Acta Derm Venereol (Stockh) 1992; 72: 292–293

Familial Occurrence of Fixed Drug Eruptions

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Fixed drug eruptions following the use of pyrazolone derivatives occurred in 4 members of the same family: a 12-year-old girl, her grandmother, and two of her great aunts. Although the pathophysiologic events leading to this type of reaction are unknown, these cases of familial occurrence suggest that genetic predisposition might be an important causal factor. ***Key words: HLA; Pyrazolone derivatives.***

(Accepted December 2, 1991.)

Acta Derm Venereol (Stockh) 1992; 72: 292–293.

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Fixed drug eruptions (FDE) are considered to be the most classic form of cutaneous reactions to drugs. Clinical manifestations include the appearance of one or several round or oval erythematous lesions with clearly defined borders. The lesions are dusky red in colour. In some cases a central blister forms. After the acute phase of the reaction has subsided, the affected areas usually show hyperpigmentation that varies in shade from brown to brownish purple or even black (1). These lesions reappear in the same sites each time the offending drug is used. They may occur in any area of the body and involve either skin or mucous membranes. The number of reaction sites may gradually increase if the patient continues to use the drug from time to time (2).

The drugs that have most frequently been implicated in fixed drug eruptions include phenazones, barbiturates, sulfonamides, phenolphthalein, salicylates, tetracyclines and penicillin (3–6).

The pathogenesis of fixed drug eruptions remains uncertain. It is believed that the immune system plays a major role in these reactions (1), but there is also data to suggest that immunological mechanisms may not be the only causative factor (6). The present study describes 4 members of a single family who experienced FDE following administration of pyrazolone derivatives. Our findings in these cases suggest that there may be a genetic basis for this form of drug reaction.

CASE REPORTS

Case 1

A 12-year-old girl (Fig. 1) was seen in our outpatient clinic for stomatitis that had appeared three days before. Approximately 10 h prior to the appearance of the first symptoms, the child had taken 100 mg of feprazone (Zepelin, Istituto De Angeli) for treatment of cold symptoms.

Physical examination showed both lips to be edematous and covered with hemorrhagic scabs. There were several areas of edema with surrounding patches of erosion within the oral cavity itself. The clinical features of these lesions were compatible with a diagnosis of FDE. The symptoms resolved in about eight days with topical therapy.

The child had a history of atopy. She and her family clearly remembered three previous episodes of bullous stomatitis, all of which had occurred following the use of feprazone.

Case 2

The maternal grandmother of the child described above was seen in our clinic. The woman, 59 years old, presented a cutaneous rash and complained of dysphagia. She reported that three days prior to our observation, she had also taken 100 mg of feprazone. Five minutes later she experienced an intense burning sensation in the genital area and generalized pruritus. During the following 24 h, the patient noted the appearance of purplish erythematous lesions on her wrists, thighs, face and neck, areas of erosion in the vulva and erythema of the oral cavity with slight dysphagia.

Physical examination revealed the presence of four round lilac-coloured lesions approximatley 4 cm in diameter. The lesions were situated symmetrically, one on each forearm and one on each thigh. There were two other erythematous lesions, one on her right cheek and the other on the back of her neck. At the centers of some of these lesions there were blisters which continued to evolve, becoming more evident during the days that followed. Within the oral cavity and on the medial surface of the labia majora there were other areas of erosion with erythematous bases. She was admitted to the hospital.

The patient was afebrile and routine blood chemistry test results were within normal limits. She was started on antihistamines and topical steroids.

On the fifth day of hospitalization, a skin biopsy was performed at the margin of a blister on the patient's forearm. Histological examination of the hematoxylin-eosin stained sections showed separation of the epidermis from the dermis secondary to blister formation and epidermal necrosis. Further away from the blister, edematous degeneration of the basal and superbasal keratinocytes could be seen with isolated areas of necrosis. There was a slight lympho-histiocyte reaction in the perivascular dermis with incontinentia pigmenti. By the 15th day of hospitalization, the bullous lesions had for the most part resolved, leaving behind areas of light brown pigmentation.

This patient also reported the previous occurrence of a similar episode which was also related to feprazone use.

Cases 3 and 4

Following the hospitalization of Case 2, the patient's two sisters both reported that they too had experienced reactions to drugs in the past. The first sister (Case 3, Fig. 1), 48 years old, described three episodes, the most recent of which had occurred three years earlier. These reactions took place following the consumption of a capsule containing feprazone (Zepelin). Thirty minutes after taking the drug, the sister was stricken with generalized pruritus and facial erythema. A few hours later, hemorrhagic vesicles appeared on her lips, making it impossible to eat. During the next hours, round, purple lesions appeared on both her wrists. These latter lesions evolved into blisters. At the time of our interview with this woman, i.e. three years after the third and final episode, hyperpigmented areas were still apparent on her cheeks and wrists.

The second sister (Case 4, Fig. 1), 52 years old, reported three episodes of bullous stomatitis with a dark purple, intensely pruritic lesion on the elft wrist. All three episodes had their onsets approxi-

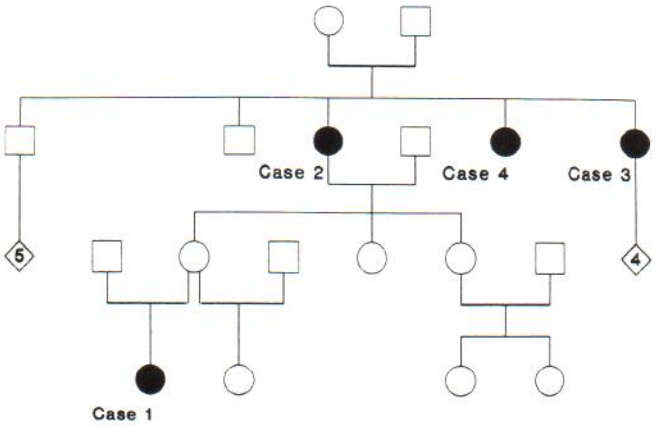

Fig. 1. Family pedigree.

mately 6–8 h after the woman had taken a drug containing propyphenazone and butalbital (Optalidon, Sandoz).

Laboratory findings

IgE levels were determined in all four subjects. Patients 2, 3 and 4 had levels of less than 15 IU/ml. Patient 1 had 180 IU/ml.

HLA typing was in patient 1: A1, A3, Bw55(w22), B35, Cw3, Cw4, Drw11(5), DRw6, DQw1, DQw3; in patient 2: A1, A2, Bw55(w22), B12, Cw3, DR4, DRw13(w6), DQw1, DQw3; in patient 3: A1, A2, Bw55(w22), B12, Cw3, DR4, DRw13(w6), DQw1, DQw3; in patient 4: A2, A28, Bw55(w22), B35, Cw3, DR4, DQw3.

Skin testing

All four patients were subjected to occlusive patch testing with feprazone (10% in white petrolatum) using the Finn chamber technique. Case 4 was also tested with propyphenazone (10% in white petrolatum). In Cases 1 and 2, the patch tests were performed six months after the cutaneous eruption had resolved. The patches were applied to normal skin on the back in Cases 1 and 4. In Cases 2 and 3, the patches were applied to areas previously involved in the cutaneous reactions. The patches were left in place for 24 h. Only Cases 2 and 3 presented positive reactions with local provocation of FDE, while patch tests performed on normal skin in cases 1 and 4 were, as expected (7), negative.

COMMENTS

Familial occurrence of fixed drug eruptions would seem to be fairly rare. In spite of the fact that these reactions are quite common, reports of even large series of patients either fail to consider familiarity or describe non-contributory family histories (2).

Fixed drug eruptions are one of the most common forms of adverse reactions to the pyrazolone derivatives (5).

Possible involvement of the HLA system had already been suggested for other types of drug reactions (8).

The HLA antigen B12 has, in fact, been found with increased frequency in patients with Stevens–Johnson syndrome with ocular complications as well as in those with Toxic epidermal necrolysis (9, 10). At this point, it is also interesting to note that the two cases with the more severe symptomatology reported here, Cases 2 and 3, were both positive for the HLA B12.

To our knowledge, there is no other data in the literature on HLA typing in patients with fixed drug reactions.

Although the pathophysiological events that lead to fixed drug eruptions remain unknown, our observation of this reaction in four members of the same family raises the possibility of genetic predisposition to this condition. Further study on a larger series of patients will be needed to determine whether there is indeed a consistent association between one or more HLA antigens and fixed drug eruptions.

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