



Subsequent Autoimmune or Related Disease in Asthma Patients: Clustering of Diseases or Medical Care?

KARI HEMMINKI, MD, PhD, XINJUN LI, MD, PhD, JAN SUNDQUIST, MD, PhD, AND KRISTINA SUNDQUIST, MD, PhD

PURPOSE: Asthma includes immunological components that may share mechanisms with autoimmune diseases. We analyzed the subsequent occurrence of any of 22 autoimmune and related conditions in hospitalized asthma patients.

METHODS: A nationwide study was conducted in Sweden on subsequent diseases of asthma patients on the basis of the Hospital Discharge Register. Standardized incidence ratios (SIRs) were calculated for subsequent autoimmune diseases.

RESULTS: A total of 4006 patients were hospitalized for an autoimmune condition after last hospitalization for asthma. The SIRs were increased for 11 subsequent autoimmune conditions, diagnosed at least 5 years after asthma. The highest SIRs were noted for polyarteritis nodosa (4.29) and Addison disease (3.62). SIRs for these diseases and others, including the most common autoimmune disease rheumatoid arthritis, were increased even when the follow-up was started 5 years after the last asthma hospitalization. Addison disease and Crohn disease were increased in asthma patients hospitalized at various ages, whereas young asthma patients presented with celiac disease and immune thrombocytopenic purpura.

CONCLUSIONS: Hospitalized asthma patients presented with a number of subsequent autoimmune and related diseases. Although we were unable to exclude the effects of environmental factors, the data suggest that shared genetic factors or gene-environment interactions may explain coexistence of some of these diseases. *Ann Epidemiol* 2010;■:■. © 2010 Elsevier Inc. All rights reserved.

KEY WORDS: Disease Aggregation, Immunological Diseases, Individual Risks, National Database.

INTRODUCTION

The purpose of the present study was to investigate the association between asthma, a relatively common, mainly an atopic disorder, and subsequent autoimmune or related diseases. T-helper (Th) 1 and Th2 lymphocytes and the distinct cytokines produced by them constitute an important component of cell-mediated adaptive immunity (1–3). An excessive proinflammatory response by Th1 lymphocytes has been considered a common basis of autoimmune diseases, whereas Th2 lymphocytes mediate the IgE response characteristics of atopic conditions, such as

asthma. As a possible mechanism, it has been suggested that the predominant Th2 profile in atopic conditions may be a result of the increased tendency to activation and apoptosis of high interferon-gamma-producing Th1 cells (4).

The Th2-mediated pathway is also thought to operate in nonallergic adult-onset asthma (1–3). It has been hypothesized that establishment of one Th phenotype, autoimmune or atopic one, would be protective of the other. Numerous studies (5–8) have tested the hypothesis with conflicting results). Many large and relatively recent studies (6–8) suggest that autoimmune and atopic diseases are risk factors of each other. Some support to the partially shared etiology between the two types of diseases is provided by genetic studies on asthma susceptibility genes, such as NOD1 and NOD2 and components of the interleukin and HLA systems, which have also been implicated in autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes, and inflammatory bowel disease (9–11).

Few population-level studies have analyzed the occurrence of autoimmune diseases after diagnosis of asthma (12), the subject of the present study. We wanted to examine the specific aim about co-occurrence of asthma with 22 autoimmune and related conditions in individual patients. To address this aim, we harnessed the Swedish

From the Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany (K.H.); Center for Family and Community Medicine, Karolinska Institute, Huddinge, Sweden (K.H., K.S.); Center for Primary Health Care Research, Lund University, Malmö, Sweden (X.L., J.S., K.H., K.S.); and Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA (J.S.).

Address correspondence to: K. Hemminki, DKFZ, Im Neuenheimer Feld 580, D-69120 Heidelberg, Germany. Tel: 49-6221-421800. Fax 49-6221-421810. E-mail: k.hemminki@dkfz.de.

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Selected Abbreviations and Acronyms

Th = T-helper
ICD = International Classification of Diseases
SIR = standardized incidence ratio
95% CI = 95% confidence interval

nationwide data resources on medically diagnosed diseases. We wanted specifically to examine the reasons for the possible comorbidity, which could be genetic, environmental, sociomedical, or combination of these. By socio-medical reasons we imply a tendency for multiple hospitalizations for various reasons, such as a labile disease control, referred to as “brittle” diseases (13, 14). The study included 148,295 hospitalized asthma patients who were followed for the diagnosis of autoimmune diseases. The present study is unique in its scope and size.

MATERIAL AND METHODS

The research database used for this study, the autoimmune disease database, is a subset of the national MigMed database at Center for Primary Health Care Research Lund University. The MigMed database was compiled by the use of data from several national Swedish registers provided by Statistics

Sweden, including the Multigeneration Register, National Census Data (1960–1990), and the Swedish population register (1990–2007). The total population in the database is close to 12 million, and it has been used in many previous studies on, for example, autoimmune diseases (15, 16). Dates of hospitalization for asthma and autoimmune diseases were obtained during the study period from the Swedish Hospital Discharge Register for years 1964 to 2007. Patients registered for hospitalization stayed at least one night in the hospital, usually in wards with specialists; the Register does not include outpatients in hospitals or health-care centers.

Diagnoses were reported according to the different versions of the International Classification of Diseases (ICD), classified in 22 autoimmune and related diseases. Asthma was identified in ICD-7 (years 1964–1968 code 241), ICD-8 (1969–1986 code 493), ICD-9 (1987–1996 code 493), and ICD-10 (1997 code J45 and J46). The selection of the diseases into study was on the basis of ad-hoc considerations, such as previous suggested associations, without implications of the underlying pathogenic mechanisms; however, at least 25 cases had to be diagnosed after hospitalization for asthma. The diagnostic age of type 1 diabetes mellitus was limited to 20 years because type 1 and type 2 diabetes were first distinguished in ICD-10. All linkages were performed by use of the national 10-digit civic

TABLE 1. SIR for subsequent autoimmune disorders in patients with asthma

Autoimmune condition	Follow-up intervals, year											
	All				All 1+				All 5+			
	O	SIR	95% CI		O	SIR	95% CI		O	SIR	95% CI	
Addison disease	58	4.56	3.46	5.90	51	4.17	3.11	5.49	33	3.62	2.49	5.09
Amyotrophic lateral sclerosis	65	1.69	1.30	2.16	53	1.46	1.09	1.91	34	1.33	0.92	1.85
Ankylosing spondylitis	25	1.24	0.80	1.84	22	1.14	0.71	1.73	15	1.04	0.58	1.72
Celiac disease	128	1.97	1.64	2.34	83	1.50	1.19	1.86	23	1.44	0.91	2.16
Chronic rheumatic heart disease	165	2.56	2.19	2.99	114	1.91	1.58	2.30	43	1.17	0.85	1.58
Crohn disease	208	1.64	1.42	1.87	191	1.54	1.33	1.78	149	1.49	1.26	1.75
Diabetes mellitus type I	307	1.26	1.12	1.41	279	1.18	1.05	1.33	182	1.12	0.96	1.29
Graves, hyperthyroidism	294	1.69	1.50	1.90	242	1.46	1.28	1.66	156	1.30	1.10	1.52
Hashimoto/hypothyroidism	109	2.07	1.70	2.50	97	1.97	1.60	2.41	58	1.81	1.37	2.34
Immune thrombocytopenic purpura	60	1.51	1.15	1.94	51	1.37	1.02	1.80	29	1.32	0.88	1.89
Multiple sclerosis	60	1.12	0.85	1.44	56	1.08	0.82	1.41	38	0.96	0.68	1.31
Myasthenia gravis	32	2.18	1.49	3.07	30	2.13	1.44	3.05	19	1.84	1.11	2.88
Pernicious anemia	34	1.06	0.73	1.48	28	0.96	0.63	1.38	18	1.09	0.64	1.72
Polyarteritis nodosa	39	6.07	4.31	8.30	29	4.79	3.21	6.89	17	4.29	2.49	6.89
Polymyalgia rheumatica	335	2.13	1.91	2.37	297	2.00	1.78	2.24	186	1.84	1.59	2.13
Psoriasis	119	1.83	1.51	2.19	107	1.73	1.42	2.09	66	1.54	1.19	1.96
Rheumatoid arthritis	490	1.81	1.66	1.98	445	1.75	1.59	1.92	310	1.83	1.63	2.04
Sarcoidosis	75	1.89	1.49	2.38	61	1.61	1.23	2.07	38	1.34	0.95	1.84
Systemic lupus erythematosus	32	1.22	0.83	1.72	27	1.08	0.71	1.57	19	1.04	0.62	1.62
Systemic sclerosis	40	1.96	1.40	2.68	31	1.63	1.11	2.32	17	1.37	0.80	2.20
Ulcerative colitis	263	1.54	1.36	1.73	245	1.48	1.30	1.67	178	1.36	1.17	1.57
Wegener granulomatosis	68	1.68	1.30	2.13	57	1.55	1.17	2.01	32	1.48	1.01	2.10
All	3006	1.73	1.67	1.79	2596	1.58	1.52	1.64	1660	1.46	1.39	1.54

SIR = standardized incidence ratio; O = observed number of cases; CI = confidence interval.
Bold type indicates that 95% CI does not include 1.00.

identification number that is assigned to each person in Sweden for his or her lifetime. This number was replaced by a serial number for each person in order to provide anonymity.

Hospitalization rates of subsequent autoimmune diseases among asthma patients were compared with the hospitalization rates of these diseases in the whole population, that is, first hospitalization for autoimmune disease for those who had not been diagnosed with asthma in the national MigMed population. Standardized incidence ratios (SIRs) were used as measure of relative risk for which 95% confidence intervals (95% CIs) assuming a Poisson distribution. SIRs were calculated as the ratio of observed (i.e., autoimmune disease after asthma) to expected (i.e., autoimmune disease without previous asthma) number of cases. Person-years for subsequent autoimmune diseases were calculated from the last hospitalization for asthma after January 1, 1964, until hospitalization for an autoimmune disease (any of 22 diseases), death, emigration, or closing date, December 31, 2007. Patients whose autoimmune disease was diagnosed before the last hospitalization for asthma were excluded from the study. The expected number of cases was calculated for covariates age (5-year groups), sex, period (5-year groups), region (3 groups), and socioeconomic status (6 groups)-specific standard hospitalization rates for each of the 22 autoimmune diseases.

RESULTS

The total number of patients diagnosed with asthma was 148,295, divided in 78,996 men and 69,299 women. It should be noted the data only include autoimmune diseases first diagnosed after the last hospitalization for asthma, which included 3006 patents, that is, 2.0% of all asthma patients. The individual risks for the first hospitalizations for any of the 22 autoimmune and related diseases after the last hospitalization for asthma are shown in Table 1. We show the risk for the total follow-up time ("All") and for follow-up that started either 1 year or 5 years after the last hospitalization for asthma ("All 1+" and "All 5+," respectively). For "All," the SIR for all but four diseases were increased, with highest SIRs for polyarteritis nodosa (6.07) and Addison disease (4.56); the overall SIR was 1.73. For "All 1+" the overall SIR decreased to 1.58, but the two diseases still showed the highest SIRs, 4.79 and 4.17, respectively. For "All 5+," the overall SIR decreased further to 1.46, with polyarteritis nodosa (4.29) and Addison disease (3.62) showing the highest SIRs. Only one half (11) of the diseases were increased for "All 5+," but SIRs for some (Crohn disease, Hashimoto/hypothyroidism, myasthenia gravis, polymyalgia rheumatica and psoriasis) demonstrated a small decrease only compared with SIRs for "All"; notable, the SIR for rheumatoid arthritis was stable.

The risk of autoimmune and other diseases after 1 year of the last asthma hospitalization is shown in Table 2 according to the age at the last hospitalization for asthma. Some diseases were increased only in young asthma patients, that is, celiac disease, immune thrombocytopenic purpura, and type 1 diabetes; for type 1 diabetes the age restriction limited the cases to young age. Some of the autoimmune diseases were increased through all hospitalization ages, including Addison disease and Crohn disease, yet with the greatest SIRs in mid or old age. For most other diseases the increased risks were only found in asthma patients last hospitalized in mid or old age.

The risk of autoimmune and other diseases after asthma was analyzed according to the number of hospitalizations for asthma in mutually exclusive categories (data not shown). Overall the risk increased from 1.50 after one hospitalization (1499 patients) to 2.06 after more than five hospitalizations (291 patients). The increase in SIR was notable for Addison disease (from 2.51 to 10.83), but it was relatively systematic also for polymyalgia rheumatica (from 1.82 to 2.83) and psoriasis (from 1.56 to 2.62). The SIRs for polyarteritis nodosa and rheumatoid arthritis did not depend on the number of hospitalizations, and they were increased in all categories.

DISCUSSION

The use of hospital discharge data has great advantages, such as an access to nationwide data and reasonably high diagnostic accuracy because the discharge diagnosis is often delivered by specialists during extended examinations in the clinic. The diagnostic accuracy in the Swedish Hospital Discharge Register has been referred to as being 88% to 90% on main diagnoses (17). We have reviewed several ad-hoc studies on diagnostic accuracy and coverage elsewhere (15, 18). A further limitation is that hospitalization may involve selections, whereby persons once hospitalized may be more likely to be hospitalized again for reasons such as co-morbidity or diagnosis/observation bias. "Brittle" asthma, type 1 diabetes, and Addison disease have been described in the literature among patients whose disease is unstable or unpredictable, thereby leading to frequent hospitalizations (13, 14). Although the described "brittle" conditions have involved frequent hospitalizations for the particular diseases, it is conceivable that other symptoms and diseases were found during the hospital visits.

To reduce the likelihood of diagnosis/observation bias of simultaneous diagnoses of several conditions during a single hospital stay, we limited the present patients to those whose first autoimmune or related condition was diagnosed after the last hospitalization for asthma. This choice reduced

TABLE 2. SIR for subsequent autoimmune disorders in patients with asthma

Autoimmune condition	Age at diagnosis of asthma, years											
	<20			20–49			50–64			>64		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Addison disease	11	2.78	1.38	4.99	11	3.61	1.79	6.48	13	5.53	2.93	9.49
Amyotrophic lateral sclerosis	1	0.85	0.00	4.86	8	1.21	0.52	2.39	17	1.21	0.70	1.94
Ankylosing spondylitis	4	0.70	0.18	1.82	12	1.47	0.76	2.58	3	0.91	0.17	2.69
Celiac disease	65	1.42	1.09	1.80	6	1.79	0.64	3.92	6	1.98	0.71	4.34
Chronic rheumatic heart disease	2	0.92	0.09	3.37	18	1.95	1.15	3.08	44	1.94	1.41	2.61
Crohn disease	101	1.42	1.16	1.73	44	1.52	1.11	2.05	26	1.93	1.26	2.83
Diabetes mellitus type I	279	1.18	1.05	1.33	0				0			
Graves, hyperthyroidism	50	1.31	0.97	1.73	68	1.33	1.04	1.69	58	1.68	1.27	2.17
Hashimoto/hypothyroidism	19	2.41	1.45	3.77	22	2.63	1.65	4.00	22	1.87	1.17	2.84
Immune thrombocytopenic purpura	34	1.47	1.02	2.06	3	0.77	0.15	2.29	5	1.19	0.38	2.80
Multiple sclerosis	16	1.04	0.59	1.70	32	1.33	0.91	1.88	5	0.57	0.18	1.33
Myasthenia gravis	3	1.08	0.20	3.21	7	2.22	0.88	4.59	8	2.12	0.90	4.19
Pernicious anemia	1	2.00	0.00	11.46	5	2.27	0.72	5.35	10	1.31	0.62	2.42
Polyarteritis nodosa	0				7	6.31	2.50	13.07	12	6.52	3.35	11.43
Polymyalgia rheumatica	3	1.09	0.20	3.22	21	1.31	0.81	2.01	77	1.76	1.39	2.20
Psoriasis	15	1.19	0.66	1.96	32	1.67	1.14	2.36	35	2.19	1.52	3.05
Rheumatoid arthritis	28	1.03	0.69	1.50	117	1.92	1.59	2.31	153	1.75	1.49	2.06
Sarcoidosis	7	0.71	0.28	1.46	21	1.50	0.93	2.30	17	1.92	1.12	3.08
Systemic lupus erythematosus	9	1.25	0.57	2.39	10	1.26	0.60	2.33	4	0.70	0.18	1.80
Systemic sclerosis	6	1.46	0.53	3.21	10	1.90	0.91	3.52	8	1.49	0.64	2.96
Ulcerative colitis	75	0.90	0.71	1.13	84	2.10	1.67	2.60	43	1.95	1.41	2.63
Wegener granulomatosis	3	1.60	0.30	4.75	10	2.29	1.09	4.22	17	1.29	0.75	2.07
All	732	1.22	1.13	1.31	548	1.71	1.57	1.86	583	1.75	1.61	1.90

SIR = standardized incidence ratio; O = observed number of cases; CI = confidence interval.
Follow-up was started 1 year after last asthma hospitalization.
Bold type indicates that 95% CI does not include 1.00.

case numbers, and only 2% of all asthma patients were diagnosed with any subsequent autoimmune disease. It is conceivable that this choice eliminated some clustering of conditions that might have been of interest. Moreover, because approximately 50% of the asthma patients were hospitalized more than once, the follow-up was always started after the last hospitalization. The data in Table 1 show that the longer time had elapsed from the last asthma hospitalization, the lower the SIRs were for most diseases, suggesting that, for various reasons, a recent hospitalization increased the likelihood of a subsequent diagnosis. However, Addison, Crohn and thyroid diseases, myasthenia gravis, polyarteritis nodosa, polymyalgia rheumatica, psoriasis, rheumatoid arthritis, ulcerative colitis, and Wegener granulomatosis associated with asthma even when first diagnosed 5 years after the last asthma hospitalization, "All 5+." Notably, the most common autoimmune disease, rheumatoid arthritis, showed no decrease in SIR in "All 5+," and even for many other diseases the decrease was small. This is strong evidence against diagnosis/observation bias and suggests shared disease mechanisms between these diseases and asthma.

Polyarteritis nodosa and Addison disease showed the greatest risks in all analyses, including "All 5+," and these where the disease with the highest risk in difficult, "brittle" asthma patients, that is, those hospitalized more than five times. Addison disease had the largest proportion of patients in this category, 22% compared with 9.7% for all diseases. One reason for the high risk may be that most of the asthma patients with many hospitalizations were treated with corticosteroids, whereby acute Addison disease might be provoked by changes in therapeutic regimens, exacerbated by psychosocial factors (13, 19). The risk for subsequent autoimmune and related diseases increased by to the number of hospitalizations for asthma, suggesting a relationship with the severity of asthma and supporting a true biological etiology but cannot exclude confounding by observation bias.

The analysis by age at last hospitalization for asthma showed some distinct differences for the occurrence of subsequent autoimmune diseases. Some, such as Addison disease and Crohn disease, were increased through all hospitalization ages; celiac disease, type 1 diabetes, and immune thrombocytopenic purpura were increased only in young asthma patients; most others were increased in asthma patients first hospitalized as adults, but for many of them, including Hashimoto/hypothyroidism, polyarteritis nodosa, and Wegener granulomatosis, the highest risk was in young adulthood. These results show heterogeneity among studied autoimmune diseases with typical ages of onset; early onset diseases, such as celiac disease and type 1 diabetes, had to occur in early onset asthma patients because, by definition, they had to follow asthma hospitalization.

The association of polyarteritis nodosa with asthma is known as Churg Strauss syndrome or allergic granulomatous angiitis, which has been considered a variant or a separate entity of polyarteritis nodosa (20, 21). In this syndrome, asthma is usually of adult onset, which is in agreement with the present findings showing the highest risk for polyarteritis nodosa in old asthma patients. Moreover, Wegener granulomatosis may also be a manifestation in this syndrome and, indeed, an association was noted in the present study. The association of Addison disease with asthma is also known in the literature and covered as case reports (22).

The incidence of atopic diseases has increased markedly in the developed countries during the past decades (1–3). One proposed explanation to the increase is the hygiene hypothesis, according to which allergic diseases are increased because early childhood infections are reduced and the Th2 profile that predominate at birth is perpetuated. As a consequence, the biased Th2 response will lead to a generally weaker Th1 response, thus resulting in a dichotomous outcome, either increasing allergies and decreasing autoimmune responses or vice versa (5–8). However, an alternative hypothesis posits that the recent environmental changes have modified in parallel Th1 and Th2 responses (5–8). The present results favored coaggregation of many autoimmune diseases with asthma, probably explained by the host immunological factors and by their interplay with environmental factors.

To our knowledge this is a first attempt to assess co-occurrence of asthma with a large number of autoimmune and related diseases using unified data. The present data are in agreement with the relatively recent studies that have considered the coexistence of atopic and autoimmune related conditions (6–8). However, in these studies autoimmune diseases were considered jointly or by specifying only some common ones and without giving the sequence of the disease occurrence. However, many studies with opposite results have also been published, as reviewed (5); these included a recent study on Israeli conscripts but these were followed only for 2 to 3 years (12). None of the previous studies have tried and distinguish host genetic, environmental, and sociomedical factors in the observed co-morbidity.

In summary, hospitalized asthma patients presented with a number of subsequent autoimmune and related diseases. Although we were unable to exclude the effects of environmental factors, it is likely that host genetic/immunological factors or gene-environment interactions may explain coexistence of some of these diseases. To some degree, the high risks for subsequent diseases may probably be explained by frequent hospitalization leading to new diagnosis, yet leaving the main explanation to the observed biological factors and their possible interactions with environmental factors.

The registers used in the present study are maintained at Statistics Sweden and the National Board of Health and Welfare.

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