Diabetes-related autoantibodies in children with acute lymphoblastic leukemia.

Bizzarri, C; Pinto, RM; Pitocco, D; Astorri, E; Cappa, M; Hawa, M; Giannone, G; Palermo, A; Maddaloni, E; Leslie, DR; Pozzilli, P; IMDIAB Group

OBSERVATIONS

Diabetes-Related Autoantibodies in Children With Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common subtype of leukemia in children. Although ALL and type 1 diabetes appear to be biologically unrelated, there are common threads in both epidemiology and etiology. Rising incidence rates of both ALL (1) and type 1 diabetes (2) observed over recent decades in many Western countries seem to support common etiological factors (3).

In the current study, we report on diabetes-related autoantibodies (Abs) in a group of patients with ALL. Thirty-four consecutive children (19 males and 15 females, mean age 6.2 ± 4.6 years) were referred to our institution in 2004 for newly diagnosed ALL. Patients were tested for Abs to islet and thyroid antigens. After the initial investigation and treatment, 31/34 (91%) patients (3 died in the mean time) were followedup for 6 years to evaluate the evolution of the autoimmune markers and progression toward type 1 diabetes.

Glutamic acid decarboxylase (GAD) Abs by direct radioligand assay (Centak, Medipan, Germany), insulin Abs (IAA) by a semiquantitative radioimmunoassay (AIA −100; DIAsource, Nivelles, Belgium), IA2 Abs by a direct radioligand assay (Centak, Medipan, Germany), and thyroperoxidase Abs (TPOAbs) by an ultrasensitive chemiluminescent enzyme immunoassays by Advia Centaur (Bayer HealthCare LLC Division, Tarrytown, NY) were measured twice at diagnosis and after 6 years. Our laboratory participated in the latest 2010 Diabetes Antibody Standardization Program.

Seven children (20.5%) showed at least one diabetes-related Ab; two children (5.9%) were found positive for all three Abs (GAD, IAA, and IA2) with one of the two also showing TPOAbs positivity; isolated IAA positivity was found in five (14.7%) children. Autoantibodies retested in the 31 surviving children 6 years later were found to be negative in all patients. Also, none of the children who were Abs negative at ALL diagnosis became Abs positive at follow-up. No patient manifested hyperglycemia during ALL therapy, and none developed type 1 diabetes and/or autoimmune thyroiditis during follow-up.

Finally, in Abs-positive ALL patients HLA type was not typical of type 1 diabetes, and indeed, only one patient showed a moderate risk HLA genotype for type 1 diabetes.

Our data suggest that the activation of the immune system against self-antigens in childhood ALL is nonspecific and self-limiting, even though chemotherapy may contribute to suppress autoimmunity during follow-up. The dysregulation of the immune response in ALL is probably related to the profound functional derangement of the immune response during malignancy. The relatively low Ab titer in ALL children supports the hypothesis that the autoimmune process in ALL is not an aggressive one.

Genome-wide association studies identified an ALL susceptibility locus near the *IKZF1* gene (4). Recently, one of these single nucleotide polymorphisms (rs10272724) conferring susceptibility to ALL was found to be protective against type 1 diabetes in a large population of patients of European ancestry (5). Very likely genetic susceptibility to type 1 diabetes and ALL is regulated by distinct genes. In conclusion, the autoimmune humoral response may start in ALL children as a consequence of the disease, but it should be considered as an epiphenomenon related to the general immune dysregulation.

Carla Bizzarri, MD[1]
Rita M. Pinto, MD[2]
Dario Pitocco, MD[3]
Elisa Astorri, MD, PhD[4]
Marco Cappa, MD[1]
Mohammed Hawa, MD[4]
Germana Giannone, MD[5]
Andrea Palermo, MD[6]
Ernesto Maddaloni, MD[6]
David R.G. Leslie, MD[4]
Paolo Pozzilli, MD[4,6]
on behalf of the IMDIAB Group*

From the [1]Department of Endocrinology and Diabetes, Bambino Gesù Children's Hospital, Rome, Italy; the [2]Department of Hematology and Oncology, Bambino Gesù Children's Hospital, Rome, Italy; the [3]Department of Diabetology, Catholic University, Rome, Italy; the [4]Centre of Diabetes, St. Bartholomews & The London School of Medicine, Queen Mary, University of London, London, U.K.; the [5]Department of Chemistry, Bambino Gesù Children's Hospital, Rome, Italy; and the [6]Department of Endocrinology and Diabetes, University Campus Bio-Medico, Rome, Italy.

Corresponding author: Paolo Pozzilli, p.pozzilli@unicampus.it.

DOI: 10.2337/dc11-1946

*A complete list of the members of the IMDIAB Study Group can be found in the APPENDIX.

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

C.B. and R.M.P. performed research, analyzed data, and wrote the manuscript. D.P., E.A., M.H., and G.G. performed research and contributed to the manuscript. M.C. analyzed data and critically revised the manuscript. A.P. and E.M. contributed to the discussion and critically reviewed the manuscript. D.R.G.L. and P.P. designed research, analyzed data, and critically reviewed and edited the manuscript. All authors approved the final version of the manuscript. C.B. 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.

APPENDIX—Members of the IMDIAB Group: Altomare M, Astorri E, Barchetta I, Benevento D, Beretta Anguissola G, Bizzarri C, Buzzetti R, Capizzi M, Cappa M, Cassone Faldetta M.R., Cavallo M.G., Cipolloni L, Cipponeri E, Costantino F, Crinò A, Defeudis G, Di Stasio E, Fallucca S, Fioriti E, Ghirlanda G, Guglielmi C, Khazrai Yeganeh M, Kyanvash S, Lauria A, Maddaloni E, Maggi D, Manfrini S, Maurizi A.R., Moretti C, Morviducci L, Napoli N, Palermo A, Patera P, Pitocco D, Portuesi R, Pozzilli P, Schiaffini R, Scrocca R, Spera S, Strollo R, Suraci C, Tubili C, Tuccinardi D, Valente L, and Visalli N.

References

1. Pui CH. Recent advances in acute lymphoblastic leukemia. Oncology (Williston Park) 2011;25:341, 346–347
2. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 2009;373:2027–2033
3. Feltbower RG, McKinney PA, Greaves MF, Parslow RC, Bodansky HJ. International parallels in leukaemia and diabetes epidemiology. Arch Dis Child 2004;89:54–56
4. Papaemmanuil E, Hosking FJ, Vijayakrishnan J, et al. Loci on 7p12.2, 10q21.2 and 14q11.2 are associated with risk of childhood acute lymphoblastic leukemia. Nat Genet 2009;41:1006–1010
5. Swafford AD, Howson JM, Davison LJ, et al. An allele of IKZF1 (Ikaros) conferring susceptibility to childhood acute lymphoblastic leukemia protects against type 1 diabetes. Diabetes 2011;60:1041–1044