Higher Relative Risk for Multiple Sclerosis in a Pediatric and Adolescent Diabetic Population: Analysis From DPV Database

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OBJECTIVE

Type 1 diabetes and multiple sclerosis (MS) are typical autoimmune diseases in children and young adults. We assessed the co-occurrence of type 1 diabetes and MS by estimating the relative risk (RR) for MS in a pediatric and adolescent diabetic population and looked for possible influencing factors.

RESEARCH DESIGN AND METHODS

Within the Diabetes Patienten Verlaufsdokumentation (DPV)-Wiss Project, from January 1995 to October 2012, data from 56,653 patients with type 1 diabetes were collected in 248 centers in Germany and Austria. Published data on German and Mid-European MS prevalence were taken for comparison. Multivariable regression analysis was used to identify confounders for co-occurrence of type 1 diabetes and MS.

RESULTS

The RR for MS in patients with type 1 diabetes was estimated at 3.35–4.79 (95% CI 1.56–7.21 and 2.01–11.39, respectively). Immigration status in all patients ($P < 0.05$) and the presence of thyroid antibodies in male patients only ($P = 0.05$) were identified as influencing factors on MS incidence within the DPV database. The month-of-birth pattern revealed that risk was higher during the spring and summer months in the population with type 1 diabetes and MS in comparison with the population with type 1 diabetes.

CONCLUSIONS

The present cohort study demonstrates a higher risk of co-occurrence of MS in a pediatric and adolescent diabetic population. Immigration status and thyroid antibodies in male patients were independent risk indicators for the incidental rate of MS. Diabetic patients born during spring and summer had a higher risk for the development of MS. We suggest that environmental factors modulate the individual's risk for the co-occurrence of both diseases.

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Type 1 diabetes and multiple sclerosis (MS) are organ-specific inflammatory diseases, which result from an autoimmune attack against either pancreatic β-cells or the central nervous system; a combined appearance has been described repeatedly (1–3). For children and adolescents below the age of 21 years, the prevalence of type 1 diabetes in Germany and Austria is ~19.4 cases per 100,000 population, and for MS it is 7–10 per 100,000 population (4–6). A Danish cohort study revealed a three times higher risk for the development of MS in patients with type 1 diabetes (7). Further, an Italian study conducted in Sardinia showed a five times higher risk for the development of type 1 diabetes in MS patients (8,9). An American study on female adults in whom diabetes developed before the age of 21 years yielded an up to 20 times higher risk for the development of MS (10).

These findings support the hypothesis of clustering between type 1 diabetes and MS. The pathogenesis behind this association is still unclear, but T-cell cross-reactivity was discussed as well as shared disease associations due to the HLA-DRB1-DQB1 gene loci (8,11). The geographical appearances of diabetes and MS are quite similar; therefore, besides a genetic component, environmental factors might be relevant in both diseases (10). Ponsonby et al. (12) speculated that the higher incidence of diabetes and MS might depend on the month of birth and the intake of vitamin D during pregnancy.

Most previous observations on co-occurrence of the two autoimmune diseases have been based on case reports, patient series, or smaller epidemiologic studies limited by a modest number of patients with MS and type 1 diabetes. Therefore, the reported co-occurrence of type 1 diabetes and MS needs further confirmation. Most studies investigated an MS population and searched for type 1 diabetes, while we investigated a large pediatric and adolescent diabetic population and investigated the co-occurrence of MS.

The aim of this study was to evaluate the prevalence of MS in a diabetic population and to look for possible factors related to the co-occurrence of MS in children and adolescents with type 1 diabetes using a large multicenter survey from the Diabetes Patienten Verlaufsdokumentation (DPV) database. We hypothesize that antibodies (i.e., diabetes-specific antibodies, celiac disease–specific antibodies, or thyroid-specific antibodies), BMI, immigration background, or month of birth might have a major impact on the coincidence of type 1 diabetes and MS.

RESEARCH DESIGN AND METHODS

DPV is a prospective, observational, multicenter survey for continuous diabetes data acquisition. Twice a year, anonymous longitudinal data from patients are transmitted for central validation from 248 diabetes centers in Germany (n = 235) and Austria (n = 13). Inconsistent data were reported back to the centers for correction and then re-entered into the database (13).

According to the guidelines of the German Diabetes Association, all centers are advised to document age at diabetes manifestation, initial presence of diabetes-specific antibodies, weight, height, BMI, blood pressure, immigration background, insulin therapy, further diseases, concomitant medications, and HbA_{1c} levels. From January 1995 to October 2012, data from 56,653 children and adolescents with type 1 diabetes under the age of 21 years were collected. Patients with MS were searched for and identified either by ICD-10 code for MS or written diagnosis.

For the analysis, data on present age, month of birth, age at the onset of type 1 diabetes and MS, diabetes duration, insulin dose, BMI, immigration background, diabetes-specific antibodies, celiac disease–specific antibodies (tissue transglutaminase antibody or endomysium antibody), and thyroid antibodies (thyroid peroxidase antibody or transglutaminase antibody) were collected. Patients were subdivided according to their age into prepubertal (<11 years of age), pubertal (11–16 years of age), and postpubertal (>16 years of age) groups.

Published data on German and Mid-European MS prevalence were used for comparison. The estimated prevalence of MS cases in the pediatric and adolescent age groups of patients <21 years of age is 7–10 cases per 100,000 population in central Europe (5,6,14,15).

Statistical Methods

The standardized prevalence ratio (i.e., the ratio of observed to expected numbers of patients with MS in the diabetic cohort) served as a measure of relative risk (RR). The expected numbers of patients with MS were calculated as the sum of age-specific persons at risk in the type 1 diabetic cohort multiplied by corresponding national age-specific MS prevalence rates available from the Mid-European and German MS pediatric and adult registers (5,14,15). Ninety-five percent CIs for the RRs were estimated from the Wald test, assuming a Poisson distribution of the observed cases.

Descriptive statistics (mean, SD, and percentage) were calculated. Multivariable linear mixed-regression models were applied to assess the effects of possible confounders on the prevalence of MS within the diabetic population. Age, sex, diabetes duration, immigration background, therapy regimen, and daily insulin dose were included as fixed independent effects. Dependent variables were month of birth; BMI-SDS levels; and thyroid-specific, celiac disease–specific, and diabetes-specific antibodies. Asymmetrical CIs for fixed-effects parameters were constructed, and standardized coefficients were used to assess the relative importance of independent confounders. Estimates of regression coefficients (and SEs) and respective Wald and F tests were used to assess the relative importance of influencing factors. P values <0.05 were considered to be statistically significant.

RESULTS

RR

We observed 19 patients with MS among 56,653 registered type 1 diabetic patients within the DPV database. With a prevalence for MS of 7–10 patients per 100,000 population under the age of 21 years, a group of 3 to 5 patients with type 1 diabetes and MS would be expected. Therefore, the RR for the co-occurrence of both diseases within the diabetic population was increased from 3.35-fold to 4.79-fold

(95% CI 1.56–7.21 and 2.01–11.39, respectively).

Comparing the type 1 diabetic-MS population with the remaining pediatric DPV population, mean age at evaluation and duration of diabetes were higher within the type 1 diabetic-MS patients ($P < 0.05$) (Table 1). Age at diabetes onset and insulin dose per body weight did not differ significantly. However, the proportion of patients with an immigrant background and BMI-SDS levels was significantly higher in the type 1 diabetic-MS group ($P < 0.05$). In 9 of 19 type 1 diabetic-MS patients, patient age at MS onset was registered. Within those nine patients, diabetes developed first in seven patients, but two patients received their MS diagnosis before or in parallel with their type 1 diabetes diagnosis.

Dividing the type 1 diabetic-MS population according to pubertal stage, information was available in nine patients: two patients (two male) were prepubertal; three patients (one male) were pubertal; and four patients (two male) were postpubertal. As in the pediatric MS population, most patients were pubertal or postpubertal at disease onset. There was a tendency for a higher rate of male patients with type 1 diabetes and MS than expected from the pediatric MS population (RR 1.2 [95% CI 0.45–3.26]; $P = 0.071$)

Possible Influencing Factors

Results of multivariable linear regression models showed that BMI or BMI-SDS, and thyroid-specific or celiac disease–specific antibodies were not different between the type 1 diabetic and type 1 diabetic-MS groups. After separation for sex, male patients with thyroid-specific antibodies had an elevated probability for the development of MS that was close to a P value of 0.05 (β −0.18, $P = 0.053$).

Looking at the distribution of month of birth within the type 1 diabetic-MS population, there were two peaks in June and August, and a lower birth rate in April. Splitting the month of birth based on the sun exposition during pregnancy, we divided the population in groups of lower vitamin D exposure from May to October and higher exposure from November to April. Fourteen patients were born in the lower-exposure month, whereas 5 patients were born in the vitamin D higher-exposure month. In contrast, there was an almost equal distribution of month of birth in the MS population (16) and in the total type 1 diabetic population within DPV.

Table 1—Auxological, disease-specific data of type 1 diabetic patients with and without MS

Variables	Type 1 diabetes and MS (n = 19)	Type 1 diabetes (n = 56,634)	P value
Age at evaluation (years)	17.75 ± 2.23	14.25 ± 4.33	<0.01
Age at diabetes manifestation (years)	8.33 ± 3.93	8.61 ± 4.34	NS
Age at MS manifestation (years)	15.57 ± 4.65 (n = 9)	—	—
Diabetes duration (years)	9.42 ± 4.98	5.64 ± 4.31	<0.05
Insulin dose (IU/kg body weight/day)	0.89 ± 0.19 (n = 17)	0.85 ± 0.31 (n = 53,377)	NS
Male sex (%)	52.6	52.5	NS
BMI-SD (kg/m^2)	1.01 ± 1.16	0.53 ± 0.98	<0.05
Immigration background (%)	31.58	13.39	0.04
B-cell–specific antibodies positive	42.9 (n = 7)	84.65 (n = 22,161)	NS
GAD-antibody positive (%)	33.3 (n = 6)	68.7 (n = 17,819)	NS
Positive thyroid-specific antibodies (%)	50.00 (n = 12)	18.91 (n = 36,196)	0.026
Positive celiac disease–specific antibodies (%)	30.77 (n = 13)	22.37 (n = 33,452)	NS
Diagnosis of celiac disease (%)	10.53	3.20	NS
Diagnosis of autoimmune thyroiditis (%)	31.58	8.20	0.04

CONCLUSIONS

We used a large database of pediatric and adolescent type 1 diabetic patients to analyze the RR of MS co-occurrence. The DPV database includes ~98% of the pediatric diabetic population in Germany and Austria below the age of 21 years. In children and adolescents, the RR for MS in type 1 diabetes was estimated to be three to almost five times higher in comparison with the healthy population. Our findings are comparable with data from Sardinia in which a twofold to fivefold higher prevalence of type 1 diabetes was observed in adult patients with MS compared with the general population (8,9). A Danish study using three population-based disease registers showed a threefold increased risk in adult type 1 diabetic patients for the development of MS (7).

In this diabetic population, sex distribution was comparable between patients with type 1 diabetes and those with type 1 diabetes-MS. There was a trend for a higher number of males with co-occurrence of type 1 diabetes and MS, as expected from MS data in pubertal and postpubertal populations (14). However, because of the low number of MS patients this did not reach statistical significance. The diabetic patients in whom MS developed did not differ from the diabetic-only population with respect to age at diabetes onset and insulin dose. BMI-SDS level was significantly higher, but whether this was biased by higher age and possible MS relapse treatment with glucocorticoid pulses can only be speculated.

The pathomechanism behind the co-occurrence of type 1 diabetes and MS is quite unclear. MS and type 1 diabetes are associated with several immune abnormalities directed against different autoantigens. A common predisposing HLA haplotype in patients with type 1 diabetes-MS has not been found in adult studies (17,18). Both diseases are considered to be T-cell–mediated, as

characterized by decreased T-cell–suppressor activity and autoantigen-specific T-helper–cell response and the presence of numerous autoantibodies (11). However, a polymorphism in the T-cell receptor did not influence the susceptibility to type 1 diabetes and MS in the Sardinian population (19). Interleukin-2 receptor polymorphism was discussed as reflecting the existence of a heterogeneous association between type 1 diabetes and MS, suggesting different immunopathological mechanisms for the IL-2 receptor antagonist in the two diseases (20,21). The higher rate of thyroid-specific antibodies in male type 1 diabetic-MS patients in this population might fit with the hypothesis of autoreactive T cells (10).

The underlying mechanisms may involve both genetic and environmental causes. Therefore, we looked for possible factors such as age at diabetes manifestation and rates of diabetes-specific antibodies, thyroid-specific antibodies, and celiac disease–specific antibodies. None of these factors turned out to be significantly different from those of the type 1 diabetic-only population with the exception of an almost significantly higher rate of thyroid-specific antibodies in male type 1 diabetic-MS patients. Evidence for a link between viral infection and the autoimmune process has been repeatedly shown in patients with type 1 diabetes, MS, and other autoimmune diseases (22–24). One might assume that autoimmune diseases have—despite different antigens and antibodies—a common trigger in the initiation of an autoimmune process such as viral infections or vitamin D level in the fetal or perinatal period (25). In a series of epidemiologic studies performed in different populations, it has been reported that children and adolescents with type 1 diabetes or autoimmune diseases such as celiac disease and thyroiditis have a different rhythmic pattern of month of birth (25–29). In an Australian study, there was an inverse correlation between ambient ultraviolet radiation in the first trimester and risk of MS (30). Further, the latitude gradient is environmentally related to type 1 diabetes and MS because the prevalence is higher as grade of latitude away from the equator. This would support an underlying seasonal or latitudinal factor (31). The risk of autoimmune diseases might be linked to month of birth through seasonal maternal vitamin D deficiencies (32). Lower ultraviolet radiation exposure might predict a higher autoimmune susceptibility, explaining the co-occurrence of several autoimmune diseases in one person (30,33). In this population, two-thirds of patients with type 1 diabetes and MS had a month of birth that was consistent with the fetus having experienced lower levels of ultraviolet radiation exposure during early pregnancy. The month-of-birth distribution of the whole DPV population without co-occurrence of MS had no sigmoid distribution.

The higher MS risk in patients with immigrant background was found to be independent of the seasonal variation, and, thus, we assume that variations in the genetic, environmental, or cultural backgrounds of patients with this significantly increased risk caused simultaneous development of type 1 diabetes and MS. The major population groups with immigrant status in Germany and Austria come from Turkey, the Middle East, or Eastern Europe, and thus are very heterogeneous in terms of population genetics and socioeconomic factors.

One limitation of this analysis of the diabetes-centered database is that MS-related information is not documented systematically, and so we could not give detailed information on family history, number of relapses, and type of MS (e.g., type of progression) experienced while receiving certain current medications, which would be of interest for anyone dealing with MS patients. In some patients, we did not obtain all patient-related data (e.g., age at onset of MS). Furthermore, the elevated RR for co-occurrence could only be an estimation. On the one hand, age distribution within the type 1 diabetic and type 1 diabetic-MS populations is not similar, and a correction for age was not performed. On the other hand, the data might be biased, since it is possible that patients with type 1 diabetes are more likely to receive a diagnosis of MS faster than the general population, and cases of MS in the MS registry could be under-reported. In addition, the number of type 1 diabetic-MS patients is small. Data on month-of-birth distribution are therefore speculative and need proof from a larger population. In terms of month of birth, a subdivision of the whole diabetic population into sex or ethnicity and a comparison with patients with MS and type 1 diabetes would be of interest. However, the number of patients with co-occurrence of the two diseases is too small for analysis in subgroups. The strength of the study is the multicenter approach and the long-term standardized follow-up of a large population of children and adolescents with type 1 diabetes.

In conclusion, we found an approximately three to five times higher rate of patients with the co-occurrence of type 1 diabetes and MS within a pediatric diabetic population. This also might be due to a higher common susceptibility to multiple autoimmune diseases if MS and autoimmune diabetes are not classified under one of the established autoimmune syndromes. We also found that the strong predominance of female sex in MS patients was lower in this type 1 diabetic-MS cohort, and type 1 diabetic-MS male patients had an almost significantly higher rate of additional thyroid-specific antibodies. Besides genetic factors, environmental factors such as vitamin D, and its levels during early pregnancy, and immigration background might be a modulator of autoimmune disease. These specific effects, found only in the type 1 diabetic-MS group, draw attention to a subtype of immune disease that results in combined autoimmunity against endocrine and neuronal antigens. To follow up on this interesting topic, prospective documentation of detailed disease-related data from type 1 diabetic-MS patients is needed.

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Schwenningen Schwarzwald-Baar-Klinikum Innere; Waiblingen Kinderklinik; Waldshut Kinderpraxis; Waldshut-Tiengen Kinderpraxis Biberbau; Weiden Kinderklinik; Weingarten Kinderarztpraxis; Wernberg-Köblitz SPP; Wetzlar Praxis Klewer/Teichner; Wetzlar/Braunfels Innere; Wien Uni-Kinderklinik; Wiesbaden Horst-Schmidt-Kinderkliniken; Wiesbaden Kinderklinik Deutsche Klinik für Diagnostik; Wilhelmshaven Reinhard-Nieter-Kinderklinik; Wilhelmshaven St. Willehad Innere; Wittenberg Kinderklinik; Wolgast Innere Medizin; Worms Kinderklinik; Wuppertal Kinderklinik.

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