Preeti Jaggi, MD, joined Nationwide Children's Hospital in 2006 as a member of the Section of Infectious Diseases and an assistant professor of clinical pediatrics at The Ohio State University College of Medicine. Her research interests include Kawasaki disease, Group A streptococcal infections and adenovirus infections.

Karen M. Texter, MD, joined Nationwide Children's Hospital in 2008 as a pediatric cardiologist in The Heart Center and a clinical assistant professor of pediatrics at The Ohio State University College of Medicine. Her special interests include echocardiography in congenital and acquired heart disease and fetal cardiology.

Recent Publications:

Jaggi P, Mejias A, Xu Z, Tremoulet A, Pascual V, Ramilo O. Transcriptional Profiling to Discriminate Complete and Incomplete Kawasaki Disease (KD) from Other Febrile Conditions. Poster session presented at: Pediatric Academy Societies 2013 Annual Meeting;2013 May 4-7; Washington, D.C.

Jaggi P, Kajon AE, Mejias A, Ramilo O, Leber A. Human adenovirus infection in Kawasaki disease: a confounding bystander? *Clinical Infectious Disease*. 2013 Jan;56(1):58-64. PMID: 23011145. Epub 2012 Sep 25.

Referrals and Consultations

The Kawasaki Disease Program at Nationwide Children's Hospital accepts referrals from across the country.

Online: NationwideChildrens.org
Fax: (614) 722-4000
Phone: (614) 722-6200 or 1(877)722-6220

Physician Direct Connect Line for urgent physician consultations:
(614) 355-0221 or 1(877) 355-0221

Proud to be consistently ranked among the top 10 in the nation by *U.S.News & World Report*.

Case Study: Kawasaki Disease

The Heart Center
Karen Texter, MD

Section of Infectious Diseases
Preeti Jaggi, MD

Once found only in Japan, Kawasaki disease now affects thousands of children in the United States, with the Centers for Disease Control and Prevention reporting more than 5,000 new cases each year. The disorder is characterized by a fever lasting five days or longer; a rash; red eyes; red and swollen hands and feet; peeling of fingertips and toes; strawberry tongue with bright red spots, and swollen and cracked lips. The severity of symptoms varies dramatically from patient to patient, which can lead to missed diagnoses. Kawasaki disease can cause inflammation in the coronary arteries and heart. Left unchecked, this damage can lead to vasculitis, arrhythmias and heart valve malfunctions.

Here we profile two patients who presented to Nationwide Children's Hospital and were referred to our Kawasaki Disease Program, a multidisciplinary partnership between physicians in The Heart Center and the Section of Infectious Diseases. Launched in November 2012, the program's goal is to improve patient outcomes and advance research into the disorder. Faculty in the program are conducting studies into the biological basis of the disease, a vital step toward developing a diagnostic test for Kawasaki disease.

PATIENT 1: COMPLETE KAWASAKI DISEASE

PHASE I:
Presentation, admission, diagnosis

8-month-old male presented to Emergency Department at Nationwide Children's Hospital after four days of fever, accompanied by non-exudative bulbar conjunctivitis with limbic sparing, diffuse maculopapular rash that involved the palms and soles, as well as erythematous of the lips, tongue and pharynx. No evidence of cervical lymphadenopathy. Met criteria for Kawasaki disease.

PHASE II:
Testing, treatment, cardiac monitoring

Patient was admitted and received IVIG 2g/Kg x 1 and ASA 80 mg/Kg/day divided four times daily. Sedated echocardiogram revealed enlargement in the left anterior descending artery and right coronary aneurysm. Patient responded to treatment and was released after three days. Echocardiograms administered at six and 21 days post-discharge showed continued improvement. At three months post-discharge, imaging tests indicated no cardiac enlargement or aneurysm.

PHASE III:
The follow-up

Patient will be followed through the Kawasaki Disease Program through age 18 to monitor for any residual sequelae, such as valve abnormalities, changes in aortic dimensions and subtle changes in ventricular function. Follow-up testing will include cardiac assessment lipid testing and, if examinations suggest potential problems, additional echocardiograms.

PATIENT 2: ATYPICAL KAWASAKI DISEASE

PHASE I:
Presentation, admission, diagnosis

10-year-old otherwise healthy boy with prolonged low-grade fever that responded to ibuprofen. Tests for routine pathogens administered by the child's pediatrician were negative. Three weeks after onset of fever, patient developed diffuse maculopapular rash over his palms and soles and erythematous of eyes, lips and tongue. Patient was referred to the Kawasaki Disease Program at Nationwide Children's for suspected Kawasaki disease.

PHASE II:
Testing, treatment, cardiac monitoring

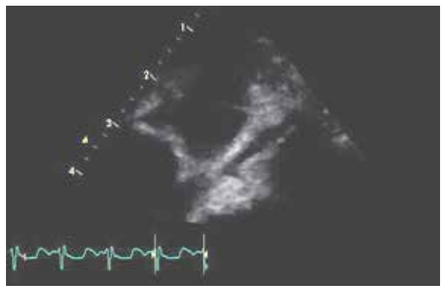
Patient was admitted to Nationwide Children's Hospital. Sedated echocardiogram revealed dilation of the right coronary artery, confirming Kawasaki diagnosis. Patient received IVIG 2g/Kg x 1 and ASA 80 mg/Kg/day divided four times daily. Symptoms resolved within three days of admission and patient was discharged. Sedated echocardiogram at eight weeks post-discharge indicated normal cardiac size and function.

PHASE III:
The follow-up

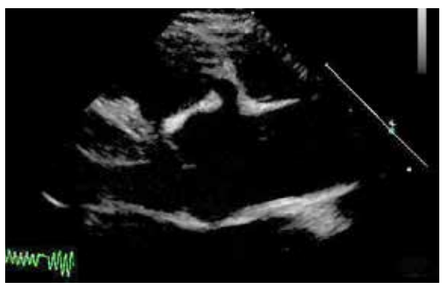
Patient will be followed through the Kawasaki Disease Program through age 18 to monitor for any residual sequelae, such as valve abnormalities, changes in aortic dimensions and subtle changes in ventricular function. Follow-up testing will include cardiac assessment lipid testing and, if examinations suggest potential problems, additional echocardiograms.

Hospitalizations in the United States due to Kawasaki disease have increased in recent years. According to the Centers for Disease Control and Prevention, approximately 5,447 children—most under the age of 5—were admitted for treatment in 2009, the most recent year for which statistics are available.

The lack of a diagnostic test for the disease makes the diagnosis one of exclusion. Kawasaki disease can mimic other febrile illnesses, such as adenovirus infections and Group A streptococcus. While echocardiography can detect cardiac damage caused by the disease, only 3 to 5 percent of patients with Kawasaki suffer cardiac injury. In the absence of obvious symptoms, the disorder is often misdiagnosed in children under 1 year of age and in teenagers. A multidisciplinary, comprehensive program at Nationwide Children's Hospital is advancing the standard of care through an innovative program that combines the expertise of physicians in The Heart Center and the Section of Infectious Diseases with an ambitious scientific research effort to develop a much-needed diagnostic test.



Echocardiogram for Patient 1 at presentation showing ectasia of the left anterior descending coronary, 2.5mm, and a small aneurysm more distally measuring 3.5mm.



Echocardiogram for patient 2 at presentation showing ectasia of the proximal right coronary artery, measures 4mm.

The Kawasaki Disease Program

More than 50 patients have been seen through the Kawasaki Disease Program at Nationwide Children's Hospital since its inception in November 2012. Among these patients is a 10-year-old boy who showed no outward symptoms of Kawasaki until three weeks after the onset of a low-grade fever. Upon referral to Nationwide Children's, the patient was diagnosed with atypical Kawasaki disease.

Case Elements

The elements of this case represent the challenge inherent in the majority of Kawasaki disease patients. The boy was not very ill and his fever responded initially to ibuprofen. Had it not been for the telltale peeling of his fingertips, his pediatrician may not have referred him as a potential Kawasaki patient. The joint efforts of infectious disease specialists and cardiologists increase the likelihood that even subtle presentations will be caught early.

Patient Follow-Up

All patients treated for Kawasaki at Nationwide Children's are followed through the Kawasaki Disease Program for two months following discharge. During this time, patients are seen by both an infectious disease specialist and a cardiologist. After the initial follow-up period, patients are monitored by a cardiologist throughout adolescence into adulthood to monitor cardiac function.

Toward the Development of a Diagnostic Test

When caught early, Kawasaki disease can be successfully treated and cardiac damage prevented or reversed. However, the lack of a diagnostic test means that many cases aren't caught early—if at all. Researchers at Nationwide Children's are analyzing genetic profiles of Kawasaki disease, looking for a pattern that distinguishes the disorder from other febrile illnesses.

An Emerging Pattern

Utilizing a database from 100 Kawasaki disease patients treated at Nationwide Children's since 2009, scientists have narrowed their focus from tens of thousands of genes to about 7,000 that are over- or under-expressed in Kawasaki disease. In a recent study, samples were analyzed from 77 pediatric patients with complete Kawasaki disease, 14 patients with incomplete disease, as defined using American Heart Association guidelines, and from patients with other febrile illnesses [invasive group A streptococcal infection (GAS, n=17), adenovirus (n=19), unexplained fever (n=18)], and age- and sex-matched healthy controls.

The research, presented in May 2013 at the Pediatric Academy Societies annual meeting, found that patients with complete Kawasaki disease demonstrated overexpression of cells associated with the innate immune response and underexpression of monocyte and natural killer cell genes compared to patients with other febrile illnesses.

Implications and Future Direction

The findings suggest that gene expression profiling modular analysis is a promising tool to help characterize Kawasaki disease immunopathogenesis. Because molecular distance to health (MDTH) indicates a higher molecular perturbation in Kawasaki disease compared to other febrile illnesses, there is a potential to use MDTH to predict which patients may not respond to treatment.

Scientists are pursuing this work, which is supported in part by the American Heart Association. These and future findings could finally create the etiological picture of Kawasaki disease that is key to the development of a diagnostic tool.