Association of Epilepsy and Type 1 Diabetes Mellitus in Children and Adolescents: Is There an Increased Risk for Diabetic Ketoacidosis?

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Objective To estimate the prevalence of epilepsy and possible risk factors in children and adolescents with diabetes mellitus.

Study design We conducted an observational cohort study based on the Diabetes Patienten Verlaufsdokumentation database including data from 45 851 patients (52% male) with type 1 diabetes mellitus, age 13.9 ± 4.3 years (mean ± SD) and duration of diabetes mellitus 5.4 ± 4.2 years. The database was searched for the concomitant diagnosis of epilepsy or epileptic convulsions and for antiepileptic medication.

Results A total of 705 patients with epilepsy were identified, giving a prevalence of 15.5 of 1000. A total of 375 patients were treated with antiepileptic medication, and 330 patients were without anticonvulsive therapy. Patients with epilepsy were younger at onset of diabetes mellitus and shorter than patients without epilepsy, and their weight and body mass index were comparable. No difference could be demonstrated for metabolic control, type of insulin treatment, insulin dose, and prevalence of B-cell specific autoantibodies. The frequency of severe hypoglycemia was lower in patients treated with antiepileptic medication. The risk for diabetic ketoacidosis was almost double in patients with epilepsy compared with patients with type 1 diabetes mellitus alone ($P < .01$).

Conclusion Children and adolescents with diabetes mellitus show an increased prevalence of epileptic seizures. For unknown reasons, there is an association between epilepsy and diabetic ketoacidosis in children with type 1 diabetes mellitus. *(J Pediatr 2012;160:662-6)*.

Seizures caused by hypoglycemia in patients with type 1 diabetes mellitus are relatively frequent events, with 18.2 to 62.0 per 100 patient years depending on age, type of treatment, and residual insulin secretion,[1,2] but seizures also can occur during diabetic ketoacidosis (DKA) because of metabolic derangement or cerebral edema.[3] In adults, an association between diabetes mellitus and idiopathic generalized epilepsy has been described. In a recent study, a four-fold excess of type 1 diabetes mellitus was found in a cohort of adults with epilepsy.[4] Diagnosis of diabetes mellitus preceded the onset of epilepsy by several years.

Studies in children have shown conflicting results. A study in Italy found a higher prevalence of epilepsy in adolescents with diabetes mellitus compared with healthy control subjects.[5] O'Connell found no increase in risk for epilepsy in children and adolescents with diabetes mellitus in Australia.[6]

The aim of our study was to estimate the prevalence of epileptic seizures in children and adolescents with type 1 diabetes mellitus in Germany and Austria on the basis of a large cohort.

Methods

The observational cohort analysis was based on the continuous diabetes data acquisition system for prospective surveillance, Diabetes Patienten Verlaufsdokumentation (DPV).[7] The data documentation DPV started on a bi-national level (Germany and Austria) in 1995 and comprises complete demographic characteristics and diabetes-related findings. Anonymous longitudinal data from patients are transmitted for central validation and analyzed twice yearly. Analysis of anonymized DPV data was approved by the Institutional Review

BMI	Body mass index
DKA	Diabetic ketoacidosis
DPV	Diabetes Patienten Verlaufsdokumentation
GAD	Glutamic acid decarboxylase
HbA1c	Hemoglobin A1c

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Board at the University of Ulm. Inconsistent data are verified and, when necessary, corrected at the participating centers and re-entered in the joint database.

Data from children and adolescents with type 1 diabetes mellitus <20 years old who were treated in 184 pediatric departments of university and general hospitals in Germany and Austria were included. For each patient, the most recent year of follow-up was used. For the calculation of event rates, the interval between visits was used as time under risk.[8]

Sex and age at diabetes mellitus onset were available for all subjects.

According to the guidelines of the German Diabetes Association, all centers are requested to document weight, height, body mass index (BMI), hemoglobin A1c (HbA1c) levels, blood pressure, and acute complications (severe hypoglycemia or DKA) at least every 6 months. BMI (kg/m^2) was expressed as BMI-SDS on the basis of German normative data by Kromeyer-Hauschild.[9] HbA1c values were mathematically standardized. DKA was defined as pH <7.3, hospital admission because of DKA, or both. Hypoglycemic episodes were classified as severe when mental status was altered and help from another person was required and as hypoglycemic coma when seizures or loss of consciousness occurred at blood glucose levels <3.3 mmol/L.

Concomitant diseases, associated autoimmune conditions, and additional medication other than insulin treatment also are documented in the database. In DPV, epilepsy was diagnosed on the basis of at least two unprovoked seizures in normoglycemia (capillary blood glucose >3.9 mmol/L) with >24 hours between the seizures. Blood glucose measurement is recommended in every episode of seizures or unconsciousness.

To ensure that all possible epilepsy cases were identified, a broad search was undertaken. The database was searched for the concomitant diagnoses epilepsy or epileptic convulsions and for antiepileptic medication including all marketed antiepileptic drugs, including acetolamide, beclamide, carbamazepine, clobazam, ethosuximide, gabapentin, lamotrigene, levetircetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, sulthiam, tiagabine, topiramate, valproate, vigabatrin and zonisamide.

Statistical Methods

Data were analyzed with SAS software version 9.1 (SAS Institute, Cary, North Carolina). Data are presented as means ± SD for normal distributed variables or median and range for non-Gaussian distributed parameters. For group comparisons, non-parametric statistical tests (Kruskal-Wallis) were used, with adjustment for multiple comparisons by using the method of Holm.

Differences of frequencies for categorical variables were tested by the χ^2 test.

To adjust comparisons between patients with diabetes mellitus with additional epilepsy and patients with diabetes mellitus without additional epilepsy, hierarchic linear models were applied with age at onset, sex, and diabetes mellitus duration as fixed effects and treatment center as random effect (random intercept model with Cholesky co-variance structure). Degrees of freedom were calculated according to Kenward-Roger, by using a conjugate-gradient-optimization technique (SAS version 9.2, proc glimmix). For comparison of event rates (hypoglycemia, DKA), Poisson distribution was assumed with a logarithmic link function, by using the interval between the respective outpatient visits as time under risk. Poisson models were corrected for overdispersion.

Results

From January 1995 to March 2010, 45 847 patients (52% male) with type 1 diabetes mellitus aged 0.1 to 20.0 years were registered in the DPV database. The mean age of the cohort was 13.9 ± 4.3 years, the mean age at diagnosis was 8.5 ± 4.3 years, and the mean duration of diabetes mellitus was 5.4 ± 4.2 years.

A total of 705 of these patients with type 1 diabetes mellitus additionally were categorized as patients with epilepsy, giving a prevalence of 15.5 of 1000.

A total of 375 patients (53%) were treated with antiepileptic medication, and 330 patients (47%) were not. Considering only patients currently on antiepileptic medication, the prevalence of treated epilepsy in our cohort was 8.2 of 1000.

Clinical characteristics of the patients are given in **Table I**.

Patients with epilepsy were younger at onset of diabetes mellitus and were shorter than patients without epilepsy, and weight and BMI were comparable in the groups. No difference could be demonstrated for metabolic control for HbA1c. Both groups used an average of >3 daily insulin injections, and the insulin dosage per kg bodyweight was similar. There was no difference in the groups for the number of daily insulin injections (5.4 ± 2.2 versus 5.4 ± 2.1 injections per day) or type of treatment as continuous subcutaneous insulin infusion and multiple daily insulin injection.

There was no difference in the prevalence of B-cell specific autoantibodies, including glutamic acid decarboxylase (GAD) autoantibodies.

The numbers of severe hypoglycemic events and hypoglycemic coma per 100 patient years were higher in the group with epilepsy, but after adjustment for confounders as age at onset, sex, and duration of the disease, the difference was no longer significant. In the group of patients with diabetes mellitus and epilepsy, the frequency of severe hypoglycemic events was lower in patients taking antiepileptic medication compared with patients not taking the medication (19.9 ± 3.3 per 100 patient years versus 38.2 ± 5.3 per 100 patient years, $P < .01$; **Table II**).

The risk for DKA was almost double in the patients with epilepsy compared with patients with type 1 diabetes mellitus alone. The difference in risk for DKA in the groups persisted even when considering only severe DKA with a pH value <7.1 (**Table II**).

Analyzing the type of antiepileptic treatment, 82 patients were treated with either topiramate or sulthiame, 293