

Chemical atopy

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Summary

Background. Although atopic disease is associated with protein allergy, its relationship with chemicals (haptens/contact allergens and irritants) is less clearly defined. The 'haptent-atopy' hypothesis, whereby significant hapten and irritant exposure during times of natural T helper (Th)2 bias (pregnancy and first year of life) promotes the development of atopy and atopic disease in the resulting child, has been previously proposed. Supporting evidence includes the practice of repeated cutaneous application of haptens in generating animal models of atopic dermatitis, and the observation of a significant increase in atopic disease in children born to mothers with occupations associated with high chemical exposure during pregnancy.

Objectives. To observe the relationship between personal chemical exposure and atopic disease in a particular case series.

Methods. We report a case series of exacerbation of atopic dermatitis after repeated cutaneous chemical exposure.

Results. Most of the patients had atopic dermatitis in young childhood that had resolved. However, after repeated chemical exposure, either occupationally as an adult or after starting to use cosmetics as a teenager, there was clear exacerbation of atopic dermatitis. Patch tests gave negative results in most cases.

Conclusions. We propose that repeated exposure to chemicals in patients with an atopic background can occasionally lead to reactivation of atopic dermatitis.

Key words: allergic contact dermatitis; atopic dermatitis; atopy; DAMP; extra domain A-positive fibronectin; hapten.

The frequency of atopic dermatitis has increased by >300% in the last 60 years. The cause of this increase remains unclear, but this time period has coincided with an increase in personal chemical (hapten and irritant) exposure through both the skin (fragrances, preservatives, surfactants, resins, dyes, and metal) and the gut (processed food, formula milk, and drugs) in industrialized countries. The relationship between personal chemical exposure and atopic disease is worthy of further research.

It has been previously postulated that hapten exposure in the personal environment during natural periods of T helper (Th)2 bias (pregnancy and the first year of life) may lead to the subsequent development of atopic disease in the resulting child (1). Supportive evidence includes the observations that many animal models of atopic dermatitis are based on repeated topical applications of haptens (2), and that maternal occupations during pregnancy involving significant exposure to hapten/irritant chemicals are associated with an increased prevalence of atopic diseases in the resulting children (3). At other periods with increased chemical exposure, for example entering some manual jobs or starting to use facial cosmetics, the development of atopic dermatitis-like rashes is not usually observed. However, we have occasionally observed this phenomenon. We now report a

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series of cases of exacerbation of atopic dermatitis after repeated chemical exposure (Table 1).

Case Report

Case 1

A 14-year-old girl presented with a history of dry itchy eczema since she was an infant. She has had hay fever, exercise-induced asthma, and oral allergy syndrome after eating apples. There was a family history of atopy. The eczema resolved almost completely while she was attending primary school (age 7–11 years), but has recurred over the last 2 years on her face, neck, elbows, and antecubital fossa. She gave a history of stinging reactions to many products, such as cosmetics, shampoo, and sunscreen, after 2–6 months of use. Her cosmetics included creams for sensitive skin, moisturizer, eye shadow, strawberry lip salve, facial wipes, deodorant, and nail varnish. She used cosmetics on a daily basis, and used a cleanser to remove the cosmetics. On examination, she had periorbital, perioral eczema with involvement of the philtrum, mild cheilitis, Dennie–Morgan fold, and keratosis pilaris. There was also inflammation of the antecubital fossa. Patch testing with an extended European baseline series and a face series gave negative results.

Case 2

A 24-year-old female beauty therapist presented with a 1-year history of itching on the back of the hands. She had been using a specific hand wash in the previous year. She recently developed a flare-up of eczema that affected both medial forearms and forearm flexures, and extended to the axilla. She had a past history of childhood atopic dermatitis and generalized dry skin. Previous patch testing in 2008 showed a positive reaction to *Narcissus* absolute essential oil. She was patch tested with an extended European baseline series, and face and fragrance series, as well as with products used in her job, including hand treatment cream, massage cream, hand lotion, face cleanser, and a hand wash. She reacted positively (+) to the hand wash (1% aqua) on D4. We were unable to determine which of the constituents of the product she had specifically reacted to. The rest of the patch testing series gave negative results. We concluded that she experienced a reactivation of atopic dermatitis after exposure to this hand wash.

Case 3

A 29-year-old woman had a history of trivial atopic dermatitis as a toddler. She had then developed atopic

dermatitis while at university. The rashes started on the cheeks. The eczema had spread to the chest and flexural aspect of the arms. Since attending university, she had increased her use of toiletries such as perfumes, foundation, eyeliner, and pencil. She was patch tested with an extended European baseline series, and face, fragrance and clothing dye series. These all gave negative results. She was diagnosed as having active atopic dermatitis.

Case 4

A 49-year-old woman with a history of eczema and asthma as a child underwent a facial peel. The face became inflamed the next day, and this was presumed to be an irritant dermatitis reaction to the facial peel. However, she presented 2 weeks later with inflammation in the philtrum and periorbital inflammation associated with dry skin and pruritus. A diagnosis of local recurrence of atopic dermatitis was made.

Case 5

An 18-year-old woman with a history of childhood atopic dermatitis started work as a hairdresser. Her work included both shampooing and styling/dyeing hair. After 2 months of work, she developed generalized dry skin and itchy hand dermatitis. The dermatitis spread to the forearm flexures. Her IgE level was raised (419 IU/l). She was patch test-positive to *p*-phenylenediamine. A diagnosis of local reactivation of atopic dermatitis was made.

Case 6

A 14-year-old girl had a history of atopic eczema as a toddler that had cleared. She started using facial cosmetics on a daily basis. After 1 year, she developed pruritic facial eczema involving the philtrum and perioral and periorbital area with prominent Dennie–Morgan folds and dry skin. Her IgE level was raised (259 IU/l). A diagnosis of atopic dermatitis was made.

Case 7

A 19-year-old man presented with pruritic hand and facial dermatitis. He had a history of atopic dermatitis as a child. He started acting, and was using stage cosmetics. After ~6 months, he presented with perioral and periorbital dermatitis with dry skin. The dermatitis spread to the neck flexures. He had also started a part-time job in a public bar, which involved frequent wet work and exposure to detergents. He subsequently developed a

Table 1. Clinical characteristic of 7 patients with reactivation of atopic dermatitis

No.	Age (years)/sex	Job	Eczema onset	Atopy	Atopic features	Exposure	Clinical presentations	Patch test
1	14/F	Student	Infant; recurred at age 12 years	Allergic rhinitis, asthma, oral allergy syndrome	Flexural, philtrum, periorbital, perioral eczema, cheilitis, Dennie–Morgan fold, keratosis pilaris	Moisturizer, eye shadow, strawberry lip salve, facial wipes, deodorant, nail varnish	Eczema on the face, neck, and elbow, sensitive to shampoo, sunscreen, and toothpaste	Negative
2	24/F	Beauty therapist	23	Atopic dermatitis	Flexural eczema	Perfume, hand treatment cream, massage cream, hand lotion, face cleanser, hand wash	Itching on back of both hands, eczema on the hands, forearms, arms, and axilla	Essential oil, hand wash
3	29/F	NA	Toddler, university	Atopic dermatitis	Flexural eczema	Perfume, eyeliner, eye pencil	Eczema on the face and chest	Negative
4	49/F	NA	Child	Atopic dermatitis, asthma	Philtrum, periorbital eczema, dry skin	Facial peel	Recurrent facial eczema	Negative
5	18/F	Hairdresser	Child	Atopic dermatitis, IgE 419 IU/l	Flexural eczema	Hair dye	Hand eczema spread to forearm	PPD
6	14/F	Student	Toddler	Atopic dermatitis, IgE 259 IU/l	Philtrum, periorbital, perioral eczema, dry skin, Dennie–Morgan fold	Facial cosmetics	Facial eczema occurred 1 year after cosmetic use	Negative
7	19/M	Actor, bartender	Child	Atopic dermatitis	Flexural, perioral, periorbital eczema, dry skin	Stage cosmetics, water	Hand eczema spread to forearm flexures, eczema on the face and neck	Negative

F, female; M, male; NA, not available; PPD, *p*-phenylenediamine.

generalized hand dermatitis that spread to the forearm flexures. Patch testing gave negative results. A diagnosis of atopic dermatitis was made.

Discussion

All patients described fulfilled the UK Working Party's diagnostic criteria for atopic dermatitis (4). These cases show the development of atopic-type dermatitis after prolonged exposure to irritant/allergic chemicals, from either occupational or cosmetic sources. The Melbourne group (5) described a series of 6 patients who initially developed occupational contact dermatitis after exposure to irritants and/or contact allergens, usually of the hands, which then precipitated a flare of more generalized eczema. The eczema appeared to be clinically consistent with atopic eczema. All of these patients had a background of atopic diseases. This pattern is also reminiscent of patients who developed 'auto-eczematization' with spread to distant sites involving flexural areas (6, 7). There have also been occasional single case reports of atopic dermatitis triggered by irritant exposure (8). Interestingly, hairdressers with a high level of occupational exposure to allergenic/irritant chemicals had significantly higher serum IgE levels than office worker controls (9, 10). Chronic skin irritation with croton oil in CC chemokine ligand (CCL)17 mice (which are biased towards atopy) induced dermatitis with an elevation of IgE (11).

Atopic dermatitis has not been shown to predispose to contact sensitization, although an association has recently been reported (12). Contact allergens such as nickel have been shown to have the ability to induce not only Th1-type but also Th2-type cytokines (13). Atopic dermatitis has been shown to predispose to irritant contact dermatitis (14). Barrier function deficiency, such as that resulting from filaggrin mutations, has been postulated as a possible link (15). In contrast, our case series supports the Melbourne group's report that prolonged irritant/allergen exposure can, on occasion, cause reflare of atopic dermatitis (5). Although it is difficult in experimental models to distinguish between chronic contact dermatitis involving Th2 switch and chemically induced atopic dermatitis, one can make a clinical distinction, in that atopic dermatitis diagnostic criteria are not fulfilled in the former, whereas they are in the latter (4).

The mechanisms underlying a model of hapten–atopy pathogenesis have been detailed elsewhere (1). Briefly, animal models of atopic dermatitis are often based upon repeated cutaneous topical application of hapten (2). Although initial hapten application leads to a Th1

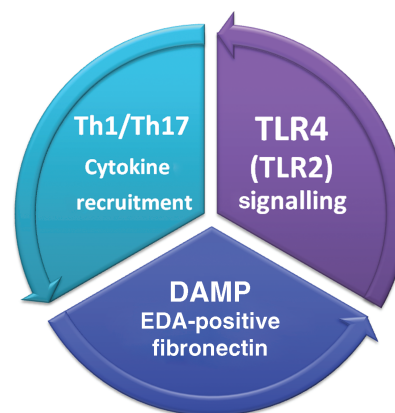


Fig. 1. A simplified model of the cutaneous extracellular damage-associated molecular patterns (DAMP) immune circuit. EDA, extradomain A; Th, T helper; TLR, toll-like receptor.

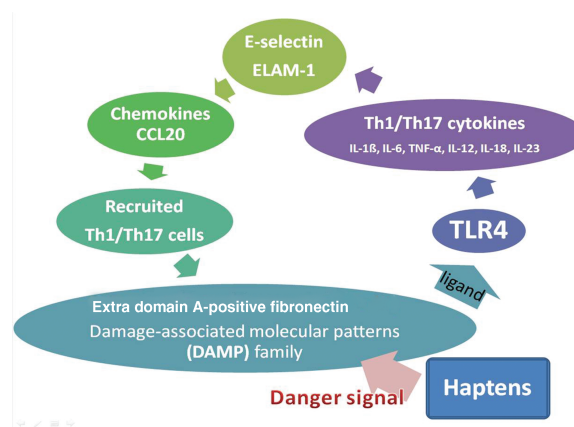


Fig. 2. Cutaneous extracellular damage-associated molecular patterns (DAMP) immune circuit. Initial cutaneous chemical exposure results in release of extracellular DAMP molecules that stimulate TLR4 to produce interleukin (IL)-1 β , tumour necrosis factor (TNF)- α , IL-6, IL-12, IL-18, and IL-23. Subsequent expression of vascular adhesion molecules, such as endothelial cell leukocyte adhesion molecule (ELAM)-1, and chemokines, such as CCL20, leads to recruitment of T helper (Th)1/Th17 cells. Th1 cells produce their own DAMP molecules (extradomain A-positive fibronectin), thus completing a circuit (DAMP immune circuit).

response, repeated application will lead to a Th2 inflammatory response and rash with features of atopic dermatitis (16). The inflammation consists of increased numbers of Th2 cells, mast cells, and eosinophils, and elevated interleukin (IL)-4 and IgE levels (16). It has been postulated that haptens deliver their 'danger signal' through release of endogenous ligands of toll-like receptor (TLR)4 and TLR2, proteins that are also released in skin injury and are members of the damage-associated

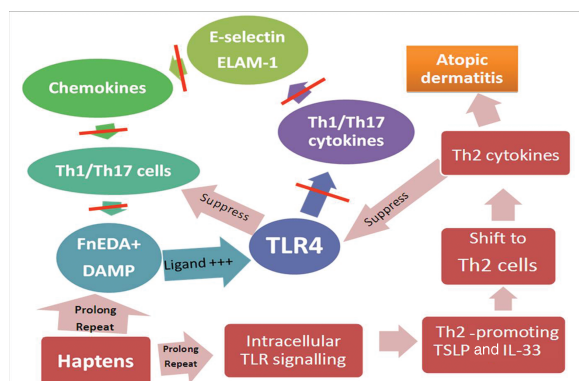


Fig. 3. A model of the possible pathogenesis of chemical atopy. Prolonged and repeated hapten application leads to intracellular toll-like receptor (TLR) signalling with release of T helper (Th)2-promoting thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33. Th2 cytokines antagonize the Th1/Th17-promoting effect of TLR4, and Th2 cells, in contrast to Th1 cells, do not release damage-associated molecular patterns (DAMP) molecules. The DAMP immune circuit is therefore shut down. ELAM, endothelial cell leukocyte adhesion molecule; FnEDA+, extradomain A-positive fibronectin.

molecular patterns (DAMP) family (16). These include extradomain A (EDA)-positive fibronectin, fibrinogen, hyaluronan, heparan sulfate, tenascin, and β -defensins. TLR4 stimulation leads to release of IL-1, tumour necrosis factor- α , IL-6, IL-12, IL-18, IL-23, and α -interferon,

which help to promote Th1/Th17-based inflammation. Recruited Th1 cells release their own DAMP ligand for TLR4 (EDA-positive fibronectin), so that a DAMP–TLR4–Th1/Th17 positive feedback loop is created (DAMP feedback loop) (Figs. 1 and 2). Indeed, allergic contact dermatitis can be abrogated by inhibiting TLR4 function (17).

In animal models, prolonged stimulation of TLR4 will abrogate the Th1 response. Prolonged hapten chemical insult appears to lead to morphological changes of chronic dermatitis and intracellular signalling, with release of the Th2-promoting thymic stromal lymphopoietin and IL-33 (2, 18). The Th2 cytokines such as IL-4, IL-13 and vasoactive intestinal peptide suppress TLR4 signalling, allowing the T cell dominance to switch from Th1 to Th2 and the development of subsequent atopic dermatitis (1) (Fig. 3). In this model, innate immune signalling will, in part, direct adaptive signalling, such as to Th1 or Th2 bias.

It has been postulated that, in stages of life where there is a natural inclination towards a Th2 bias (pregnancy and first year of life), prolonged low-dose exposure to haptens/irritants will lead to atopy in the child. In most other circumstances, hapten/irritant exposure does not lead to atopic states. However, there are reports that both occupational and non-occupational prolonged exposure to haptens/irritants in patients with atopic backgrounds (who are therefore Th2 predisposed) can occasionally lead to reactivation of atopic dermatitis (4).

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