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

Katharina Warncke, MD; Elke E Fröhlich-Reiterer, MD; Angelika Thon, MD; Sabine E Hofer, MD; Dagobert Wiemann, MD; Reinhard W Holl, MD on behalf of the DPV-Initiative of the German working group for pediatric diabetology and the German BMBF Competency Network for Diabetes Mellitus

From the 1Department of Pediatrics, Technische Universität München, Munich, Germany; 2Department of Pediatrics, Medical University of Graz, Graz, Austria; 3Department of Pediatrics, Hannover Medical School, Hannover, Germany; 4 Department of Pediatrics, Medical University of Innsbruck, Austria; 5 Department of Pediatrics, Otto-von Guericke University Magdeburg, Magdeburg, Germany; and the 6 Department of Epidemiology, University of Ulm, Ulm, Germany

Corresponding author:
Katharina Warncke, MD
Email: katharina.warncke@lrz.tu-muenchen.de

Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

Submitted 1 March 2010 and accepted 7 June 2010.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
**Objective** To investigate diabetes-specific autoantibodies and additional autoimmune phenomena in a very large cohort of young patients with type 1 diabetes (T1D).

**Research Design and methods** Data from 28,671 patients < 30 years with T1D from 242 specialized centres in Germany and Austria were analyzed.

**Results** At least one Beta-cell-antibody was present in 81.6% of patients. β-cell-Ab-negative patients were significantly younger at diabetes onset (p<0.0001). 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 3 different autoimmune phenomena were present.

**Conclusions** Thyroid autoimmunity and antibodies suggestive for celiac disease are the most prevalent additional immune phenomena in T1D. Parietal/ adrenal antibodies are rare.

Additional autoimmune phenomena like Hashimoto thyroiditis or celiac disease are a frequent observation in T1D (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 T1D.

**RESEARCH DESIGN AND METHODS**

**Data collection.** Data was 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 years; 52.2% male) with at least one autoantibody measurement (GADA, ICA, IAA, IA-2A at onset; TG, TPO, Gliadin-Ab, TGA, PCA, AA-Ab). Patients were divided into age groups according to developmental stage: age-group 1 (0.1–12 years; n= 9,431), group 2 (12–18 years; n= 15,495), and 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, USA). Data are presented as mean ± SD for normal distributed variables or median and range for non-Gaussian distributed parameters. For group comparisons, non-parametric 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 chi-square 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 CD-Ab (75.7%; TGA 49.9%), β-cell-Ab (52.6%), AA-Ab (10.0%) and PCA (6.3%).

**β-cell autoimmunity.** At least one β-cell-Ab (ICA, GAD, IA2, IAA) was present in 12,070 of 14,784 patients (81.6%). GADA were most frequently measured (n=11,150, 65.3% positive), followed by ICA (n=10,515, 58.3% positive), IAA (n=8,468, 67.6% positive) and IA-2A (n=7,488, 66.1% positive). β-cell-AB-
negative patients were significantly younger at T1D onset (8.4 ± 4.7 years vs. 9.1 ± 4.5 years, p<0.0001).

**Thyroid autoimmunity.** 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.** TGA 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.** PCA were investigated in 1,795 patients (6.3%), with a positive result in 283 cases (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).

**Antiadrenal 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 significant higher prevalence of AA-Ab compared to β-cell-Ab negative patients (3.7 vs. 1.5%, p<0.05).

**Patients with ≥ 3 autoimmune phenomena.** In 575 patients (60% female, mean age 14.4 years), at least 3 different autoimmune phenomena were present (most prevalent: β-cell-Ab, n=565; TPO, n=378). 4 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 Ab were present in about 80% of patients diagnosed with T1D (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 T1D (7), and their association to female sex and older age (8).

We can show an association between autoimmunity suggestive of celiac disease (CD) and a longer duration of T1D. The hypothesis of T1D as the first autoimmune disease, followed by CD (9, 10) is confirmed and emphasizes the need for repeated antibody testing for CD.

PCA are characteristic for autoimmune gastritis and are directed to the H+,K+-ATPase of parietal cells. This is the first study to investigate PCA in a large cohort of young patients with T1D. The prevalence of PCA increased with age and longer duration of T1D.

In a study of adults with T1D, De Block reported a prevalence of 20.9% patients with PCA (11), with iron deficiency anemia in 15.4% and pernicious anemia in 10.5%.

Tests for AA-Ab were performed in 10% (3% positive). Barker et al. studied AA-Ab in patients with T1D in 2005 (12) with a positive result in 1.4%. In previous studies, the development of Addisons 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 maybe due to selection factors like underlying disorders, or even cost factors. Further studies on prevalence of PCA and AA-Ab in T1D 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 in discussion. We are aware of the weakness of decentralised antibody testing, but centralised measurements were not practicable because of organisational/financial difficulties and the involvement of 242 centers. Nevertheless, they reflect the situation clinicians are dealing with. All of the laboratories have taken part at a nationwide quality control circle and gave consent to international standardization workshops (15).

**Author contributions:** K.W. researched data and wrote the manuscript. E.F., S.H., A.T., D.W. and R.H. researched data, contributed to discussion and reviewed/edited the manuscript.

**ACKNOWLEDGEMENTS**
No potential conflicts of interest relevant to this article were reported.

We kindly acknowledge the participating diabetes centers in Germany and Austria. These centers are listed in the online appendix available at [http://care.diabetesjournals.org](http://care.diabetesjournals.org). “This work was supported by the Kompetenzzentrum Diabetes mellitus (Competition Network for Diabetes mellitus)” funded by the Federal Ministry of Education and Research (FKZ 01GI0859). In addition, the DPV initiative is supported by the Bundesärztekammer, Dr. Dr. Bürger Büsing-Stiftung, Exzellenzzentrum „Stoffwechselkrankheiten“ Baden Württemberg, the European Foundation for the study of diabetes (EFSD), and Novo Nordisk Germany.

**REFERENCES**
Table 1. Screening frequency and number of patients with positive autoantibodies (in brackets) in 28,671 patients with type 1 diabetes (divided into three age groups) from the German-Austrian DPV Wiss Cohort.
(1) Thyroid-Ab include antibodies against thyreoperoxidase and against thyreoglobulin.
(2) CD-Ab include autoantibodies against Gliadin (IgA/ IgG) and anti-tissue transglutaminase.
*N: the N-numbers refer to the patients with at least one autoantibody determination

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