ORIGINAL PAPER

Neurodevelopmental and neurological disorders in children and adolescents with type 1 diabetes in central Poland. A study on one heterogenous region of Poland

Hanna Maria Kuśmierczyk-Kozieł[1], Martyna Supernat[1,2], Martyna Plisiecka-Olesiejuk[1,3], Anna Kaczmarek[1], Krystyna Wyka[4], Agnieszka Szadkowska[1], Anna Hogendorf[1]

[1]Department of Paediatrics, Diabetology, Endocrinology and Nephrology, Medical University of Lodz, Lodz, Poland
[2]Department of Paediatrics and Allergy, Medical University of Lodz, Lodz, Poland
[3]Department of Rheumatology and Clinical Immunology with Internal Medicine Subdivision, University Clinical Hospital of the Military Academy of Medicine, Lodz, Poland
[4]Department of Paediatrics, Oncology and Haematology, Medical University of Lodz, Lodz, Poland

ABSTRACT

INTRODUCTION: Some recent research has shown an increased prevalence of epilepsy and autism spectrum disorder (ASD) in children with type 1 diabetes (T1D) compared with the general population. This study aimed to evaluate the prevalence and clinical characteristics of the above-mentioned and other neurological disorders among children with T1D.

MATERIAL AND METHODS: The study included youths aged 1–16 with T1D from a single paediatric diabetes centre in Central Poland. Children with both T1D and neurological/neurodevelopmental diagnoses were identified by a retrospective medical records review of all patients. The prevalence was compared to the general prevalence among Polish children based on the official electronic databases.

RESULTS: The study comprised 669 children with T1D, mean age 11.23 ±3.43 years. Twenty nine (4.3%) had at least one neurological disorder, mostly epilepsy (12, 1.8%) and ASD (8, 1.2%). Nine participants had ≥ 1 neurological diagnosis.

The prevalence of ASD among children with T1D was similar to the overall population patients aged ≤ 16 in Poland: 1.2% vs. 1.15% (OR = 1.044, 95% CI: 0.52–2.096, p = 0.9032), but it was higher for epilepsy: 1.8% vs. 1.02% (OR = 2.0112, 95% CI: 0.8427–4.7999, p = 0.11). Metabolic control in children with ASD was similar to those with T1D only, but significantly worse for other neurological disorders, especially epilepsy (HbA_{1c} 7.9 ±1.6% vs. 7.2 ±1.0%, p = 0.0014 and 7.6 ±1.0% vs. 7.2 ±1.0%, p = 0.0029, respectively).

CONCLUSIONS: In our study there is a small, but important group of individuals with T1D and neurological disorders comprising mostly boys. This group does not differ significantly from their peers with T1D only in terms of age or diabetes onset but has different immunological patterns and worse metabolic control.

KEY WORDS: neurology, autoimmunity, type 1 diabetes, autism spectrum disorder, epilepsy.

Current Topics in Diabetes 2026; 6 (2): 1–6

DOI: https://doi.org/10.5114/ctd/221495

Introduction

Type 1 diabetes (T1D) is an autoimmune disease that affects over 1.2 million children and adolescents worldwide [1] and over 18 000 young people in Poland [2]. Its prevalence increased significantly over the past several decades. Its pathogenesis and clinical course seems to be very heterogeneous, suggesting the existence of specific phenotypes and endotypes of the disease [3], and making finding a cure for T1D extremely difficult. Moreover, frequent coexistence of T1D with multiple autoimmune and non-autoimmune disorders may suggest common, yet not completely identified, genetic background. Finding this background and dividing patients into specific subpopulations is essential to improve the results of targeted therapies and optimize their treatment.

Some recent studies have shown an increased prevalence of epilepsy and autism spectrum disorder (ASD) in children with T1D compared with the general population. Therefore, we aimed to focus on this special group of youths with clinically apparent neurological deficits to evaluate the prevalence, and to describe their clinical characteristics.

Material and methods

The study included children and adolescents with T1D, recruited from a single paediatric diabetes care centre, which is the only reference unit for the population of 2.47 million inhabitants from Central Poland (Lodzkie region), diagnosed with T1D before 31.12.2019. Children with both T1D and diagnoses such as ASD, epilepsy and other neurological disorders were identified by a retrospective medical records review of all patients aged 1–16 with T1D (n = 669).

The diagnosis of T1D was confirmed by positivity for at least two of anti-islet autoantibodies: islet cell autoantibodies (ICA), glutamic acid decarboxylase (GAD), tyrosine phosphatase (IA2A), insulin (IA/IAA), or zinc transporter 8 (ZnT8) autoantibodies. The conventional autoantibodies were measured in serum: ICA with immunofluorescence, autoantibodies to GAD, islet antigen 2 (IA/IAA) and ZnT8 with ELISA (RSR Ltd., UK) and IA2 with specific radio binding assays RIA (CIS International, France or RSR Ltd., USA). Levels of ICA were quantified according to the International Workshop on the Standardization of ICA, with indirect immunofluorescence of pancreatic tissue obtained from a human donor. The cut-off values for ICA, GAD, IA2A/IA2, and IA/IAA positivity were 10 Juvenile Diabetes Foundation units, 10 and 20 U/ml and 7%/0.4 U/ml, respectively. According to the IASP2020 (Islet Autoantibody Standardization Program) – the disease sensitivity of the antibody was ICA – 72.0% and 94.4%, GAD 82% and 98.9%, IA2 – 70% and 95.6%, ZnT8 – 76% and 97.8%, and for IA/IAA – 42% and 100%.

Neurological diagnoses had been confirmed by a neurologist or psychiatrist (documented in medical history).

For comparison of the prevalence of ASD among the Polish group of children with the same age we used the data from the electronic system monitoring certification of disability (EKSMOoN) [4].

For comparison of the prevalence of epilepsy, data for 2014–2019 were obtained from the National Health Fund [5].

Statistical analysis

Continuous variables were presented as medians followed by interquartile ranges, while nominal variables as numbers and percentages. To present the overlap between detected neurological problems, Venn's diagram was created with online tool Venny 2.1.20 [6]. The Shapiro-Wilk test was used to assess the continuous variables for normal distribution. Most continuous variables displayed non-normal distribution – therefore, they were compared between groups using the Mann-Whitney U test or Kruskal-Wallis ANOVA. For those tests, participants with T1D without any neurological disorders were considered as reference. Categorical variables between the groups were compared with χ^2 test or Fisher's exact test for small subgroups. Associations between each neurological disorder (considered exposure) and qualitative outcomes (presence of comorbidities, *etc.*) were assessed with odds ratios (OR) and corresponding 95% confidence intervals (95% CI). The Statistica package (StatSoft, TIBCO, Palo Alto, CA, USA) was used for the analysis. P-values < 0.05 and OR with 95% CI not overlapping one were considered statistically significant.

Results

The final cohort comprised 669 consenting participants (349 boys [52%] and 320 girls), of mean age of 11.23 ±3.43 years. The groups were similar in age, age at T1D onset and number and structure of other autoimmune comorbidities (autoimmune hypothyroidism, celiac disease, asthma or allergy).

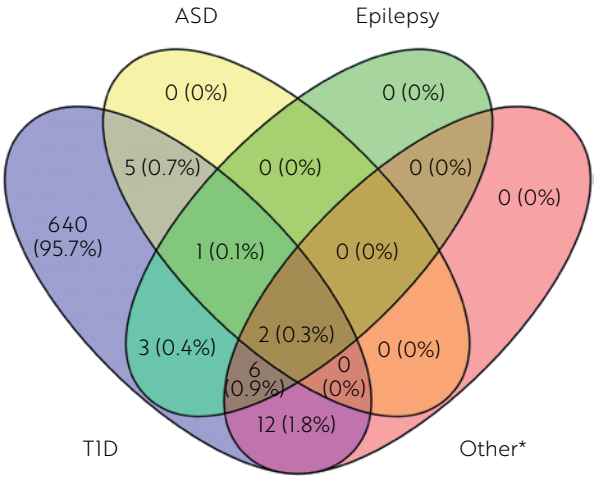
Overall, 29 (4.4%) children had at least one neurological disorder and/or ASD: 12 (1.8%) had

epilepsy, 8 (1.2%) had ASD, and 20 (3%) other neurological diseases (Supplementary Table 1). Nine participants (1.35%) had more than one neurological diagnosis (most commonly epilepsy with another neurological condition) (Figure 1). Table 1 shows the comparison between the "T1D neurological" and "T1D non-neurological" control groups and the detailed clinical characteristics of each "neurological" participant is presented in Supplementary Table 1.

According to sex, ASD was diagnosed only in boys (p = 0.0065), and more boys than girls (75% vs. 25%) suffered from epilepsy (p = 0.1076). In the whole group with neurological disorders, the disproportion was not that profound, though still visible (66% vs. 34%, p = 0.1416)

The only statistical difference (p = 0.0464) was that two children (6.9%) with neurological disorders had other autoimmune disorders than mentioned above (vitiligo and IgA deficiency), while in the control group it was 1.7% (n = 11).

All children with ASD were diagnosed before the diagnosis of T1D. Among children with epilepsy, most (75%, n = 9) displayed symptoms after the diagnosis of T1D. In terms of other neurological



ASD – autism spectrum disorder, T1D – type 1 diabetes
** Other: attention-deficit hyperactivity disorder, paroxysmal cerebral dysrhythmia, multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, hearing loss, oligophrenia, mutism*

Figure 1. Distribution of patients 1–16 years old with type 1 diabetes in the Department

disorders, 10 (50%) were diagnosed before, 7 (35%) after and 3 (15%) simultaneously with T1D.

Among children with ASD, 75% (n = 6) had a relative with autoimmune disease, most com-

Table 1. Group characteristics and comparison

Parameters	Overall T1D (n = 669)	T1D only (n = 640)	T1D + all neurological disorders (n = 29)	p-value	T1D + ASD (n = 8)	p-value	T1D + epilepsy (n = 12)	p-value
Age [years]	M = 11, 23 ±3.43	M = 11, 29 ±3.41	M = 10, 1 ±3.89	0.0682	M = 11, 0 ±3.74	0.8113	M = 9, 92 ±4.033	0.1698
Sex (men), n (%)	349 (52.16)	330 (51.56)	19 (65.5)	0.1416	8 (100)	0.0065	9 (75)	0.1076
Age at T1D onset [years]	M = 6,24 ±3.58	M = 6,23 ±3.55	M = 5,9 ±4.21	0.6275	M = 6,88 ±3.40	0.6068	M = 5.0 ±3.71	0.2352
Positive anti-GAD antibodies, n/N (%)	445/651 (68.3)	427/622 (68.6)	18/29 (62.0)	0.4556	3/8 (37.5)	0.0607	9/12 (75)	0.6360
Thyroid disease, n (%)	124 (18.5)	117 (18.3)	7 (24.1)	0.4323	2 (25)	0.6271	1 (8.3)	0.3732
Coeliac disease, n (%)	76 (11.3)	73 (11.4)	3 (10.3)	0.8552	2 (25)	0.2324	1 (8.3)	0.7374
Asthma/allergy, n (%)	95 (14.2)	91 (14.2)	4 (13.8)	0.9519	3 (37.5)	0.0630	1 (8.3)	0.5609
IgA deficiency, n (%)	7 (1.1)	6 (0.9)	1 (3.4)	0.1878	0 (0)	0.7877	0 (0)	0.7415
Other immune comorbidities, n (%)	13 (1.9)	11 (1.7)	2 (6.9)	0.0464	0 (0)	0.7102	1 (8.3)	0.6490
Mean HbA_{1c} [mmol/mol] (%)	56 ±11 7.3 ±1.0	56 ±11 7.3 ±1.0	63 ±17 7.9 ±1.6	0.0014	59 ±11 7.6 ±1.0	0.3779	63 ±20 7.9 ±2.2	0.0290

ASD – autism spectrum disorder, T1D – type 1 diabetes

monly T1D. In children with epilepsy and other neurological disorders, only 3 (14%) had a family member with autoimmune disease.

Anti-GAD antibodies were positive in 75% of participants with concomitant epilepsy, 37.5% of children with T1D and ASD, and in 68.6% of control children (p = 0.6360 and p = 0.0607, respectively).

For 18 participants in the control group, data about occurrence of anti-GAD antibodies was not possible to obtain (they were primarily diagnosed in another centre).

There was no significant difference in metabolic control (measured by % HbA_{1c}) in children with ASD, but those with other neurological disorders had significantly worse results than their peers with T1D only (63 ±17 mmol/mol, 7.9 ±1.6% vs. 56 ±11 mmol/mol, 7.2 ±1.0%, p = 0.0014 in the whole group, 63 ±20 mmol/mol, 7.9 ±2.2% vs. 56 ±11 mmol/mol, 7.2 ±1.0%, p = 0.0029 in children with epilepsy).

Discussion

One of the approaches to achieve the goal of applying precision medicine in diabetes mellitus is to identify endotypes (that is, well-defined subtypes) of the disease each of which has a distinct etiopathogenesis that might be amenable to specific interventions [7].

Our study demonstrated that among children with autoimmune diabetes there is a group (4.4%) with additional clinically apparent symptoms of neurological conditions. Some children had multiple neurological problems suggesting specific genetic syndromes and even existence of some unknown diabetic phenotypes and endotypes of T1D (like previously described by us children with 18q – deletion syndrome and Treg deficiency) [8, 9]. Their physical and/or intellectual uniqueness makes them especially interesting for further research on causes of these extremely heterogenous disorders.

The prevalence of epilepsy was higher in the T1D group than in the general Polish population: 1.8% vs. 1.0% (OR = 2.0112, 95% CI: 0.8427–4.7999, p = 0.11). Recent studies, like the one based on a much larger cohort from the German/Austrian/Swiss/Luxembourgian Diabetes-Patienten-Verlaufsdokumentation Registry, showed that epilepsy was found to be even 2–5 times more frequent in children with T1D [10–13], what would suggest common genetic or immunological background. In recent years, there has been a growing interest in immunological pathogenesis and treatment in epilepsy, as it was discovered that patients with autoimmune diseases more often suffer from drug-resistant forms of epileptic seizures [14–16].

We found that the prevalence of autism spectrum disorders among children with T1D is similar to the overall population under 16 years in Poland: 1.2% vs. 1.15% (OR = 1.044, 95% CI: 0.52–2.096, p = 0.9032) which is in line with the results obtained by other authors [17, 18]. Some other studies suggest that the prevalence of diabetes might be higher in children with ASD [19, 20].

Interestingly, our data showed that only boys were diagnosed with ASD, while in the whole outpatient clinic (control group) the proportion of boys vs. girls was about 50/50.

This fact was not entirely surprising, taking into account that in general males are more commonly diagnosed with autism, even though such striking disproportion had reported so far [17, 18, 21, 22].

We did not observe any correlation between other autoimmune diseases and neurological disorders and results from previous studies in different regions are sometimes contradictory [15, 23, 24].

It is worth noticing that children with neurological conditions overall had significantly worse metabolic control (measured by HbA_{1c}) than the control group, and while the tendency proved significant also for children with epilepsy, children with ASD had similar metabolic control to their T1D peers. While reasons for this might vary (e.g. fear of risk of seizures due to hypoglycaemia [19, 21, 22, 25, 26], problems with adapting to therapeutic regime [27]), as those children are usually under closer parental guidance, most studies indicated better metabolic control in those groups, which should be a warning for the Polish medical system.

The major strength of our study is that the group is ethnically and therefore genetically similar (all included subjects were of Caucasian, Polish ancestry). Moreover, we used first reliable data on the prevalence of children with ASD in Poland [28], based on reports.

The anti-GAD measurements were performed centrally, by the same investigator, while in the study by de Sousa et al. [12] it came from different laboratories.

There are however some limitations. The first one is a relatively low number of participants, from a single centre, as Poland does not have any national T1D registry. Therefore, some of the results, though interesting, lack statistical significance. For further research in this field, we will include more patients from other centres all patients are registered.

Moreover, it is possible that the results of the national database of children with disabilities are incomplete, as social shame of disability (and the fear of being socially stigmatized) may cause some parents to refrain from registering ASD in the database.

Conclusions

Nevertheless, our study has shown that among children with T1D there is a small, but important group of individuals with neurological disorders with possible common genetic/autoimmune background, with a notable overrepresentation in boys. This group does not differ significantly from all the children in terms of age or of T1D onset but has different immunological patterns. Most differences are not statistically significant in small populations; however, tendencies are interesting enough to broaden the research. Further genetic and immunological evaluation may reveal causes of these phenotypes.

Disclosures

1. Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of the Medical University of Lodz (approval decision no. RNN/46/20/KE, dated: 11.02.2020).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.
5. Patient consent: Written informed consent was obtained from the patient's legal guardian for publication of this case study.

REFERENCES

1. IDF Diabetes Atlas. 10th ed. Available from: www.diabetesatlas.org (accessed: 15.10.2022).
2. Chobot A, Polanska J, Brandt A, Deja G, Glowinska-Olszewska B, Pilecki O, et al. Updated 24-year trend of type 1 diabetes incidence in children in Poland reveals a sinusoidal pattern and sustained increase. Diabet Med 2017; 34: 1252-1258.
3. Battaglia M, Ahmed S, Anderson MS, Atkinson MA, Becker D, Bingley PJ, et al. Introducing the endotype concept to address the challenge of disease heterogeneity in type 1 diabetes. Diabetes Care 2020; 43: 5-12.
4. Walendzik G, Nowak V. Wsparcie osób z autyzmem i zespołem Aspergera: przygotowanie do samodzielnego funkcjonowania. Kontrola Państw 2021; 66: 59-74.
5. Ministerstwo Zdrowia. NFZ o zdrowiu. Padaczka. Avalable from: https://ezdrowie.gov.pl/portal/home/badania-i-dane/zdrowe-dane/raporty/nfz-o-zdrowiu-padaczka (accessed: 2020).
6. Venny 2.1.0. Available from: https://bioinfogp.cnb.csic.es/tools/venny/ (accessed: 13.02.2024).
7. Redondo MJ, Morgan NG. Heterogeneity and endotypes in type 1 diabetes mellitus. Nat Rev Endocrinol 2023; 19: 542-554.
8. Hogendorf A, Lipska-Zietkiewicz BS, Szadkowska A, Borowiec M, Koczkowska M, Trzonkowski P, et al. Chromosome 18q deletion syndrome with autoimmune diabetes mellitus: putative genomic loci for autoimmunity and immunodeficiency. Pediatr Diabetes 2016; 17: 153-159.
9. Hogendorf A, Zieliński M, Constantinou M, Śmigiel R, Wierzba J, Wyka K, et al. Immune dysregulation in patients with chromosome 18q deletions-searching for putative loci for autoimmunity and immunodeficiency. Front Immunol 2021; 12: 742834.
10. Verrotti A, Scaparrotta A, Olivieri C, Chiarelli F. Seizures and type 1 diabetes mellitus: current state of knowledge. Eur J Endocrinol 2012; 167: 749-758.
11. Dafoulas GE, Toulis KA, Mccorry D, Kumarendran B, Thomas GN, Willis BH, et al. Type 1 diabetes mellitus and risk of incident epilepsy: a population-based, open-cohort study. Diabetologia 2017; 60: 258-261. 12.
12. De Sousa GJ, Tittel SR, Häusler M, Holterhus PM, Berger G, Holder M, et al. 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. Pediatr Diabetes 2020; 21: 766-773.
13. Wu S, Ding Y. Type 1 diabetes and the risk of epilepsy: a meta-analysis. J Diabetes Investig 2023; 15: 364-373.
14. Amanat M, Thijs RD, Salehi M, Sander JW. Seizures as a clinical manifestation in somatic autoimmune disorders. Seizure 2019; 64: 59-64.
15. Steriade C, Titulaer MJ, Vezzani A, Sander JW, Thijs RD. The association between systemic autoimmune disorders and epilepsy and its clinical implications. Brain 2021; 144: 372-390.
16. Yoshimoto T, Doi M, Fukai N, Izumiyama H, Wago T, Minami I, et al. Type 1 diabetes mellitus and drug-resistant epilepsy: presence of high titer of anti-glutamic acid decarboxylase autoantibodies in serum and cerebrospinal fluid. Intern Med 2005; 44: 1174-1177.
17. Bethin KE, Kanapka LG, Laffel LM, Majidi S, Chaytor NS, MacLeish S, et al. Autism spectrum disorder in children with type 1 diabetes. Diabet Med 2019; 36: 1282-1286.
18. Freeman SJ, Roberts W, Daneman D. Type 1 diabetes and autism: Is there a link? Diabetes Care 2005; 28: 925-926.
19. Tromans S, Yao G, Alexander R, Mukaetova-Ladinska E, Kiani R, Al-Uzri M, et al. The prevalence of diabetes in autistic persons: a systematic review. Clin Pract Epidemiol Ment Health 2020: 16: 212-225.

20. Kohane IS, McMurry A, Weber G, MacFadden D, Rappaport L, Kunkel L, et al. The co-morbidity burden of children and young adults with autism spectrum disorders. PLoS One 2012; 7: e33224.
21. Stanek KR, Youngkin EM, Pyle LL, Raymond JK, Driscoll KA, Majidi S. Prevalence, characteristics, and diabetes management in children with comorbid autism spectrum disorder and type 1 diabetes. Pediatr Diabetes 2019; 20: 645-651.
22. Lemay JF, Lanzinger S, Pacaud D, Plener PL, Fürst-Burger A, Biester T, et al. Metabolic control of type 1 diabetes in youth with autism spectrum disorder: a multicenter Diabetes-Patienten-Verlaufsdokumentation analysis based on 61 749 patients up to 20 years of age. Pediatr Diabetes 2018; 19: 930-936.
23. Zerbo O, Leong A, Barcellos L, Bernal P, Fireman B, Croen LA. Immune mediated conditions in autism spectrum disorders. Brain Behav Immun 2015; 46: 232.
24. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH, et al. Comorbidity of allergic and autoimmune diseases in patients with autism spectrum disorder: a nationwide population-based study. Res Autism Spectr Disord 2013; 7: 205-212.
25. Bartolini E, Ferrari AR, Fiori S, Della Vecchia S. Glycaemic imbalances in seizures and epilepsy of paediatric age: a literature review. J Clin Med 2023; 12: 2580.
26. Imad H, Johan Z, Eva K. Hypoglycemia and risk of seizures: a retrospective cross-sectional study. Seizure 2015; 25: 147-149.
27. Oser TK, Oser SM, Parascando JA, Grisolano LA, Krishna KB, Hale DE, et al. Challenges and successes in raising a child with type 1 diabetes and autism spectrum disorder: mixed methods study. J Med Internet Res 2020; 22: e17184.
28. Płatosa M (red.). Ogólnopolski spis autyzmu. Sytuacja młodzieży i dorosłych z autyzmem w Polsce. Stowarzyszenie Innowacji Społecznych „Mary i Max", Warszawa 2016.