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Review

Viruses and vitamin D in the etiology of type 1 diabetes mellitus and multiple sclerosis

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ABSTRACT

Although specific viruses have been associated with autoimmune diseases, none fulfill Koch's criteria of causation. The etiologies of such diseases appear to be complex and multifactorial. For example, one might propose that the etiology of type 1 diabetes mellitus results from a toxic metabolite of nitrosamines during an enteroviral infection. Multiple sclerosis might result from a cascade of events involving several herpes virus infections activated during periods of vitamin D deficiency. We encourage investigators to consider Rotman's sufficient-component causal model when developing hypotheses for testing for the etiology of chronic diseases. Delineating the web of causation may lead to additional strategies for prevention and treatment of several autoimmune diseases.

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Contents

1. Introduction

Autoimmune diseases arise from an overactive immune response against substances or tissues normally present in the body. The target organs are quite specific, i.e., beta cells of the pancreas in diabetes, connective tissue in rheumatoid arthritis, and basement membrane of lung and kidney in Goodpasture's disease. For many autoimmune diseases the onset occurs in adolescence or young adulthood and affects females more frequently than males. The exact etiology of autoimmune diseases is unknown. Genetic predisposition may exist for some, but many researchers acknowledge that environmental factors are necessary to trigger onset of illness (Cho and Gregersen, 2011). The low concordance rates in monozygotic twin and geographic distribution of disease point toward environmental factors, including viruses, as cofactors in the etiology and pathogenesis of autoimmune diseases.

How might viral infection trigger autoimmunity? Several mechanisms have been described to explain how viruses might activate and expand T cells and other components of the immune system to initiate and/or promote autoimmune diseases. Two of the most cited mechanisms are referred to as "molecular mimicry" and "bystander activation." Molecular mimicry occurs when a T- or B-cell receptor recognizes a viral peptide that is structural similar to a self-peptide. The immune response initially directed at the virus spreads to tissues presenting the cross-reactive peptide. Bystander activation refers to the activation and/or expansion of an immune response directed at tissues altered by inflammation surrounding a viral infection (Munz et al., 2009; Delogu et al., 2011).

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We will focus on two autoimmune diseases that have unique epidemiologic characteristics related to seasonality and geographic variation. The increased incidence of type 1 diabetes mellitus and multiple sclerosis in northern latitudes relative to equatorial areas raises the possibility that infectious agents and vitamin D deficiency may play a role in etiology. Like others, we postulate that the cause(s) of selected autoimmune diseases may be complex and multifactorial. We will invoke Kenneth Rothman's sufficient-component causal model to explain the etiology of diabetes and multiple sclerosis. In the model he suggests that the cause of a disease is not due to a single agent or virus, and testable by Koch's postulates. Rather, Rothman defines a sufficient cause as a set of minimal conditions and events that invariably produce disease (Rothman, 1976). We will review the epidemiology of type 1 diabetes mellitus and multiple sclerosis, list hypotheses of causation, and suggest research approaches to test them.

2. Type 1 diabetes mellitus (DM1)

Type 1 diabetes mellitus (DM1) is the most common life-threatening endocrine disorder of children and young adults worldwide and its incidence appears to be increasing. Originally coined juvenile diabetes or insulin-dependent diabetes, DM1 has traditionally been considered a pediatric disease. In a recent multicenter American study the incidence of DM1 was approximately 20 per 100,000 among youth less than 20 years of age; no gender differences were noted (SEARCH, 2007). There are currently limited population-based estimates of DM1 among adults; however the medical literature suggests that up to 40% of new cases of DM1 occur in persons over age 18 years (Blohme et al., 1992; Pundziute-Lycka et al., 2003; Thunander et al., 2008). There is a clear genetic predisposition, and the process of pancreatic beta-cell destruction is autoimmune-mediated (Concannon et al., 2009; Eisenbarth, 2007). The triggers of beta-cell destruction are unknown, although a number of environmental factors have been proposed.

Investigators have sought an infectious cause of DM1 for several decades. In 1926 Adams reported a seasonal variation in the onset of symptomatic diabetes in the fall, winter and spring, and noted a higher incidence of acute diabetes in northern US states compared to southern states (Adams, 1926). The search for an etiology of DM1 eventually focused on the family Picornaviridae, genus Enterovirus (Helfand et al., 1995; Haverkos, 1997; Haverkos et al., 2003; Oberste and Pallansch, 2003; Yeung et al., 2011). Enteroviruses are a common cause of childhood 'flu-like" infections during late summer/early fall. In 1968, Craighead et al. reported induction of hyperglycemia and pancreatic lesions in mice following infection with a non-human family Piocornaviridae, genus, Cardiovirus, species, Encephalomyocarditis virus (EMCV) (Craighead and McLane, 1968). Yoon et al. (1979) reported a 10-year-old previously healthy boy who presented to the National Naval Medical Center in Bethesda, MD in diabetic ketoacidosis, and he died one week later. "Coxsackie B4 virus", family Picornaviridae, genus Enterovirus, species Human enterovirus B4, was grown from his pancreas at autopsy; inoculation of that virus into mice produced hyperglycemia and beta-cell necrosis. Since then, several epidemiologic studies have linked onset of DM1 with enterovirus B4 and/or other enteroviral infections. In 1995, University of Pittsburgh investigators working with the CDC conducted a case-control study of 128 newly diagnosed patients and reported serologic evidence of an association between enteroviral infections and onset of DM1 (Helfand et al., 1995).

The observation of Adams and others that symptomatic diabetes occurred more frequently at higher latitudes suggests that Vitamin D deficiency might play a role in DM1 (Adams, 1926; Ponsonby et al., 2002; Cantorna and Mahon, 2004; Hollick, 2007; Mohr et al., 2008). Finland has one of the highest rates of DM1 in the world. In 1966, investigators recruited every woman in two Finnish cities whose pregnancy continued beyond 24 weeks and enrolled their children for follow-up. Vitamin D supplementation, 2000 IU of vitamin D3 per day, was encouraged for 10,366 infants and usage was assessed for those children at one year of age by evaluation of medical charts. Eighty-one children were diagnosed with DM1 before 1998; median age of diagnosis was 14 years. The incidence rate per 100,000 years of observation was 204 for those using no Vitamin D supplements at one year of age, 33 for those using supplements irregularly, and 24 using supplements regularly (relative risk, 0.22; 95% CI 0.05–0.89) (Hypponen et al., 2001). Unfortunately, serum concentrations of 25 (OH) D_3 were not collected at one year of age or at time of DM1 diagnosis.

So how might vitamin D deficiency play a role in the etiology of DM1? It might involve a direct effect on insulin production, as suggested by one study; vitamin D deficiency decreased insulin production, and increasing vitamin D intake during pregnancy reduced the development of islet cell autoantibodies (Chiu et al., 2004). Others have suggested that vitamin D is an immunomodulator. For example, 1,25-dihydroxyvitamin D(3) modulators various immune cells, including monocytes, macrophages, T-lymphocytes and B-lymphocyte (Baeke et al., 2010).

Several epidemiologic observations suggest that "enhanced" nutrition may trigger DM1 (Virtanen and Knip, 2003). A reduced incidence of DM1 was observed in Germany and Sweden during World War II (Dorner et al., 1985). Conversely, several studies have suggested that children of higher socioeconomic status have higher rates of DM1, specifically in Finland, Estonia, and in Alleghany County, Pennsylvania (Kalits and Podar, 1990; LaPorte et al., 1986). An increase in DM1 has also been observed among migrant populations in Polynesia and Micronesia, and attributed to nutritional changes (Elliott, 1992). Several investigators have reported an association between an increase in height and weight of children prior to onset of DM1 (Baum et al., 1975; Blom et al., 1992; Ljungkrantz et al., 2008). Even though polyphagia is considered an early symptom of DM1, could it also be a symptom associated with an etiological factor? Several dietary components, including proteins, carbohydrates, and nitrosamines have been associated with DM1. The Swedish Childhood Diabetes Study was established to evaluate risk factors for DM1 and included a study of different nutrients and food additives. They compared the dietary histories of 339 children aged 0–14 years with newly diagnosed DM1 with 528 control children matched for age, sex, and residence. The Swedish investigators found a direct relationship between frequency of intake of foods rich in meat protein, complex carbohydrates, nitrosamines and nitrates/nitrites and DM1 (Dahlquist et al., 1990, 1991).

A genetic component of DM1 etiology is suggested by the strong familial clustering of disease. Emerging data from linkage studies indicate that genes encoding for HLA-DR proteins on chromosome 6 confer most, but not all, of the genetic risk of DM1 (Concannon et al., 2005, 2009; Eisenbarth, 2007). Children who carry both of the highest risk haplotypes (DR3-DQ2 and DR4-DQ8) have a 5% risk of DM1 by age 15 years (Concannon et al., 2005, 2009). However, only about one in 15 children in the general population with high risk alleles and one in five with a first degree relative with DM1 with high risk alleles develop disease. Other disease susceptibility loci, such as INS on chromosome 11p15, PTPN22 on chromosome 1p13, and CTLA4 on chromosome 2, have also been linked to DM1 (Concannon et al., 2005, 2009). It is still not clear how high risk alleles on chromosome 6 and those on other chromosomes interact to predict onset of DM1.

Although most studies have linked a single environmental factor with DM1 etiology, a Swedish group of investigators conducted an interactive analysis of selected pairs of variables. As cited above, The Swedish Childhood Diabetes Study compared risk factors of 339 children aged 0–14 years with newly diagnosed DM1 with factors of