Diagnostic Test for Kawasaki May Be Near Reality

BY BRUCE JANCIN

VAIL, COLO. — By far the greatest need in Kawasaki disease is for a diagnostic laboratory test—and recent developments suggest that gene expression testing may be the answer.

"I don't think we're going to have a diagnostic test tomorrow, but with refinement I'm hopeful that gene expression profiling might be the basis of a diagnostic test," Dr. Marsha Anderson said at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

"We really, really, really need a diagnostic test," added Dr. Anderson, a pediatric infectious disease specialist at the University of Colorado, Denver.

The need is desperate because it's clear that patients who meet the original Kawasaki disease case definition are just the tip of the iceberg. That was acknowledged 5 years ago in the revised American Heart Association Kawasaki disease guidelines, which highlighted the diagnosis and treatment of what has come to be termed incomplete Kawasaki disease (Circulation 2004;110:2,747-71).

Patients with incomplete Kawasaki disease—that is, with fewer than four of the standard criteria—are at increased risk of coronary artery complications, just like patients who meet the original diagnostic criteria, and they too respond to intravenous immunoglobulin. But familiarity with the revised guidelines isn't all that great outside the centers of expertise in Kawasaki disease, and the lack of a diagnostic test results in delays in diagnosis and treatment, which can have critical long-term impact.

"I suspect that once we get a diagnostic test, we're going to quadruple the number of patients. We're going to have patients we never dreamed had Kawasaki disease who turn out to have very mild forms of it. That's been seen in many other diseases once a diagnostic test was available," Dr. Anderson observed.

Strong evidence suggesting that genetic predisposition plays a role in the development of Kawasaki disease comes from Japan, where the disease incidence is 10- to 15-fold higher than in white populations. Japanese studies indicate that within 1 year after a first case occurs in a family, the incidence of Kawasaki disease in a sibling is 2.1%. Moreover, Kawasaki disease is twice as common in children whose parents had the disease.

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Investigators at Stanford (Calif.) University are pursuing the genetic connection using DNA microarray technology to examine patterns of gene expression in whole blood from patients with acute and convalescent Kawasaki disease. They demonstrated that patients with Kawasaki disease had increased expression of clusters of genes associated with platelet and neutrophil activation, including genes coding for cell adhesion, innate immunity, and B-cell activation, whereas interferon-gamma was turned off.

They also reported that gene clusters that were turned on in Kawasaki disease were by and large turned off in adenovirus infection, whereas those that were turned off in Kawasaki disease were turned on in adenovirus infection. Whole-blood samples from patients with group A streptococcal infection showed a gene expression profile somewhat similar to that of Kawasaki disease, whereas samples from patients with systemic drug reactions were more akin to the adenovirus infection pattern.

When blinded evaluators were asked to use a set of 38 gene transcripts to categorize 23 Kawasaki disease patients and 8 with adenovirus infections, they got the diagnosis right in 21 of 23 Kawasaki disease patients and in 7 of 8 with adenovirus (J. Infect. Dis. 2009;200:657-66).

This is the most promising lead to date in the effort to develop a diagnostic test for Kawasaki disease, in Dr. Anderson's view. ■

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