COXSACKIE B4–INDUCED PANCREOPATHY

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ABSTRACT

Supporting the hypothesis that Coxsackie B4 (CB4) may cause pancreopathy and/or be important in the pathogenesis of human diabetes mellitus are virologic, serologic, immunologic, genetic and pathologic studies. The most direct evidence for this relationship is isolation of the virus from a human pancreas showing histopathologic change consistent with the patient's diagnosis, juvenile (type 1) diabetes mellitus. Other laboratory assays, including measurement of islet cell antibodies and CB4 antibodies in populations of patients with juvenile diabetes mellitus provide further evidence for viral etiology of this disease. In the context of epidemiologic study, these and other observations, including age, sex and seasonal variation have been assessed. Additionally, positive correlations between certain human leukocyte antigen (HLA) determinants and viral antigenic responses, including CB4, have been found in studies of diabetic individuals.

INTRODUCTION

A temporal relationship between the onset of some viral infections and subsequent development of diabetes mellitus has been recognized since the turn of the century (1). It is generally accepted that there is hereditary predisposition to diabetes, however, there is little agreement on its mode of inheritance. The influence of viruses and other environmental factors on expression of these genotypes as clinical diabetes mellitus is uncertain (1-4).

Juvenile insulin–dependent (type 1) and adult onset non-insulin-dependent (type 2) diabetes are thought to be distinct entities, based on epidemiologic, genetic and immunologic studies (5). The concordance rate for diabetes in studies of identical twins has
been reported to be 92% in adult-onset diabetes as compared to 53% in juvenile diabetes (6). While these observations indicate a strong genetic influence on the occurrence of adult-onset diabetes, the discordant results in juvenile diabetics suggest environmental factors may be important in the etiology of this disease (2).

The hypothesis that viruses are important in the pathogenesis of juvenile diabetes is supported by its seasonal incidence, abrupt clinical onset and accumulating serologic, immunologic and pathologic studies of patients with the disease (1,7,8,9). Implicated viruses include mumps, rubella, Coxsackie B, encephalomyocarditis virus, Epstein-Barr virus and cytomegalovirus (1,6,7,8,10). The most direct explanation for viral pathogenesis of the diabetic syndrome is infection and ultimate destruction of the insulin-producing beta cells of the islets of Langerhans in the pancreas, however, other hypotheses include altered immunoresponsiveness in the presence of viral antigens triggering autoimmune destruction of beta cells (11,12). Additionally, relationships have been noted between certain HLA serotypes and immunocompetence in the presence of CB4 and other viruses (13). Similar to viral oncogenesis, it has also been postulated that viruses may function as initiators of disease but may not be present at the time of disease expression (14). This later suggestion would obviously explain how a virus might be part of the etiology of a disease when all traces of the virus are absent at the time of diagnosis.

Animal studies have been performed to help elucidate the association between diabetes and viruses. CB4 has been implicated in studies including isolation of the virus from a ten-year-old patient with newly diagnosed diabetes mellitus. The diabetogenic potential of this virus was supported by mouse inoculation with the human isolate and subsequent demonstration of hyperglycemia and pancreopathy including beta-cell necrosis and inflammation in the islets of Langerhans (9).

CB4 and other picornaviruses have been further studied in various inbred strains of mice to assess their diabetogenic potential. As with human studies, multiple factors appear to influence susceptibility to viral-induced pancreopathy and abnormal glucose tolerance. Pancreatic damage related to these viruses and resulting in hyperglycemia appear