiring intermittent topical treatment, was present. The reason behind this improvement in the majority of patients is not clear, but is most probably multifactorial. The natural history of patients with late onset atopic eczema, like that of endogenous unclassified eczema, is not well described, but it is possible that a proportion of patients will improve with time. 80% of patients with IgE levels >100 IU/ml reported an improvement in their eczema over the follow-up period.

Another reason for the improvement, apart from the natural course of the disease, could be improved treatment. All patients assessed at our clinic are given thorough advice on general measures and specific treatment for their eczema. Although this information has often already been given by the referring dermatologist, we are able to reinforce this advice over the 3 visits required for patch testing.

The 26 biopsies performed did not help with the classification or aetiology of these patients due to the non-specific appearance of one type of eczema compared to another on histology. However in the future, with different types of eczema having different cytokine profiles (11, 12), immunostaining may allow histological diagnoses of eczema subtypes to be made. Also recently, it has been shown that there is an association of atopy with a gain of function mutation in the (alpha) subunit of the interleukin-4 receptor (13). Thus genetic markers for atopy may also be available in the future.

In summary, we bring to the attention of other dermatologists this puzzling and often unhappy group of patients. These patients are relatively common, comprising just under 10% of the patients seen in our patch testing clinic. This % would, of course, vary with referral patterns in other clinics. Because of the elevated IgE levels in 1/3 of the patients investigated, we think that a significant proportion of these patients may have late onset atopic dermatitis, despite no past history or family history of eczema, asthma or hayfever.

However, further investigation is necessary to define this group of patients.

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