

Risk for multiple sclerosis in relatives and spouses of patients diagnosed with autoimmune and related conditions

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Abstract In the era of complex disease genetics, the consideration of familial risks is important in the assessment of the likely success of these studies. In the present article, we study familial risks for multiple sclerosis (MS) among parents and offspring, singleton siblings, twins, and spouses when a family member was diagnosed with MS or any of 33 other autoimmune diseases. The availability of a Multigeneration Register in Sweden provides a reliable access to families throughout the last century. The diseases in individual family members were obtained through linkage to the Hospital Discharge Register. With a total patient population of 425,102 of whom 11,154 were diagnosed with MS, this is the largest population-based family study on these diseases to date. Standardized incidence ratio (SIR) was calculated for family member of MS patients compared to those lacking an affected family member. SIR for MS was 5.94 (6.12 when parents were aged <73 years) in offspring of affected parents, 6.25 in singleton siblings, 9.09 in twins, and 1.50 (nonsignificant) in spouses; the SIRs did not depend on the gender. The SIRs for MS were 1.84 when a parent was diagnosed with amyotrophic lateral sclerosis and 1.14 with parental asthma. The overall risk of MS was 1.21 when a parent was

diagnosed with any autoimmune disease. The genes, so far associated with MS, explain little of the familial aggregation of MS, calling for further efforts in gene identification. The shared familial risks of MS with amyotrophic lateral sclerosis and asthma suggest shared genetic basis.

Keywords Familial risk · Sibling risk · Twins · Amyotrophic lateral sclerosis · Disease genes

Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disease with a population prevalence of the order of 0.1% or higher in Scandinavia and Canada [1–3]. MS is a demyelinating disease of the central nervous system affecting multiple foci and with a tendency to become chronically progressive [4]. The typical pathological findings in MS involve focal lesions, plaques, with infiltrating dysregulated, lymphocytes reacting against oligodendrocytic self-antigens at the myelin sheaths [4]. A family history of MS is a known risk factor of MS, and studies on twins have shown a higher concordance between monozygotic compared to dizygotic twins, consistent with a heritable cause [1, 5]. However, there are inconsistencies as to the magnitude of the familial risk among first-degree relatives, which are cited as being 15–40-fold according to older reports and around sevenfold according to two nationwide studies from Scandinavia [3, 6]. The HLA locus has been implicated in the genetics of MS with class II alleles showing the strongest evidence [7, 8]. Other recently confirmed genes are interleukin receptors IL2RA and IL7RA, and additionally, many genes await conformation [7].

An important question is to what extent the different autoimmune diseases share genetic risk factors [9–11]. Some older and recent literature states that MS does not

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share familial clustering with other autoimmune diseases [4, 12] while other studies report association of multiple types of autoimmune disease with MS [13, 14]. The HLA associations are shared between many autoimmune disease, but the same alleles may not be involved [7, 8]. Also, other genes maintaining immune function, such as interleukins and their receptors, are associated with many autoimmune diseases, IL2RA, for example, with MS, type 1 diabetes and Graves disease [15]. However, the genotype relative risks of many of the newly detected variants have been very small, and their contribution to the familial aggregation has been marginal [15]. The reasons can be that the genetic effects are truly small for the tested variants which may not capture all the genetic effects of the gene or that the variants are only markers of the true causative variants which are rarer and, hence, of higher familial risk [16].

Reliable data on family history has become increasingly important in studies on complex diseases because they are the only direct indicator of a possible heritable etiology [17–19]. Familial risks need to be considered before gene finding studies in order to estimate their likelihood of success, and they can be considered after obtaining the results to estimate their significance [20]. In autoimmune diseases of assumed shared etiology, family studies would help to estimate the level of genetic sharing. All family members also share environmental experiences, which can be assessed through disease correlation between spouses [21]. The availability of a Multigeneration Register in Sweden provides a reliable access to families throughout the last century. This register has been extensively used to study any hospitalized diseases through linkage to the Hospital Discharge Register, including familial autoimmune diseases [11, 19]. In the present article, we study familial risks for MS among parents and offspring, singleton siblings, twins, and spouses. Both concordant (MS–MS) and discordant associations are studied with any other of the 33 autoimmune diseases. With a total patient population of 425,102 of whom 11,154 were diagnosed with MS, this is among the largest family study published on these diseases with the advantage that all the results emanate from a single population of medically confirmed cases in a country of high medical standard and reasonably uniform diagnostics.

Material and methods

The research database used for this study, the autoimmune disease database, is a subset of the national MigraMed database at Karolinska Institute, Center for Family and Community Medicine. The MigMed database was compiled using data from several national Swedish registers provided by Statistics Sweden, including the Multigenera-

tion Register in which persons (second generation) born in Sweden in 1932 and thereafter are registered shortly after birth and are linked to their parents (first generation). Sibships could only be defined for the second generation, which was the present study population. National Census Data (1960–1990) and the Swedish population register (1990–2001) were incorporated into the database to obtain information on individuals' socioeconomic status. Dates of hospitalization for autoimmune diseases were obtained during the study period from the Swedish Hospital Discharge Register for years 1964 to 2004. 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 34 autoimmune groups of diseases. All linkages were performed using the national ten-digit civic 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 and to check that each individual was only entered once, for his or her first hospitalization for an autoimmune disease. Over 7.4 million individuals were included in the second generation of the autoimmune database.

Person-years were calculated from start of follow-up on January 1, 1964, until hospitalization for the first autoimmune disease, death, emigration, or closing date, December 31, 2004. Age-specific incidence rates were calculated for the whole follow-up period, divided into five 5-year periods. Standardized incidence ratios (SIRs) were calculated as the ratio of observed (O) to expected (E) number of cases. The expected number of cases was calculated for age (5-year groups), sex, period (5-year groups), region, and socioeconomic status-specific standard incidence rates. Familial risks were calculated for men and women with parents, singleton siblings, or twins affected with concordant (same) or discordant (different) autoimmune diseases, compared with men and women whose relatives were not affected by these conditions, using the cohort methods as described [22]. Spouses were defined for the population older than 25 years through common children. In rare families where more than two siblings were affected, each was counted as an individual patient. Confidence intervals (95% CI) were calculated assuming a Poisson distribution, and they were adjusted for dependence between the sibling pairs [22].

In the present results, an estimate of the degree of environmental contribution to the familial risk is given by risks between spouses. When this is lower than the risk between siblings, a genetic contribution is likely, and the risk between twins would be expected to exceed that of singleton siblings. As another measure of environmental sharing, we estimate risks for singleton siblings by their age

difference; if the risk is higher for siblings close in age compared to those with a large age difference, childhood environmental sharing may be the cause. We do not have data on zygosity.

Results

The total numbers of patients with autoimmune diseases was 425,015 of whom 11,154 were diagnosed with MS. The largest diagnostic groups were asthma 134,011, type 1 diabetes 53,694, and rheumatoid arthritis 47,550 patients. Among the MS patients, women (7,180) outnumbered men (3,974). In the whole patient population, women slightly outnumbered men, but there were over twofold sex differences according to the type of autoimmune disease: male patients were more common in ankylosing spondylitis, Behcet disease, Reiter disease, and rheumatic fever, whereas female patients outnumbered males for discoid lupus erythematosus, Graves disease, Hashimoto thyroiditis, localized scleroderma, rheumatoid arthritis, Sjogren syndrome, and systemic lupus erythematosus.

Familial risks for MS are shown in Table 1 for offspring of affected parents, singleton siblings, twins, and spouses. The SIR for offspring was 5.94 when a parent was diagnosed with MS. The SIRs for offspring MS were also significant when a parent was diagnosed with amyotrophic lateral sclerosis (1.84) and asthma (1.14, borderline significance). When the analysis considered only Graves disease, instead of Graves disease with hyperthyroidism, the association was significant ($N=39$, SIR 1.44, 95% CIs 1.03–1.97). For any autoimmune disease, the SIR was 1.21. Among siblings, only concordant MS was significant (6.25). The SIR for twins was 9.09, but only two pairs were found. The SIR for concordant MS was nonsignificant for spouses (1.50, 95% CIs 0.93–2.30). There was an increase also for MS when a spouse was diagnosed with psoriasis (1.64), and a decrease when a spouse was diagnosed with chronic rheumatic heart disease (0.41).

In these analyses, the ages of the parents were not limited whereas all offspring were below 73 years of age. Thus, to enable a comparison with risks between siblings, the above analyses were repeated by limiting the parental age to 72 years (data not shown). The SIRs were somewhat increased for concordant MS (6.18), but for the other significant associations, the SIRs were identical to the first decimal.

Hospitalization for MS was more common for women as for men in all age groups (Fig. 1). The question of sex-specific familial associations was addressed by comparing familial risk between sons of affected fathers and daughters of affected mothers (data not shown). For MS, there was no difference, the male SIR was 5.50 (13 affected pairs) compared to the female SIR of 6.10 (50 affected pairs). For

most discordant associations between MS and other autoimmune disease, sex-specific SIRs did not appear to differ, but the numbers of cases were small. The only apparent sex-specific discordant associations were for MS-amyotrophic lateral sclerosis (females SIR 2.65, 95% CIs 1.41–4.55, 13 affected female pairs, six affected male pairs, SIR 1.97, 95% CIs 0.71–4.31, note that the 95% CIs overlap indicating no gender difference) and Graves disease without hyperthyroidism (female SIR 1.95, 95% CIs 1.32–2.79, 30 affected female pairs, three affected male pairs with an SIR of 1.87, 95% CIs 0.35–5.53, not significant). MS was increased in men when parents of both sexes were diagnosed with sarcoidosis (SIR for male offspring 2.34, 95% CIs 1.27–3.93, 14 affected male offspring); however, there was no increase for any other sex-specific analyses between offspring and parents.

Discussion

To our knowledge, this is a first attempt to assess familial risks for MS and a large number of autoimmune diseases and related conditions using unified nationwide data. The selection of the 33 diseases to the association study with MS covered those with known immunological or inflammatory manifestations but without strict etiological delineations. The use of hospitalized cases may offer advantages and disadvantages to etiological studies. Hospitalization may involve selections whereby family members of hospitalized cases may preferentially seek hospitalization or family members may tend to be diagnosed close in time (i.e., surveillance bias). However, such selections should be largest among cohabiting spouses, and no evidence was noted to this effect; the largest spouse correlation was 1.64 for MS and psoriasis and a nonsignificant 1.50 for concordant MS. Although there is evidence of surveillance bias for diseases such as cancer, the bias was limited to a period shortly after the diagnosis of cancer in the first family member and the effect on the overall familial risk was negligible [23]. Another limitation would be that all patients are not hospitalized. Thus, the case numbers would be decreased and probably preferentially include severe disease presentation. We do not know to what extent MS patients have been hospitalized, but the number of MS patients who received disability pensions during years 1971 to 1994 was 11,371 [2], close to the number of 11,154 for the present hospitalizations from 1964 through 2004. As most patients hospitalized between 1964 and 1971 would have been receiving pensions in 1971, we have probably not lost many patients in the early period; however, new pensions have been issues after 1994 which would account for the MS patients missing from the discharge data. Moreover, all MS patients have not qualified for the

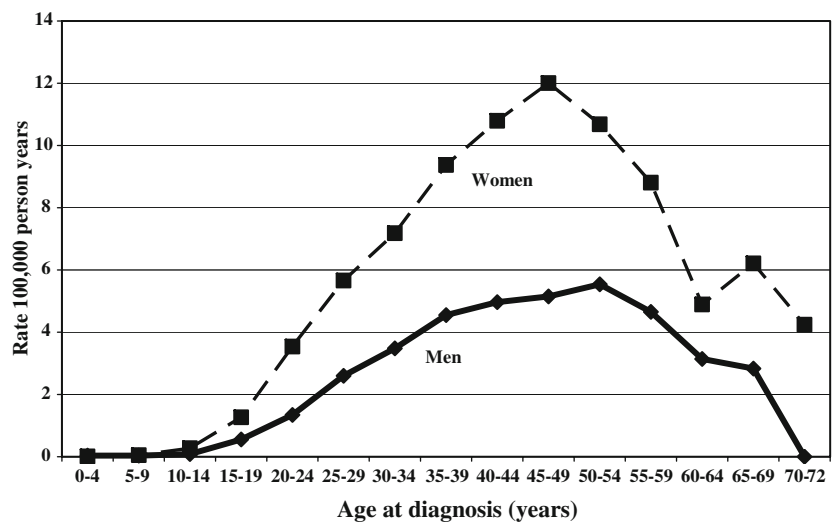
Table 1 Familial SIR for multiple sclerosis and autoimmune disorders according to the proband

	Parents				Singleton sibling				Twin				Spouses			
	O	SIR	95%	CI	O	SIR	95%	CI	O	SIR	95%	CI	O	SIR	95%	CI
Addison disease	6	2.40	0.86	5.25	2	1.08	0.07	5.61	0				0			
Anyotrophic lateral sclerosis	29	1.84	1.23	2.64	3	0.91	0.12	3.81	0				5	0.65	0.20	1.52
Ankylosing spondylitis	14	1.77	0.96	2.97	13	1.22	0.46	2.96	0				13	1.58	0.84	2.71
Asthma	238	1.14	1.00	1.30	79	0.82	0.46	1.44	2	1.09	0.07	5.66	93	0.97	0.78	1.19
Autoimmune hemolytic anemia	0				1	2.09	0.00	16.95	0				0			
Behcet disease	6	1.18	0.43	2.59	1	0.24	0.00	1.98	0				1	0.30	0.00	1.72
Celiac disease	4	0.86	0.22	2.22	4	0.61	0.11	2.24	0				2	0.68	0.06	2.48
Chorea minor	0				0				0				1	39.53	0.02	226.57
Chronic rheumatic heart disease	52	1.04	0.77	1.36	6	1.17	0.30	3.64	0				8	0.41	0.17	0.81
Crohn disease	19	0.95	0.57	1.49	26	0.78	0.36	1.62	3	4.90	0.65	20.50	14	0.78	0.42	1.31
Diabetes mellitus type I	80	1.18	0.93	1.46	68	1.01	0.55	1.81	1	0.80	0.00	6.48	46	1.05	0.77	1.40
Discoid lupus erythematosus	0				2	2.94	0.20	15.29	0				0			
Graves, hyperthyroidism	74	0.98	0.77	1.23	50	1.26	0.66	2.36	0				25	0.75	0.49	1.11
Hashimoto/hypothyroidism	29	1.28	0.86	1.84	7	1.16	0.33	3.40	0				10	1.37	0.65	2.54
Immune thrombocytopenic purpura	5	1.26	0.40	2.97	6	2.09	0.53	6.46	0				4	1.78	0.46	4.61
Localized scleroderma	2	0.99	0.09	3.64	1	1.72	0.00	13.92	0				0			
Lupoid hepatitis	1	2.84	0.00	16.31	1	3.27	0.00	26.48	0				0			
Multiple sclerosis	110	5.94	4.88	7.16	118	6.25	3.66	10.60	4	9.09	1.67	33.24	21	1.50	0.93	2.30
Myasthenia gravis	2	0.43	0.04	1.58	5	1.91	0.43	6.36	0				5	1.87	0.59	4.39
Pernicious anemia	24	1.15	0.74	1.71	0				0				11	1.81	0.90	3.25
Polyarteritis nodosa	2	0.70	0.07	2.58	0				0				0			
Polymyalgia rheumatica	55	0.91	0.69	1.19	21	1.63	0.71	3.53	0				21	0.85	0.53	1.30
Polymyositis/dermatomyositis	5	1.84	0.58	4.34	1	0.74	0.00	6.02	0				2	1.36	0.13	5.01
Primary biliary cirrhosis	5	1.63	0.51	3.83	2	2.27	0.15	11.79	0				2	1.47	0.14	5.40
Psoriasis	30	0.96	0.65	1.37	18	0.79	0.33	1.77	0				30	1.64	1.10	2.34
Reiter disease	0				0				0				0			
Rheumatic fever	3	0.47	0.09	1.39	4	0.77	0.14	2.81	0				5	1.06	0.33	2.49
Rheumatoid arthritis	165	1.10	0.94	1.28	39	0.97	0.49	1.88	1	1.36	0.00	11.05	67	1.14	0.88	1.44
Sarcoidosis	25	1.29	0.84	1.91	24	1.43	0.65	3.02	0				16	1.26	0.72	2.04
Sjören syndrome	2	0.68	0.06	2.51	1	0.70	0.00	5.68	0				1	0.72	0.00	4.15
Systemic lupus erythematosus	13	1.27	0.67	2.18	11	1.72	0.60	4.36	0				2	0.40	0.04	1.48
Systemic sclerosis	12	1.18	0.61	2.07	4	0.80	0.15	2.91	0				6	1.13	0.41	2.48
Ulcerative colitis	35	1.11	0.78	1.55	47	1.01	0.53	1.91	1	1.26	0.00	10.18	27	0.95	0.63	1.39
Wegener granulomatosis	40	1.24	0.89	1.69	1	0.48	0.00	3.86	0				12	1.31	0.68	2.30
All	1087	1.21	1.14	1.28	566	1.22	0.79	1.87	12	1.34	0.49	3.32	450	1.02	0.93	1.12

Bold type: 95% CI does not include 1.00

O observed number of cases, SIR standardized incidence ratio, CI confidence interval

Fig. 1 Age-specific hospitalizations for multiple sclerosis in men and women aged 0 to 72 years



pensions and the exact number of MS patients remains open [2]. Similarly, the degree of hospitalization for the other 33 diseases is likely to be variable and related to the severity of the disease. A further problem is the differential age at presentation of the 34 diseases under study, which influenced statistical power; for example, low numbers of offspring and siblings were detected for diseases with late onset.

The advantages of using hospitalized cases include a nationwide recruitment of cases and high diagnostic accuracy. Hospitalizations normally require a doctor's pass from the primary care. Thus, each hospitalized patient is seen at least by two medical doctors, of which the one in the hospital is likely to be a neurologist. The diagnoses were those by which the patients were discharged. Many patients have been hospitalized multiple times. Moreover, differential diagnostics towards the end of the study should not have been difficult. Neuromyelitis optica did not have a separate diagnosis code in ICD-8 but the number of patients in ICD-9 and ICD-10 was only about 2% of the number of MS patients, in line with the literature [24]. The weakness in many published case-control studies is that the diagnosis is obtained anecdotally on medical conditions diagnosed a long time earlier; yet, in a UK study where the reported diagnoses in relatives were controlled through general practitioners, the diagnostic accuracy was better for MS (positive predictive value 87% for cases and 100% for controls) than for autoimmune diseases in general (70% and 78%, respectively) [13].

The results provide several pieces of novel data or new data on controversial issues. In the present population where the parental population was of any age and the offspring population aged below 72 years, the familial relative risks were essentially similar even if the parental age was limited to 72 years. The familial risk of MS in offspring of affected parents was 6.18 compared to sibling

risk of 6.25 and the risk for twins of 9.09. The essentially identical risks for offspring of affected parents and for siblings suggest that no major recessive or shared childhood effects influence the familial clustering of MS. There was no gender-difference implying that, in spite of the higher female hospitalization rate, the familial risk was a constant multiplier over the background rate of MS. The number of affected first-degree family members was 342 (i.e., 2×110 for offspring and parents and 118 for singleton siblings and four twins). The present familial risks are somewhat lower than the ones reported by a Danish study on 90 familial cases but the results are in full agreement because of younger patient population in the Danish study. Diagnostic misclassification would reduce familial risks but limited to the early years of the present study. It is possible that the earlier cited familial risks ranging from 15 to 40 may be due to selected patient series recruiting high proportions of patients from multiplex families.

For discordant diseases, offspring had an increased risk of MS when parents were hospitalized for amyotrophic lateral sclerosis (SIR 1.84), Graves disease (1.44) and asthma (1.16). Because the hospitalization rates for many autoimmune diseases showed large sex differences, we analyzed sex-specific familial risks. However, the numbers of cases swindled and no evidence was found for sex-specific effects; much larger studies would be needed to demonstrate such effects. The only significant sex-specific discordant associations were for female MS-amyotrophic lateral sclerosis (SIR 2.65) and Graves disease (SIR 1.95). These SIRs were well above the overall SIRs of 1.84 and 1.44, respectively; even the male SIRs were also above unity, but they were not significant. Interestingly, the present data showed no parent of origin effects for MS as the risk for males (SIR 5.50) equaled the risk for females (SIR 6.10), contrary to the previous hypothesis [25]. In previous studies, associations of MS with Hashimoto

thyroiditis or hypothyroidism, Graves disease, and psoriasis have been observed [13, 14]. Thus, we could only confirm the association with Graves disease while a novel association with asthma has observed, but this was of borderline significance. The spouse correlation between MS and psoriasis could be due to chance, but psychosocial stress triggered by spouse's MS could be an alternative explanation. The overall familial risks of autoimmune disease in the studied MS families have been higher than the present 1.21, i.e., 1.65 (sibling risk with 95% CIs 1.0–3.4) in the UK study [13] and 3.5 in the US study on multiplex families (any first-degree relative with 95% CIs 1.6–7.6); the present low overall familial risk of 1.21 is also due to our broad inclusion of autoimmune and related conditions. A recent Danish study on 12,403 MS patients also found an overall risk of 1.2 for autoimmune diseases and an increased risk for polyarteritis nodosa and borderline increases for sarcoidosis, Crohn disease, and ulcerative colitis [26]; amyotrophic lateral sclerosis and asthma were not included in that study.

In summary, the present population-based study on hospitalized patients observed a familial risk for MS of about 6.0 in first-degree relatives of patients and it was independent of the type and sex and the proband. The genes so far associated with MS explain little of the familial aggregation of MS, calling for further efforts in gene identification. The shared familial risks of MS with amyotrophic lateral sclerosis, Graves disease, and asthma suggest a shared genetic basis.

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Conflict of interest None

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