Enterovirus Risk Is 10-Fold Greater in Type 1

BY KERRI WACHTER

FROM BMJ

Patients with type 1 diabetes are almost 10 times more likely to be infected with enterovirus than are individuals without diabetes, according to results of the first meta-analysis of studies using molecular diagnosis of the virus.

Although it has been suggested in the literature that enterovirus might play a role in the development of type 1 diabetes, to date there has been no systematic review of molecular studies. Researchers in Australia performed such a review of 25 controlled studies that used molecular methods to investigate such an association. They found a summary odds ratio of 9.8 (*P* less than .001) for identifying enterovirus in patients with type 1 diabetes, compared with patients without it.

"While the findings from this meta-analysis of observational studies cannot prove that enterovirus infection has a causal role in pathogenesis of diabetes, the results provide additional support to the direct evidence of enterovirus infection in pancreatic tissue of individuals with type 1 diabetes," wrote authors Wing-Chi Yeung, Dr. William D. Rawlinson and Dr. Maria E. Craig of the University of New South Wales (BMJ 2011;342:d35).

For this meta-analysis, two reviewers independently conducted systematic searches for controlled observational studies of enterovirus and type 1 diabetes. They searched the PubMed (from 1965 to May 2010) and Embase (from 1974 to May 2010) databases.

They included only case-control or cohort studies that used molecular methods for viral detection (such as reverse transcription-polymerase chain reaction [RT-PCR], in situ hybridization, or immunostaining for detection of viral capsid protein) to identify current or recent infection in blood, stool, or tissue of patients with prediabetes and diabetes. "Molecular testing is now standard for diagnosis of acute enterovirus infection," they noted.

They classified the studies into two groups – prediabetes and diabetes – depending on whether autoimmunity or type 1 diabetes (newly diagnosed, es-

VIEW ON THE NEWS

New Therapies To Come?

In an accompanying editorial, Dr. Didier Hober and Famara Sane, Pharm.D., noted that prospective studies have suggested "an association between enterovirus infections and the subsequent production of autoantibodies directed against pancreatic beta-cells that result in type 1 diabetes." In fact, it is possible that persistent or consecutive enterovirus infections may play a role in progression or acceleration of type 1 diabetes (BMJ 2011; 341:c7072).

"The link between enteroviruses and the pathogenesis of type 1 diabetes probably involves and interplay between viruses, pancreatic beta-cells, the innate and adaptive immune systems, and the genotype of the patient," they wrote.

While additional studies are necessary to understand these associations and to establish pathogenic mechanisms of enterovirus infections, clear evidence of an association between enteroviruses and type 1 diabetes "opens up the possibility of developing new preventive and therapeutic strategies to fight this disease."

Dr. Hober is a professor of virology at the University of Lille in France. Dr. Sane is a virology research assistant at the University of Lille. The authors reported that they have no relevant financial relationships.

VITALS

Major Finding: Patients with type 1 diabetes are 10 times more likely to have an enterovirus infection, compared with patients without diabetes.

Data Source: A meta-analysis of 34 case-controlled studies using molecular diagnosis of enterovirus.

Disclosures: The investigators reported that they have no relevant financial relationships.

tablished type and eventual type 1 diabetes) was the outcome. This systematic review of 33 prevalence studies, involving 1,931 patients and 2,517 nondiabetic individuals.

They identified 34 studies – 9 involving patients with prediabetes (198 cases and 733 controls) and 25 studies of diabetes patients (1,733 cases and 1,784 controls).

Thirty studies used RT-PCR or in situ hybridization to detect enterovirus RNA; immunostaining for the enterovirus capsid protein vp1 on autopsy pancreas specimens was used on four studies. Most studies investigated children and adolescents up to age 16 years, though some included adults up to age 53 years.

The summary odds ratio of identifying enterovirus in patients with prediabetes compared with patients without diabetes was 3.7 (*P* less than .001). All but one of the 25 studies of patients with type 1 diabetes had odds ratios greater than one for patients with diabetes testing positive for enterovirus, with a summary odds ratio of 9.8 (*P* less than .001).

They used sensitivity analyses to test the robustness of the results by country and study quality.

In all, 19 studies were conducted in Europe. "There was some evidence for geographical differences; in non-European studies the odds ratio was 13.5, compared with 8.6 in European studies, though there was considerably overlap in the confidence intervals," they wrote.

In addition, "the odds of having an enterovirus infection in people with established diabetes (OR, 11) suggest that persistent enterovirus infection is also common among patients with type 1 diabetes." ■

Insulin Regulator Gene Tied to Type 2 Diabetes

FROM JAMA

Patients with type 2 diabetes were more likely to have genetic variations for a key protein regulating cells' insulin receptors, according to a multinational case-control study.

The variants' presence could serve as an early predictive marker of insulin resistance and type 2 diabetes, particularly in patients with a family history of the disease, the study's authors noted.

The investigators examined variations in the high-mobility group A1 protein, or HMGA1, a key regulator of insulin receptor gene expression. The protein's most frequent functional variant was found in 7.2% of the study's 3,278 Italian patients with type 2 diabetes, compared with 0.4% and 3.3% of two Italian control groups (2,544 and 784 patients) without diabetes, significant differences resulting in adjusted odds ratios of 15.8 and 2.0, respectively.

In addition, the variant was found in 7.7% of 970 U.S. case patients, compared with 4.7% of 958 U.S. control patients (adjusted odds ratio, 1.6), a significant difference, and in 7.6% of 354 French case patients vs. 0% of 50 French controls, also a significant difference, reported Dr. Eusebio Chiefari of the University of Catanzaro (Italy) and colleagues (JAMA 2011;305:903-12).

Three other functional variants also were observed in the Italian population, although those variants were not studied in the U.S. and French populations because of the relatively small sample sizes.

Overall, when all four variants were analyzed, nearly 10% of Italian patients with type 2 diabetes were found to have HMGA1 defects, compared with less than 1% of controls.

The four variants of the HMGA1 gene were also shown to be associated with decreased insulin receptor gene and insulin receptor protein expression.

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–Sharon Worcester