HIGHER RELATIVE RISK FOR MULTIPLE SCLEROSIS IN A PEDIATRIC AND ADOLESCENT DIABETES POPULATION: ANALYSIS FROM DPV DATA BASE

Susanne Bechtold, MD, 1, Astrid Blaschek, MD 1, Klemens Raile, MD 2, Axel Dost, MD 3, Clemens Freiberg, MD 4, Meik Askenas, MD 5, Elke Fröhlich-Reiterer, MD 6, Esther Molz 7, Reinhard W. Holl, MD PHD 7

1 Department of Pediatrics, Medical University Munich, Germany
2 Department of Pediatrics, Medical University of Berlin, Germany
3 Department of Pediatrics, University Hospital Jena, Germany
4 Department of Pediatrics, Medical University of Göttingen, Germany
5 Department of Pediatrics, Evangelisches Krankenhaus Bielefeld, Germany
6 Department of Pediatrics, Medical University of Graz, Austria
7 Institute of Epidemiology and medical Biometry, University of Ulm, Germany

Running title: Higher risk for multiple sclerosis in type 1 diabetes

Corresponding author
Susanne Bechtold, MD
Kinderklinik und Kinderpoliklinik
Dr. von Haunersches Kinderspital, Pediatric Endocrinology and Diabetology
Ludwig-Maximilians University
Lindwurmstr. 4
D-80337 München, Germany
Phone: +49-89-5160-2811
Fax: +49-89-5160-2894
e-mail: Susanne.Bechtold@med.uni-muenchen.de

Word count: 2477

Table: 1
ABSTRACT

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 for MS in a pediatric and adolescent diabetes population and looked for possible influencing factors.

RESEARCH DESIGN AND METHODS: Within the DPV-Wiss-project, from January 1995 to October 2012, data of 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: Relative risk for MS in type 1 diabetes was estimated at 3.35 to 4.79 (95% CI: 1.56 to 7.21 and 2.01 to 11.39, respectively). As influencing factors on MS incidence within the DPV database could be identified immigration status in all (p<0.05) and thyroid antibodies in males only (p= 0.05). The month of birth pattern was higher during the spring and summer months in the type 1 diabetes with MS in comparison to the type 1 diabetes population.

CONCLUSION: The present cohort study demonstrates a higher risk of co-occurrence of MS in a pediatric and adolescent diabetes population. Immigration status and thyroid antibodies in males were independent risk indicators for incidental rate of MS. Diabetic patients born during spring and summer had a higher risk to develop MS. We suggest that environmental factors modulate the individual’s risk for the co-occurrence of both diseases.
INTRODUCTION

Type 1 diabetes and Multiple Sclerosis (MS) are organ specific inflammatory diseases, which result from an autoimmune attack against either pancreatic β-cells or central nervous system; a combined appearance has been described repeatedly (1-3). For children and adolescents below the age of 21 the prevalence for type 1 diabetes in Germany and Austria is about 19.4 per 100,000 and for MS it ranges from 7 to 10 /100,000 (4-6). A Danish cohort study revealed a three times higher risk for patients with type 1 diabetes to develop MS (7). Further, an Italian study from Sardinia could show an even five times increased risk for MS patients to get type 1 diabetes (8; 9). An American study on female adults with diabetes manifestation before the age of 21 yielded an up to 20 times higher risk in the prevalence 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 gen loci (8; 11). The geographical appearance of diabetes and multiple sclerosis are quite similar, therefore, besides a genetic component environmental factors might be relevant in both diseases (10). Ponsonby et al. speculated that the higher incidence of diabetes and multiple sclerosis might depend on the month of birth and the vitamin D exposition during pregnancy (12).

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 MS population and searched for type 1 diabetes, while we investigated a
large pediatric and adolescent diabetes population and investigated the co-occurrence of MS.

The aim of this study was to evaluate the prevalence of multiple sclerosis in a diabetes population and to look for possible factors related to the co-occurrence of multiple sclerosis in children and adolescents with type 1 diabetes using a large multicenter survey from the DPV (Diabetes Patienten Verlaufsdokumentation-DPV) database. We hypothesize that antibodies (namely diabetes specific antibody, celiac disease or thyroid specific antibodies), BMI, immigrant 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 diabetes specific antibodies, weight, height, BMI, blood pressure, immigration background, insulin therapy, further diseases, concomitant medication and HbA1c levels. From January 1995 to October 2012 data from 56,653 children and adolescents with type 1 diabetes mellitus under the age of 21 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 disease onset of type 1 diabetes and MS, diabetes duration, insulin dose, BMI, immigrant background, diabetes specific antibodies, celiac disease specific antibodies (tTgAb or EMAb) and
thyroid antibodies (TPO-, TgAb) were collected. Patients were subdivided according to their age group in prepubertal (<11 years of age), pubertal (age 11 to 16 years) and postpubertal (> 16 years of age).

Published data on German and Mid-European MS prevalence were used for comparison. Estimated prevalence of MS cases in pediatric and adolescent age group younger than 21 years is 7 to 10 cases /100,000 in central Europe (5; 6; 14; 15).

**Statistical methods:**

The standardized prevalence ratio, that is the ratio of observed to expected numbers of patients with MS in the diabetes cohort, served as a measure of relative risk (RR). The expected numbers of patients with MS were calculated as the sum of age-specific person at risk in the type 1 diabetes 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 confidence intervals (CI’s) for the RR’s were estimated from the Wald test, assuming a Poisson distribution of the observed cases.

Descriptive statistics (mean, SD, percentage) were calculated. Multivariable linear mixed regression models were applied to assess the effect of possible confounders on the prevalence of MS within the diabetes population. Age, sex, diabetes duration, migration background, therapy regime and daily insulin dose were included as fixed independent effects. Dependent variables were month of birth, BMI-SDS, thyroid, celiac disease and diabetes specific antibodies. Asymmetrical confidence intervals for fixed-effect parameters were constructed, and standardized coefficients were used to assess the relative importance of independent confounders. Estimates of regression coefficients (and standard errors) and respective Wald and F-tests were
used to assess the relative importance of influencing factors. P-value less than 0.05 were considered as statistically significant.

RESULTS

Relative risk

We observed 19 patients with MS among 56,653 registered type 1 diabetes patients within the DPV data base. With prevalence for MS of 7 to 10 patients per 100,000 under the age of 21 3 to 5 patients would be expected. Therefore, the relative risk for the co-occurrence of both diseases within the diabetes population was increased 3.35 to 4.79-fold (CI: 1.56 to 7.21 and 2.01 to 11.39, respectively).

Comparing the type 1 diabetes-MS population with the remaining pediatric DPV population, mean age at evaluation and duration of diabetes were higher within the type 1 diabetes-MS patients (p<0.05) (Table 1). Age at diabetes onset and insulin dose per body weight did not differ significantly. However, proportion of immigrant background and BMI SDS were significantly higher in the type 1 diabetes-MS group (p<0.05). In 9 out of 19 type 1 diabetes-MS patient age at MS onset was registered. Within those five developed diabetes first, but 2 experienced their MS diagnose before or in parallel with type 1 diabetes.

Dividing the type 1 diabetes-MS population according to the pubertal stage information was available in 9 patients: 2 (2 male) were prepubertal, 3 (1 male) pubertal and 4 (2 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, CI: 0.45, 3.26; p=0.071)

Possible influencing factors
Results of multivariable linear regression models showed that BMI or BMI SDS, thyroid or celiac disease specific antibodies were not different between the type 1 diabetes and type 1 diabetes-MS groups. After separation for sex, male patients with thyroid specific antibodies had an elevated probability to develop MS that was close to a p-value of 0.05 ($\beta$ -0.18, p= 0.053).

Looking at the distribution of month of birth within the type 1 diabetes-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. 14 patients were born in the lower exposure month, whereas 5 patients were born in the vitamin D higher exposure. In contrast, there was an almost equal distribution of month of birth in the MS (16) and the total type 1 diabetes population within DPV.

**Discussion**

We used a large database of pediatric and adolescent type 1 diabetes patients to analyze the relative risk of MS co-occurrence. The DPV database includes about 98% of pediatric diabetes population in Germany and Austria below the age of 21. In children and adolescents the relative risk for MS in type 1 diabetes was estimated 3 to almost 5 times higher in comparison to the healthy population. Our findings are comparable with data from Sardinia in which 2 to 5-fold higher prevalence of type 1 diabetes were observed in adult patients with MS, compared with the general population (8;9). A Danish study using three population based disease-registers showed a 3-fold increased risk in adult type 1 diabetes patients for the development of MS (7).
In this diabetes population, sex distribution was comparable between type 1 diabetes and type 1 diabetes-MS patients. There was a trend for a higher number of males with co-occurrence of type 1 diabetes-MS as expected from MS data in pubertal and postpubertal population (14). However, due the low number of MS patients this did not reach statistical significance. The diabetic patients who developed MS did not differ from the diabetes only population with respect to age at diabetes onset and insulin dose. BMI-SDS was significantly higher but whether this was biased by higher age and possible MS relapse treatment with glucocorticoid pulses could 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. Predisposing common 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 autoantigene-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). IL-2 receptor polymorphism was discussed to reflect the existence of a heterogeneous association between type 1 diabetes and MS, suggesting different immunopathological mechanisms of IL2RA in the two diseases (20; 21). The higher rate of thyroid specific antibodies in male type 1 diabetes-MS patients in this population might fit to the hypothesis of autoreactive T-cells (10).

The underlying mechanisms may involve both genetic and environmental causes. Therefore we looked for possible factors like age at diabetes manifestation, rate of diabetes specific antibodies, thyroid specific antibodies and celiac disease specific antibodies. None of these factors turned out to be significantly different from the type
1 diabetes only population with the exception of an almost significantly higher rate of thyroid specific antibodies in male type 1 diabetes -MS patients. Evidence for a link between viral infection and the autoimmune process has been repeatedly shown in 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 the autoimmune process like 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 like 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 one move 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 UV exposure might predict for a higher autoimmune susceptibility explaining the co-occurrence of several autoimmune diseases in one person (30; 33). In this population 2/3 of patients with type 1 diabetes and MS had a month of birth consistent with the fetus having experienced lower levels of ultra violet 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 independently to the seasonal variation and thus we assume that variations in their genetic, environmental or cultural background caused this significantly increased risk to simultaneously develop type 1 diabetes and MS. The major population groups with
immigrant status in Germany and Austria come from Turkey, Middle East or Eastern Europe and thus are very heterogeneous in terms of population genetics and socioeconomic factors.

One limitation of this analysis from 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) under certain current medication that would be of interest for anyone, dealing with MS patients. In some patients we did not get the whole information of patient related data (e.g. age at onset of MS). Furthermore, the elevated relative risk for the co-occurrence could only be estimation. On the one hand, age distribution within the type 1 diabetes and type 1 diabetes-MS population is not similar and a correction for age was not performed. On the other hand, data might be biased, since it is possible that patients with type 1 diabetes are more likely to be diagnosed with MS faster than the general population and cases of MS in the MS registry could be underreported. In addition, the number of type 1 diabetes-MS patients is small. Data on month of birth distribution are therefore speculative and need proof on a larger population. In terms of month of birth a subdivision of the whole diabetes population into gender 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 about a 3 to 5-times higher rate of patients with the co-occurrence of type 1 diabetes and MS within a pediatric diabetes population. This might be due to a higher common susceptibility to multiple autoimmune diseases also if multiple sclerosis and autoimmune diabetes are not classified under one of the
established autoimmune syndromes. We also found that the strong predominance of female gender in MS patients was lower in this type 1 diabetes-MS cohort and type 1 diabetes-MS males had an almost significant higher rate of additional thyroid specific antibodies. Beside genetic, environmental factors like 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 diabetes-MS group draw attention to a subtype of immune disease that results in combined autoimmunity against endocrine and neuronal antigens. To follow this interesting topic, prospective documentation of detailed disease related data of type 1 diabetes-MS patients is needed.

Author Contributions: S.B. wrote manuscript, researched data; A.B. reviewed/edited manuscript; K.R. and A.D. reviewed manuscript and contributed to discussion; M.A., C.F and E.F.-R. reviewed/edited manuscript; E.M. researched data; R.W.H. contributed to discussion and reviewed/edited manuscript.

Acknowledgements:

Dr. Susanne Bechtold is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. There is no conflict of interest for any author.

The DPV initiative is financially supported by the German Ministry of Health, the German Diabetes Foundation, the German Diabetes Association, the BM BF competence network for diabetes mellitus and competence net obesity (Förderkennzeichen): 01G1106, excellence center “Metabolism” of the state at Baden Württemberg, the Dr. Bürger-Büsing F dation, the German Medical Association (BÄK) and Novo Nordisk Germany.

Reference


22. Songini M, Casu A, Ashkenazi I, Laron Z: Seasonality of birth in children (0-14 years) and young adults (0-29 years) with type 1 diabetes mellitus in Sardinia differs from that in the general population. The Sardinian Collaborative Group for Epidemiology of IDDM. Journal of pediatric endocrinology & metabolism : JPEM 2001;14:781-783
31. Watson PE, McDonald BW: Seasonal variation of nutrient intake in pregnancy: effects on infant measures and possible influence on diseases related to season of birth. Eur J Clin Nutr 2007;61:1271-1280
Table 1: Auxological, disease specific data of type 1 diabetes patients with and without MS

<table>
<thead>
<tr>
<th></th>
<th>Type 1 diabetes &amp; MS (n=19)</th>
<th>Type 1 diabetes (n= 56,634)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at evaluation (yr)</td>
<td>17.75 ± 2.23</td>
<td>14.25 ± 4.33</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Age at diabetes manifestation (yr)</td>
<td>8.33 ± 3.93</td>
<td>8.61 ± 4.34</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age at MS manifestation (yr)</td>
<td>15.57 ± 4.65 (n=9)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Diabetes duration (yr)</td>
<td>9.42 ± 4.98</td>
<td>5.64 ± 4.31</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Insulin dose (IU/kgBW/d)</td>
<td>0.89 ± 0.19 (n=17)</td>
<td>0.85 ± 0.31 (n=53,377)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex (male %)</td>
<td>52.6</td>
<td>52.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI-SD</td>
<td>1.01 ± 1.16</td>
<td>0.53 ± 0.98</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Immigration background (%)</td>
<td>31.58</td>
<td>13.39</td>
<td>P=0.04</td>
</tr>
<tr>
<td>B-cell specific antibodies positive</td>
<td>42.9 (n=7)</td>
<td>84.65 (n=22,161)</td>
<td>n.s.</td>
</tr>
<tr>
<td>GAD-antibody positive (%)</td>
<td>33.3 (n=6)</td>
<td>68.7 (n=17,819)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pos. thyroid specific antibodies (%)</td>
<td>50.00 (n=12)</td>
<td>18.91 (n=36,196)</td>
<td>P=0.026</td>
</tr>
<tr>
<td>Pos. celiac disease specific antibodies (%)</td>
<td>30.77 (n=13)</td>
<td>22.37 (n=33,452)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diagnosis of celiac disease (%)</td>
<td>10.53</td>
<td>3.20</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diagnosis of autoimmune thyroiditis (%)</td>
<td>31.58</td>
<td>8.20</td>
<td>P=0.04</td>
</tr>
</tbody>
</table>