Polyendocrinopathy in Children, Adolescents, and Young Adults With Type 1 Diabetes

A multicenter analysis of 28,671 patients from the German/Austrian DPV-Wiss database

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OBJECTIVE — To investigate diabetes-specific autoantibodies and additional autoimmune phenomena in a large cohort of young patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Data from 28,671 patients <30 years with type 1 diabetes from 242 specialized centers in Germany and Austria were analyzed.

RESULTS — At least one β-cell antibody was present in 81.6% of patients. β-cell–Ab-negative patients were significantly younger at diabetes onset ($P < 0.0001$). A total of 19.6% had positive thyroid antibodies with female predominance (62%, $P < 0.0001$). Antibodies to tissue transglutaminase were present in 10.7%, with a significantly longer duration of diabetes ($P < 0.0001$). Parietal cell antibodies were found in 283 patients, associated with older age ($P < 0.001$), and adrenal antibodies were present in 94 patients. In 575 patients, at least three different autoimmune phenomena were present.

CONCLUSIONS — Thyroid autoimmunity and antibodies suggestive for celiac disease are the most prevalent additional immune phenomena in type 1 diabetes. Parietal/adrenal antibodies are rare.

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Additional autoimmune phenomena such as Hashimoto thyroiditis or celiac disease are a frequent observation in type 1 diabetes (1,2). The appearance of autoantibodies is often the first detectable sign of autoimmune diseases (3). The aim of this study was to investigate screening frequency and prevalence of autoimmune phenomena in a large cohort of children, adolescents, and young adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Data collection

Data were collected from 242 departments in Germany/Austria by means of a computerized follow-up program called the Diabetes Prospective Documentation Initiative (Diabetes Patienten Verlaufsdokumentation [DPV]) (4).

Patient characteristics

Data from 46,342 patients between 1990 and 2008 were included in the database. We analyzed 28,671 patients (mean age 13.7 years; range 0–30; 52.2% male) with at least one autoantibody measurement (GADA, ICA, IAA, and IA-2A at onset; TG, TPO, Gliadin-Ab, TGA, PCA, and AA-Ab). Patients were divided into age-groups according to developmental stage: age-group 1 (0.1–12 years; $n = 9,431$), age-group 2 (12–18 years; $n = 15,495$), and age-group 3 (18–30 years; $n = 3,745$).

Statistical analysis

Data were analyzed using the SAS statistical software package, version 9.1 (SAS Institute, Cary, NC). Data are presented as mean ± SD for normal distributed variables or median and range for non-Gaussian distributed parameters. For group comparisons, nonparametric statistical tests (Kruskall-Wallis test) were used, with adjustment for multiple comparisons (method of Holm). Differences of frequencies for categorical variables were tested by the χ^2 test. A P value ≤0.05 was considered as statistically significant.

RESULTS

Screening frequency

Thyroid autoantibodies were screened in 87.3% of patients, followed by celiac disease antibody (75.7%), TGA (49.9%), β-cell–Ab (52.6%), AA-Ab (10.0%), and PCA (6.3%); all listed in Table 1.

β-Cell autoimmunity

At least one β-cell–Ab (ICA, GAD, IA2, IAA) was present in 12,070 of 14,784 patients (81.6%). GADAs were most frequently measured ($n = 11,150$, 65.3% positive), followed by ICAs ($n = 10,515$, 58.3% positive), IAAs ($n = 8,468$, 67.6% positive), and IA-2As ($n = 7,488$, 66.1% positive). β-Cell–AB-negative patients were significantly younger at type 1 dia-

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Table 1—*Screening frequency and number of patients with positive autoantibodies (in parentheses) in 28,671 patients with type 1 diabetes (divided into three age-groups) from the German-Austrian DPV-Wiss cohort*

	<12 years	12–18 years	18–30 years
N	9,431	15,495	3,745
β-Cell–Ab	5,622 (84.1)	7,414 (81.4)	1,748 (74.5)
GADA	4,710 (63.5)	5,380 (66.6)	1,060 (67.5)
ICA	3,855 (58.4)	5,331 (59.0)	1,329 (55.6)
IA-2A	3,148 (67.8)	3,609 (66.4)	731 (57.3)
IAA	3,145 (66.2)	4,373 (68.1)	1,027 (72.0)
Thyroid-Ab†	8,023 (11.4)	13,791 (22.6)	3,232 (26.9)
TPO	7,874 (8.8)	13,547 (18.6)	3,142 (20.5)
TG	5,713 (9.3)	10,291 (16.6)	2,750 (21.4)
CD-Ab‡	7,512 (20.7)	11,693 (21.0)	2,504 (19.2)
Gliadin-IgA	5,520 (6.9)	9,378 (6.8)	2,220 (6.6)
Gliadin-IgG	4,796 (20.2)	8,098 (18.1)	1,749 (14.5)
TGA	5,557 (10.1)	7,599 (10.7)	1,145 (13.0)
PCA	494 (11.1)	949 (15.6)	352 (22.7)
AA-Ab	764 (3.0)	1,588 (3.3)	525 (3.6)

*Data are *n* (% positive) (*n* refers to the number of patients with at least one autoantibody determination). †Thyroid-Ab includes antibodies against thyreoperoxidase and against thyreoglobulin. ‡CD-Ab includes autoantibodies against Gliadin (IgA/ IgG) and anti-tissue transglutaminase.

betes onset (8.4 ± 4.7 vs. 9.1 ± 4.5 years, $P < 0.0001$).

Thyroid autoimmunity

A total of 4,901 patients (19.6%) were found to have elevated titers of at least one thyroid Ab. Thyroid autoimmunity was associated to female sex (62 vs. 44% in thyroid-Ab–negative patients, $P < 0.0001$), older age (15.3 ± 3.8 vs. 13.4 ± 4.6 years), and longer duration of diabetes (6.7 ± 4.5 vs. 5.3 ± 4.1 years; both $P < 0.0001$).

Celiac disease autoimmunity

TGAs were measured in 14,301 patients, with a positive result in 10.7% (n = 1,529). TGA-positive patients showed a significantly longer duration of diabetes (5.6 ± 3.9 vs. 5.0 ± 3.9 years, $P < 0.0001$).

Parietal cell autoimmunity

PCAs were investigated in 1,795 patients (6.3%), with a positive result in 283 subjects (15.8%), associated with older age (15.8 ± 4.7 vs. 14.3 ± 4.6 years, $P < 0.001$) and longer duration of diabetes (8.3 vs. 6.1 years, $P < 0.0001$).

Anti-adrenal autoimmunity

Screening for AA-Ab was performed in 2,877 patients (10.0%), with a positive result in 94 patients (3.3%). This group did not differ clinically from patients without AA-Ab. Patients with β-cell autoimmunity showed a significantly higher prevalence of AA-Ab compared with β-cell–Ab-negative patients (3.7 vs. 1.5%, $P < 0.05$).

Patients with three or more autoimmune phenomena

In 575 patients (60% female, mean age 14.4 years), at least three different autoimmune phenomena were present (most prevalent: β-cell–Ab, n = 565; TPO, n = 378). Four organ systems were involved in 46 patients.

CONCLUSIONS — We present the results of a large patient group based on the DPV documentation system. This involved the participation of 242 diabetes centers, 28,671 documented patients, and an observation period ≥10 years.

As previously shown, β-cell antibodies were present in ~80% of patients diagnosed with type 1 diabetes (5). The observation that β-cell–Ab-negative subjects were younger is not consistent with previous findings, suggesting β-cell–Ab-negative diabetes forms at an older age in a cohort of patients <18 years, but this might have been also patients with clinical type 2 diabetes (6).

Our data support previous studies documenting the high prevalence of thyroid autoimmunity in young patients with type 1 diabetes (7) and their association to female sex and older age (8).

We can show an association between autoimmunity suggestive of celiac disease and a longer duration of type 1 diabetes. The hypothesis of type 1 diabetes as the first autoimmune disease, followed by celiac disease (9,10), is confirmed and emphasizes the need for repeated antibody testing for celiac disease.

PCAs are characteristic for autoimmune gastritis and are directed to the H+,K+-ATPase of parietal cells. This is the first study to investigate PCAs in a large cohort of young patients with type 1 diabetes. The prevalence of PCAs increased with age and longer duration of type 1 diabetes.

In a study of adults with type 1 diabetes, De Block et al. (11) reported a prevalence of 20.9% of patients with PCA, with iron deficiency anemia in 15.4% and pernicious anemia in 10.5%.

Tests for AA-Abs were performed in 10% (3% positive). Barker et al. (12) studied AA-Ab in patients with type 1 diabetes in 2005 with a positive result in 1.4%. In previous studies, the development of Addison's disease in patients with AA-Ab varies between 18 and 45% (13,14).

Unfortunately, we do not have data on the reasons for PCA and AA-Ab testing, nor do we know about clinical outcome. Thus, the unexpected high number of positive patients may be due to selection factors such as underlying disorders, or even cost factors. Further studies on prevalence of PCA and AA-Ab in type 1 diabetes and associated clinical features are preferable.

Apart from a slightly higher prevalence of AA-Ab in the β-cell–Ab-positive groups, no differences between β-cell–Ab-positive and -negative patients were detected. Thus, the proof of β-cell autoimmunity cannot be seen as a predictor of additional autoimmunity.

Multicenter studies on autoimmune phenomena are under way. We are aware of the weakness of decentralized antibody testing, but centralized measurements were not practicable because of organizational/financial difficulties and the involvement of 242 centers. Nevertheless, they reflect the situation with which clinicians are dealing. All of the laboratories have taken part at a nationwide quality control circle and gave consent to international standardization workshops (15).

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