

Urticaria is associated with birch-pollen sensitization

Hesselmar B, Eriksson B, Åberg N. Urticaria is associated with birch-pollen sensitization.

Pediatr Allergy Immunol 2007; 18: 692–695.

© 2007 The Authors

Journal compilation © 2007 Blackwell Munksgaard

Urticaria is a common condition, seldom of allergic origin. It is however not always possible to find the provoking allergen. The aim of the present study was to analyze if there was a relationship between urticaria and sensitization to common airborne allergens. A representative sample of 402 12 to 13-yr-old children answered a questionnaire on allergic diseases, 397 were interviewed by the study nurse and 371 underwent skin prick tests to cat, dog, horse, birch, timothy-grass, house dust mites and *Cladosporium* mould. Specific IgE-antibodies were analyzed to birch pollen and cat dander. Urticaria was more common in sensitized children, but the relationship between urticaria and sensitization was only statistically significant for birch pollen sensitization (OR 1.99, 95% CL 1.04–3.83), when tested in a multiple logistic regression model with the specified allergens as independent variables. A similar pattern was seen for birch-specific IgE-antibody levels, which was higher in children reporting urticaria than in those without. IgE-levels to cat dander did not show such a difference. Urticaria was statistically significantly associated with sensitization to birch-pollen, but not to other common inhalant allergens. We propose that intake of birch-pollen cross-reactive food-stuffs may be a neglected cause of urticaria and relapsing urticaria, in birch-pollen sensitized subjects.

B. Hesselmar¹, B. Eriksson² and N. Åberg¹

¹Department of Paediatrics, Institute of Clinical Sciences, Sahlgrenska Academy of Göteborg University, Göteborg, Sweden, ²Nordic School of Public Health, Göteborg, Sweden

Key words: allergens; urticaria; pollens; food-allergens

Bill Hesselmar, The Queen Silvia Children's Hospital, Göteborg, Sweden

Tel.: +46 (0)31 343 4000

Fax: +46 (0)31 343 4760

E-mail: bill.hesselmar@vgregion.se

Accepted for publication 24 February 2007

Urticaria, and especially relapsing urticaria, is a troublesome condition in both children and in adults. Sometimes it is caused by infections, drugs or physical stimuli and sometimes by allergy. Food allergens are often suspected in allergic urticaria, but it is not always possible to find a triggering allergen. The aim of the present study was to analyze if there is a relationship between urticaria and sensitization to common airborne allergens in a representative sample of Swedish school children.

Methods

A Swedish questionnaire study comprising 1649 7-yr-old children in Göteborg and 832 7 to 9-yr-old children in Kiruna was conducted in 1991 (1). In 1992 a representative sub-sample of 412 children was selected for interview and skin prick testing for common allergens. This sub-sample was approached once again in 1996 for a follow-

up. The children were at the time 12 yr old in Göteborg, and 12–13 yr old in Kiruna. Four hundred and two of the initial 412 children responded to the questionnaire, 397 underwent a structured interview by the study nurse, and complete skin prick test (SPT) results were achieved from 371 children. The study population, the selection and stratification of the sub-sample and the follow-up procedure are previously described in detail (2). This paper is based on the questionnaire reports, the interviews and the SPTs from 1996.

Data on current (symptoms during the last 12 months) asthma, rhinoconjunctivitis and eczema were collected from the questionnaire. Data on urticaria (nettle rash) were collected from the structured interviews; urticaria being defined as at least one episode with at least solitary urticaric efflorescence's during the last 12 months. If the child reported at least one episode in the last 12 months with multiple or large urticaric

efflorescence's with or without angioedema, it was classified as 'generalized urticaria' (GU). Provoking or causative agents were asked for and categorized into four groups; insects sting, drugs, food-stuff and other/unknown cause.

The SPTs were carried out by a trained nurse according to the standards from the subcommittee on skin tests of the European Academy of Allergy and Clinical Immunology (3). The allergen extracts used were all of ALK make (ALK, Hørsholm, Denmark); Soluprick SQ 10 HEP: birch, timothy-grass, dog, cat, horse, *Dermatophagoides pteronyssinus*, *D. farinae*. *Cladosporium herbarum* was represented by Soluprick in dilution 1:20. Positive control was histamine 10 mg/ml Soluprick. A positive SPT corresponds to a weal with a diameter exceeding the negative control (NaCl 9 mg/ml) with at least 3 mm.

Venous blood samples were obtained from 309 children, and serum was stored in -20°C until analysis. The levels of specific IgE-antibodies to birch pollen and cat dander were analyzed with the high-sensitive protocol (incubation of serum samples overnight) of Magic LiteTM, a commercial chemoluminometric method, according to the recommendations of the manufacturer (ALK).

Statistical analyses were performed with SPSS 12.0.1 (SPSS Inc., Chicago, IL, USA) and EPI-INFO version 3.2.2 (CDC, United States Department of Health and Human Services). Prevalence's were calculated in the sub-sample as weighted proportions using estimates from the individual strata and weights from the original 1991 sample. Chi-squared tests were used to calculate differences between proportions. Logistic regression with the 'Forced Entry method' was used to test the relationship between urticaria/GU and the independent disease- and SPT-variables. The non-parametric median test was used to investigate if the antibody levels in different samples have different median values.

The etiological fraction (or the population attributable risk) is expressed as a percentage, and was calculated as: the number of urticaria cases in the birch-sensitized part of the population that are in excess of what can generally be expected to occur in the population, divided by the total number of urticaria cases.

The study was approved by the Ethic Committee of The Sahlgrenska Academy, Göteborg University.

Results

In the stratified and weighted analyses, the estimated prevalence of at least one episode with urticaria during the last 12 months was 30.6%

(S.E. 2.34). The corresponding figure for GU was 23% (S.E. 2.11). When insect stings and known drug reactions as causative agents were excluded, the urticaria prevalence was to 17.2% (S.E. 1.92).

Urticaria was more common in children with other types of current allergic diseases. A multiple logistic regression model with urticaria or GU as the dependent variable revealed that this covariation was most evident for eczema and allergic rhinoconjunctivitis, but less for asthma (Table 1). Urticaria was also more often reported by sensitized children, as measured by at least one positive SPT (Crude OR 1.6, 95% CL 1.0–2.5). However, the relationship between sensitization and urticaria was in the multiple logistic regression model only statistically significant for sensitization to birch pollen (Table 2). The relation between urticaria and birch pollen allergy was further strengthened when known provoking agents were taken into account. Urticaria caused by food, or when the provoking agent was unknown, was related to birch-pollen sensitization (OR 2.43, 95% CL 1.24–4.72, $p = 0.004$). A corresponding relation could however not be demonstrated when the reactions were caused by insect stings or drugs (OR 1.45, 95% CL 0.64–3.22, $p = 0.33$). No trend was noticed for the rate of birch-pollen sensitization over increasing

Table 1. Relationship between urticaria/generalized urticaria and allergic diseases

	Urticaria adjusted OR (95% CL)	GU adjusted OR (95% CL)
Allergic rhinoconjunctivitis	1.65 (1.01–2.70)	2.03 (1.21–3.39)
Eczema	1.87 (1.16–3.00)	2.14 (1.31–3.52)
Asthma	1.89 (1.00–3.57)	1.49 (0.76–2.90)

GU = generalized/widespread urticaria; adjusted OR = multiple logistic regression with allergic rhinoconjunctivitis, eczema and asthma as independent variables.

Table 2. Relationship between urticaria/generalized urticaria and specific sensitization to common airborne allergens

	Urticaria adjusted OR (95% CL)	GU adjusted OR (95% CL)
Cat	1.06 (0.54–2.10)	0.85 (0.41–1.74)
Dog	0.98 (0.39–2.45)	0.91 (0.35–2.41)
Horse	0.80 (0.30–2.11)	1.01 (0.37–2.78)
Birch	1.99 (1.04–3.83)	2.02 (1.02–4.00)
Timothy-grass	1.33 (0.73–2.41)	1.55 (0.83–2.88)
HDM	0.62 (0.24–1.63)	0.68 (0.25–1.88)
Cladosporium herbarium	1.28 (0.19–8.51)	1.65 (0.25–11.17)

GU = generalized/widespread urticaria; adjusted OR = multiple logistic regression with cat, dog, horse, birch, timothy-grass, *D. pteronyssinus* and *D. farinae* as independent variables; HDM = house dust mite, *D. pteronyssinus* and/or *D. farinae*.

Table 3. IgE-antibody levels to birch pollen and cat dander in relationship to urticaria and provoking agent

	IgE to birch pollen*	IgE to cat dander*
No urticaria	47	47
Urticaria caused by drugs or insects stings	35	39
Urticaria caused by food stuff or of unknown origin	66	52
p-value**	0.005	0.393

*Percentage of IgE-antibody levels above overall median value.

**Non-parametric median test.

frequency of urticaria (Chi-square for trend, data not shown).

The levels of IgE-antibodies to birch pollen and cat dander showed a similar pattern in the relationship to urticaria, as the SPTs. IgE-antibodies to birch pollen was higher in children reporting urticaria caused by food, or when the provoking agent was unknown, than those without urticaria, or when urticaria was caused by drugs or insect stings. No such relationship was seen between IgE-antibody levels to cat dander and urticaria (Table 3).

The etiological fraction (population attributable risk) for urticaria due to birch-pollen cross-reactive food-stuff was estimated as 16.7% (95% CI 2.8–37.3).

Discussion

The study confirms urticaria as a common condition. Population based prevalence figures for urticaria is however seldom reported, but it is generally accepted that about 20–25% of a population will experience urticaria at least once during life time. In the interventional ETAC-study of cetirizine treatment in young children with eczema, 16% of the children in the control group reported urticaria during the 18-month follow-up period (4). We report higher prevalence figures for urticaria, as we also included drug-induced urticaria, and localized urticaric reactions due to insect stings. If excluding these specific provoking agents, urticaria was reported in 17% of our children.

Very often it is not possible to find out what factors triggering an acute attack. Sometimes an episode is secondary to infections (5), sometimes physical stimuli such as cold or heat are eliciting rash (6). Sometimes a typical food-allergen could be recognized. Exercise may also potentate an allergic reaction, especially to food allergens, and exercise induced anaphylaxis has been reported (7). Very often, however, no single causative or triggering factor can be identified. We found that

urticaria was strongly related to birch-pollen sensitization, but we could not demonstrate relations to the other inhaled allergens tested. Many fruits, vegetables and nuts cross-react with birch-pollen, mainly causing the 'oral allergy syndrome' in birch-pollen allergic subjects (8). But very little is mentioned in the literature about their potential role in causing urticaria or relapsing urticaria. Our results indicate however that birch-pollen cross-reactive food-stuff may be a plausible trigger also for urticaria in birch-pollen sensitized subjects, a mechanism supported by Bircher et al. (9). They found that IgE antibodies to food allergens were common in pollen-allergic subjects. Furthermore, clinical reactions to food allergens, including urticaria, were seen in subjects with IgE-antibodies to food allergens. No such relationship was seen in the non-allergic control group or in subjects allergic to house dust mites or animal dander. Contact urticaria could be an alternative mechanism to cross-reactive food-stuff, as birch can cause contact urticaria on direct skin contact in sensitized subjects (10). Such an explanation is however not very likely, because contact urticaria could be caused also by animals on direct skin contact. If that had been the mechanism, we should have seen an association also between animal-sensitization and urticaria (11).

The weakness of the study is that it is observational; it does not give direct evidence for a connection between the reported episodes of urticaria and food stuff that cross-react with birch-pollen. Further studies have to be made to establish if there is a causative relationship. Still, the results are intriguing and may help the clinician in the often unavailing search for underlying causes including a triggering allergen in relapsing urticaria. If no obvious causative allergen could be found by the medical history, the further investigations with allergy testing could also include inhalant allergens, especially birch-pollen. It is not unlikely that birch-pollen cross-reactive food-stuffs may act as allergens in relapsing urticaria in birch-pollen sensitized subjects, at least in Sweden and other countries where birch-trees are common. In this study, we estimate that 17% of all urticaria cases could be due to food-stuff cross-reacting with birch pollen, although the confidence interval was wide, the share could be just a few percent but also as much as 37%.

Acknowledgments

The authors would like to express their gratitude to the staff at the Paediatric Clinic, Kiruna Hospital, Sweden, and to Maria Jenmalm (PhD) at the KFC/Division of Paediatrics,

Linköping University Hospital, Sweden, for performing the antibody analysis. The study was supported by grants from The Swedish Foundation for Health Care Sciences and Allergy Research and the Swedish Association against Asthma and Allergy.

References

1. ABERG N, HESSELMAR B, ABERG B, ERIKSSON B. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy* 1995; 25: 815–9.
2. HESSELMAR B, ABERG N, ABERG B, ERIKSSON B, BJORKSTEN B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy* 1999; 29: 611–7.
3. Skin tests used in type I allergy testing position paper. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. *Allergy* 1989; 44 (Suppl. 10): 1–59.
4. DIEPGEN TL. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. *Pediatr Allergy Immunol* 2002; 13: 278–86.
5. SACKESSEN C, SEKEREL BE, ORHAN F, KOCABAS CN, TUNCER A, ADALIOGLU G. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol* 2004; 21: 102–8.
6. DICE JP. Physical urticaria. *Immunol Allergy Clin North Am* 2004; 24: 225–46, vi.
7. BEAUDOUIN E, RENAUDIN JM, MORISSET M, CODREANU F, KANNY G, MONERET-VAUTRIN DA. Food-dependent exercise-induced anaphylaxis—update and current data. *Allerg Immunol (Paris)* 2006; 38: 45–51.
8. ORTOLANI C, ISPANO M, PASTORELLO E, BIGI A, ANSALONI R. The oral allergy syndrome. *Ann Allergy* 1988; 61: 47–52.
9. BIRCHER AJ, VAN MELLE G, HALLER E, CURTY B, FREI PC. IgE to food allergens are highly prevalent in patients allergic to pollens, with and without symptoms of food allergy. *Clin Exp Allergy* 1994; 24: 367–74.
10. LAHTI A, HANNUKSELA M. Immediate contact allergy to birch leaves and sap. *Contact Derm* 1980; 6: 464–5.
11. AGRUP G, SJOSTEDT L. Contact urticaria in laboratory technicians working with animals. *Acta Derm Venereol* 1985; 65: 111–5.