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Comparison of autoantibody-positive and autoantibody-negative pediatric participants enrolled in the T1D Exchange clinic registry

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Abstract

Objective—To compare characteristics of autoantibody (aAb)-positive and -negative cases of type 1 diabetes (T1D) <18 years old in the T1D Exchange clinic registry.

Methods—An aAb-positive status ($n = 6239$) required at least one of the aAbs to be positive; an aAb-negative status ($n = 485$) required negative results on testing of at least two different aAbs.

Results—The percentage of males was higher (58% vs 51%; $P = 0.002$) and total daily insulin dose lower ($P = 0.003$) in aAb-negative compared with aAb-positive groups, but both groups had similar distributions of race–ethnicity, diagnosis age, family history of T1D, ketoacidosis at diagnosis, body mass index at diagnosis and at most recent office visit, and current HbA1c.

Conclusions—Male gender and lower total daily insulin dose were more likely in aAb-negative than aAb-positive children with T1D, but no other distinguishing characteristics were identified. Further examination of characteristics of aAb-negative cases may help characterize the heterogeneous nature of T1D.

Keywords

autoantibodies; autoantibody; childhood type 1 diabetes; pediatric diabetes

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Timing of antibody measurements.

Disclosures

A.S., M.R., B.O., A.G., P.C., S.D., and K.M. have nothing to declare. R.B.'s non-profit employer has received consultant payments on his behalf from Sanofi and Animas and a research grant from NovoNordisk with no personal compensation to R.B.

Introduction

Type 1 diabetes (T1D) results from immune-mediated destruction of insulin-producing β-cells, leading to insulin deficiency.[1] Autoantibodies (aAbs) are markers of an autoimmune response, but in 10%–20% of cases of presumed T1D testing is negative.[2–5] There have been limited efforts to further understand the physiopathology behind this group of patients, with some data suggesting a higher incidence of aAb negativity among those of African or Asian ancestry.[5–8] Using the large T1D Exchange clinic registry database,[9] the present study compared the characteristics of youth with T1D who were aAb-positive with those who were aAb-negative.

Methods

The T1D Exchange Clinic Network includes 67 US-based pediatric and adult endocrinology practices. A registry of individuals with T1D commenced enrollment in September 2010[9] and, as of 1 August 2012, included 25 833 participants, with 14 592 aged <18 years. To be enrolled in the clinic registry, an individual must have a clinical diagnosis of presumed autoimmune T1D and either islet cell antibodies present or, if antibodies are negative or unknown, then insulin must have been started at or shortly after diagnosis and used continually thereafter (except in the case of a pancreas or islet cell transplant). Each clinic received approval from an institutional review board (IRB). Informed consent and assent from minors were obtained according to IRB requirements. Data were collected for the registry's central database from the participant's medical record and by having the participant or parent complete a comprehensive questionnaire, as described previously.[9]

Clinic registry participants <18 years old who had aAb measurements available were considered for the present analysis. Pancreatic aAb test results, which were obtained from the clinic's medical records, included islet cell (ICA), glutamate decarboxylase (GAD), tyrosine phosphatase (IA-2 or ICA-512), and zinc cotransporter (ZnT8); insulin aAb results were not used because of uncertainty in determining the timing of assessment relative to the initiation of insulin therapy. Only the 6724 participants who met the criteria for either aAb-positive or aAb-negative, as described below, were included in the analysis. An aAb-positive status ($n = 6239$) required at least one autoantibody to be positive at any time relative to diagnosis; an aAb-negative status ($n = 485$) required negative results on testing of at least two different aAbs, at least one of them within 12 months after diagnosis (Tables 1–3 show the autoantibodies tested and the results for the aAb-positive and aAb-negative cases; Table S1, available as Supplementary Material to this paper, shows the timing of measurements relative to diagnosis.)

Differences in clinical characteristics comparing aAbpositive and aAb-negative participants were assessed using Chi-squared tests for categorical variables and *t*-tests or Wilcoxon rank tests for continuous variables. When assessing the differences in current body mass index (BMI), HbA1c, and total daily insulin dose, participants with diabetes of <1 year duration were excluded from the analysis. All *P*-values are two-sided. Due to multiple comparisons, only $P < 0.01$ were considered to be potentially clinically meaningful. Analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

As shown in Table 4, diagnosis age was similar in aAb-positive and aAb-negative cases. The aAb-negative cases were more likely than aAb-positive cases to be male (58% vs 51%, respectively; $P = 0.002$), but both groups had similar race–ethnicity distributions and a similar frequency of family history of T1D.

At the time of diagnosis, aAb-positive and aAb-negative cases were similar in terms of the proportion that presented with ketoacidosis ($P = 0.36$) and median BMI percentile ($P = 0.13$). At the time of registry enrollment, aAb-positive and aAb-negative cases had similar age and diabetes duration distributions (both with mean age 10.9 years and mean duration 2.7 years) and a similar proportion were using an insulin pump (41% vs 43%, respectively). Most recent HbA1c and BMI levels appeared similar between groups, whereas total daily insulin dose tended to be slightly higher among aAb-positive cases ($P = 0.003$; Table 4).

Discussion

Although one of the hallmarks of T1D is the presence of one or more aAbs, it is well recognized that there is a subset of presumed T1D patients who are aAb-negative at diagnosis.[3,5]

In the present study, we found that characteristics of aAb-negative and aAb-positive cases were similar, with the exception that a higher proportion of aAb-negative participants were male and that the aAb-negative participants had a lower total daily insulin dose than the aAb-positive participants, associations that could be due to chance because we do not have plausible explanations. Of note, we did not find a difference in race–ethnicity distribution between positive and negative cases, in contrast with other studies reporting a higher frequency of negative cases among individuals with African or Asian ancestry.[8] It is also of interest that the frequency of a family history of T1D was similar in aAb-positive and aAb-negative cases.

The main limitations of the present study are that all aAbs were not collected on all participants, particularly ZnT8, which was measured in a small percentage, and measurements were not made at a standardized time point from diagnosis or in a single reference laboratory. As a result, we cannot determine whether all those without aAbs present were indeed wholly aAb-negative.

There are several key questions that remain to be answered in aAb-negative patients, including whether they have a fundamentally different process leading to diabetes. Preliminary insights from the Hvidore Study Group, a cohort of children with T1D from Europe and Japan, suggested that GADA-, IA-2A-, and ICA-negative children have a slower decline in β-cell function and improved glycemic control 12 months after diagnosis.[10] However, that study had a small number of participants, included wide ethnic backgrounds, and did not include ZnT8 aAbs. In our data, there was a suggestion of a lower total daily insulin dose among aAb-negative compared with aAb-positive individuals, which could be an indirect sign of greater β-cell function in aAb-negative subjects. An additional consideration is that the aAb-negative patients may have another form of diabetes, such as

maturity onset diabetes of youth resulting from a monogenic defect, a mitochondrial defect, or other rare causes.[11,12] Further characterization of aAb-negative cases with presumed T1D may uncover novel defects regulating β-cell growth and differentiation. Whole exome sequencing or other analyses may help define such causes for diabetes.[13]

A better understanding of the disease process in aAb-negative cases may help to project the expected clinical course for aAb-negative individuals with diabetes and lead to alternative therapies, such as oral agents rather than exogenous insulin or new family screening practices. Furthermore, such aAb-negative patients are excluded from new onset T1D intervention studies that aim to preserve β-cell function. Further insight into their disease process may lead to therapies that help preserve β-cell function and that differ from therapies offered to those with aAb positivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix I. Staff of the Type 1 Diabetes (T1D) Exchange Clinic Network Coordinating Center and sites of the T1D Exchange Clinic Network

The T1D Exchange Clinic Network Coordinating Center staff are Roy Beck, Brian Becker, Christina Carpenter, Vincent Chen, Peiyao Cheng, Elizaveta Dolzhenko, Stephanie DuBose, Heidi Gillespie, Russell Guzzetta, Callyn Hall, Kellee Miller, Dan Raghinaru, Tricia Rampersad, Nicole Reese, Alysa Sampson, Ashleigh Saenz, Jeffrey Saunders, Heidi Strayer, and Dongyuan Xing.

The T1D Exchange Clinic Network sites with participating principal investigators (PI), co-investigators (I), and coordinators (C) ordered according to the number of participants recruited per site as of 1 August, 2012 are listed below.

Philadelphia, PA Children’s Hospital of Philadelphia (n = 1451)

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Significant findings of the study

The phenotype of non-autoimmune type 1 diabetes (T1D) patients was characterized in a large cohort. We noted differences consistent with a different pathopysiologic process. Further prospective studies are needed to characterize non-autoimmune T1D and could lead to the discovery of novel genes.

What this study adds

Significant information to current knowledge on the natural history and phenotype of non-autoimmune T1D. It adds valuable information on autoantibody trends, and stresses the importance of further studies to discover novel genes involved and to gain an understanding of the heterogeneity of T1D.

Table 1

Cross-tabulation for combinations of autoantibodies tested and autoantibody positivity within the autoantibody-positive group (n = 6239)

		Autoantibody positive													
	All	**Anti-GAD**	**Anti-GAD/anti-IA2**	**Anti-GAD/anti-IA2/ZnT**	**Anti-GAD/ZnT**	**Anti-IA2**	**Anti-IA2/ZnT**	**ICA**	**ICA/anti-GAD**	**ICA/anti-GAD/anti-IA2**	**ICA/anti-GAD/anti-IA2/ZnT**	**ICA/anti-GAD/ZnT**	**ICA/anti-IA2**	**ICA/anti-IA2/ZnT**	**ICA/ZnT**	**ZnT**
Autoantibody tested																
Anti-GAD	633	633														
Anti-GAD/anti-IA2	1825	395	1175			255										
Anti-GAD/anti-IA2/ZnT	249	30	33	109	13	19	31									14
Anti-GAD/ZnT	19	8			10											1
Anti-IA2	47					47										
Anti-IA2/ZnT	6						6									
ICA	210							210								
ICA/anti-GAD	2677	666						497	1514							
ICA/anti-GAD/anti-IA2	300	42	79			20		7	25	104			23			
ICA/anti-GAD/anti-IA2/ZnT	33	6	1	1	3	1	1	1		6	6			5		2
ICA/anti-GAD/ZnT	216	21			20			28	32			56			47	12
ICA/anti-IA2	19					6		2					11			
ICA/ZnT	1														1	
ZnT	4															4

Data show the number of individuals in each group.

GAD, glutamic acid decarboxylase; IA2, islet antigen 2; ZnT, zinc transporter; ICA, islet cell antibodies.

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Table 2

Combination of autoantibody tested within the negative antibody group ($n = 485$)

	n
Autoantibody tested	
Anti-GAD/anti-IA2/	114
Anti-GAD/anti-IA2/ZnT	28
Anti-GAD/ZnT	1
ICA/anti-GAD	284
ICA/anti-GAD/anti-IA2	22
ICA/anti-GAD/anti-IA2/ZnT	2
ICA/anti-GAD/ZnT	31
ICA/anti-IA2	3

GAD, glutamic acid decarboxylase; IA2, islet antigen 2; ZnT, zinc transporter; ICA, islet cell antibodies.

Table 3

Frequency for testing of each autoantibody, within each antibody group

	Autoantibody positive (*n* = 6239)		Autoantibody negative (*n* = 485)
	No. tested	**No. positive (%)**	**No. tested**
ICA	3456	2575 (75)	342
GAD	5952	4988 (84)	482
IA2	2479	1939 (78)	169
ZnT8	528	342 (65)	62

GAD, glutamic acid decarboxylase; IA2, islet antigen 2; ZnT8, zinc transporter 8; ICA, islet cell antibodies.

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Table 4

Characteristics of antibody-positive and antibody-negative participants

	Antibody positive (*n* = 6239)	Antibody negative (*n* = 485)	*P*-value*
Age at diagnosis (years)	7.8 ± 3.9	7.7 ± 4.2	0.770
Males (%)	3187 (51)	283 (58)	0.002
Race–ethnicity†			0.510
White non-Hispanic	4628 (74%)	347 (72%)	
Black non-Hispanic	396 (6%)	35 (7%)	
Hispanic–Latino	784 (13%)	66 (14%)	
Asian	101 (2%)	12 (2%)	
Other	300 (5%)	24 (5%)	
Family history (first-degree relative) of T1D‡	741 (12%)	66 (14%)	0.250
BMI percentile at diagnosis§	47 (15, 83)	39 (12, 79)	0.130
No. normal/underweight (%)	2586 (77)	218 (78)	
No. overweight (%)	373 (11)	25 (9)	
No. obese (%)	396 (12)	35 (13)	
Current BMI percentile§	77 (57, 91)	77 (54, 90)	0.320
No. normal/underweight (%)	2755 (63)	229 (65)	
No. overweight (%)	974 (22)	71 (20)	
No. obese (%)	666 (15)	51 (15)	
DKA at diagnosis**	2029 (35%)	151 (33%)	0.360
Current HbA1c†† (%)	8.4 ± 1.5	8.4 ± 1.5	0.810
Current total daily insulin dose‡‡ (units/kg per day)	0.83 ± 0.38	0.77 ± 0.35	0.003

Unless indicated otherwise, data are given as either the mean ± SD or the number of subjects in each group, with percentages in parentheses.

**P*-values were calculated for categorical variables using a Chi-squared test and for continuous variables using either a *t*-test (when mean values are shown) or Wilcoxon's rank test (when median values are shown).

†Race/ethnicity data were unavailable for 31 participants.

‡Family history data of type 1 diabetes (T1D) were unavailable for 224 participants.

[§]Current body mass index (BMI) and BMI at diagnosis are given as the median, with 25th and 75th percentiles in parentheses. Data for BMI at diagnosis were unavailable for 3091 participants. Current BMI data exclude results for 1942 participants with a duration of diabetes <1 year (n = 1810 in the antibody-positive group and 132 in the antibody-negative group) and was unavailable in a further 36 participants. The results for current BMI were similar in both groups when the analysis included those with diabetes of <1 year duration.

[**]Diabetic ketoacidosis (DKA) data at diagnosis were unavailable for 539 participants.

[††]Current HbA1c data exclude results for 1942 individuals with diabetes of <1 year duration and was unavailable for a further 73 participants.

[##]Current total daily insulin dose data exclude results for 1942 individuals with diabetes of <1 year duration and was unavailable for a further 268 participants.