

Possible Source of Kawasaki Disease Found

Deadly childhood condition may be triggered by aerosols from northeast China



An international team of scientists, including researchers at the UC San Diego School of Medicine and Scripps Institution of Oceanography, report that the likely cause of Kawasaki disease in Japan is a windborne agent originating from northeast China, a region characterized by dense cereal croplands.

Actress Sarah Chalke Becomes Advocate for Kawasaki Disease Research and Treatment in Wake of Son's Illness

It was clear to Actress Sarah Chalke in late 2011 that her 15-month-old son was sick. But his constellation of symptoms – a full body rash, persistent fever, aching joints, red lips, vomiting, and dehydration – stubbornly defied official medical diagnosis.

Or rather, they produced multiple diagnoses. “He was misdiagnosed for ten days. Allergic reaction, adenovirus, Scarlet fever were a few of the diagnoses we received,” said Chalke, perhaps best known for her role as Dr. Eliot Reid in the TV medical comedy-drama series “Scrubs.”

What he had was Kawasaki disease (KD), a largely mysterious condition that can result in permanent damage to blood vessels and is the most common cause of acquired heart disease in children.

“The website kdfoundation.org helped save his life,” Chalke said. “It clearly listed the symptoms and my son had all of them. We went to his pediatrician almost every day for the next nine days, and the ER on day four, and everyone said it was not Kawasaki’s. It was the KD website that I would visit every day and where I would read the symptoms and other parent’s stories that encouraged me to keep pushing to see an infectious disease doctor.

Chalke's son was examined by a specialist on day ten, and the doctor diagnosed him with Kawasaki's on the spot. "My son received the IVIG treatment (an infusion of intravenous immunoglobulin) that day and we are very grateful his heart is okay," Chalke said. "Because there is little known about the long-term effects of KD, he will have an echocardiogram every year and our whole family eats heart healthy."

The experience left a lasting mark. Chalke was alarmed by how little was known about KD, how hard it was to diagnose quickly and accurately and by the potential for future harm. An estimated 25 percent of children with KD develop coronary artery aneurysms – balloon-like bulges of heart vessels – that may eventually result in heart attacks, congestive heart failure or sudden death.

"What I learned is that the first ten days is the ideal window to get treatment, but that coronary damage can happen anytime. I have met parents whose children got coronary aneurysms on day five," Chalke said. "Early diagnosis and early treatment is key."

As a result, Chalke has become a vocal and public advocate for Kawasaki disease research and treatment, most notably of efforts by Dr. Jane C. Burns, professor and director of the Kawasaki Disease Research Center at UC San Diego School of Medicine and Rady Children's Hospital-San Diego, and colleagues to develop an effective diagnostic test and to better understand how the disease is caused and spread.

Working with the Kawasaki Disease Foundation, she has helped raise more than \$250,000 in crowdsource funding for research and last year portrayed the mother of a child with KD in an episode of "Grey's Anatomy."

"We were hoping to reach a wide audience and, through a dramatic story, talk about and show the visual symptoms of KD," she said. She urges parents to advocate for their children.

"For parents who find themselves in a similar situation, I would say trust your gut. Whether it is KD or something else, don't be afraid to go back to your doctor. Don't be afraid to get a second or third opinion. Far better to make an unnecessary trip to the ER than to miss something big. And for things that are time-sensitive like KD, fight to see a specialist."

Symptoms of Kawasaki disease

If your child has had a fever for at least five days with two or more of the following symptoms: bloodshot eyes, body rash, red palms and soles, swollen hands and feet, red and cracked lips, strawberry tongue, swollen lymph node in neck.

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Kawasaki disease (KD) is the most common cause of acquired heart disease in children, most notably in Japan, though incidence rates are also rising in the United States and Western Europe. For decades, it has stubbornly resisted scientific explanation. The disease is difficult to diagnose and, without treatment, 25 percent of children with the condition develop coronary artery aneurysms – balloon-like bulges of heart vessels – that may eventually result in heart attacks, congestive heart failure or sudden death. Prevalence rates of KD are rising among children in Asia, the United States and Western Europe. Predictive models estimate that by 2020 one in every 1,600 adults in the U.S. will be affected by the disease.



Jane Burns, MD

First described in Japan in 1967 and named after its discoverer, Dr. Tomisaku Kawasaki, the cause of KD has eluded two generations of researchers. Dr. Jane C. Burns, professor and director of the Kawasaki Disease Research Center at the UC San Diego School of Medicine and Rady Children's Hospital-San Diego, assembled an international team to help decipher the distinct seasonality of this devastating childhood illness.

Noting that the timing of KD outbreaks in Japan coincides with certain wind patterns from Asia, climate scientist Xavier Rodó and colleagues at the Catalan Institution for Research and Advanced Studies and the Catalan Institute of Climate Sciences, both in Barcelona, used computer models to simulate air currents and airborne particle transport for all days since 1977 with high numbers of KD cases in Japan, based on data compiled by Dr. Yoshikazu Nakamura and colleagues at Jichi Medical University in Japan. The modeling indicated that KD cases in many Japanese locations, both in and out of epidemic years, peaked only when winds originated from a densely-cultivated region in northeastern China characterized by vast cereal croplands.

In 2011, the Barcelona researchers equipped an aircraft based in Japan with a newly designed large-volume air-filtering device to collect aerosol samples. With help from Hiroshi Tanimoto and colleagues at the National Institute of Environmental Science in Tsukuba, Japan, the plane sampled at altitudes between two and three kilometers above Japan to avoid surface contaminants, and on days during the KD season when air currents originated only from northeastern China. Detailed microbiome analyses of the samples by Brent Williams and Dr. Ian Lipkin at Columbia University in New York City identified *Candida* species as the dominant airborne fungus, a finding not previously reported from other aerosol sampling campaigns in other regions of the globe. *Candida* is a genus of yeasts and the most common cause of diverse human fungal infections worldwide.

In their new *PNAS* paper, the multidisciplinary team of Rodó, Burns, Dan Cayan, a climate researcher at UC San Diego's Scripps Institution of Oceanography and co-authors in New York, Barcelona and Japan, say the new evidence suggests that the most likely cause of KD is a "preformed toxin or molecule" originating from northeastern China, possibly related to *Candida*, which has been linked to Kawasaki-like coronary artery vasculitis in mouse models.

Burns summarized the major findings:

- Prevailing wind patterns associated with KD cases in Japan track back to northeastern China, which is the country's main cereal grain-growing region.
- KD has a short incubation time (less than 24 hours between exposure and fever onset), suggesting the cause is not a traditional infectious organism, but more likely a toxin, perhaps fungal in origin, that readily triggers a host immune response in genetically susceptible children.
- Air sampling in Japan during the winter KD season found unexpectedly high levels of *Candida* species within the rich microbiome of tropospheric winds.

Burns, who has published extensively on KD, said these combined factors point to a pathogenic airborne toxin or molecule associated with areas of intensive agriculture, which is lofted into the winds and causes idiosyncratic immune reactions in genetically susceptible children.

“This is a Sherlock Holmes situation,” said Burns. “The data suggest that people are doing something new (since World War II) in northeastern China. Could they be burning a biomass fuel in winter that carries the agent on aerosolized ash to Japan? Could there be some agricultural practice or crop or activity that is new since the 1960s when KD first started to appear in Japan? Could it be that the aerosolized particle is chemically altered to become pathogenic as it travels through clouds on its way to Japan?”

“We need to figure out what the activity or condition is that creates these aerosols carried by the winds. There are certainly other source regions around the globe, but focusing on the link between northeastern China, Japan, Hawaii, and the west coast of North America is our best bet for figuring this out.”



Burns said rising KD cases elsewhere in the world, notably in the Philippines and India, may involve the same agent originating from different source regions. She said the findings have broader implications as well.

“I think that KD represents a new disease paradigm,” she said. In years of searching for its source, “we kept trying to shove a round peg into a square hole. Now I think the door has been opened to thinking about this disease in a new way that may well liberate our thinking about other diseases as well.”

