Additional Autoimmune Disease Found in 33% of Patients at Type 1 Diabetes Onset

Taylor M. Triolo, bs¹ Taylor K. Armstrong, bs¹ Kim McFann, phd² Liping Yu, md¹ Marian J. Rewers, md, phd¹ Georgeanna J. Klingensmith, md¹ George S. Eisenbarth, md, phd¹ Jennifer M. Barker, md¹

OBJECTIVE—We sought to define the prevalence of nonislet, organ-specific autoantibodies at diagnosis of type 1 diabetes and to determine the prevalence of comorbid autoimmune diseases.

RESEARCH DESIGN AND METHODS—Children (n = 491) diagnosed with type 1 diabetes at the Barbara Davis Center for Childhood Diabetes were screened for autoimmune thyroid disease (thyroid peroxidase autoantibodies [TPOAb]), celiac disease (tissue transglutaminase autoantibodies [TTGAb]), and Addison disease (21-hydroxylase autoantibodies [210HAb]).

RESULTS—Of the 491 children, 161 had at least one nonislet autoantibody, and of these, 122 (24.8%) were positive for TPOAb, and 15 of the 122 (12.3%) had autoimmune thyroid disease. There were 57 (11.6%) who were positive for TTGAb, of whom 14 (24.6%) had celiac disease. Five (1.0%) were positive for 21OHAb, of whom one had Addison disease.

CONCLUSIONS—Many autoantibody-positive subjects present with additional autoimmune disorders. Detection of these autoantibodies at type 1 diabetes onset may prevent complications associated with delayed diagnosis of these disorders.

ype 1 diabetes occurs in one in 300 individuals (1) and is associated with other autoimmune diseases, including autoimmune thyroid disease (AIT) in 15-30%, celiac disease (CD) in 4-9%, and Addison disease (AD) in 0.5% (2); detection of which is crucial to prevent morbidity related to unrecognized disease. Assays for thyroid peroxidase autoantibodies (TPOAb) in AIT, tissue transglutaminase autoantibodies (TTGAb) in CD, and 21hydroxylase autoantibodies (210HAb) in AD, may be used to screen for asymptomatic disease to identify risk of progression to overt disease. Previous studies have examined multiple autoantibodies in cohorts of patients with type 1 diabetes (3). We sought to define the prevalence of nonislet, organspecific autoantibodies at the diagnosis of type 1 diabetes and to determine the prevalence of comorbid autoimmune diseases.

Diabetes Care 34:1211-1213, 2011

RESEARCH DESIGN AND

METHODS—We studied 491 individuals with type 1A diabetes diagnosed by the American Diabetes Association criteria (4) at the Barbara Davis Center for Childhood Diabetes from 2004 to 2009. GAD antibody (GADAb), islet cell antibody (ICA512Ab), insulin autoantibody (IAA), and zinc transporter 8 antibody (ZnT8Ab) were used to confirm the diagnosis of type 1 diabetes and were measured as described (5,6). TPOAb, TTGAb, and 210HAb were measured within a mean \pm SD of 16 \pm 39 days of diagnosis, as described (7,8). TPOAb was measured using a RIA kit (KRONUS Inc., Star, ID). Patients were diagnosed with AIT, CD, and/or AD within 45 ± 43 days of type 1 diabetes diagnosis. HLA class II DQAB genotyping was performed on 457 subjects for whom DNA was available, as

From the ¹Barbara Davis Center for Childhood Diabetes, Aurora, Colorado; and the ²Colorado Biostatistics Consortium, Colorado School of Public Health, University of Colorado Denver, Aurora, Colorado.

Corresponding author: Taylor M. Triolo, taylor.triolo@ucdenver.edu. Received 10 September 2010 and accepted 21 February 2011. described (9). Subjects were enrolled with informed consent, and the study was approved by the University of Colorado Institutional Review Board.

Our current clinical practice is to obtain thyroid-simulating hormone (TSH) and thyroid hormone levels (T4 or free T4) biannually or with symptoms of AIT. TPOAb screening is solely for research purposes to identify individuals with AIT. Subjects with positive TPOAb were defined as having hypo- or hyperthyroidism according to abnormal results of laboratory testing or by treatment, or both. The date of TSH abnormalities was recorded as the onset of AIT.

Patients with symptoms or persistently high TTGAb were referred to gastroenterology for evaluation and a small-intestinal biopsy to confirm CD diagnosis. Several subjects refused the confirmatory smallintestinal biopsy, and CD was diagnosed by two positive TTGAb results at an index of >0.05 (10) and a gluten-free diet. None of the patients with positive TTGAb who were not diagnosed with CD had a small-intestinal biopsy, and thus it is possible that some children might have had undiagnosed CD. Individuals with positive 210HAb had ACTH stimulation testing, as previously described (11).

GraphPad Prism 5.00 software (Graph-Pad Software, San Diego, CA) was used for statistical analysis. Descriptive statistics are reported as the mean \pm SD. Proportions were compared using a χ^2 test unless 20% of the cells had an expected value of <5, in which case the Fisher exact test was used. Results were considered statistically significant with $\alpha < 0.05$.

RESULTS—Of the 491 children diagnosed with type 1 diabetes, 408 (82.7%) were non-Hispanic white and 262 (53.4%) were boys. The mean age of type 1 diabetes diagnosis was 9.6 ± 4.4 years, and the average HbA_{1c} at diagnosis was $11.6 \pm 2.6\%$. Upon diagnosis of type 1 diabetes, 160 children (32.6%) had at least one positive nonislet organ-specific autoantibody (TPOAb, TTGAb, or 21OHAb; Fig. 1), and 122 (24.8%) were positive for TPOAb, of whom 15 (12.3%) had AIT. Five (1.0%) were positive for 21OHAb,

DOI: 10.2337/dc10-1756

DOI: 10.2337/dc10-1756

^{© 2011} by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/ licenses/by-nc-nd/3.0/ for details.

Autoimmune disorders at type 1 diabetes onset



Figure 1—Frequency of nonislet, organ-specific autoantibodies is shown in 491 children with type 1 diabetes. Of these, 160 (32.6%) were positive for at least one nonislet, organ-specific autoantibody.

of whom one had AD. TTGAb was positive in 57 (11.6%), of whom 14 (24.6%) had CD. Of these 14 diagnosed with CD, six were diagnosed by analysis of an intestinal biopsy specimen and eight were diagnosed from two consecutive TTGAb results at an index of >0.05 (10) and report of symptoms or gluten-free diet, or both. The mean initial TTGAb for these eight subjects was 0.88 ± 0.33 (99th percentile of normal = index 0.05). Of the 161 children with at least one nonislet, organspecific autoantibody, 30 (18.6%) were diagnosed with an additional autoimmune disease within an average of 46 ± 43 days of presentation. The HLA-DR3 allele was found 33 of 53 (62.3%) of TTGAb⁺ subjects compared with 181 of 457 (44.8%) $TTGAb^{-}$ children (P = 0.012).

CONCLUSIONS—This study has confirmed the high prevalence of nonislet, organ-specific autoantibodies in individuals with type 1 diabetes and indicates that for many, these autoantibodies are present at diagnosis. Previous studies have confirmed the prevalence of these antibodies (3) and the effect of these autoantibodies on type 1 diabetes control (12). Additionally, within an average of 45 days after type 1 diabetes diagnosis, 19% of individuals with nonislet, organ-specific autoantibodies were diagnosed with clinical disease. These comorbid conditions were likely present at type 1 diabetes onset, given clinical practice to repeat positive autoantibody tests and perform confirmatory testing, which may take several months to coordinate.

Twice as many children were positive for TPOAb as TTGAb. However, an equal number of children were diagnosed with CD as with AIT. Analysis of HLA confirms a relationship between the *HLA-DR3* allele and TTGAb positivity (7). Further genetic typing will be important to identify additional genes that may contribute to the presence of organ-specific autoimmunity and development of disease.

This study is limited because it only monitored subjects for a short period after their diagnosis of type 1 diabetes, and confirmatory small-intestinal biopsies for CD were not performed on all TTGAb⁺ subjects.

Ongoing follow-up of this cohort will be important to determine the natural history of organ-specific autoimmunity in patients with type 1 diabetes. Key questions remain, including the incidence of autoantibodies over time, the evolution from positive antibodies to disease, the genetic influences on autoimmunity and disease, and patient characteristics that may influence antibody or disease development.

The strategy for screening for these autoantibodies is a source of ongoing debate (13–15). However, given the high preponderance of these antibodies at the onset of type 1 diabetes, we recommend screening for AIT, CD, and AD.

We have shown that 32.6% of patients with type 1 diabetes are positive for at least one additional organ-specific autoantibody at the diagnosis of type 1 diabetes, and 18.6% had clinical disease. This is important for the clinical care of patients with type 1 diabetes and may provide insight into the pathogenesis of these complex diseases.

Acknowledgments—T.M.T. is supported by a National Institute of Diabetes and Digestive and Kidney Diseases Medical Student Training Grant at the University of Colorado–School of Medicine (3T32-DK-0063687-07S1), and her contribution to this project is in partial fulfillment of the Mentored Scholarly Activity thesis requirement at the University of Colorado– School of Medicine. J.M.B. is supported by the Juvenile Diabetes Research Foundation (11-2005-15). Research was supported by National Institutes of Health grants DK-32083, DK-50970, P30-DK-57516, and AI-46374, and grants to the General Clinical Research Centers (RR-00051 and RR-00069).

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

T.M.T., T.K.A., and K.M. researched data and wrote the manuscript. L.Y. wrote the manuscript. M.J.R., G.J.K., G.S.E., and J.M.B. contributed to discussion and reviewed the manuscript.

Parts of this study were presented in abstract form at the 69th Scientific Sessions of the American Diabetes Association, New Orleans, Louisiana, 5–9 June 2009.

The authors acknowledge the study participants and their families for their contributions, which made this research possible. The authors acknowledge the technical assistance of Laura A. Scrimgeour and Dong Mei Miao, MD, University of Colorado–Barbara Davis Center for Childhood Diabetes.

References

- 1. Libman I, Songer T, LaPorte R. How many people in the U.S. have IDDM? Diabetes Care 1993;16:841–842
- 2. Barker JM. Clinical review: type 1 diabetesassociated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab 2006;91:1210–1217
- 3. Barker JM, Yu J, Yu L, et al. Autoantibody "subspecificity" in type 1 diabetes: risk for

organ-specific autoimmunity clusters in distinct groups. Diabetes Care 2005;28: 850–855

- American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27(Suppl. 1):S5–S10
- Wenzlau JM, Juhl K, Yu L, et al. The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes. Proc Natl Acad Sci USA 2007;104: 17040–17045
- Wang J, Miao D, Babu S, et al. Prevalence of autoantibody-negative diabetes is not rare at all ages and increases with older age and obesity. J Clin Endocrinol Metab 2007; 92:88–92
- 7. Bao F, Yu L, Babu S, et al. One third of HLA DQ2 homozygous patients with type 1 diabetes express celiac disease-associated transglutaminase autoantibodies. J Autoimmun 1999;13:143–148

- Falorni A, Nikoshkov A, Laureti S, et al. High diagnostic accuracy for idiopathic Addison's disease with a sensitive radiobinding assay for autoantibodies against recombinant human 21-hydroxylase. J Clin Endocrinol Metab 1995;80:2752–2755
- 9. Erlich H, Valdes AM, Noble J, et al.; Type 1 Diabetes Genetics Consortium. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk: analysis of the type 1 diabetes genetics consortium families. Diabetes 2008;57:1084–1092
- Liu E, Li M, Bao F, et al. Need for quantitative assessment of transglutaminase autoantibodies for celiac disease in screeningidentified children. J Pediatr 2005;146: 494–499
- 11. Barker JM, Ide A, Hostetler C, et al. Endocrine and immunogenetic testing in individuals with type 1 diabetes and 21hydroxylase autoantibodies: Addison's

disease in a high-risk population. J Clin Endocrinol Metab 2005;90:128–134

- Prázný M, Skrha J, Límanová Z, et al. Screening for associated autoimmunity in type 1 diabetes mellitus with respect to diabetes control. Physiol Res 2005;54: 41–48
- Freemark M, Levitsky LL. Screening for celiac disease in children with type 1 diabetes: two views of the controversy. Diabetes Care 2003;26:1932–1939
- Marks SD, Girgis R, Couch RM. Screening for adrenal antibodies in children with type 1 diabetes and autoimmune thyroid disease. Diabetes Care 2003;26:3187–3188
- Bilimoria KY, Pescovitz OH, DiMeglio LA. Autoimmune thyroid dysfunction in children with type 1 diabetes mellitus: screening guidelines based on a retrospective analysis. J Pediatr Endocrinol Metab 2003; 16:1111–1117