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TYPE 1 DIABETES: PATHOPHYSIOLOGY AND PREVENTION

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Type 1 diabetes and epilepsy in childhood and adolescence: Do glutamic acid decarboxylase autoantibodies play a role? Data from the German/Austrian/Swiss/Luxembourgian DPV Registry

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Abstract

Aims: We aimed to analyze the relationship between epilepsy and glutamic acid decarboxylase autoantibodies (GADA) in patients with type 1 diabetes mellitus (T1DM) and the impact of GADA on demographic, clinical, and metabolic data in T1DM patients with epilepsy.

Methods: We searched for patients with T1DM ≤20 years and GADA measurements, and within this group for patients with epilepsy. We formed groups: T1DM + Epilepsy + GADA positive; T1DM + Epilepsy + GADA negative; T1DM + GADA positive; T1DM + GADA negative. We used logistic regression to analyze the relationship between epilepsy and GADA with odds ratio adjusted for sex, duration of diabetes (DOD), and age at diabetes onset (ADO). We used logistic regression with odds ratio adjusted for DOD and ADO onset using epilepsy as a dependent variable and GADA, HbA1c, ketoacidosis, severe hypoglycemia (SH), sex, celiac disease, and autoimmune thyroiditis as independent variables. We conducted regression analyses

adjusted for sex, DOD, and ADO to analyze differences in clinical/metabolic parameters between the groups.

Results: Epilepsy was not more frequent in GADA-positive patients (GPP). Logistic regression including all patients with GADA measurements showed that hypoglycemia with coma (HC) correlated with epilepsy when compared to no SH. We found no differences in clinical and metabolic data between GPP and GADA-negative patients (GNP) with epilepsy. SH occurred more often in GPP with epilepsy in comparison to GPP without epilepsy. GNP with epilepsy had a higher rate of HC than GPP without epilepsy.

Conclusion: We found no relationship between epilepsy and GADA. A relationship between T1DM and epilepsy might be explainable by SH.

KEYWORDS

children and adolescents, diabetes mellitus type 1, epilepsy, glutamic acid decarboxylase autoantibodies, severe hypoglycemia

1 | INTRODUCTION

The pathogenesis of type 1 diabetes mellitus (T1DM) is characterized by autoimmune destruction of beta cells in the pancreas.[1] Being an autoimmune disorder, T1DM is associated with other immune-mediated diseases, such as autoimmune thyroid disease (AIT),[2] celiac disease,[3,4] and Addison's disease,[5] suggesting a common genetic susceptibility.[6]

The relationship between T1DM and epilepsy remains a topic of controversy although most evidence points toward an increased risk of epilepsy for patients with T1DM.[7-11] Factors considered to contribute to neuronal damage finally causing epilepsy in T1DM are immune-mediated processes linked to the autoimmune pathogenesis of T1DM itself including autoantibodies to glutamic acid decarboxylase autoantibodies (GADA), metabolic abnormalities (hypo- and hyperglycemia), cerebrovascular disease, and genetic risks. The exact mechanisms, however, are not fully understood.[12]

GADA are directed against secretory vesicles in the pancreatic islet cells and are proven to play an important pathogenic role in the development of T1DM, contributing to the destruction of the insulin-producing pancreatic cells.[13] As for the central nervous system (CNS), GADA are directed against the enzyme glutamic acid decarboxylase, which is essential for the formation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Among others, GADA have been linked to autoimmune encephalitis, Stiff man syndrome, cerebellar ataxia, and severe epilepsy particularly affecting the temporal lobe.[14] This leads to the question of whether GADA might disturb inhibitory GABA-mediated neurotransmission in the CNS and contribute to the pathogenesis of epilepsy among patients with T1DM.[15] So far, only few studies have addressed this question. Aguiar et al studying 375 adults with T1DM found similar rates of GADA among patients with and without epilepsy. Patients with epilepsy, however, showed higher GADA serum titers.[16] Moloney et al compared 25 patients with T1DM and epilepsy with 36 matched pairs without epilepsy. They found an increased rate of GADA among patients with epilepsy.[17]

To the best of our knowledge, studies analyzing the relationship between GADA and epilepsy in a cohort of young patients with T1DM and epilepsy have not been published so far as has the relationship between positive GADA and demographic, clinical, and metabolic parameters among these patients.

We therefore aimed to address this question based on data of the German/Austrian/Swiss/Luxembourgian DPV registry.

2 | RESEARCH DESIGN AND METHODS

2.1 | Data source

The multicenter, prospective, computer-based diabetes data acquisition system DPV (www.d-p-v.eu) was used in this study. The DPV initiative currently comprises 485 specialized diabetes care centers from Germany, Austria, Switzerland, and Luxembourg using the DPV software for standardized documentation of diabetes diagnosis and patient care. The electronic health record contains demographic data, type and onset of diabetes, data on metabolic control and treatment regimen, and information on comorbidities. The locally documented information is pseudonymized and subsequently transmitted twice a year to Ulm, Germany, for central analyses and quality assurance.[18,19] If necessary, centers are requested to correct inconsistent data. All plausible data are then aggregated into a cumulative database. The DPV initiative has been approved by the ethics committee of the University of Ulm and the anonymized data documentation by the local review boards. Until September 2019, demographic and clinical data of 534 756 patients with any type of diabetes were recorded in the database, including 84 267 T1DM patients ≤20 years of age.

2.2 | Subjects

For the present study, we considered patients with T1DM ≤ 20 years in which GADA measurements had been documented. In this cohort, we identified patients with comorbid epilepsy by searching the database for the additional lifetime diagnosis of epilepsy using ICD-10 codes (G 40) and German search terms considering different terminologies and synonyms for epilepsy (eg, "Epilepsie," "Anfallsleiden," "Krampfleiden," "epileptische Anfälle," "Krampfanfälle"). For the comparison of data, we divided the patients into four groups: Group 1: T1DM + Epilepsy + GADA positive; Group 2: T1DM + Epilepsy + GADA negative; Group 3: T1DM + GADA positive; Group 4: T1DM + GADA negative. In order to analyze the impact of GADA in T1DM patients with epilepsy, we compared clinical and metabolic parameters between the four groups. The final study population comprised 31 601 patients from 155 German, 13 Austrian, 1 Swiss, and 1 Luxembourgian centers. From the 31 601 patients with T1DM, we identified 368 T1DM patients with comorbid epilepsy.

2.3 | Variables analyzed

For the present study, data from the most recent documented treatment year of each patient were considered. We analyzed demographic data (age, sex, body mass index [BMI], duration of diabetes [DOD], age at diabetes manifestation, as well as glycemic control [HbA1c] and insulin dose in international units kg^{-1} d^{-1}). We used the LMS method to calculate the standard deviation score of BMI (BMI-SDS) or BMI *z*-score as a measure for the degree of overweight due to the skewness of BMI distribution based on reference data.[20] Furthermore, our analysis also evaluated the rates of documented diabetic ketoacidosis (DKA) (venous pH < 7.3 and/or bicarbonate < 15 mM/L), severe hypoglycemia (SH) (an event requiring assistance of another person to actively administer carbohydrates, glucagon, or intravenous glucose), or hypoglycemia with coma (HC) (loss of consciousness or occurrence of seizures) in events per patient-year aggregated over the most recent treatment year per patient based on Poisson regression with individual time under risk as offset. Finally, we analyzed the frequency of additional disorders, such as celiac disease (biopsy-proven) and AIT.

To adjust for differences between laboratory methods, the multiple of the mean method was applied to mathematically standardize HbA1c measurements to the Diabetes Control and Complications Trial (DCCT) reference range (20.7-42.6 mM/mol or 4.04%-6.05%).[21]

2.4 | Statistics

Data analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). Logistic regression was used to analyze the relationship between epilepsy and GADA with odds ratio adjusted for sex, DOD, and age at diabetes onset (ADO). We used logistic regression with odds ratio adjusted for DOD and ADO to calculate the contribution of possible pathophysiologically relevant factors to the pathogenesis of epilepsy in patients with T1DM. Hereby, we used epilepsy (yes/no) as dependent variable and serum GADA titers (GADA negative/GADA ≤ 5-fold elevated/GADA > 5-fold elevated), HbA1c (<7.5% or ≥7.5%), DKA (yes/no), severe hypoglycemia (no severe hypoglycemia/severe hypoglycemia/hypoglycemia with coma), sex (male/female), celiac disease (yes/no), and AIT (yes/no) as independent variables. Results are presented as median with quartiles or proportion. We compared demographic parameters between the groups using Wilcoxon's rank sum test for continuous and χ^2-test for binary variables. *P* values were corrected for multiple comparisons using the Holm step-down method. To account for potential confounding effects (ADO, sex, and DOD), multivariable regression models were created to compare diabetes-related outcome variables between the groups. Linear regression was used for continuous variables, logistic regression for binary data, and Poisson regression for event rates. Restricted maximum likelihood was used as estimation technique in linear regression and maximum likelihood for logistic regression. Results are given as adjusted means with SEM. Two-sided *P* values < .05 were defined as statistically significant.

3 | RESULTS

3.1 | GADA are detected more frequently among female patients

Three hundred sixty-eight patients with and 31 233 patients without epilepsy were included into the analysis. Table 1 summarizes demographic data, including age at analysis, ADO, sex, and DOD distinguishing between patients with and without epilepsy as well as patients with positive and negative GADA findings, respectively. We found differences with regard to demographic data, particularly a higher rate of females among GADA-positive patients (GPP).

3.2 | GADA-positive and GADA-negative patients do not differ in their rates of epilepsy

Epilepsy was not more frequent in GPP (*P* = .77; odds ratio 0.97 [95% CI 0.79-1.20]).

3.3 | GADA-positive and GADA-negative patients with epilepsy do not differ in clinical and metabolic data

After adjustment for ADO, sex, and DOD, we found no significant differences between GADA-positive and GADA-negative patients (GNP) with T1DM and epilepsy regarding BMI, BMI-SDS, HbA1c, insulin dose, rate of DKA, rate of SH, rate of HC, and the frequency of celiac disease and autoimmune thyroiditis (Table 2).

TABLE 1 Demographic data of GADA positive and GADA negative patients with T1DM with and without epilepsy

Parameter	Group 1: T1DM and epilepsy, GADA positive	Group 2: T1DM and Epilepsy, GADA negative	Group 3: T1DM without epilepsy, GADA positive	Group 4: T1DM without epilepsy, GADA negative	*P* value group 1 vs group 2	*P* value group 1 vs group 3	*P* value group 1 vs group 4	*P* value group 2 vs group 3	*P* value group 2 vs group 4	*P* value group 3 vs group 4
Number of patients	210	158	18 660	12 573						
Age at analysis (y)	16.7 (13.0-17.8)	16.6 (12.6-17.7)	15.5 (11.7-17.5)	15.5 (11.5-17.5)	.63	***<.001***	***<.001***	***.03***	***.03***	.35
Age at diabetes onset (y)	9.3 (5.7-11.7)	7.4 (4.5-11.3)	10.0 (6.4-13.0)	8.6 (5.1-12.2)	.07	***.007***	.63	***<.001***	.05	***<.001***
Male patients	46%	59%	50%	60%	***.03***	.33	***<.001***	***.03***	.89	***<.001***
Duration of diabetes (y)	6.2 (3.8-9.1)	7.5 (3.7-10.0)	4.0 (1.6-7.0)	4.9 (2.0-8.4)						

Note: *P* values were adjusted for multiple comparisons using Tukey-Kramer; values presented as median with quartiles or proportion; no statistical comparisons were made for duration of diabetes as duration of diabetes is not an independent parameter (directly dependent on age at analysis and age at diabetes onset); significant differences in bold and italic.
Abbreviations: GADA, glutamic acid decarboxylase autoantibodies; T1DM, type 1 diabetes mellitus.

3.4 | The occurrence of SH/HC correlates with an increased risk of epilepsy

Adjusted comparisons of parameters possibly contributing to the pathogenesis of epilepsy between the four groups showed that SH occurred significantly more often in GPP with epilepsy in comparison to GPP without epilepsy ($P = .04$). Moreover, GNP with epilepsy had a higher rate of HC than GPP without epilepsy ($P = .01$) (Table 2).

After adjusting for DOD and ADO, logistic regression did not show any correlation between epilepsy and serum GADA titers, HbA1c, DKA, sex, celiac disease, or AIT. HC when compared to no SH showed a correlation with epilepsy ($P < .001$; odds ratio 2.73 [95% CI 1.68-4.44]).

4 | DISCUSSION

To the best of our knowledge, this is the first study analyzing the relationship between epilepsy and GADA in young patients with T1DM and epilepsy as well as the impact of GADA on demographic, clinical, and metabolic parameters in patients with T1DM and epilepsy. In our cohort of patients, epilepsy was not more frequent in GPP. Therefore, it remains unclear whether GADA are involved in the pathogenesis of epilepsy in patients with T1DM.

Epilepsy affects 0.5% to 1% of children in the general population. However, the validity of epilepsy diagnoses from different data sources varies, and contemporary population-based incidence studies are lacking.[22] In our cohort of 84 267 young patients with T1DM, we found 368 patients with comorbid epilepsy (~0.44%), that is, the incidence of epilepsy in young T1DM patients would seem comparable to that in the general population.

However, epilepsy is an umbrella term for different types of epileptic disorders, and GADA have previously been discussed to be associated with distinct types of epilepsy only.[14] For example, Caietta et al characterized idiopathic generalized epilepsy and non-idiopathic temporal epilepsy as the two most common types of epilepsy in their cohort of children with T1DM.[23] McCorry et al compared the population prevalence of T1DM in 15- to 30-year-olds to a cohort of 518 15- to 30-year-olds with idiopathic generalized epilepsy and found that the prevalence of T1DM is increased by the factor of four in young adults with idiopathic generalized epilepsy.[24] Studying 233 patients with epilepsy, Errichiello et al detected GADA in six (2.58%) patients. Two of these patients had idiopathic generalized epilepsy and T1DM, the other four patients had cryptogenic temporal epilepsy.[25] In the DPV registry, the type(s) of epilepsy are not documented. We therefore do not have data on the distinct types of epilepsy in our studied cohort. Furthermore, we have to keep in mind that although GADA have been discussed to be a possible link between T1DM and epilepsy,[24] up to now, the pathomechanism and relevance of GADA in epilepsy remain unclear, and evidence of a pathomechanistic association between GADA, T1DM, and epilepsy/types of epilepsy is, as for now, lacking.

TABLE 2 Clinical and metabolic data of GADA positive and GADA negative patients with T1DM with and without epilepsy

Parameter	Group 1: T1DM and epilepsy, GADA positive	Group 2: T1DM and epilepsy, GADA negative	Group 3: T1DM without epilepsy, GADA positive	Group 4: T1DM without epilepsy, GADA negative	*P* value group 1 vs group 2	*P* value group 1 vs group 3	*P* value group 1 vs group 4	*P* value group 2 vs group 3	*P* value group 2 vs group 4	*P* value group 3 vs group 4
BMI (kg/m^2)	21.43 ± 0.26	21.49 ± 0.30	21.48 ± 0.03	21.60 ± 0.03	1.00	1.00	.91	1.00	.98	***.02***
BMI-SDS	0.19 ± 0.06	0.23 ± 0.08	0.27 ± 0.01	0.30 ± 0.01	.97	.61	.35	.96	.83	.05
Insulin dose (IE kg^{-1} d^{-1})	0.84 ± 0.02	0.90 ± 0.03	0.86 ± 0.00	0.86 ± 0.00	.38	.73	.87	.62	.47	.36
HbA1c (%)	7.99 ± 0.12	8.47 ± 0.14	8.14 ± 0.01	8.16 ± 0.01	.05	.60	.48	.09	.13	.68
HbA1c (mM/mol)	63.83 ± 1.31	69.07 ± 1.54	65.46 ± 0.14	65.70 ± 0.17	.05	.60	.48	.09	.13	.68
Celiac disease	3%	2%	3%	2%	.82	.97	.86	.88	.96	.35
Autoimmune thyroid disease	7%	6%	6%	5%	.96	.99	.36	.98	.91	***<.001***
Diabetic ketoacidosis (events/ patient-year)	0.05 ± 0.02	0.08 ± 0.03	0.04 ± 0.00	0.04 ± 0.00	.83	.97	.96	.38	.33	.95
Severe hypoglycemia (events/ patient-year)	0.25 ± 0.08	0.16 ± 0.06	0.11 ± 0.00	0.11 ± 0.00	.82	***.04***	.05	.74	.78	.97
Hypoglycemia with coma (events/ patient-year)	0.06 ± 0.02	0.08 ± 0.04	0.02 ± 0.00	0.03 ± 0.00	.92	.06	.25	***.01***	.06	.05

Note: Adjusted values ± SEM and proportions with adjustments for age at diabetes onset, sex, and diabetes duration; significant differences in bold and italic.
Abbreviations: BMI, body mass index; BMI-SDS, standard deviation score of BMI; GADA, glutamic acid decarboxylase autoantibodies; T1DM, type 1 diabetes mellitus.

In the discussion of whether GADA are involved in the pathogenesis of epilepsy in patients with T1DM, we additionally have to keep in mind that the production of GADA in T1DM patients is not always stable, that is, during the course of T1DM, patients can change from GADA positivity to GADA negativity and vice versa.[26] Furthermore, the possible lack of an association between GADA and epilepsy in T1DM patients is strengthened by the fact that most patients with GADA associated autoimmune epilepsy do not have T1DM.[27]

Finally, GADA-related epilepsy in T1DM might not be mediated by GADA in the serum but by GADA in the cerebrospinal fluid (CSF). Accordingly, children and adults with T1DM and consecutive epilepsy have been described with high titers of GADA in the serum and CSF.[28,29] The intrathecal production of GADA could be essential for the development of certain neurological diseases, as serum GADA are not able to cross the blood-brain barrier.[30] Interestingly, Lilleker et al were able to observe that adult patients with epilepsy and high serum titers of GADA had high CSF GADA titers, as well.[31] Furthermore, Aguiar et al were able to show that adult patients with T1DM and epilepsy had higher serum GADA titers than T1DM patients without epilepsy.[16] In our study with pediatric patients with T1DM and epilepsy, however, the degree of elevation of serum GADA titers did not correlate with the occurrence of epilepsy suggesting that the pathomechanisms leading to epilepsy in patients with T1DM differ to a certain extent between children and adults.

According to meta-analytic data,[12] other pathomechanistic links between T1DM and epilepsy than GADA must also be discussed. This includes the metabolic abnormalities of T1DM, such as hypoglycemia and hyperglycemia, which may damage the CNS,[8] alter the balance between the neuronal inhibition and excitation, and cause seizures.[32-34] In our study, HC when compared to no SH showed a correlation with epilepsy. Furthermore, we were able to show that GNP with epilepsy had a higher rate of HC than GPP without epilepsy indicating that HC might be a stronger factor in the pathogenesis of epilepsy in patients with T1DM than GADA. This thought is strengthened by our observation that SH occurred significantly more often in GPP with epilepsy in comparison to GPP without epilepsy. Finally, both groups with epilepsy (+/− GADA) had higher mean rates of SH with coma than both groups without epilepsy although these differences were not statistically significant. As pointed out by Tricò and Herzog, the acute and functional injuries induced by SH, that is, the lack of glucose as a source of energy for brain metabolism, can persist even after normal glucose levels are restored, leading to abnormalities in the electroencephalogram and perhaps to a predisposition for unprovoked seizures.[35] Therefore, repeated episodes of SH/HC in patients with T1DM may cause neuronal damage resulting in epilepsy. This mechanism, however, can only partially explain the relationship between T1DM and epilepsy. As shown by Moloney et al, in 44% of patients with T1DM and epilepsy, epilepsy precedes T1DM suggesting that the two diseases can arise independently through partially overlapping mechanisms.[17] In the DPV registry, the date of epilepsy diagnosis is not documented. We therefore do not have data on which is the preceding diagnosis in our cohort of T1DM patients with epilepsy.

Hyperglycemia, as well, is an important risk factor for focal seizures in patients with T1DM, predisposing to cerebrovascular dysfunction and a secondary decrease of cerebral blood flow enhanced by neuronal hyperosmolarity and dehydration.[36] In line with these studies, Yun and Xuefeng reported that patients with diabetes who experienced episodes of DKA also have seizures more frequently.[37] As an earlier study from the DPV registry was able to demonstrate that the risk for DKA in pediatric patients with T1DM and epilepsy was almost double in comparison to patients with T1DM only,[38] patients with T1DM and epilepsy would seem to have the risk of entering a vicious circle consisting of seizures and DKA. In our study, DKA did not correlate with the occurrence of epilepsy, and the rate of DKA did not differ between the four groups. A possible explanation for this seeming discrepancy could be the fact that the risk for DKA is influenced by numerous factors such as age, sex, ethnicity, personal skills, level of diabetes education, concomitant medication, and so on.[39]

Cerebrovascular damage could be another pathomechanistic link between T1DM and epilepsy, as diabetes can result in pathological capillary changes, leading to neurological disorders such as epilepsy.[12] Hyperglycemia can induce different structural and functional damages in blood vessels of the brain, which could result in ischemic events and subsequent seizures secondary to impaired metabolism of endothelial nitrite oxide, dysfunctions of coagulation and fibrinolytic networks, malfunctioning of recanalization, or increased reperfusion injuries.[40] The relevance of these mechanisms in the pathogenesis of epilepsy in patients with T1DM, however, is controversial.[36]

We need to mention potential limitations of this study. The GADA measurements were not performed centrally but in the individual laboratories associated to the respective participating centers. We well understand the drawbacks of decentralized GADA testing but centralized GADA measurements were not feasible for organizational and financial reasons. Furthermore, we used serum GADA measurements for our analyses, as CSF GADA measurements are not available in the DPV registry. Finally, it has to be mentioned that a potential limitation of a multicenter-database, such as DPV with 485 participating centers, is underreporting, that is, the possibility exists that T1DM patients with epilepsy are not recorded due to overlooking in individual centers.

In conclusion, we found no relationship between epilepsy and GADA in our study irrespective of serum GADA titers. We were able to demonstrate a correlation between epilepsy and HC which is supported by the comparisons of the rates of SH/HC between the four groups. In our study, the impact of GADA-positive autoimmunity in young patients with T1DM and epilepsy seems limited.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Gideon John de Sousa created tables, wrote, and edited the manuscript. S. R. Tittel edited the manuscript and performed the data analyses. M. Häusler, P. M. Holterhus, G. Berger, M. Holder, C. Kamrath, S. Golembowski, and S. Herrlinger researched data and reviewed the manuscript. R. W. Holl conceptualized the study and reviewed the manuscript. R. W. Holl 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 and the accuracy of the data. All authors have approved the final article.

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