

Reduced allergy rates in atopic eczema to contact allergens used in both skin products and foods: atopy and the 'hapten-atopy hypothesis'

JOHN P. MCFADDEN¹, JONATHAN M. L. WHITE¹, DAVID A. BASKETTER¹ AND IAN KIMBER²

¹Department of Cutaneous Allergy, St John's Institute of Dermatology, St Thomas' Hospital, London SE1 7EH, UK, and ²Faculty of Life Sciences, University of Manchester, Manchester M13 9PL, UK

Background: Food allergy is strongly associated with atopy. This retrospective study investigates whether atopic status affects responses to contact allergens also found in food. We compared incidences of atopic dermatitis/eczema (AD) in subjects who were patch-test positive (PT+) to diallyl disulfide from handling garlic and parabens used as a skin cream/ointment and food preservative with the incidence in those subjects who were PT+ to chemicals encountered at skin surfaces (lanolin and nickel).

Results: 36 658 patients with eczema/dermatitis were patch tested (1980–2006). 10 326 (28.2%) had AD. 13/83 (15.6%) PT+ subjects to diallyl disulfide/garlic had AD (AD/total population versus AD/diallyl disulfide PT+, $P = 0.011$). 54/239 parabens PT+ had AD (22.6%), while 181/608 lanolin PT+ had AD (29.8%) ($P < 0.05$).

Conclusions: Contact allergy to haptens with oral and skin exposure is reduced in AD compared with non-AD, unlike food protein hypersensitivity. Lanolin frequency was not decreased. Possible explanations include (i) confounding factors, e.g. AD subjects handle garlic less than non-AD subjects, or (ii) AD patients tolerate haptens efficiently, secondary to their atopic status, or (iii) oral tolerance of haptens antagonizes tolerance of food proteins, contributing to development of atopy (hapten-atopy hypothesis). The recent upsurge of atopy took place when gut exposure to haptens in processed foods increased dramatically.

Key words: allergic contact dermatitis; atopic dermatitis; hapten; hapten-atopy hypothesis; oral tolerance. © Blackwell Munksgaard, 2008.

Accepted for publication 18 September 2007

Food protein allergens are large (10–75 kDa) stable glycoproteins, which are absorbed intact. Haptens are small (<800 kDa) chemicals, which usually bind to small peptides to render them antigenic. Exposure to haptens (low molecular weight chemical agents) can be through the skin (skin+ exposure pattern, contact allergens) or through the gut (gut+ exposure pattern). While allergy to food proteins is predominantly seen in association with atopy (1), it is our impression that this does not hold true for haptens/contact allergens present in our diet. Diallyl disulfide is the major haptenic allergen in garlic, and allergic contact dermatitis to this has been described in people who handle garlic while preparing food (2) (skin+ gut+). Cosmetic and medicament creams commonly contain

parabens and lanolin, which are both known contact allergens. However, unlike lanolin (skin+ gut–), the preservative parabens is used in some processed foods (skin+ gut+). Nickel is an example of a contact allergen with mainly skin exposure but only trace elements are present in the diet (skin+ gut trace). We retrospectively reviewed data from our patch test clinic, comparing the frequency of allergy rates [patch-test positive (PT+)] to these haptens between atopic eczema/dermatitis (AD) and non-AD dermatitis patients.

Methods

All patients attending for patch testing between 1980 and 2006 had results entered in a database.

The presence or absence of present/past AD, as witnessed by flexural eczema with childhood involvement, was recorded. Patch testing was performed, read, and recorded according to the protocol recommended by the International Contact Dermatitis Research Group (3). Readings were performed at 2/3 and 4/5 days. Frequencies of positive reactions to diallyl disulfide, lanolin, parabens, and nickel were reviewed with respect to the presence or absence of past/present AD. Statistical comparison of different groups regarding presence/absence of AD was performed using chi-squared test with 1 degree of freedom, and 2-tailed *P* value.

Results

Between 1980 and 2006, 36 658 patients with dermatitis/eczema were patch tested. Of these, 10 326 (28.2%) were recorded as having past/present AD (Table 1).

The frequency of AD was reduced in diallyl disulfide PT+ group compared with all patch-test patients ($P = 0.011$), as was the nickel PT+ group ($P < 0.05$). AD in lanolin PT+ subjects was significantly higher than either diallyl disulfide or nickel subjects ($P < 0.01$). The frequency of AD in parabens PT+ group is significantly reduced in comparison with the lanolin PT+ group ($P < 0.05$).

Discussion

AD was noted mainly by history or presence of a flexural rash and childhood involvement. Flexural involvement was recently highlighted as the most reliable indicator of AD (4).

The results show that the groups having contact allergy to haptens with both oral and significant gut exposure show reduced incidence of AD compared with groups allergic to haptens with cutaneous exposure only. This difference is not, however,

seen in the group with only trace exposure in the gut (nickel). Type 1 hypersensitivity to garlic food protein has almost exclusively only ever been reported in atopics (5, 6); yet, we have shown that allergic contact dermatitis to the garlic hapten diallyl disulfide is significantly associated with the absence of AD. Both parabens and lanolin are contained in topical medicaments which AD patients rub onto their inflamed skin, so one may expect the frequency of AD to be slightly raised in both PT+ groups. However, the incidence of AD in the group PT+ to parabens (which is also used in foods) is significantly reduced in comparison with the relatively high incidence of AD in the lanolin PT+ group.

There are other haptens with oral/gut (skin+ gut+) exposure. While some of these have so few PT+ in our data that studying them individually is open to considerable bias when compared with PT+ groups from 'skin+ gut-' exposure haptens, there is a trend of reduced incidence of AD in the 'skin+ gut+' group (Fig. 1).

There are many possible explanations for these observations. First, this was a retrospective study of a heterogeneous collection of AD and non-AD subjects. There is always a possibility of confounding factors being at play in such an unselected group. AD patients, for example, may handle garlic less and may use fewer cosmetics on their skin. Conceivably, this could lead to a reduction in the incidence of AD in the relevant PT+ groups. The second possibility is that there is an established atopic state that, as a secondary phenomenon, in some way leads to more efficient oral tolerance of haptens. However, we speculate that oral tolerance of haptens may be directly contributing to the development of the atopic state (the hapten-atopy hypothesis).

Of all the body surfaces interacting with the environment, the gastrointestinal (GI) tract has the largest amount of associated lymphoid tissue and also has the highest surface area (7). Interactions

Table 1. Prevalence of AD in different contact allergen PT+ groups

Contact allergen	Exposure pattern	AD+, <i>n</i> (%)	AD-, <i>n</i> (%)	Total
Total patch-test population		10 326 (28.2)	26 332	36 658
Diallyl disulfide (garlic)	Skin+ gut+	13 (15.6)	70	83
Nickel	Skin+ gut trace only	1605 (25.2)	4761	6366
Lanolin	Skin+ gut-	181 (29.8)	427	608
Parabens	Skin+ gut+	54 (22.6)	185	239

AD, atopic dermatitis/eczema; PT+, patch-test positive.

Diallyl disulfide PT+ AD+ versus total patch-test population AD+, $P = 0.011$.

Diallyl disulfide PT+ AD+ versus lanolin PT+ AD+, $P < 0.01$.

Diallyl disulfide PT+ AD+ versus nickel PT+ AD+, $P < 0.05$.

Parabens PT+ AD+ versus lanolin PT+ AD+, $P < 0.05$.

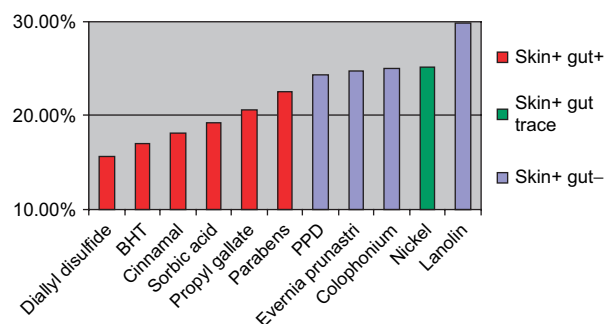


Fig. 1. Incidence of AD in PT+ groups with different exposure patterns. BHT, butyl hydroxytoluene; PPD, para-phenylenediamine.

with foreign proteins/haptens in the GI tract have an influence on interaction elsewhere such as the skin (8, 9). The GI tract is designed for active tolerance to food proteins. The mechanisms of oral tolerance to food proteins and haptens have some common pathways, such as the use of Treg cells (10, 11) (although not necessarily the same subsets), and involvement of cytokines (12) such as transforming growth factor- β . However, significant differences also exist – Peyer's patches are required for oral tolerance to food proteins but not for oral tolerance to haptens (13). Atopics having reduced oral tolerance to food proteins, but appearing to be super-efficient at tolerating haptens from oral exposure may suggest that mechanisms of oral tolerance to haptens and proteins are, in some ways, different and possibly competitive/antagonistic. Over the past 30–40 years, there has been a marked increase in atopic disorders. This increase has occurred during a period when there has been an increased use of processed food and milk (with artificially high hapten/chemical content) in the diet of industrialized countries. We speculate that an increased dietary load of hapten from processed food/milk, especially at an early age, may lead to a breakdown in oral tolerance to food proteins and also promote a shift, priming the generalized immunity towards an atopic state. Other factors in organs such as the skin (impaired surface barrier leading to an increased exposure to atopic proteins) may then lead to atopic disease of that organ (AD). Implicating dietary haptens in the aetiology of atopy would not necessarily exclude other causations [e.g. the hygiene hypothesis (14, 15)] as there could be multiple factors involved.

Acknowledgement

The authors thank Professor Adrian Hayday, King's College School of Medicine, for his help and advice in the preparation of this manuscript.

References

1. Schafer T, Bohler E, Ruhdorfer S et al. Epidemiology of food allergy/intolerance in adults: associations with other manifestations of atopy. *Allergy* 2001; 56: 1172–1179.
2. Jappe U, Bonnekoh B, Hausen B M, Gollnick H. Garlic-related dermatoses: case report and review of the literature. *Am J Contact Dermat* 1999; 10: 37–39.
3. Fregert S. *Manual of Contact Dermatitis*, 2nd edition. Copenhagen, Munksgaard, 1981.
4. Chalmers D A, Todd G, Saxo N. Validation of U.K. working party diagnostic criteria for atopic eczema in a Xhosa-speaking African population. *Br J Dermatol* 2007; 156: 111–116.
5. Anbarro B, Fontela J L, De La Hoz F. Occupational asthma induced by garlic dust. *J Allergy Clin Immunol* 1997; 100: 734–738.
6. Perez-Piemiento A J, Moneo I, Santolalla M et al. Anaphylactic reaction to young garlic. *Allergy* 1999; 54: 626–629.
7. Moog F. The finding of the small intestine. *Sci Am* 1981; 245: 116–125.
8. van Hoogstraten I M, Boos C, Boden D et al. Oral induction of tolerance to nickel sensitisation. *J Invest Dermatol* 1993; 101: 26–31.
9. Kahn G, Phanuphak P, Henry N et al. Propyl gallate-contact sensitization and orally-induced tolerance. *Arch Dermatol* 1974; 109: 506–509.
10. Brandtzaeg P. Current understanding of gastrointestinal immunoregulation and its relation to food allergy. *Ann N Y Acad Sci* 2002; 964: 13–45.
11. Dubois B, Chapat L, Goubier A et al. Innate CD4+ CD25+ regulatory T cells are required for oral tolerance and inhibition of CD8+ T cells mediating skin inflammation. *Blood* 2003; 102: 3295–3301.
12. Faria A M, Weiner H L. Oral tolerance. *Immunol Rev* 2005; 206: 232–259.
13. Fujihashi K, Dohi T, Rennert P D et al. Peyer's patches are required for oral tolerance to proteins. *Proc Natl Acad Sci U S A* 2001; 98: 3310–3315.
14. Strachan D P. Hay fever hygiene and household size. *Br Med J* 1989; 299: 1259–1260.
15. Holt P G, Sly P D, Bjorkstein B. Atopic versus infectious diseases in childhood: a question of balance? *Pediatr Allergy Immunol* 1997; 8: 638–640.

Address:

Jonathan White
Department of Cutaneous Allergy
St John's Institute of Dermatology
St Thomas' Hospital
London SE1 7EH
UK
Tel: +44 2071886272
Fax: +44 2071887473
e-mail: jonathan.3.white@kcl.ac.uk