EDITORIAL

Predawn reflections on genetic studies of insulin-dependent diabetes mellitus

BYRON HOOGWERF, MD, DEPARTMENT OF ENDOCRINOLOGY

DIABETES mellitus was described by Pyke,[1] a decade ago, as "the graveyard of the geneticist's reputation" and a "geneticist's nightmare." To a lesser extent, attempting to tell patients about the risk of diabetes mellitus is a clinician's nightmare. Increased knowledge has made this task a little less fearsome, and the following article by McFarland et al[2] may bring us a little closer to the dawn.

■ *See McFarland et al (pp 217–219)*

Studies from the 1930s to 1970s, which evaluated concordance rates for diabetes mellitus in twins, showed that in all probability both non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM) had a genetic basis. In monozygotic twins, concordance rates for diabetes mellitus were nearly 100% for NIDDM and 35%–50% for IDDM. These rates were higher than for dizygotic twins and other siblings. Such marked differences between monozygotic and dizygotic twins indicated that environmental factors were not the sole reason for development of diabetes mellitus.

Further understanding of the genetic mechanism for IDDM has been provided by studying the association of diabetes mellitus with specific antigens in the major histocompatibility complex (HLA) on the short arm of chromosome 6. A number of studies have shown linkage disequilibrium with specific HLA antigens including B8, B15, DR3, DR4, and, more recently, DQ. In studies of families with two or more siblings with IDDM siblings who share both HLA haplotypes with their IDDM probands are at increased risk to develop IDDM (55%); the risk decreases with one (40%) or no shared haplotypes (5%).[3] The predicted rates with no genetic association would be 25%, 50%, and 25%, respectively. Despite this clear genetic association with HLA, there are major gaps in our understanding of the etiology of IDDM. First, there is evidence to support immunologic or other environmental triggers for beta-cell destruction. Second, data support the concept that other genetic factors may contribute to the risk of developing diabetes mellitus. Third, recent findings suggest that there may be genetic relationships between IDDM and NIDDM. Kobayashi et al[4] have shown that patients with clinically defined NIDDM may have islet-cell antibodies in plasma and that this is associated with decreasing beta-cell function as measured by C-peptide determinations. More recently, Groop et al[5] have confirmed these observations in patients characterized as NIDDM and noted an association with HLA antigens DR3 and DR4.

In the face of all this "sophisticated science," efforts to determine the prevalence of diabetes mellitus in the parents and grandparents of children with IDDM as reported by McFarland et al[2] may seem to have done little to enlighten us. In fact, questions and criticisms may be raised about their ability to ascertain the incidence of diabetes mellitus in relatives of patients with and without IDDM who do not have NIDDM, the validity of their statistical methods, their failure to explain the apparent increased prevalence of diabetes in the paternal side of the family, and the possibility that an autosomal dominant form of diabetes[6] may have confounded their data. Nevertheless, some useful points may be taken from the article.

Practicing physicians dealing with diabetes mellitus are frequently asked these questions: Why did my child get diabetes when no one in my family has it? What are my children's chances of getting diabetes since it runs in

my family? Should I have tests run? McFarland et al remark that their data may help with genetic counseling. The observation that IDDM frequently occurs in the absence of a family history of diabetes is a surprise to patients (and sometimes to practitioners) who know something about genetic transmission of disease. The relatively low prevalence of insulin-treated diabetes in the parents and grandparents of children with IDDM is clearly shown by the data presented by McFarland et al. Furthermore, it is evident from such studies that the ability to predict the risk of developing IDDM in any child with a family history of diabetes mellitus is still limited and will remain so, outside of carefully designed trials,[7] in the absence of a clear understanding of exact genetic patterns, specific environmental triggers, and definite immunologic markers. Extensive HLA testing and screening with markers such as pancreatic islet-cell antibodies, even in patients with a family history of diabetes mellitus, is probably not warranted outside of carefully designed protocols.

Investigators involved in family genetic studies of diabetes mellitus may also extract useful information from the data of McFarland et al. The data, generated from a large number of patients, may be helpful for future trial designs, when combined with data from other investigators. The data also suggest a possible genetic relationship between insulin-requiring NIDDM and IDDM. Additionally, the observation of the paternal influence of the transmission of IDDM confirm data from other investigators. McFarland et al mention several mechanisms for the latter observation. They do not suggest the possibility of genetically induced alterations in sperm motility or penetration that may be associated with diabetes-related genes. Such information may be useful for family screening, genetic counseling, or reducing the risk of IDDM. Altering the transmission of IDDM by treating sperms that carry the susceptible genes would truly represent a "new day" in the era of diabetes management.

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