OBSERVATIONS

No Relation Between Cystic Fibrosis–Related Diabetes and Type 1 Diabetes Autoimmunity

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DOI: 10.2337/dc11-2327

Diabetes is the most common comorbidity in individuals with cystic fibrosis. The etiology is poorly understood. Data on the presence of diabetes autoantibodies are conflicting, and little is known about type 1 diabetes gene associations. Our goal was to determine the prevalence of antibodies and HLA haplotypes known to be associated with type 1 diabetes in cystic fibrosis–related diabetes (CFRD).

Patients with CFRD with fasting hyperglycemia were recruited from the University of Minnesota. Serum for antibodies and buffy coats for HLA were sent for analysis to the Barbara Davis Center for Childhood Diabetes (BDC). All patients gave informed consent. The Eisenbarth laboratory at BDC serves as the autoantibody/HLA reference laboratory for large national diabetes studies. Insulin, insulinoma-associated protein 2 (IA-2), GAD65, and zinc transporter 8 (ZnT8) autoantibodies were measured by radioimmunoassay (1,2). HLA class II alleles were determined for DQB1 loci (3). Comparison data were obtained from new-onset diabetes and population studies collected at BDC (1–3).

Of 76 CFRD patients, 50% were female, the average age was 34 years (range 15–55), and the average duration of diabetes was 10 years (range 1–33). All received constant or intermittent insulin therapy.

In the general population, ~2% of individuals are positive for one of IA-2, GAD, ZnT8, or insulin autoantibodies (1). In contrast, 55–98% of individuals with type 1 diabetes are positive for at least one of these autoantibodies (2). Only 5% of CFRD patients had autoantibodies, including three subjects with antibodies to GAD and one subject with antibodies to IA-2. Insulin administration itself induces insulin antibodies, which were found in 32% of CFRD patients. Thirty-six percent of CFRD patients had high-risk alleles compared with 47% of the general population and more than 90% of those with type 1 diabetes (3). Seventeen percent of CFRD patients were DR3+, 14% DR4+, and 5% DR3+/DR4+.

The etiology of CFRD is poorly understood and probably multifactorial. The primary defect is insulin insufficiency. Pancreatic fibrosis leads to ~50% reduction in islet mass. However, the correlation between the degree of islet destruction and clinical diabetes is poor, leading to speculation that there are other factors causing diabetes, including autoimmunity.

Because these CFRD patients all had fasting hyperglycemia, they represent the severe end of the glucose intolerance spectrum and might be the most likely to exhibit associations with type 1 diabetes. Although autoantibody levels can drop after diagnosis and subjects in this study may have had diabetes for some time, their low levels of IA-2, GAD, and ZnT8 antibodies appear more similar to the general population than to those with type 1 diabetes and are consistent with the normal HLA haplotype profiles we found in patients with CFRD. Insulin antibodies are common in patients receiving exogenous insulin. The fact that a higher percentage of CFRD patients did not have these may be related to the relatively low doses of insulin required in this population. Autoantibody assays are of varying quality, which may explain differences in previous reports; we used highly sensitive and specific validated assays.

In summary, the presence of autoantibodies and HLA haplotypes associated with type 1 diabetes appears to be no greater in CFRD than in the general population.

Acknowledgments—This project was supported by a grant from Pennsylvania Cystic Fibrosis, Inc.

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

P.A.G. and A.M. conceived and supervised the study, interpreted the data, and wrote the manuscript. L.Y., J.W., and S.B. supervised or performed the analyses and edited the manuscript. B.I.F. and M.B. collected the samples and edited the manuscript. A.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.

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