

Case 24

C.G. is the only child born to his parents. His growth and development were normal and he excelled at school. When he was 6 years old he began to lose weight and developed enormous thirst such that he was consuming over three liters of liquid a day. The thirst and excess fluid consumption was accompanied by frequent urination. He was taken to the family doctor who found the patient was hyperglycemic and diagnosed with Type 1 diabetes mellitus. It turned out that a paternal uncle had also developed juvenile-onset diabetes.

C.G. was started on diet and daily insulin injections. His blood glucose was easy to control in the first 6 months after diagnosis, but then became more difficult. He experienced glucose levels over 200 mg/dl after meals and about three episodes of hypoglycemia (glucose level < 70 mg/dl) each week. His hemoglobin A1c levels (a measure of chronic glucose control) were generally 8.0 – 9.0% (nl to 6.0%). When he was 35 years old, a routine annual physical examination revealed an elevated blood pressure and proteinuria (presence of increased protein in the urine). A serum creatinine was 7.5 mg/dl (normal < 1.2 mg/dl). On the basis of this result, Christopher's physician suspected that he had developed renal complications of diabetes. An ultrasonogram of the kidneys revealed small kidneys bilaterally (evidence of chronic, irreversible renal failure). He ultimately underwent hemodialysis (passing blood over a semi-permeable membrane to remove waste products such as urea) twice weekly. He had few dialysis-related complications but had several episodes of ulcerations and cellulitis (inflammation of the skin, usually infectious in etiology) of both feet. He was put on a waiting list for a kidney transplant; as part of his pre-transplant evaluation, he was found to be blood group B, Rh-positive; HLA A2,24; B50,51; DR3,4, DQA1-0501, DQB1-0201, and DQA1-0301 and DQB1-0302.

Questions for Case 24

- (1) There was little family history of juvenile diabetes for this patient, yet the disease has been linked to genes of the MHC. Can you suggest a genetic or environmental interaction that might explain this discordance?
- (2) C.G. is HLA-DR3,4 and has DQ alleles highly associated with Type 1 diabetes (about 50 times more than individuals without these alleles). How might specific MHC class II alleles confer increased susceptibility to IDDM?
- (3) In mice, it has been shown that a number of islet “antigens” that are thought to be targets of the autoimmune response in diabetes are expressed in the thymus. Explain how abnormalities in antigen presentation in the thymus and/or thymic development could contribute to the development of DM.
- (4) In the same mouse model of DM, expression of a transgene encoding for TNF- α in islet cells in neonatal mice was sufficient to accelerate diabetes progression. Explain how this might have occurred.
- (5) Considering the fact that Type 1 diabetes is an autoimmune disease thought to be mediated by Th1 cells, what approaches would you consider to arrest the process?