Screening for Type 1 Diabetes–, Thyroid-, Gastric-, and Adrenal-Specific Humoral Autoimmunity in 529 Children and Adolescents With Celiac Disease at Diagnosis Identifies as Positive One in Every Nine Patients

Claudio Tiberti,[1] Monica Montuori,[2] Francesca Panimolle,[1] Chiara M. Trovato,[2] Caterina Anania,[2] Francesco Valitutti,[2] Anna R. Vestri,[3] Andrea Lenzi,[1] Salvatore Cucchiara,[2] and Susanna Morano[1]

Diabetes Care 2017;40:e10–e11 | DOI: 10.2337/dc16-2095

Organ-specific autoimmune disorders are often associated with celiac disease (CD) (1,2). Most studies investigated the frequency of CD humoral autoimmunity in patients at diagnosis of an organ-specific autoimmune disorder or along its course. Conversely, only two studies, dating back to the early 2000s, were aimed at determining the frequency and co-occurrence of organ-specific autoimmunity in CD patients at diagnosis (3,4). These studies reported discordant, excessively high positivities for diabetes-specific autoimmunity (12.2% and 31.6%, respectively) that may be explained by the small number of patients investigated and the use of, at least in part, outdated techniques such as islet cell autoantibody assay.

On these bases, our aim was to evaluate in a large cohort of CD patients at diagnosis the real frequency and co-occurrence of humoral immunoreactivity specific of four organ-specific autoimmune disorders known to be associated to CD, namely, type 1 diabetes (T1D), autoimmune thyroid disease (HT), autoimmune atrophic gastritis (AG), and Addison disease (AD). In particular, the immune response directed against insulin (INS), GAD, tyrosine phosphatase $2_{(aa\ 605\text{-}979)}$ (IA-2), zinc cation efflux transporter (ZnT8), thyroid peroxidase, enzyme steroid 21-hydroxylase, and parietal cells was investigated in 529 biopsy-confirmed CD patients at disease diagnosis (332 girls/197 boys, age range 3.0–17.7 years) and compared with that found in 264 anti-transglutaminase autoantibody–negative healthy control subjects (104 girls/160 boys; age range 3.0–18.0 years).

Of 529 CD patients, 11.7% were positive for at least one of the organ-specific

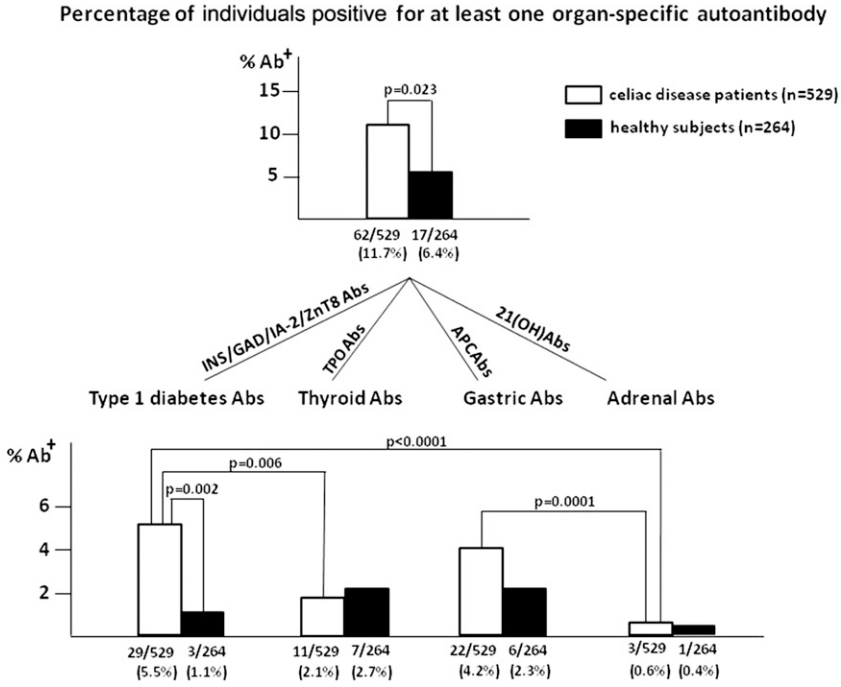

Figure 1—The upper part of the figure shows the frequencies of CD patients and healthy control subjects positive for at least one of the organ-specific autoantibodies (Abs) investigated in the study. The lower part of the figure shows the frequency distribution of the organ-specific autoantibody-positive CD patients and healthy control subjects according to each single disease. 21(OH), steroid 21-hydroxylase; APC, parietal cell; TPO, thyroid peroxidase.

[1]*Department of Experimental Medicine, "Sapienza" University of Rome, Rome, Italy*
[2]*Department of Pediatrics, Pediatric Gastroenterology and Liver Unit, "Sapienza" University of Rome, Rome, Italy*
[3]*Department of Public Health and Infectious Diseases, "Sapienza" University of Rome, Rome, Italy*

Corresponding author: Susanna Morano, susanna.morano@uniroma1.it.

Received 20 September 2016 and accepted 28 October 2016.

antibodies investigated (Fig. 1) more frequently than control subjects (6.4%, $P = 0.023$), with T1D-specific immune response significantly higher compared with HT and adrenal (2.1%, $P = 0.006$ and 0.6%, $P < 0.0001$, respectively) but not gastric immunoreactivities (4.2%). Only 4.8% of autoantibody-positive CD patients showed more than one disease-specific immunoreactivity. Among CD T1D-specific immunoreactivities, GAD autoantibodies were significantly more frequent (62.1%) relative to INS, IA-2, and ZnT8 autoantibodies (31.0%, $P = 0.034$; 20.7%, $P = 0.003$; and 13.8%, $P = 0.0003$, respectively). More than 20% of CD patients with T1D autoimmunity were positive for two to three related autoantibodies. A high percentage of CD patients (91.9%), which includes among others all of the T1D, AG, and AD autoantibody-positive patients, did not present with the clinical signs of the related disease. Organ-specific autoantibody-positive CD patients increased with age at diagnosis (P for trend $= 0.018$). The overall frequency of organ-specific autoimmunity in CD boys/girls and symptomatic/asymptomatic patients was not significantly different.

The finding that about one of every nine CD patients was positive for at least one T1D-, HT-, AG-, or adrenal-specific humoral autoantibody demonstrates the importance to evaluate the organ-specific autoimmunity at CD diagnosis. Our results revalue downward the prevalences reported so far in literature, which date back to the early 2000s. Most of the organ-specific autoantibody-positive CD patients identified in this study were not diagnosed for, but are just at risk to develop, an organ-specific disease. In this light, it will be extremely important for future evaluation of the gluten-withdrawal effects on the development of organ-specific diseases after CD diagnosis. Finally, our data provide the first experimental confirmation of the hypothesis (5) that age at diagnosis is the only significant predictor variable of developing an additional autoimmune disease in CD patients.

Acknowledgments. The authors thank Flavia Amaro and Lucilla Pezza (Department of Pediatrics, Pediatric Gastroenterology and Liver Unit, "Sapienza" University of Rome) for their contributions to the data collection.

Funding. This work was supported by the Italian Research Ministry (PRIN no. 2010JS3PMZ_011) (to S.M.).

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

Author Contributions. C.T. contributed to data collection, statistical analysis, and data interpretation and wrote and revised the manuscript. M.M. and S.M. contributed to data collection and interpretation and revised the manuscript. F.P. and C.M.T. contributed to data collection and revised the manuscript. C.A., F.V., A.L., and S.C. contributed to data interpretation and revised the manuscript. A.R.V. contributed to statistical analysis and revised the manuscript. S.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Kelly CP, Bai JC, Liu E, Leffler DA. Celiac disease: clinical spectrum and management. Gastroenterology 2015;148:1175–1186

2. Lauret E, Rodrigo L. Celiac disease and autoimmune-associated conditions. Biomed Res Int 2013;2013:12759

3. Ventura A, Neri E, Ughi C, Leopaldi A, Città A, Not T. Gluten-dependent diabetes-related and thyroid-related autoantibodies in patients with celiac disease. J Pediatr 2000;137:263–265

4. Toscano V, Conti FG, Anastasi E, et al. Importance of gluten in the induction of endocrine autoantibodies and organ dysfunction in adolescent celiac patients. Am J Gastroenterol 2000;95:1742–1748

5. Ventura A, Magazzù G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Gastroenterology 1999;117:297–303