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Allergy and autoimmune disease: a registry-based study

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Summary

Background Allergy and autoimmunity are two potential outcomes of a dysregulated immune system, but the relationship between them is unclear. It has been hypothesized that they could be inversely associated because of different T helper cell reactivity patterns. However, both positive and negative associations have been reported. Therefore, our aim was to perform a large epidemiological study with a defined allergic disease cohort.

Methods During the years 1990–2002, 68 770 subjects were tested for total serum IgE (Total-IgE) and 72 228 were tested with Phadiatop for diagnosing allergic disease at Karolinska University Hospital, Stockholm, Sweden. This cohort was then linked with the Swedish Inpatient Registry 1968–2004 for a follow-up with regard to recorded discharges for 28 autoimmune diseases. We then used Cox regression and logistic regression to estimate the risk of autoimmune diseases in general in the allergy-tested subjects.

Results Subjects with positive Phadiatop test were at a statistically decreased risk of subsequent autoimmune disease in comparison with subjects with negative test; hazard ratio (HR): 0.80 [95% (Confidence interval) CI: 0.68–0.94]. Prior autoimmune disease was associated with a decreased risk of positive Phadiatop test [odds ratio: 0.83 (95% CI: 0.72–0.96)] in comparison with negative test. Subjects with highly elevated Total-IgE were at a statistically increased risk of a subsequent autoimmune disease in comparison with subjects with normal levels [HR: 1.36 (95% CI: 1.09–1.70)], but no association was found between prior autoimmune disease and different Total-IgE levels.

Conclusion The study supports the hypothesis that allergy, defined as positive Phadiatop test, could be inversely related to autoimmune disease but this association is weak.

Keywords allergy, autoimmune, epidemiology, IgE, Phadiatop

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Introduction

The functional classification of T helper cell clones into distinct subtypes, designated type 1 T helper (Th1) and Th2, based on their pattern of cytokine production, has greatly enhanced the understanding of immune responses [1]. Accordingly, the balance between Th1 and Th2 cytokines appears to be important in the expression of allergic and autoimmune diseases. A Th1 phenotype response is associated with autoimmune disease and a Th2 response with allergic disease [1].

Previous research has suggested an inverse relationship between Th1-related disorders and Th2-related disorders. To date, a number of studies have reported a protective

effect of atopy/allergy status against the development of autoimmune disorders [2–11], but other studies have found allergy to be a risk factor for autoimmune disease [12–14] and some have found no such correlation [15–18]. In these studies, the definition of allergy status has varied considerably, most often based on questionnaires about atopic symptoms [2–5, 8–10, 14–16] or interviews in medical records [6, 11, 13, 17]. Very few of them have included any form of allergy testing: total serum IgE (Total-IgE) [7, 15, 17] and skin prick testing [14, 15]. The studied autoimmune diseases have also varied a lot, from analysis of a single autoimmune disease (diabetes mellitus type 1 [3, 5, 7, 9, 15, 16], rheumatoid arthritis [2, 4, 8], systemic lupus erythematosus (SLE)

[17, 18], multiple sclerosis [6], thyroid autoimmunity [12]) to groups of 3–17 different autoimmune diseases taken together [10, 11, 13, 14]. Why allergy should have a protective effect against autoimmune disease is unclear. Some argue that environmental influences have acted to increase allergic diseases by promoting a shift from Th1 to Th2 immune responses, and consequently, a decrease in number of autoimmune diseases. It has also been suggested that a possible autoimmune protective effect of allergy rather may be a consequence of the therapeutic approach to the allergy, i.e. inhaled or systemic corticosteroids [11]. Furthermore, the Th1/Th2 paradigm has been proposed as an explanation for the hygiene hypothesis; that is, the risk of allergic diseases is reduced by infections in early childhood [13].

The fact that the available data is very difficult to interpret has led us to perform a large epidemiological study with a defined allergic disease cohort followed up for a large number of autoimmune diseases. The main objective of this study was to assess the association between allergy and autoimmune disorders in general. The second objective was to study if any of the 28 included autoimmune or probable autoimmune diseases revealed a different pattern in comparison with the autoimmune disorders as a group.

Methods

This study was approved by the Ethics Committee at the Karolinska Institute, Stockholm, Sweden. None of the participants was contacted. Patient information was anonymized before the analysis.

Study population

During the years 1990–2002, 68 770 subjects with valid personal registration numbers were tested for Total-IgE for diagnosing allergic disease at the Department of Clinical Immunology, Karolinska University Hospital, Stockholm, Sweden. Of these, 27 663 (40.2%) were men and 41 107 (59.8%) were women. The number of subjects in different age groups was as follows: 0–19 years: 17 846 (26.0%), 20–39 years: 25 641 (37.3%), 40–59 years: 19 091 (27.7%) and ≥ 60 years: 6192 (9.0%). The mean age was 33.3 years (range 1–89) and the total follow-up time was 478 453 person years.

A total of 72 228 Phadiatop-tested subjects with valid personal registration numbers were included in the study. Of these, 29 970 (41.5%) were men and 42 258 (58.5%) were women. The number of subjects in different age groups was as follows: 0–19 years: 21 450 (29.7%), 20–39 years: 25 631 (35.5%), 40–59 years: 18 763 (26.0%) and ≥ 60 years: 6384 (8.8%). The mean age was 32.5 years (range 0–92) and the total follow-up time was 511 509 person years.

Table 1. Total serum IgE: definitions

Age of patients	IgE range (kU/L)		
	Normal	Slightly elevated	Highly elevated
> 20 years	< 122	122–500	> 500
6–20 years	< 263	263–500	> 500
10 months–5 years	< 22.3	22.3–200	> 200
3–9 months	< 16.3	16.3–100	> 100
6–12 weeks	< 4.9	6–100	> 100
< 6 weeks	< 1.3	1.3–100	> 100

Immunoglobulin E testing

Total-IgE concentrations were determined by using Pharmacia CAP System (Pharmacia Diagnostics AB, Uppsala, Sweden). Concentrations were expressed as kU/L, and levels are characterized and defined in Table 1. A total of 51 235 (74.5%) of the subjects had normal, 12 582 (18.3%) had slightly elevated and 4953 (7.2%) had highly elevated levels of Total-IgE. About 89.6% of the subjects were tested only once. The level of Total-IgE for the first test was used in the analysis when multiple testing was performed.

Phadiatop[®] (a mixture of 11 airborne allergens) was determined by using Pharmacia CAP System[™] (Pharmacia Diagnostics AB, Uppsala, Sweden). A value of 0.35 kU/L or more was considered positive. A total of 47 865 (66.3%) of the subjects had negative and 24 363 (33.3%) had positive Phadiatop test.

A total of 107 570 subjects were tested. A total of 33 428 (31.1%) were tested with both Total-IgE and Phadiatop test, 35 342 (32.7%) were tested only for Total-IgE and 38 800 (36.1%) were tested only with Phadiatop.

The Swedish inpatient registry

We used the national in-patient registry (IPR) to identify all allergy-tested subjects with a hospital discharge diagnosis of any autoimmune disease between 1968 and 2004. The autoimmune diseases were defined according to the appropriate International Classification of Disease (ICD) codes (Table 2). Since 1964, the Swedish National Board of Health and Welfare has compiled data on individual hospital discharges in the IPR. For each discharge, date of admission, date of discharge, main and up to five contributory discharge diagnoses (coded according to ICD-7: 1964–1968, ICD-8: 1968–1986 and ICD-9: 1987–1996 and ICD-10 thereafter), surgical procedures, department and hospital are recorded together with the individual's national registration number. This register was not nationwide until 1987. In 1969, the register covered 60% of the Swedish population, in 1978, 75%, and by the end of 1983, 85%. Validation of the register by analysing medical records both in 1986 and 1990 confirmed a correct ICD code at the four-digit level in 86% of the

Table 2. List of autoimmune diseases included in the study and employed International Classification of Disease codes

Autoimmune disease	ICD-8	ICD-9	ICD-10
Addison's disease	255,10	255E	E271
Antiphospholipid syndrome			D668B
Autoimmune hepatitis			K754
Autoimmune haemolytic anaemia		283A	D591
Celiac disease	269,00	579A	K900
Diabetes mellitus type 1	250	250	E10–E14
Grave's disease	242	242	E05
Hashimoto's disease		245C	E063
SLE	734,10	710A	M32
Myasthenia gravis	733	358	G700
Pemphigus	694	694E	L100
Pemphigoid	694	694F	L12
Pernicious anaemia	281,00/281,09	281A	D510
Rheumatoid arthritis	712,00/712,10/712,20/712,38/712,39/712,50	714	M05
Systemic scleroderma	734,00	710B	M34
Wegeners granulomatosis	446,20	446E	M313
<i>Probable autoimmune</i>			
Bechterew's disease	712,40	720A/720X/721G/721W	M459
Crohn's disease	563,00	555	K50
Dermatomyositis	716,00	710D	M330/M331/M339
Polymyositis	716,10	710E	M332
Guillain barré		357	G610
Multiple sclerosis	340	340	G35
Temporal arteritis	446,30	446F	M315
Polymyalgia reumatica	446,38	725	M353
Primary biliary cirrhosis		571G	K743
Psoriasis	696,00/696,10/696,19	696A/696B	L40
Ulcerative colitis	563,10	556	K51

principal discharge diagnosis [19]. As an example, for ulcerative colitis and Crohn's disease, a correct diagnosis was assigned to 84–89% [20].

In the analysis of all autoimmune diseases or possible autoimmune diseases taken together as a group, diabetes mellitus type 1 was included only from 1997 (ICD-10). The reason for this is that before this date, the code (ICD-8, ICD-9) for diabetes mellitus included both type 1 (autoimmune) and type 2 and could not be distinguished. However, in the specific analysis for the single disease, all years were included.

The individually unique 10-digit national registration number ascribed to every Swedish citizen, since 1 January 1947, ensures accurate identification and follow-up of each patient.

Analysis and statistics

Cox's regression was applied to investigate the association between the result of the allergy test (Phadiatop positive/negative, Total-IgE normal/slightly elevated/highly elevated) and the risk of being admitted with an autoimmune disease, as main or contributory diagnosis. The Cox model was conditioned on sex, calendar year and age in 5-year

bands. Risk estimates are given as hazard ratios (HRs). Follow-up started at the time of the allergy test for all persons without a prior diagnosis of an autoimmune disease, and ended on the date of first discharge diagnosis of an autoimmune disease, date of emigration, death or the end of the study period (31 December 2004), whichever occurred first.

The association between the prevalence of having a diagnosis of an autoimmune disease before the allergy test and the result of the test was analysed by logistic regression, conditioned on sex, calendar year and age in 5-year bands. Measure of associations is given as odds ratios (ORs).

The 95% confidence intervals (CIs) for HRs and ORs not including 1.00 were considered statistically significant. All analyses were performed using procedures PHREG and LOGISTIC in the Statistical Analysis System (SAS[®]) package.

Results

Result of allergy test and risk of subsequent autoimmune disease

Table 3 provides summary information. Subjects with positive Phadiatop tests were at a statistically decreased

Table 3. Risk of subsequent autoimmune disease* in allergy-tested subjects according to positive or negative Phadiatop or level of total serum immunoglobulin E

	No. of subjects (%)	No. of events [†] after test	HR [‡]	95% confidence interval
<i>Phadiatop</i>				
Negative	46 376 (66)	709	1.0	
Positive	23 895 (34)	211	0.80	0.68–0.94
Total	70 271			
<i>IgE</i>				
Normal	49 414 (75)	879	1.0	
Slightly elevated	12 202 (18)	210	1.08	0.93–1.26
Highly elevated	4807 (7)	89	1.36	1.09–1.70
Total	66 423			

*For definition, see Table 2.

[†]Number of patients with a discharge diagnosis of autoimmune disease recorded in the Swedish Inpatient Registry.

[‡]HR, hazard ratio. Estimates derived from Cox regression internally stratified for sex, age and year of study entry.

risk of subsequent autoimmune disease in comparison with subjects with negative tests [HR: 0.80 (95% CI: 0.68–0.94)]. Subjects with highly elevated Total-IgE were at a statistically increased risk of a subsequent autoimmune disease in comparison with subjects with normal levels [HR: 1.36 (95% CI: 1.09–1.70)]. In patients where both the IgE and Phadiatop tests were performed, the associations found were further strengthened. Positive Phadiatop/normal IgE – HR: 0.65 (95% CI: 0.48–0.87), and highly elevated IgE/negative Phadiatop – HR: 1.94 (95% CI: 1.01–3.73).

Result of allergy test and prior history of autoimmune disease

Prior autoimmune disease was associated with a decreased risk of positive Phadiatop test [OR: 0.83 (95% CI: 0.72–0.96)]. No association was found for different Total-IgE levels.

Individual analyses of included autoimmune diseases

Each of the 28 included autoimmune diseases was also analysed separately by logistic regression (prior history of disease before test in relation to test result, risk estimates given as ORs) and Cox regression (risk of subsequent disease, risk estimates given as HRs) when the number of events was sufficient.

Prior coeliac disease was associated with a decreased risk of positive Phadiatop test [OR: 0.50 (95% CI: 0.25–0.98)].

Subjects with highly elevated Total-IgE were at a statistically increased risk of a subsequent Graves disease [HR: 2.38 (95% CI: 1.29–4.02)] and psoriasis [HR: 2.40

(95% CI: 1.07–5.38)] in comparison with subjects with normal levels.

For the rest of the tested diseases, no statistically significant decrease or increase in risks was found. For the Phadiatop positive test vs. Phadiatop negative test, these results can be summarized as follows: rheumatoid arthritis – OR: 0.74 (95% CI: 0.48–1.14), HR: 0.74 (95% CI: 0.38–1.45). Diabetes mellitus type 1 and 2 – OR: 0.89 (95% CI: 0.72–1.10), HR: 0.90 (95% CI: 0.73–1.10). SLE – OR: 0.64 (95% CI: 0.28–1.48), HR: 1.32 (95% CI: 0.51–3.40); Crohn's disease – OR: 0.94 (95% CI: 0.65–1.39), HR: 0.84 (95% CI: 0.54–1.32) and ulcerative colitis – OR: 0.81 (95% CI: 0.58–1.13), HR: 0.62 (95% CI: 0.37–1.04).

Discussion

Our findings indicate that allergy, defined as positive Phadiatop test (a mixture of 11 airborne allergens), may be protective against the development of autoimmune diseases as a group and are consistent with the immunologic concept of Th1 (autoimmune) and Th2 (atopy) diseases being mutually exclusive. The results has implications for the 'hygiene hypothesis' which has been cited as an example of immunomodulation by environmental factors [21], and according to this hypothesis, the clean westernized lifestyle may have led to the increased prevalence of allergic disorders over the past decades. Children are exposed to fewer pathogenic and non-pathogenic microbes, which may result in an unnatural imbalance between enhanced Th2 response and suppressed Th1 response. Our finding of an inverse relationship between Th1- and Th2-mediated disorders provides support for the hygiene hypothesis. However, the increase in allergic diseases seen in the past few decades should according to the hygiene hypothesis have been accompanied by a decrease in the prevalence of autoimmune diseases, but the converse is true; autoimmune diseases have increased in parallel with allergy [22]. Thus, some authors argue that the Th1/Th2 paradigm might be an oversimplification [13].

In this study, which is to our knowledge the most comprehensive study so far of allergic subjects, we have been able to get a more precise quantification of the risk of autoimmune disease in general, but also in separate analyses of several autoimmune diseases. Furthermore, in contrast to previous studies, the present study was based on consecutive patients tested for Total-IgE and Phadiatop in order to diagnose allergic disease, and different levels of Total-IgE (normal/slightly elevated/highly elevated) enabled us to perform a detailed analysis.

At present, no single laboratory test can define a patient being an allergic individual. Rather, the diagnosis usually is based on accumulated evidence of the patient's history and *in vivo* and *in vitro* diagnostic procedures. Many studies have shown that Total-IgE concentrations tend to

be higher in allergic compared with non-allergic individuals, but the diagnostic value of Total-IgE, as a single test, is considered to be limited. There are difficulties in defining normal limits [23], because Total-IgE levels vary widely. A number of non-allergic factors affect Total-IgE, i.e. infection, parasites, renal and liver disease and IgE myeloma. In contrast to the limited specificity of Total-IgE in diagnosing allergic disease, the detection and titration of allergen-specific IgE determined by the Phadiatop test is of great clinical importance. In a study comparing the results of Phadiatop testing with the clinical diagnosis of atopy in patients with rhino conjunctivitis and asthma, a specificity of 0.91–0.94 and a sensitivity of 0.89–0.96 were found for the test [24]. Therefore, we consider the cohort of Phadiatop-positive subjects to be a true allergic group of patients in contrast to the cohort of subjects with elevated levels of Total-IgE. As the Phadiatop test only gives a 'yes' or 'no' answer for the presence or absence of atopy and cannot be stratified, the use of a quantitative test such as allergen-specific immunocaps may have given more useful data.

The present study was not community based, but was based on consecutive patients allergy tested in a hospital laboratory. This may cause some selective effects. The cohorts probably comprised relatively more subjects with strong than weak allergy reactions, as compared with the general population in the catchment area. This is, however, not a problem, as it adds to the precision of the study without compromising its validity. It must also be pointed out that using in-patient hospital records of autoimmune disease will select more severe cases. Thus, the found associations do not refer to autoimmune disease in general, but to a particular group of severe cases.

In order to test the hypothesis of an inverse relationship between allergy and autoimmune disorders, we included a number of autoimmune diseases and possibly autoimmune diseases. The definition of an autoimmune disease seems to be simple: the patients have unusual antibodies circulating in their blood that target their own body tissues. The list of diseases that are thought to be of autoimmune origin is constantly increasing and we therefore tried to include both recognized autoimmune diseases with known autoantibody targets as well as probable autoimmune diseases with not yet discovered autoantibodies (Table 2). However, the presence of a laboratory abnormality is not enough evidence of a disease. Furthermore, we analysed the recognized autoimmune diseases, the probable autoimmune diseases and each individually included disease separately. Therefore, we consider the outcome of the study to be reliable with regard to autoimmune diseases as a group.

The analysis of the subjects tested for Total-IgE is not as valid as the Phadiatop analysis, but revealed some findings that might be of importance. Subjects with highly elevated Total-IgE were at an increased risk of subsequent

autoimmune disease in comparison with subjects with normal levels. This increased risk for autoimmune disease in general was mainly made up of two diseases, Graves' disease and psoriasis. In Graves' disease, elevated circulating IgE levels have been reported in comparison with controls, in line with our finding [25]. Psoriasis vulgaris is a Th1-mediated disorder and IgE levels should not be elevated. However, elevation of serum IgE has been reported in psoriatic erythroderma in comparison with psoriasis vulgaris [26]. Because psoriatic erythroderma is a severe form of psoriasis, patients affected by this variant of psoriasis are more likely to be admitted to hospital care, and this might explain the association of increased levels of Total-IgE and psoriasis found in this study. The finding that prior coeliac disease was associated with a decreased risk of positive Phadiatop test is a bit more puzzling. Coeliac disease has been associated with allergy [27] but no such association has also been reported [28]. Also, the effect of multiple statistical testing in our study might theoretically produce significant results by chance. Other important confounders are the immunosuppressive drugs patient with autoimmune diseases frequently are treated with. Also, we have no information on the socio-economic status of the patients or life style factors such as smoking, variables that are associated to many health outcomes.

In conclusion, this cohort study found a statistically significant decreased risk of subsequent autoimmune disease in a cohort of well-defined allergic subjects.

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