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.

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