

High frequency of psoriasis in relatives is associated with early onset in an Italian multiple sclerosis cohort

Annunziata P, Morana P, Giorgio A, Galeazzi M, Campanella V, Lore' F, Guarino E. High frequency of psoriasis in relatives is associated with early onset in an Italian multiple sclerosis cohort.

Acta Neurol Scand 2003; 108: 327–331. © Blackwell Munksgaard 2003.

Objectives – An exploratory study has been carried out to assess the association of autoimmune diseases in multiple sclerosis (MS) families with clinical features and disability of MS patients. **Material and methods** – Age at onset, symptoms and signs at onset, and disability were assessed in 177 patients with definite MS and 178 age- and sex-matched control patients with autoimmune diseases (78 with endocrine and 100 with rheumatological diseases) and correlated with the most frequent autoimmune diseases recorded in the families.

Results – Psoriasis was found in 30 relatives of 177 (16.9%) MS patients, thyroid disorders in 17 (9.6%) and allergies in 17 (9.6%). In the control group, psoriasis was found in 22 relatives of 178 (12%) patients, thyroid diseases in 19 (10.7%) and allergies in seven (3.9%). Of the 30 relatives with psoriasis in the MS group, 16 (53.3%) were fathers ($P < 0.0001$). There was a significant association of high frequency of family psoriasis with early age of MS onset ($P = 0.025$) but not with onset of symptoms or severe disability. **Conclusion** – In this Italian MS cohort, a subgroup of patients with a first- or second-degree relative with psoriasis had early onset of MS.

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Key words: multiple sclerosis; autoimmunity; psoriasis

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Accepted for publication February 20, 2003

The occurrence of autoimmune diseases in individual patients with multiple sclerosis (MS) has been the subject of several studies. Some reports have shown associations of MS with various autoimmune diseases (1, 2) although others failed to find significant differences with respect to control population (3). Relatively little work has been carried out on the frequency of autoimmune diseases in MS families and different patterns have been found in different populations (4–6) reflecting the heterogeneous findings of recent genome screening studies in European and North American MS populations (7–9). The rationale of these studies is the possibility of looking for genes shared by MS and other organ-specific autoimmune diseases, and environmental factors involved in the etiopathogenesis, which could provide information on the nature of the genes underlying genetic susceptibility to MS. None of these studies, however, has investigated whether high family incidence of an autoimmune disease may be

associated with a particular MS clinical phenotype. To address this question, we investigated the family frequency of autoimmune diseases in an Italian MS cohort compared with a similar sex- and age-matched control cohort of patients with immune-mediated endocrinological and rheumatological diseases. We also looked for associations of autoimmune diseases in MS families with particular clinical features of MS, including the age and signs at onset and progression as assessed by disability level.

Materials and methods

Patient groups

A total of 177 patients (129 females and 48 males, ratio 2.7:1) with definite MS (10) admitted to our Department up to 31 December 1999 and 178 sex- and age-matched controls who were patients with immune-mediated endocrine and rheumatological

diseases followed at the Departments of Endocrinology and Rheumatology of the University of Siena were studied. No MS multiplex pedigree was included in the study. The control group consisted of 78 patients (62 females and 16 males, ratio 3.9:1) with autoimmune endocrine diseases [Graves's disease ($n = 26$), Hashimoto's thyroiditis ($n = 38$), type-1 diabetes ($n = 14$)] and 100 patients (78 females and 22 males, ratio 3.5:1) with immune-mediated rheumatological diseases [(rheumatoid arthritis ($n = 29$), systemic lupus erythematosus ($n = 21$), Sjogren's syndrome ($n = 16$), systemic sclerosis ($n = 22$), vasculitis ($n = 4$), polymyositis ($n = 6$), anti-phospholipid syndrome ($n = 2$)].

Clinical recording and family history

Clinical assessment of MS patients included age at onset, symptoms and signs at onset, functional neurological systems and disability scoring with the expanded disability status scale (EDSS) (11). For all patients, disability was assessed at the time of investigation until 31 December 1999 and retrospectively by neurological records at the department. Family history was recorded at the time of neurological examination by questioning MS patients about a list of organ-specific autoimmune or immune-mediated disorders previously demonstrated to be associated with MS (3) also including psoriasis (4). Full biological relatives including first (parent, sibling, child) and second (grand parents, uncles/aunts, nephews/nieces) degree relatives were considered. The family history of the control population was assessed using the same criteria.

Statistical analysis

Comparison of cohort parameters was performed by the non-parametric Mann-Whitney test. Contingency tables were analyzed by Fisher's exact test and chi-square test with large tables (multiple rows). Survival analysis was used to estimate the association of age at onset and high disability level with autoimmune disorders in the MS population. Two end points were chosen: the first was the time of MS onset before or after 30 years (the average age at onset of the MS cohort studied); the second was the time to reach an EDSS 6.0 (a high disability score). Survival curves were performed by Kaplan-Meier analysis and compared by the log rank test using GraphPad Prism software (version 3.0) (GraphPad Software, Inc., San Diego, CA, USA). For each test $P < 0.05$ was considered significant.

Results

Frequency of psoriasis and other autoimmune diseases

Demographic characteristics of the MS and the control cohorts studied are given in Table 1. There were no significant differences between the cohorts with regard to age, female to male ratio and the residence areas.

The autoimmune diseases found in relatives of MS patients and control population are given in Table 2. Psoriasis was found to be the most frequent disease occurring in relatives of MS patients. Other less frequent diseases were thyroid disorders (Graves's and Hashimoto's diseases) and cutaneous and respiratory allergies. Of the other autoimmune disorders, two had type-1 diabetes and one celiac disease. A slightly significant higher incidence of allergies in relatives to MS with respect to control group was found. Furthermore, in the control group, psoriasis occurred in a lower (not significant) percentage of relatives with respect to MS patients although it was more frequent in relatives of patients with endocrine than with autoimmune rheumatological diseases (16.6% vs 9%, respectively). The relatives presenting psoriasis in MS and control populations are listed in Table 3. Most relatives with psoriasis in the MS population were fathers, others were mothers and uncles; grandparents, siblings and children were

Table 1 Characteristics of MS patients and controls

	MS	OAD
Number of subjects	177	178
F/M ratio	2.7:1	3.4:1
Age (years)*	41 ± 12 (18–70)	45 ± 15 (5–68)
Age of onset (years)*	30 ± 9 (14–57)	–
Duration of disease (years)*	11 ± 8 (1–45)	–
Residence areas (number of subjects)		
Siena	138	109
Tuscany (other provinces)	30	29
Other areas	9	40

MS, multiple sclerosis; OAD, other autoimmune diseases; F/M ratio, female/male ratio.

* Values are expressed as mean ± SD. Range values are given in parenthesis.

Table 2 Frequency of autoimmune diseases in relatives of MS patients and control cohort

Disease	MS ($n = 177$)	OAD ($n = 178$)	<i>P</i> -value
Psoriasis	30 (16.9)	22 (12.4)	0.23
Thyroid diseases	17 (9.6)	19 (10.7)	0.86
Allergies	17 (9.6)	7 (3.9)	0.036
Others	3 (1.7)	10 (5.6)	0.09

MS, multiple sclerosis; OAD, other autoimmune diseases.

Percentage values are given in parenthesis.

Table 3 Frequency of psoriasis in MS and control families

Relative	MS			OAD		
	Number	Percentage	P-value	Number	Percentage	P-value
Fathers	16	53.3	<0.0001*	3	13	—
Mothers	5	16.7	—	3	13	—
Sons	1	3.3	—	1	4.5	—
Brothers	1	3.3	—	6	27	0.19†
Cousins	0	0	—	3	13	—
Nephews	0	0	—	1	4.5	—
Maternal uncles	5	16.7	—	2	9	—
Maternal grandmothers	2	6.6	—	0	0	—
Paternal grandfathers	1	3.3	—	3	13	—
Total	31‡			22		

MS, multiple sclerosis; OAD, other autoimmune diseases.

* $\chi^2 = 67.6$, degrees freedom 8.

† $\chi^2 = 11.1$, degrees freedom 8.

‡ The total is 31 because one patient had father and paternal grandfather affected by psoriasis.

Table 4 Clinical features at onset in MS patients in relation to family psoriasis

Symptoms/signs	Psor ⁺ (n)	Psor ⁻ (n)	P-value
Pyramidal	4 (11%)	38 (19.2%)	0.25
Cerebellar	5 (14%)	27 (13.6%)	1.0
Brainstem	4 (11%)	27 (13.6%)	0.79
Sensory	12 (32%)	65 (32.9%)	1.0
Visual*	12 (32%)	39 (19.6%)	0.12

* Optic neuritis; n = number of subjects.

Psor⁺, patients with psoriasis; Psor⁻, patients without psoriasis.

The total number of subjects with clinical features is greater than the number of patients because some patients had more than one symptom or sign.

rarely affected. The frequency of psoriasis in fathers was significantly higher than in other relatives ($P < 0.0001$). In the control population, most relatives with psoriasis were brothers but this frequency was not significant with respect to other relatives.

Association of clinical parameters with psoriasis

Survival analysis of the association of age at onset of MS with respect to family psoriasis revealed that patients with a relative with psoriasis had a significant earlier onset than those without relatives: median survival was 26 years vs 29 years, respectively ($\chi^2 = 5.035$; $P = 0.025$). There were no significant differences between these two populations with respect to time to reach a high disability score ($\chi^2 = 0.003$; $P = 0.95$). To test the specificity of significant association of age at onset with psoriasis, survival analysis of age at onset in relation to frequency of thyroid disorders or allergies in relatives were performed. There were no significant differences between patients with or

without family thyroid disorders ($\chi^2 = 1.367$; $P = 0.24$) nor with or without family allergies ($\chi^2 = 0.18$; $P = 0.67$).

Association of symptoms and signs at onset with psoriasis is given in Table 4. There were no significant differences between patients with and without relatives with psoriasis with respect to symptoms and signs at onset. There were also no significant differences between patients with and without relatives with thyroid disorders or allergies (data not shown).

Discussion

In this exploratory study, we found a high but not significant frequency of psoriasis in relatives of MS patients with respect to other immune-mediated diseases. This prevalence was significantly greater in fathers of MS patients. Psoriasis was one of the autoimmune diseases occurring in MS families in two recent studies (4, 5) and was more frequent in simplex and multiplex MS families than in controls (5). The prevalence of psoriasis in the families of this Italian MS cohort was much higher than in the general Italian population (2%) estimated in a recent large epidemiological study based on data from a representative sample of specialists and general practitioners (12) but was similar to that found in our control cohort with immune-mediated diseases. The aim of using this control population was to establish whether the incidence of family autoimmune diseases was similar to that of autoimmune diseases other than MS. Although the prevalence may be overestimated because of the relatively small size of the population analyzed consisting of subjects admitted to hospital, the use of a control cohort of autoimmune diseases with demographic characteristics very similar to those of our MS population reduces this possibility and has the advantage that these patients are more motivated to answer questions about family diseases than normal healthy controls. However, the fact that either the MS or the control cohort consisted of subjects referred by physicians to hospital may have caused a potential selection bias with a possible overestimation of prevalence. The finding of a similar prevalence of psoriasis in families of MS and other organ-specific autoimmune diseases suggests that there may be common genetic susceptibility. In addition, the other finding of a higher frequency of psoriasis in fathers of MS patients than in other relatives, although has to be considered with caution because of the potential selection bias and although not a primary objective of this study, encourages the hypothesis of a possible common genetic link between MS and

psoriasis and this deserves to be verified in other future studies. However, the prevalence of psoriasis among fathers of our MS patients could simply reflect the higher prevalence of psoriasis among males in the Italian population as evidenced in a recent large epidemiological study (12). Furthermore, the prevalence of psoriasis in fathers and mothers of our MS cohort accounts for 70% of all relatives with psoriasis and is consistent with the evidence that autoimmunity is inherited as an autosomal dominant trait (13). Psoriasis is thought to be a T-cell-mediated autoimmune disease (14) with a genetic background. Genetic heterogeneity has been found in family psoriasis (15) and association of sporadic psoriasis with several human leukocyte antigen (HLA) Classes I and II antigens has also been reported (16). The demonstration of a significant association between high incidence of family psoriasis and early age at onset of MS highlights a possible relationship between genetic and immunological background of psoriasis and MS onset. Age at onset in MS has been investigated and established to be at least partly under genetic control. Indeed, studies of MS twins have found a stronger correlation of age at onset in concordant monozygotic twins than concordant non-twin subjects (17). Furthermore, in a recent study of a large cohort of MS patients, the age at onset of the disease was found to influence MS risk in siblings (18). Age at onset is a major prognostic factor in MS. Late onset is associated with high mortality of MS (19) and with increased risk of a shift toward a secondary progressive course (20). On the contrary, early onset is reported to be related to a less severe course and onset symptoms were found to predict disability (21). In our study, we did not find any relationship between high incidence of psoriasis in MS relatives and any particular clinical feature at onset or severe disability. However, the possible genetic influence of time of onset appears to be heterogeneous, depending on genes encoding cytokines or the HLA system. An interleukin (IL)-4 B1 allele was found to be correlated with late onset of MS (22) and HLA-DR15 was recently found to be associated with early age at onset (23). An IL-6 allele was associated with rapid onset (24). Our study is not population-based although the MS cohort studied consists mainly of subjects resident in the province of Siena and therefore the results must be taken into account with caution. However, a number of suggestions for future investigations are raised from these findings. Future larger population-based studies including MS multiplex families and other control groups consisting of healthy

subjects and patients with autoimmune diseases in relatives diagnosed by organ specialists are needed. Further studies are also warranted to establish whether MS patients with a first- or second-degree relative with psoriasis may be a useful subgroup to be stratified in MS linkage genetic studies for new insights into search for genes involved in MS onset and whether relatives to MS patients show a higher lifetime incidence of autoimmune diseases than the general population.

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