

Increased incidence of autoimmune disorders as a late complication in children with early onset dermatitis and/or milk allergy

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Abstract

Subjects with atopic dermatitis and autoimmune disorders share some similar immune response disorders. The aim of this study was to see whether subjects with early onset atopic dermatitis run a risk of eventually developing autoimmune diseases. The results of a questionnaire of 145 adolescents (70 f, 75 m, mean age 18.2 years, range 16–23 years) was compared with those of a group of 262 controls (112 f, 150 m, mean age 17.5 years, range 16–21 years), 164 of whom reported no atopic symptoms and were treated as a separate group for statistical analysis. As compared with the non-atopic controls, the study group subjects showed a significantly increased incidence of autoimmune disorders (9% vs. 1%), the relative risk ratio of a subject with infantile onset atopic eczema getting a gastrointestinal (GI) immune-mediated disease being 2.4 (CI₉₅ 2.1–2.8) and of getting some other autoimmune disorder 3.1 (CI₉₅ 2.8–9.7). The positive skin prick tests showed a negative association with the manifestation of a GI or other autoimmune disorder. The subjects with infantile dermatitis also reported recurrent abdominal pains (23% vs. 15%), and milk-induced gastrointestinal symptoms (19% vs. 10%) significantly more even as young adults than the controls.

Our study showed that infantile atopy increases a predisposition to autoimmune disorders, suggesting that these two entities might have a common immunological determinant. While a high incidence of chronic GI complaints among the study subjects suggests the ongoing activity of local immune responses. However, more detailed prospective studies are needed to confirm these observations.

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1. Introduction

Atopic dermatitis is a chronic inflammatory skin disease appearing early in life and with a tendency to diminish in activity towards adulthood [1]. A central pathological event in the development of an atopic disposition is an imbalance and skewing of T lymphocytes in the lymphoproliferative system, predominated by certain cytokine cascades [2,3]. Autoimmune diseases and chronic gastrointestinal (GI) inflammations such as Crohn's disease and ulcerous colitis share many of the features of the immune response with atopic disorders [4,5].

Up to half of subjects manifesting atopic dermatitis during the first year of life have some food allergy, as diagnosed by double blind challenge test [6]. There is now increasing evidence showing that subjects with untreated food allergy have the same type of skewing of the immune response as those with celiac disease (CD), a state increasing the risk of autoimmune disorders [7–9]. Moreover, we recently found that food allergy in infancy does not remit as was previously believed, the immune reactivity on the mucosa of the gastrointestinal tract apparently remaining [10,11]. Following these observations we hypothesized that the subjects with infantile onset atopic dermatitis, like subjects with CD, might be at risk of eventually manifesting autoimmune and/or immune-mediated GI disorders more than expected. The persistent and exaggerated immune response on the GI mucosa and related lymphoproliferative

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system might be the central pathogenetic mechanism for this co-occurrence.

To examine this 'gut hypothesis' in more detail we surveyed an historical cohort of subjects with infantile onset atopic dermatitis who had been examined thoroughly for food allergy in childhood. The findings are also compared with age-matched controls.

2. Patients and methods

2.1. Patient population

We enrolled an historical cohort consisting of 241 children with atopic dermatitis studied thoroughly in 1978–1980 for food allergy at Oulu University Hospital by skin prick test and oral provocation and mailed a questionnaire including detailed questions about their present chronic diseases, atopic manifestations and gastrointestinal symptoms to the 198 whose addresses were still on the Oulu University Hospital population registry. Appropriate responses came from 145 (78%) adolescents and young adults (70 females and 75 males, mean age 18.2 years, range 16–23 years).

Dermatitis among these subjects had started at 0.77 years of age on average; in 103 subjects under one year of age. It affected at least 50% of the body surface in 101 subjects at the time of the first assessment. Fifty-nine (41%) had been admitted for topical treatment, while the other 86 (59%) had been assessed and treated as outpatients.

All patients had been examined by skin prick test (SPT) with food allergens, including at least milk, the four cereals separately, egg and fish. In cases where clinical food allergy was suspected, an open challenge was performed, even though SPTs were negative. On these two criteria, 96 subjects could be considered to have food allergy, comprising 48 (50%) whose SPTs were positive and another 48 (50%) whose SPTs were negative but whose open challenges were positive. In all, 37 (26%) subjects were designated as having had milk allergy, 39 (22%) egg allergy and 51 (29%) other food allergies (Table 1).

The control group consisted of 262 students (112 females and 150 males, mean age 18.2 years, range 16–23 years), half from a local high school and half from a vocational school. They completed the same questionnaire during their health education session at school. Only eight returned it inappropriately completed and were excluded. Ninety-eight subjects (61 males and 37 females) reported having or having had some atopic manifestations (dermatitis 21, rhinitis 57 and asthma 19) and were designated as atopic controls, while the remaining 164 (75 females and 89 males) were designated as non-atopic controls.

Table 1

Present atopic manifestations and the evidence for food allergy among subjects with infantile onset eczema and among the controls, those with no atopic manifestations being treated as a separate group

	Subjects with infantile onset dermatitis (N=145)	Non-atopic controls (N=164)	Atopic controls (N=98)
Sex			
Females	70	89	37
Males	75	75	61
Active eczema	112	–	21
Allergic rhinitis	84	–	57
Asthma	62		20
Food allergy in infancy	96		
Skin prick tests+	48		
Open challenge+	48		

2.2. Questionnaire

All subjects filled in a self-administered questionnaire for registration of sociodemographic data, past medical history and symptoms of atopic dermatitis, allergic rhinitis and asthma. The questionnaire also included information about food hypersensitivity and tolerance of dairy products. The occurrence of previously diagnosed gastrointestinal or other chronic diseases as well as the experience of recurrent abdominal pain and other gastrointestinal symptoms for the year preceding the examination were also recorded. The diagnosis of asthma, allergic rhinitis or other chronic disease were accepted only if based on a medical examination. We also checked the history notes of the subjects reporting any long-term disorders to verify a proper diagnosis.

2.3. Statistical methods

Data from the questionnaires and history sheets was combined with the findings of SPT in infancy and analysed with the SPSS pack. A 95% confidence interval was always used, when appropriate, to estimate the standard error, and the Student's *t*-test and χ^2 -test were used to decide the significance of the difference between the groups.

3. Results

3.1. Chronic diseases

Thirteen study group subjects (9%) had chronic diseases other than allergy. Five (6%) had immune-mediated gastrointestinal diseases (Crohn's disease in

Table 2

The reported incidence of gastrointestinal symptoms among young adults with infantile onset eczema and among atopic and non-atopic controls. Percentages in parentheses

	Study group (N=145)	Non-atopic controls (N=164)	Atopic controls (N=98)
Abdominal pains	34 (23) ^b	25 (15)	27 (28)
Heartburn/regurgitation	43 (30)	54 (33)	36 (36)
Constipation	19 (12) ^c	7 (4)	6 (6)
Diarrhoea	10 (7)	3 (2)	5 (5)
GI symptoms after using dairy products	28 (19) ^a	16 (10)	14 (14)

Statistical significances between the study group and non-atopic controls.

^a $\chi^2=5.0$ $P=0.03$.

^b $\chi^2=5.3$ $P=0.02$.

^c $\chi^2=9.3$ $P=0.002$.

three, colitis ulcerosa in one and coeliac disease in one) and eight other autoimmune disorders (diabetes in three, rheumatoid arthritis in three and hypothyreosis and psoriasis in one each). As among the controls some chronic disorder had been diagnosed in four subjects the difference between the groups was highly significant ($\chi^2=8.8$, $P=0.003$). Of the controls, two had diabetes and another two rheumatic disease, two having also had atopic manifestations. The relative risk ratio of a subject with infantile onset eczema getting a gastrointestinal disease was 2.4 (CI₉₅ 2.1–2.7) and of getting some other autoimmune disorder 3.1 (CI₉₅ 2.8–9.7).

Neither food allergy nor severe dermatitis diagnosed in infancy or a later manifestation of asthma or rhinitis increased the risk of having some other concomitant chronic disease. However, none of the five subjects with GI diseases and two of eight with other autoimmune diseases had had positive skin prick tests, whereas half of the rest had been positive with at least one allergen ($\chi^2=5.5$, $P=0.02$, relative risk ratio 0.2, CI₉₅ 0.1–0.9).

3.2. Gastrointestinal symptoms and milk tolerance

Subjects with infantile onset dermatitis reported abdominal pains and constipation significantly more often than the non-atopic controls but only as often as the atopic controls (Table 2).

Altogether 28 (19%, CI₉₅ 16–24%) subjects with infantile dermatitis reported symptoms after using dairy products. Fourteen (50%) of them had been positive in the skin prick tests and could be considered as atopic. Among the non-atopic controls the figure was 10% (CI₉₅ 9–11%) and among the atopic controls 14% (CI₉₅ 12–16%), the difference between the study group and non-atopic controls being statistically significant ($\chi^2=5.8$, $P<0.016$). A third (32%) of the subjects with milk allergy in infancy still reported symptoms from

milk or milk products. However, only 6 out of 11 had had positive SPT. Up to 22 (15%) of the study group subjects, 12 originally SPT-positive, experienced GI symptoms even from a trace of a milk product.

4. Discussion

This historical cohort provided evidence that the prevalence of autoimmune and/or immune-mediated GI disorders among young adults with infantile onset dermatitis is greater than expected. Considering that the non-responders had no such disorders and extrapolating the prevalence to the whole material of 198 enrolled subjects, the figure is still 7%. In the subgroup analysis, the increment was not related to the co-occurrence of food allergy, the severity of dermatitis in infancy or subsequent manifestations of other atopic disorders such as asthma or allergic rhinitis. Moreover, as all but two of the 13 subjects developing an autoimmune state later had been negative in the SPT in infancy, it seems reasonable to conclude that it is the non-atopic hypersensitivity which predisposes for outcome of chronic immune-mediated disorders.

The other main finding of this study was that the subjects reported gastrointestinal complaints significantly more than the controls. These symptoms were often related to the consumption of certain foodstuffs, especially milk and dairy products. However, the construction of this study prevents us from definitively demonstrating whether these two main findings are in a causal relationship or are coincidental. Evidenced best in type 1 diabetes there is now a view that in autoimmune states the small intestine shows enhanced immune activation [12]. The present finding together with our earlier observations on the persistence of the enhanced immune reactivity on the mucosa of the GI tract after food allergies in infancy supports the view that the skewing of the immune response occurring in the gut mucosa and related lymphoproliferative tissue forms the basic milieu to risk for the development of autoimmune and chronic immune-mediated GI disorders.

Food allergy, definitely diagnosed in half of our patients in infancy, may be atopic or non-atopic [1,2]. The first abates, while the latter does not, at least not in all patients, the reactivity persisting on the mucosa of the GI tract giving only GI symptoms and mainly no skin or other symptoms [10,11]. We speculate that in the present material the increase in GI symptoms may be partly due to this reactivity, though we did not test these subjects. In a state of occult milk hypersensitivity the numbers of γ/δ positive intraepithelial and IFN- γ producing T-cells are increased on the gut mucosa like in CD patients [7,8,13,14]. Indeed, Ventura et al. found a total prevalence of autoimmune disorders of 14% among

subjects with untreated CD at the age of 16 years on average [9].

The finding that atopic dermatitis since early childhood increases the risk of autoimmune disorders as young adults seems to be in conflict with the recent findings in diabetes, multiple sclerosis and rheumatoid arthritis research, which has identified a lower incidence of atopic manifestations in cases with autoimmune disorders than in controls [15–17]. This may, however, be illusory since in our study the increment of autoimmune states was mostly due to the subjects with non-atopic dermatitis. The set-up of our study was highly different from the other studies. We identified infants and small children with dermatitis, examined their possible food allergy and SPT and followed them 15–20 years to see whether they manifest a disease. In the other studies, like in EURODIAB study, the subjects with a disease were retrospectively asked whether they have or have had atopic manifestations. This study lay-out may give a biased concept as mild and unsure cases such as infectious asthma are counted as atopic. Moreover even in our series they were mainly subjects with non-atopic allergy and having a disease early in infancy e.g. during the maturation period of immune response who developed later an autoimmune or chronic immune-mediated disorders [18].

In conclusion, this study showed that non-atopic infantile dermatitis increased the risk of the manifestation of autoimmune states later in life. However, the questionnaire-based results are suggestive and more prospective follow-up studies are needed in determining who is prone to auto-immunity and who is not.

Acknowledgements

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