

Type 1 Diabetes and Multiple Sclerosis

A Danish Population-Based Cohort Study

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Background: Type 1 diabetes mellitus (T1D) and multiple sclerosis (MS) contribute considerably to the burden of autoimmune diseases in young adults. Although HLA patterns of T1D and MS are considered mutually exclusive, individual and familial co-occurrence of the 2 diseases has been reported.

Objective: To assess the co-occurrence of T1D and MS by estimating the risk for MS in patients with T1D and the risk for T1D in first-degree relatives of patients with MS.

Design, Setting, and Participants: Two population-based disease registers, the Danish Hospital Discharge Register and the Danish Multiple Sclerosis Register were used to identify patients with T1D, defined as patients in whom diabetes was diagnosed before age 20 years (N=6078), and patients with MS (N=11 862). First-degree relatives (N=14 771) of patients with MS were identified from family information in the Danish Civil Registration System.

Main Outcome Measure: Patients with T1D and first-degree relatives of patients with MS were followed up for occurrence of MS and T1D, respectively, and the relative risks were expressed as standardized incidence ratios, that is, ratios of observed to expected numbers of outcomes based on national age, sex, and period-specific MS and T1D incidence rates.

Results: Patients with T1D were at more than 3-fold increased risk for development of MS (relative risk, 3.26; 95% confidence interval, 1.80-5.88; n=11). First-degree relatives of patients with MS were at 63% increased risk (relative risk, 1.63; 95% confidence interval, 1.26-2.12; n=56) for development of T1D. However, adjusting for familial relationship to patients with T1D reduced the excess risk to 44% (relative risk, 1.44; 95% confidence interval, 1.11-1.88; n=56).

Conclusion: The present nationwide cohort study demonstrates an intraindividual and, to a lesser degree, an intrafamilial co-occurrence of MS and T1D.

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TYPE 1 DIABETES MELLITUS (T1D) and multiple sclerosis (MS) are organ-specific autoimmune diseases that differ in clinical manifestations and pathogenesis. The chronic hyperglycemia characteristic of T1D results from destruction of the pancreatic insulin-producing β -cells, whereas the neurologic disabilities associated with MS result from myelin sheath degeneration in the central nervous system.¹⁻³

The causes of T1D and MS remain largely unknown, but both genetic and environmental factors, including infectious agents, are believed to be important.^{2,3} A possible etiologic relation between the 2 conditions has been suggested by reports of familial and intraindividual co-occurrence of T1D and MS.⁴⁻¹⁰ Most previous observations, however, have been based on case reports, patient series, or small epidemiologic studies limited by modest numbers of patients with MS and self-reported information about

family relations and familial disease history. Therefore, the reported co-occurrence of T1D and MS needs further confirmation, especially since recent genetic investigations make T1D and MS an unlikely combination because of what appears to be mutually exclusive, predisposing HLA haplotypes.^{3,11}

To assess individual and familial co-occurrence of T1D and MS, we carried out a population-based cohort study using information from nationwide registers in Denmark, including the Danish Multiple Sclerosis Register, the Danish Hospital Discharge Register, and the Danish Civil Registration System.

METHODS

REGISTERS AND SUBJECTS

The Danish Multiple Sclerosis Register was formally established in 1956 in continuation of a nationwide MS surveillance study a few years

earlier. The register has since collected information about patients with MS from all departments of neurology, neuropathology, practicing neurologists, MS rehabilitation centers, death certificates, and, since 1977, the Danish Hospital Discharge Register. Cases with onset before 1994 were classified according to the diagnostic criteria of Allison and Millar, whereas cases with onset in or after 1994 were classified according to those of Poser, including possible MS.¹² Since its inception, only 3 neurologists have been involved in the classification of MS cases in the Danish Multiple Sclerosis Register.

The Danish Civil Registration System was established on April 1, 1968, and has since assigned a unique personal identification number to all Danish residents. The Civil Registration System contains continuously updated information on vital status, residence, place of birth, and, for most individuals born since the beginning of the 1950s, information about family relations, enabling us to identify first-degree relatives.¹³

The Danish Hospital Discharge Register contains information on all nonpsychiatric hospitalizations in Denmark since January 1977, including outpatient treatments since 1995. Individual information on dates of admission and discharge, diagnoses, and surgical procedures is recorded for every hospitalization. Between 1977 and 1993, diagnoses were classified according to the World Health Organization ICD-8 (*International Classification of Diseases, Eighth Revision*), and since 1994, according to the ICD-10 (*International Statistical Classification of Diseases and Health-related Problems, 10th Revision*). No distinction was made between insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus before 1987 (ICD-8 code 250 for both types of diabetes). From 1987 to 1998, insulin-dependent diabetes mellitus was coded as 249 (ICD-8; 1987-1993) or E10 (ICD-10; 1994-present) and non-insulin-dependent diabetes mellitus as 250 (ICD-8; 1987-1993) or E11 (ICD-10; 1994-present). Although most cases of T1D and type 2 diabetes will be coded as insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus, respectively, some patients with type 2 diabetes will need insulin treatment and might, therefore, be inaccurately categorized as having insulin-dependent diabetes. Accordingly, the diagnostic classification used by the Danish Hospital Discharge Register does not enable a clear distinction between T1D and type 2 diabetes. However, in Leeds, England, most patients with diabetes (97%) diagnosed before age 20 years had T1D.¹⁴ We, therefore, used age less than 20 years at the time of first diagnosis of diabetes to identify our patients with T1D. Primary and secondary diagnoses of T1D in inpatients and outpatients were included in the present study.

DATA ANALYSIS

Risk for MS After T1D

To identify patients with MS among those with T1D, we linked the cohort of patients with T1D who were younger than 20 years at establishment of the Danish Hospital Discharge Register in 1977 (ie, those born since January 1, 1957) to the Multiple Sclerosis Register, using each individual's unique personal identification number as key. Follow-up started on the date of T1D diagnosis plus 1 year and ended on the date of MS diagnosis, death, emigration, or December 31, 1997, whichever came first. The standardized incidence ratio, that is, the ratio of observed to expected numbers of patients with MS in the cohort, served as a measure of relative risk (RR). The expected numbers of patients with MS were calculated as the sum of sex-, age-, and period-specific person-years at risk in the T1D cohort multiplied by corresponding national sex-, age-, and period-specific MS incidence rates available from the Danish Multiple Sclerosis Register. Ninety-five percent confidence intervals (CIs)

for the RRs were estimated from the Wald test, assuming a Poisson distribution of the observed cases.

Risk for T1D in Families Afflicted With MS

To identify our cohort of first-degree relatives of patients with MS, we searched the files of the Danish Multiple Sclerosis Register to identify all patients in whom MS was diagnosed between April 1, 1968, and before December 31, 1997. Information about first-degree relatives born since January 1, 1957, of the same generation (siblings) or younger generation (offspring) was obtained through the Civil Registration System. The cohort of first-degree relatives was followed up for diagnosis of T1D in the Danish Hospital Discharge Register from January 1, 1977, or birth, whichever came later, until diagnosis of T1D, death, 20th birthday, emigration, or December 31, 2001, whichever came first. The standardized incidence ratio, that is, the ratio of observed to expected numbers of patients with T1D, served as the measure of RR for T1D in the cohort of first-degree relatives of patients with MS. The expected number of patients with T1D was calculated as the sum of the sex-, age-, and period-specific person-years at risk in the cohort of first-degree relatives multiplied by corresponding national sex-, age-, and period-specific T1D incidence rates generated from the Danish Hospital Discharge Register.

The risk estimates for T1D in first-degree relatives of patients with MS could be affected by an excess risk for T1D in first-degree relatives of patients with T1D if MS and T1D are related. Therefore, in an additional analysis, we adjusted for first-degree family relationship to patients with T1D by modifying the calculation of the expected number of cases, as follows: patients with T1D and their first-degree relatives were identified from the Danish Hospital Discharge Register and the Civil Registration System, respectively. An overall estimate of the RR for T1D in first-degree relatives of patients with T1D was calculated in an exercise similar to the preceding one concerning the risk for T1D in relatives of patients with MS. The first person with T1D in a family was considered the proband, and only the nonproband family members were followed up for the occurrence of T1D, from January 1, 1977, or birth, whichever came later, until diagnosis of T1D, death, 20th birthday, emigration, or December 31, 2001, whichever came first. Overall, first-degree relatives of patients with T1D were at 15.6-fold increased risk for development of T1D compared with persons without patients with T1D among their first-degree relatives. The information on familial relationship with patients with T1D was subsequently included in a new analysis. Accordingly, the contributions to the expected numbers of patients with T1D from first-degree relatives, who in addition to being related to a patient with MS also were related to a patient with T1D, were multiplied by 15.6; all other contributions were unaltered.

RESULTS

RISK FOR MS IN PATIENTS WITH T1D

We observed 11 patients with MS among 6078 patients with T1D during 71 626 person-years of follow-up when only 3.38 cases were expected (RR, 3.26; 95% CI, 1.80-5.88). In these 11 patients, T1D and MS were diagnosed at a mean \pm SD age of 13.3 ± 3.4 years and 25.4 ± 4.9 years, respectively. The diagnosis of MS was clinically definite in 7 patients, probable in 3 patients, and possible in 1 patient. Similar results were obtained in the analyses restricted to clinically definite MS cases or clinically defi-

Table. Relative Risk (RR) for Type 1 Diabetes Mellitus Diagnosed Before Age 20 Years in a Cohort of 14 771 First-degree Relatives (Siblings and Offspring) of Patients With MS

First-degree Relatives of Patients With MS	Cohort		RR for T1D			Adjusted RR for T1D*		
	No.	Person-Years	Observed, n	Expected, n	RR (95% CI)	Observed, n	Expected, n	RR (95% CI)
Offspring								
Male	6249	70 941	25	15.59	1.60 (1.08-2.37)	25	17.35	1.44 (0.97-2.13)
Female	5901	67 013	23	12.95	1.78 (1.18-2.67)	23	14.45	1.59 (1.06-2.39)
Total	12 150	137 954	48	28.54	1.68 (1.27-2.23)	48	31.81†	1.51 (1.14-2.00)
Siblings								
Male	1299	10 975	3	2.99	1.00 (0.32-3.11)	3	3.63	0.83 (0.27-2.56)
Female	1322	11 371	5	2.79	1.79 (0.75-4.31)	5	3.32	1.51 (0.63-3.62)
Total	2621	22 347†	8	5.78	1.38 (0.69-2.77)	8	6.95	1.15 (0.58-2.30)
Overall								
Male	7548	81 916	28	18.58	1.51 (1.04-2.18)	28	20.98	1.33 (0.92-1.93)
Female	7223	78 385	28	15.73	1.78 (1.23-2.58)	28	17.78	1.58 (1.09-2.28)
Total	14 771	160 300†	56	34.32†	1.63 (1.26-2.12)	56	38.76	1.44 (1.11-1.88)

Abbreviations: CI, confidence interval; MS, multiple sclerosis; RR, relative risk; T1D, type 1 diabetes mellitus.

*Adjusted for relationship to patients with T1D.

†Totals do not sum because of rounding.

nite plus probable MS cases. The RR estimate was slightly lower in women (RR, 2.69; 95% CI, 1.21-5.98; $n=6$) than in men (RR, 4.36; 95% CI, 1.82-10.48; $n=5$), but this difference was not statistically significant ($P=.4$). The RR in patients having diabetes diagnosed before age 15 years was 4.23 (95% CI, 1.90-9.43; $n=6$).

RISK FOR T1D IN FIRST-DEGREE RELATIVES OF PATIENTS WITH MS

Overall, 14 771 offspring and siblings born since January 1, 1957, were identified for 11 862 patients with MS. These first-degree relatives had 63% increased risk of developing T1D (RR, 1.63; 95% CI, 1.26-2.12), with no significant difference between the sexes (**Table**). The RR for T1D was the same in offspring (RR, 1.68; 95% CI, 1.27-2.23; $n=48$) and in siblings (RR, 1.38; 95% CI, 0.69-2.77; $n=8$; $P=.6$; **Table**). The increased risk was uniformly distributed in follow-up periods before and after MS in the proband ($P=.4$). The excess risk of developing T1D in offspring and siblings of patients with MS was, however, partly explained because some of the first-degree relatives, in addition to being related to a patient with MS, were also related to a patient with T1D. Adjusting for first-degree family relationship to patients with T1D reduced the overall excess risk slightly (RR, 1.44; 95% CI, 1.11-1.88).

Hospital records were available for 62 (93%) of 67 T1D cases that were linked with MS in our study. All patients except 1 had typical T1D. This patient, who was overweight, was diagnosed as having diabetes at age 17 years and was treated with oral antidiabetic medication. In conjunction with an episode of ketoacidosis at the age of 26 years, insulin therapy was initiated and continued for at least 10 years. A C-peptide measurement was compatible with a diagnosis of T1D.

COMMENT

We used 3 population-based disease registers to assess co-occurrence of T1D and MS. Our analyses showed that pa-

tients with T1D are at 3-fold increased risk for development of MS and that the risk for T1D in first-degree relatives of patients with MS is increased by approximately 40%.

Our findings are compatible with a recent Sardinian study in which 5-fold and 2-fold higher prevalences of T1D were observed in patients with MS and their first-degree relatives (parents, siblings), respectively, compared with the general population.⁹ Our risk estimates for female patients with T1D are, however, lower than preliminary results from the Familial Autoimmune and Diabetes study in the United States, in which women diagnosed as having diabetes before age 17 years had a 20-fold increase in the prevalence of MS.⁴ As in our study, familial co-occurrence of T1D could not explain the increased risk for T1D in first-degree relatives of patients with MS in the Sardinian study.⁹

Patients with T1D are typically in close contact with the health care system. The patients with T1D who developed MS ($n=11$) tended to be slightly younger when diagnosed as having MS compared with other patients with MS born in the same period. However, the interval between onset and diagnosis of MS was no shorter in the 11 patients with both diseases, which would have been expected if surveillance bias should explain our results. Type 1 diabetes mellitus may result in diabetic neuropathy, which may mimic early symptoms of MS, and, accordingly, diagnostic misclassification between T1D and MS could occur. However, we obtained information on MS from the Danish Multiple Sclerosis Register, in which all reports undergo individual evaluation by experienced neurologists.¹² Consequently, we consider diagnostic misclassification an unlikely explanation for the observed association between T1D and MS.

In our study we defined T1D as diabetes mellitus diagnosed before age 20 years. Despite growing incidence rates of type 2 diabetes in Europe, the risk in children and adolescents remains low in comparison with T1D.^{14,15} Moreover, we confirmed the diagnosis of T1D in all 62 available patient records. Although we cannot entirely rule out that our approximation of T1D may have im-

plied inclusion of some type 2 diabetes cases, we consider this of no significance to our observations.

Inasmuch as almost every patient having newly diagnosed T1D will be admitted to a hospital ward or an outpatient clinic, the completeness of the Danish Hospital Discharge Register regarding T1D is considered high.¹⁶ Furthermore, we used information from 3 independent registers to ascertain the intraindividual and intrafamilial co-occurrence of MS and T1D. Thereby, we avoided bias resulting from differences in recall of family histories of diseases between cases and controls, which may have affected previous studies.^{5,7,9,17}

Because of what seems to be mutually exclusive, predisposing HLA haplotypes in patients with T1D and MS, the co-occurrence of MS and T1D has been considered unlikely.¹¹ However, genetic susceptibility to autoimmune diseases is complex and involves several genes.¹⁸ Since MS- and T1D-associated HLA haplotypes differ between populations, HLA class II alleles per se may not alone be responsible for disease susceptibility.^{19,20} It has been suggested that variation at other non-HLA class II loci and/or unknown environmental factors might contribute significantly to the co-occurrence of these 2 diseases.^{21,22}

Several similarities in immunologic features of T1D and MS may also suggest overlapping causes. Both T1D and MS are considered T-cell-mediated autoimmune disorders¹ characterized by autoantigen-specific T1-helper cell responses,²³ decreased T-cell suppressor activity,^{10,24,25} and the presence of various autoantibodies, some of which could operate in both diseases.^{2,26-28} Also, Winer et al¹ recently demonstrated that autoreactive T cells were capable of targeting both pancreatic islet and central nervous system autoantigens in patients with MS, patients with T1D, and relatives of patients with T1D.

To our knowledge, the present study is the first truly nationwide cohort study to demonstrate intraindividual and, to a lesser degree, intrafamilial co-occurrence of MS and T1D. The underlying mechanisms remain unknown but may involve both genetic and environmental factors.

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