

CLINICAL REPORT

Atopic Dermatitis and Concomitant Disease Patterns in Children up to Two Years of Age

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There are few prospective studies of atopic dermatitis and co-existing diseases such as respiratory infections in children up to 2 years of age. Using annual questionnaires, we studied the cumulative incidence of atopic dermatitis and concomitant symptoms indicating other atopic diseases and respiratory infections in 0–2-year-old children in a prospective birth cohort of 4089 children. We found associations between atopic dermatitis and asthma (ratio of proportion 1.45, 95% CI 1.16–1.80), allergic rhinoconjunctivitis (RP 2.25, CI 1.77–2.85), adverse reactions to foods (RP 3.20, CI 2.83–3.62), urticaria (RP 2.04, CI 1.80–2.31), acute otitis media (RP 1.13, CI 1.05–1.21), more than one pneumonia during the first and/or second year of life (RP 2.17, CI 1.14–4.15), and use of antibiotics at least twice yearly (RP 1.29, CI 1.07–1.56). The association between atopic dermatitis and respiratory infections persisted after stratification for asthma. There was a higher proportion of atopic disease manifestations, but not respiratory infections, in children with onset of atopic dermatitis during the first year of life than during the second. The study shows that during the first 2 years of life there is a significant association not only between atopic dermatitis and other atopic disease manifestations, but also between atopic dermatitis and respiratory infections manifested in an increased rate of acute otitis media, pneumonia and use of antibiotics. **Key words:** asthma; infections; otitis; pneumonia; rhinoconjunctivitis; urticaria.

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Atopic dermatitis (AD) is a pruritic, chronically relapsing inflammatory skin disease. Its prevalence has increased during recent decades (1–4). Swedish studies show an increase in the one-year prevalence from 7% to 16% in southern Sweden and from 10% to 22% in northern Sweden between 1979 and 1991 (3), and an increase in cumulative incidence from 15% to 23%

between 1992 and 1998 in southern Sweden (5). Other manifestations of atopic disease, such as bronchial asthma and allergic rhinoconjunctivitis, are common in patients with AD (6, 7), with a similar increase in prevalence (3). Fifty to eighty percent of all patients with AD develop asthma and/or allergic rhinoconjunctivitis (6, 8), 33% develop allergic asthma and 16% allergic rhinitis during their first 5 years of life (9). A higher incidence of recurrent upper-respiratory-tract infection has been reported in adults with past or present AD than in non-atopic controls (10).

There are few prospective studies of the prevalence of other disease manifestations in young children with AD (11, 12). The aim of the present study was to investigate the association between AD and symptoms of other atopic diseases or common infections of the respiratory tract in 0–2-year-old children. This was performed in a prospective birth cohort study of 4089 children who were followed with questionnaires annually.

PATIENTS AND METHODS

Cohort

As part of a multidisciplinary epidemiological project, a cohort of 4089 children born in the central and north-western parts of the Stockholm area between February 1994 and November 1996 was followed (the “BAMSE” study). The children were identified in the Swedish birth register and consecutively recruited to the project at their first visit to the child health centres during their first months of life (Fig. 1).

Questionnaires

A first questionnaire (Q0) focusing on heredity and environmental factors was filled in by the parents at the time of recruitment at 2 months of age (10th percentile 0 months, 90th percentile 5 months of age). At 1 and 2 years of age new mailed questionnaires (Q1 and Q2) asked questions on symptoms of atopic disease. The median age of the child when the parents answered Q1 was 12 months (10th percentile 12 months, 90th percentile 14 months) and when they answered Q2 24 months (10th percentile 23 months, 90th percentile 26 months). The questionnaires included symptoms such as wheezing, running nose, red and itchy eyes, itchy rash, and factors provoking these symptoms, as well as whether the diagnosis had been made by a physician.

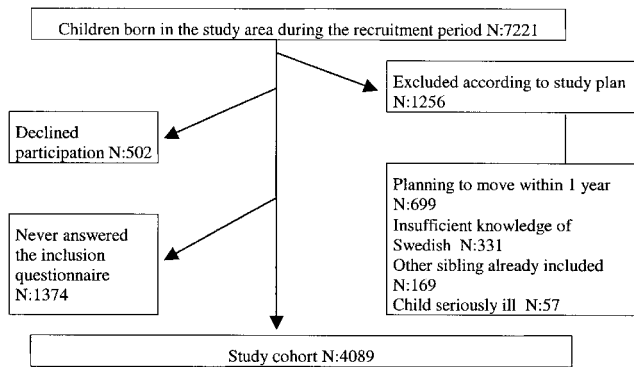


Fig. 1. Description of the cohort.

Data banking

Telephone interviews were conducted by two experienced research nurses when answers in the questionnaires were missing or ambiguous (approx. 10% of questionnaires). Data were manually registered for the first questionnaire (Q0). For the following two questionnaires (Q1, Q2) an OCR scanner was used (software: Eyes & Hands, ReadSoft AB, Helsingborg, Sweden). After data registration, established quality controls were run. All the data were stored in a database designed in Microsoft Access for Windows 95, version 7.00 (Microsoft Corporation, Washington, USA).

Definitions

Diagnoses were made by combining various symptoms (see Appendix). For stratifying and adjusting for heredity, parental atopic respiratory history was used. This history was defined as asthma and/or allergic rhinoconjunctivitis diagnosed by a doctor, in combination with reported allergy to furred animals and/or pollen in one or both parents ever. Asthma diagnosis also required that the parent at any time had been using asthma medication. Eczema was not included in the definition of heredity.

Validation of case definition

Fifty consecutive children, 0–4 years old, first-time visitors for a skin disorder to the paediatric section of the Department of Dermatology at the Karolinska Hospital, were included in a separate validation study. Their parents were asked to fill in a questionnaire before meeting the doctor. The questionnaire contained, among other questions, the questions diagnostic for eczema from the main study questionnaires. The children were then examined by a dermatologist (MB, CFW) to determine whether they had AD (“gold standard”) according to the criteria of Hanifin & Rajka (13).

Statistics

Statistical analyses were made with the Stata Statistical Software: Release 6.0 (College Station, Texas, USA). The chi-square test and the Fisher exact test were used for statistical analyses of proportions. Ratios of proportions (RP) were adjusted by stratification, and ratios within each stratum combined using Mantel-Haenszel weights. The weighted ratios are shown with exact 95% confidence intervals. Logistic regression models were used to investigate which factors might influence the associations studied.

Confounders

To investigate whether other factors influenced the association between AD and other symptoms, logistic regression models were calculated. The variables heredity, parental education, gender, age of mother, months of breastfeeding (exclusive and total), maternal smoking, gestational age and age of the child when the questionnaires were filled in were included separately and together in different combinations. With the exception of heredity, none of these variables had a strong influence on the association between AD and the symptoms studied. Therefore, all shown ratios of proportions were adjusted for heredity.

RESULTS

Response rates

Data were analysed for 3791 (93%) children where the parents had answered all three questionnaires. The response rates for Q1 and Q2 were 96% and 94%, respectively. Of these 3791 children, 3786 (952 AD, 2834 non-AD) had complete answers to the questions considered diagnostic for AD (see Appendix).

Validation of case definition

Among the 50 children with various skin disorders examined in the separate validation study, 26 (52%) fulfilled the criteria of AD. The sensitivity of the questionnaire assessment compared with the clinical diagnosis by the dermatologist was 92% and the specificity 100%.

Atopic dermatitis

In the cohort, 952 (25.1%) of the 3791 children with complete answers were reported to have symptoms defined as AD at any time during their first 2 years. The male/female ratio was 1.04. Significantly more boys (318 of 486, 65.4%) than girls (254 of 466; 54.5%) with AD were reported to have symptoms of AD already in the first questionnaire ($p = 0.009$), giving a male/female ratio of 1.25 among children with onset during the first year of life and of 0.80 among children with onset during the second year.

Other atopic disease manifestations

Asthma was reported in 321 (8.5%) children, symptoms indicating allergic rhinoconjunctivitis in 262 (7.0%), adverse reactions to foods in 768 (20.3%), and urticaria in 788 (20.9%). The combination of AD and asthma was reported in 109 (2.9%), and the combination of AD and symptoms indicating allergic rhinoconjunctivitis, adverse reactions to foods, or urticaria was reported in 115 (3.1%), 405 (10.7%) and 322 (8.5%) children, respectively (Fig. 2). Asthma, symptoms indicating allergic rhinoconjunctivitis, adverse reactions to foods, and urticaria, were all significantly more common in children with AD than in children without AD (Table I).

Infections

At least one episode of acute otitis media was reported during the first 2 years of life for 1914 children (50.7%). Three hundred children (7.9%) had had pneumonia diagnosed by a doctor, whereas 39 (1%) had had at least 2 episodes of doctor-diagnosed pneumonia during their first and/or second year of life. Oral antibiotics had been used by 1586 children (42%) at least twice a year during their first and/or second year of life, and by 445 (11.8%) at least twice a year during their first as well as second year of life (i.e. four times in all). The combination of AD and acute otitis media or the use of antibiotics at least twice a year during the first as well as the second year of life, was reported in 528 (14.0%) and 137 (3.6%) children, respectively (Fig. 2). The combination of AD and pneumonia on two or more occasions during the first and/or second year of life was reported in 16 (0.4%) children. Acute otitis media, pneumonia on more than one occasion during their first and/or second year of life, and the use of antibiotics were also more common in children with AD (Table II) even after stratification for asthma (data not shown).

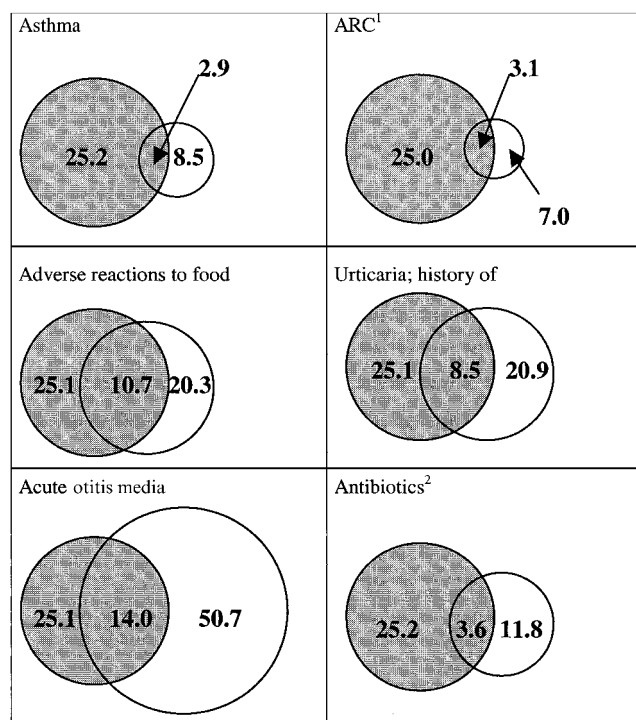


Fig. 2. Proportion (%) of atopic dermatitis (AD) and of other symptoms and signs in the cohort, and their overlap.

The filled circles illustrate AD, the unfilled circles illustrate the item mentioned at the top of each box. The percentage for AD is based on the children with complete answers both to the questions concerning AD and to the questions concerning the other item in the box. For this reason, the percentage varies.

¹Symptoms indicating allergic rhinoconjunctivitis.

²Antibiotics at least twice during first as well as second year.

Early onset of AD

Several atopic disease symptoms and diagnoses within the first 2 years were more common with AD onset during the first year than with onset during the second. The differences between proportions were highest for food reactions and urticaria. No significant differences were seen between early and later onset of AD for symptoms and signs of infections (acute otitis media, pneumonia, use of antibiotics and whooping-cough).

Gender aspects of associated disease manifestations

Lower-respiratory symptoms provoked by furred animals/pollens were significantly more common in boys with AD than in those without (RP 4.33, 95% CI 1.83–10.24). This was also true for the use of antibiotics more than twice a year during the first and/or second year (RP 1.24, CI 1.11–1.38) and more than twice a year during first as well as second year (RP 1.45, CI 1.14–1.86). These ratios were lower and non-significant in girls. On the other hand, among girls, doctor-diagnosed rhinitis and pneumonia on more than one occasion during the first and/or second year of life were significantly more common in the AD group than in the non-AD group (RP 4.46, CI 1.56–12.72 and RP 3.13, CI 1.39–7.02, respectively); whereas among boys the ratios were considerably lower and did not reach statistical significance.

DISCUSSION

In children up to 2 years of age, we found a significant association between AD and other atopic disease manifestations, and between AD and respiratory infections. The proportion of atopic disease manifestations, but not of respiratory infections, was higher when the onset of AD was during the first year rather than during the second.

Given that families with a history of atopic diseases are more willing to participate in projects studying these diseases, this would result in an overrepresentation of children with atopic diseases in the cohort. The cumulative incidences of atopic diseases in our study might, in that case, be overestimated, but this would not affect the ratios of proportions. There is also the possibility that parents with atopic diseases or with previous experience of atopic disease, e.g. among siblings, are more likely to perceive and report symptoms of such diseases in their children. Such effects could to some extent lead to an overestimation of the ratios of proportions.

When designing the study, the UK Working Party's diagnostic criteria for AD had only recently been published (14–16), and were not yet fully evaluated in children 0–4 years old. We therefore chose our own set of questions for diagnosing AD, which proved to have high accuracy when validated against clinical diagnosis.

Table I. Association with atopic disease symptoms and diagnoses cumulatively up to 2 years of age; atopic dermatitis (AD) up to 2 years of age versus non-AD

	Atopic dermatitis		Non atopic dermatitis		Ratio ^a of proportions	95% CI
	n/N	%	n/N	%		
<i>Respiratory tract</i>						
Wheezing ever	320/947	33.8	728/2816	25.9	1.27	1.14–1.42
Asthma	109/950	11.5	212/2828	7.5	1.45	1.16–1.80
Lower respiratory symptoms from furred animals/pollens	18/941	1.9	18/2802	0.6	3.06	1.57–5.98
Nasal catarrh or nasal congestion ≥ 4 weeks	362/949	38.2	835/2831	29.5	1.25	1.13–1.38
Nasal catarrh or nasal congestion ≥ 2 months	84/949	8.9	174/2830	6.1	1.40	1.09–1.80
Symptoms indicating allergic rhinoconjunctivitis (ARC)	115/936	12.3	146/2813	5.2	2.25	1.77–2.85
Rhinitis; doctor's diagnosis	14/948	1.5	15/2831	0.5	2.51	1.22–5.18
Symptoms indicating ARC from furred animals/pollens	22/940	2.3	22/2814	0.8	2.86	1.54–5.28
<i>Foods</i>						
Adverse reactions to food	405/946	42.8	362/2824	12.8	3.20	2.83–3.62
Food allergy; doctor's diagnosis	176/950	18.5	80/2829	2.8	6.14	4.73–7.97
<i>Urticaria</i>						
Urticaria; history of	322/949	33.9	466/2831	16.5	2.04	1.80–2.31
Urticaria; doctor's diagnosis	89/950	9.4	109/2829	3.9	2.43	1.85–3.20

n = number of children with the disease; *N* = number of children with complete answers to the questions diagnostic for the disease.

^aadjusted for heredity.

Table II. Association with symptoms and signs of infection cumulatively up to 2 years of age; atopic dermatitis (AD) up to 2 years of age versus non-AD

	Atopic dermatitis		Non atopic dermatitis		Ratio ^a of proportions	95% CI
	n/N	%	n/N	%		
Acute otitis media during first 2 years	528/949	55.6	1385/2827	49.0	1.13	1.05–1.21
Pneumonia; doctor's diagnosis	77/950	8.1	223/2834	7.9	1.03	0.80–1.32
Pneumonia at least twice during first and/or second year; doctor's diagnosis	16/950	1.7	23/2832	0.8	2.17	1.14–4.15
Whooping-cough	29/950	3.1	96/2819	3.4	0.88	0.59–1.31
Antibiotics at least twice during first and/or second year	450/946	47.6	1135/2826	40.2	1.17	1.08–1.27
Antibiotics at least twice during first as well as second year	137/952	14.4	308/2834	10.9	1.29	1.07–1.56

n = number of children with the disease; *N* = number of children with complete answers to the questions diagnostic for the disease.

^aadjusted for heredity.

Including “doctor’s diagnosis of eczema” as an alternative definition makes it more difficult to compare our results with the results of others. Yet, it had to be included since parents of children with eczema diagnosed by a doctor to a lower extent reported itch in their child, most likely because treatment relieving itch had been initiated by the diagnosing doctor, hence biasing the possibility to correctly diagnose AD. Further, eczema was not included in the definition of heredity since, in adults, the word “eczema” may be non-specific and in the layman’s experience include dermatoses other than AD.

The cumulative incidences of atopic diseases in our study agree with other studies (11, 17). The male/female ratios indicate an earlier age of onset in boys. In a previous case-control study with subjects from the present birth cohort, however, we were unable to detect any significant difference in age of onset between boys and girls (18).

The association between AD and bronchial asthma, allergic rhinoconjunctivitis and food allergy is well known (7). Cumulative incidences up to 5 years of age of 33% for asthma and 16% for allergic rhinitis have been reported (9), though incidences of these diseases peak later in life. Our study partly confirms the results of Gustafsson et al., who among children with AD at a mean age of 18.3 months (4 months to 3 years) found symptoms of bronchial obstruction in 26%, adverse food reactions in 63% and rhinoconjunctivitis in 14%, all in the previous year (12).

Urticaria is not generally considered common in AD (6). We found a significant association between AD and urticaria in children, and the frequency of urticaria was even higher if AD started during the first year of life, which concurs with the study by Gustafsson et al. (12). However, when we adjusted for doctor’s diagnosis of food allergy, the RP for a history of urticaria decreased

to 1.74 (95% CI 1.53–1.98) and for doctor's diagnosis of urticaria to 1.45 (1.09–1.92), indicating that some but not all cases of urticaria in children with AD are related to food allergy.

Pneumonia on more than one occasion during the first and/or second year of life, acute otitis media, and the use of antibiotics, were more frequent in children with AD. Probably this indicates that children with AD are more prone to inflammation in the airways. Yet, stratifying for asthma did not change the difference between AD and non-AD, indicating that the higher cumulative incidence was not a consequence of the higher cumulative incidence of asthma in the AD group. Hence, the children with AD seemed to be more prone to upper-respiratory-tract infection. This has also been reported in adults with past or present AD (10).

In both boys and girls, AD before one year of age led to a higher proportion of most other atopic disease manifestations during the first 2 years compared to onset of AD between 1 and 2 years of age. To what extent this difference persists later in childhood is an obvious question for a follow-up study. It could well be that later onset of AD is also associated with later onset of other atopic disease manifestations.

The material was stratified by gender to see whether the associations persisted. We have earlier reported that among 2-year-old children with ongoing AD boys are significantly more often sensitized to foods and/or airborne allergens than girls are (22% vs. 3%) (18). In the present study, the ratio of lower-respiratory symptoms induced by furred animals/pollens was higher when comparing boys with and without AD than girls with and without AD. The groups are limited in numbers of children (13/479 vs. 9/1411 in boys, 5/462 vs. 9/1391 in girls), for which reason careful interpretation of the results is required. Caution is also necessary in the interpretation of all observed gender differences. Only that for the use of antibiotics appears sufficiently large to be entirely trustworthy.

Our prospective questionnaire study showed a significant association already during the first 2 years between AD and other atopic disease manifestations; but also between AD and respiratory infections. Children with AD are more prone to the latter, and this might lead to increased health care consumption and the loss of more parental working hours in this group.

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REFERENCES

1. Taylor B, Wadsworth J, Wadsworth M, Peckham C. Changes in the reported prevalence of childhood eczema since the 1939–45 war. *Lancet* 1984; 2: 1255–1257.
2. Croner S. Atopic dermatitis – epidemiology. *Pediatr Allergy Immunol* 1991; 2 Suppl 1: 6–7.
3. Åberg N, Hesselmar B, Åberg B, Eriksson B. Increase of asthma, allergic rhinitis and eczema in Swedish school-children between 1979 and 1991. *Clin Exp Allergy* 1995; 25: 815–819.
4. Schultz Larsen F, Hanifin JM. Secular change in the occurrence of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1992; Suppl 176: 7–12.
5. Broberg A, Svensson Å, Borres M, Berg R. Atopic dermatitis in 5–6-year-old Swedish children: cumulative incidence, point prevalence, and severity scoring. *Allergy* 2000; 55: 1025–1029.
6. Rajka G. Essential aspects of atopic dermatitis. Berlin-Heidelberg: Springer-Verlag; 1989.
7. Ring J. Atopy: condition, disease, or syndrome? In: Ruzicka T, Ring J, Przybilla B, editors. *Handbook of atopic eczema*. Berlin-Heidelberg: Springer-Verlag; p. 3–8.
8. Halbert AR, Weston WL, Morelli JG. Atopic dermatitis: is it an allergic disease? *J Am Acad Dermatol* 1995; 33: 1008–1018.
9. Diepgen TL, Fartasch M. Recent epidemiological and genetic studies in atopic dermatitis. *Acta Derm Venereol* 1992; 176: 13–18.
10. Rystedt I, Strannegård IL, Strannegård Ö. Recurrent viral infections in patients with past or present atopic dermatitis. *Br J Dermatol* 1986; 114: 575–582.
11. Bergmann RL, Edenharter G, Bergmann KE, Forster J, Bauer CP, Wahn V, et al. Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. *Clin Exp Allergy* 1998; 28: 965–970.
12. Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis – a prospective follow-up to 7 years of age. *Allergy* 2000; 55: 240–245.
13. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol* 1980; Suppl 92: 44–47.
14. Williams HC, Burney PGJ, Hay RJ, Archer CB, Shipley MJ, Hunter JJA, et al. The U.K. working party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994; 131: 383–396.
15. Williams HC, Burney PGJ, Strachan D, Hay RJ. The U.K. working party's diagnostic criteria for atopic dermatitis. II. Observer variation of clinical diagnosis and signs of atopic dermatitis. *Br J Dermatol* 1994; 131: 397–405.
16. Williams HC, Burney PGJ, Pembroke AC, Hay RJ. The U.K. working party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; 131: 406–416.
17. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *Br J Dermatol* 1998; 139: 73–76.
18. Böhme M, Svensson Å, Kull I, Nordvall SL, Wahlgren C-F. Clinical features of atopic dermatitis at two years of age – a prospective population-based case-control study. *Acta Derm Venereol* 2001; 81: 193–197.

APPENDIX. Definitions used in the questionnaires

Diagnosis/manifestation	Symptoms (during the previous year) required to fulfil diagnosis
1. Atopic dermatitis	Dry skin and itchy rash with typical distribution (face/outer limbs/folds of elbows or behind knees/wrists or fronts of ankles) for ≥ 2 weeks; <i>or</i> doctor's diagnosis of eczema.
2. Wheezing ever	Any wheezing or disturbing cough at night for > 3 weeks not associated with a common cold.
3. Asthma	≥ 3 episodes of wheezing after 3 months of age; and inhalant glucocorticoids or signs of hyperreactivity ^a not associated with a common cold.
4. Lower-respiratory symptoms from furred animals/pollens	Wheezing or coughing after contact with cat, dog, horse, rodents, tree pollens (May) or grass pollens (June–August). Definite association according to parents.
5. Symptoms indicating allergic rhino-conjunctivitis (ARC)	As 6. But definite or suspected association according to parents; or doctor's diagnosis of hay fever or allergic rhinitis.
6. Symptoms indicating ARC from furred animals/pollens	Sneezing or running nose or blocked nose or red and itchy eyes after contact with cat or dog or horse or rodents or tree pollens (May) or grass pollens (June–August). Definite association according to parents.
7. Adverse reactions to food	Any of the following caused by foods/beverages: eczema, urticaria, oedema of lips or eyes, pruritus around the eyes or running nose, asthma; <i>or</i> doctor's diagnosis of food allergy.
8. Urticaria; history of	Elevated, itchy hives resembling mosquito bites or "blisters" ^b , coming and going, usually disappearing in 1 or 2 days.

^aWheezing when crying or laughing/Wheezing when playing or during outdoor activities/Coughing when laughing, playing or during outdoor activities/disturbing cough at night.

^bWheals are often described with the word "blister" by the Swedish layman.