Comorbidity of Type 1 Diabetes Mellitus in Patients with Juvenile Idiopathic Arthritis

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Objectives To determine the prevalence of type 1 diabetes mellitus (T1D) in patients with juvenile idiopathic arthritis (JIA) and to characterize patients having both.

Study design Diabetes comorbidity was recorded in the National Pediatric Rheumatologic Database since 2012. Data from the North Rhine-Westphalian diabetes registry served as the reference population for the prevalence of diabetes in the general population. The National Pediatric Rheumatologic Database data were indirectly standardized for age and sex for comparison with the general population. The diabetes prevalence ratio was calculated using the Poisson regression model.

Results The analysis included 12 269 patients with JIA. A total of 58 patients had comorbid T1D, and the diabetes prevalence was 0.5%. The mean age was 11.6 years at the time of documentation, and the mean disease duration was 4.2 years. Compared with the general population, the prevalence of diabetes in patients with JIA was significantly increased (prevalence ratio 1.76 [95% CI 1.34; 2.28], $P < .001$). The onset of diabetes in patients with JIA was earlier than that reported in the reference data. Sixty-three percent of patients developed T1D before JIA. On average, diabetes onset was 56 months before the onset of JIA. Patients who first developed JIA developed T1D on average 40 months later. The majority of patients had not received disease-modifying antirheumatic drugs before diabetes onset.

Conclusions T1D occurs more frequently in patients with JIA than in the general population. The likelihood of T1D occurrence appears to be slightly higher before JIA manifestation and without disease-modifying antirheumatic drug therapy after JIA onset. *(J Pediatr 2018;192:196-203).*

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Juvenile idiopathic arthritis (JIA) is the most common chronic childhood inflammatory rheumatic disease in Europe, with an estimated incidence of 2-20 cases per 100 000 children and adolescents.[1] JIA comprises a clinically heterogeneous group of arthritides characterized by persistent joint inflammation and a disease onset before 16 years of age. Most of the categories of JIA are related to autoimmunity.[2]

Twin and family studies have emphasized the importance of genetic predisposition for autoimmune diseases (AIDs).[3-5] Genetic analyses have shown an association between mutations in certain susceptibility gene loci and AIDs. Phenotypically different AIDs share genetic susceptibility factors.[6,7] Several single nucleotide polymorphisms associated with JIA have been identified.[7-10] Patients

AID	Autoimmune disease
AIT	Autoimmune thyroiditis
bDMARD	Biological DMARD
BMI	Body mass index
CD	Celiac disease
cJADAS	Clinical Juvenile Arthritis Disease Activity Score
DM	Diabetes mellitus
DMARD	Disease-modifying antirheumatic drug
DPV	Diabetes Patienten Verlaufsdokumentation
JIA	Juvenile idiopathic arthritis
MTX	Methotrexate
NPRD	National Pediatric Rheumatologic Database
PR	Prevalence ratio
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus

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The NPRD has been funded by the German Children Arthritis Foundation (Deutsche Kinder-Rheumastiftung), the DPV and METARTHROS (01EC1407D) are funded by the Federal Ministry of Education and Research. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.07.050

with 1 AID are at an increased risk for another AID.[11] For example, the genetic association between type 1 diabetes mellitus (T1D) and JIA has been described.[12,13]

Epidemiologic knowledge about the comorbidity of JIA and T1D is limited. Previous studies are based mostly on case reports.[14-16] A few observational studies have shown an increased frequency of diabetes mellitus (DM) in patients with JIA compared with the general population.[17,18] Detailed information about the comorbidity of T1D in patients with JIA has been limited. Two established prospective cohorts in Germany, the National Pediatric Rheumatologic Database (NPRD) for JIA and the North Rhine-Westphalian Diabetes Registry for T1D, provide a unique opportunity to investigate the co-occurrence of JIA and T1D.

In 2015, Hermann et al published data on the prevalence of JIA in patients with T1D. They showed an increased prevalence of JIA compared with the general population and an earlier onset of diabetes in patients with JIA.[19] The present study, based on the NPRD data, aimed to determine the prevalence of T1D in patients with JIA and to characterize the features of patients with JIA with T1D vs patients with JIA without T1D.

Methods

The NPRD of children and adolescents with rheumatic diseases was started in 1997 and includes incident and prevalent cases of a wide spectrum of juvenile rheumatic diseases. The majority of enrolled patients (3 of 4 patients) have JIA. Enrolled patients are followed annually by a physician and patient questionnaire. For more details, we refer to previous NPRD publications.[20-22] Patients with JIA according to the International League of Associations for Rheumatology criteria[23,24] who were 20 years of age or younger and recorded in the NPRD between 2012 and 2014, were included in this study.

Information about comorbid DM was recorded from 2012 to 2014. The presence of autoimmune thyroiditis (AIT) and celiac disease (CD) was documented by physicians only in 2013 and 2014. An additional short questionnaire on DM was used to confirm the diagnosis of DM and to provide more details regarding T1D. Patients recorded in multiple years were counted only once.

The prevalence of T1D in patients with JIA was compared with the prevalence of T1D in the general population of children and adolescents aged 0-20 years in the federal state of North Rhine-Westphalia on December 31, 2014. Independent registries for T1D exist in 4 federal German states. We chose North Rhine-Westphalia for our comparison because it comprises 22%-23% of all German children and adolescents. The prevalence data of North Rhine-Westphalia were derived from the North Rhine-Westphalian diabetes registry maintained at the German Diabetes Center since 1993. The prevalence of T1D in North Rhine-Westphalia is higher than in other parts of Germany.[25]

Incident cases between the ages of 0 and 20 years for the period 2002-2014 were selected from the registry to estimate the cumulative age distribution of T1D onset in the general population compared with the distribution of T1D onset in patients with JIA. This registry ascertains newly diagnosed cases of T1D from 3 data sources: a prospective hospital-based active surveillance system (Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland [ESPED]), annual inquiries among medical practices (pediatricians, general practitioners, and internal specialists), and the diabetes prospective follow-up (Diabetes-Patienten-Verlaufsdokumentation [DPV]) database. DPV is a computer-based system for longitudinal documentation of treatment and outcomes in routine diabetes care.[26] The DPV software is used in more than 420 diabetes centers in Germany. Completeness of the North Rhine-Westphalian diabetes registry is estimated at 99%.

Sociodemographic and clinical characteristics, and patient-reported outcome measures were annually recorded in the NPRD. These included age, sex, body height, and weight, JIA duration, age at JIA onset, JIA category, treatment, and others. Body mass index (BMI) was calculated by dividing body weight (in kg) by squared body height (in meters). Categories of underweight, normal weight, overweight, and obesity were defined according to sex- and age-specific BMI percentile curves for German children as suggested by Kromeyer-Hauschild et al.[27] The physicians recorded treatments with conventional synthetic and biological disease-modifying antirheumatic drugs (DMARD) as well as glucocorticoids, including low dose (<0.2 mg/kg), high dose (≥0.2 mg/kg), and pulse therapy. In addition, physicians recorded comorbidities of DM, AIT, and CD and their onset dates.

The patient's JIA disease activity was assessed by the pediatric rheumatologist using a numeric rating scale (0-10, 0-no disease activity). The clinical Juvenile Arthritis Disease Activity Score (cJADAS)[28] is a composite index for assessment of JIA disease activity. The cJADAS-10 is the sum of the physician's and patient's/parent's global assessment and the number of active joints (maximum = 10). Functional ability was reported by patients or parents using the Childhood Health Assessment Questionnaire, calculated as a disability index ranging between 0 and 3 (0-no disability).[29]

The DM questionnaire was sent to pediatric rheumatology centers that recorded a DM case between 2012 and 2014 and included questions regarding the type of DM (T1D, type 2 diabetes mellitus [T2D], steroid-induced diabetes, maturity-onset diabetes of the young-type, and others), age at DM diagnosis, insulin treatment, diagnosis of other AIDs (including AIT and CD), and family history of AIDs.

Statistical Analyses

Cross-sectional data from the NPRD for the years 2012, 2013, and 2014 were used to determine the diabetes rate in patients with JIA. Descriptive analyses included absolute and relative frequencies for categorical variables, means and SDs or median and IQR, if appropriate, for continuously distributed variables.

The frequency of T1D in patients with JIA was compared with the population-based data of the North Rhine-Westphalian diabetes registry.[25] Crude diabetes prevalence and respective