COVID-19 Pandemic Sets New Clues on the Transmission Pathways in Kawasaki Disease

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Many theories have been formulated through decades regarding the causes of the mysterious syndrome known as Kawasaki disease (KD). This pediatric self-limited vasculitis has been escaping full characterization since Tomizaku Kawasaki, PhD, identified the disease that was then named after him. In many of the clinical histories, the role of external factors seems already clear, because the appearance of respiratory symptoms is reported to occur a few days before KD symptoms emerge (eg, an abnormal immune response characterized by increased levels of inflammatory cytokines and chemokines during the acute phase). However, the many attempts to characterize a unique agent have been unsuccessful so far. Whether this is an indication of a multiplicity of agents (ie, multiple-agent disease) or a complex interplay of factors interacting with the immune system of children who are genetically predisposed still remains an open question. However, in this race against time, a study by Hara and colleagues takes advantage of the unique epidemiological situation caused by the COVID-19 pandemic in Japan to perform a natural experiment that sheds new light on the hidden etiological processes of KD. Indeed, the pandemic itself already has provided KD research with other interesting hints, such as multisystem inflammatory syndrome in children (MIS-C), which was originally named Kawasaki-like multisystem inflammatory syndrome, with symptoms including shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorders. MIS-C was temporally associated with SARS-CoV-2 infection. Despite MIS-C later having been found to have characteristics different from those of classic Kawasaki disease, the nature of MIS-C gives further credibility to the idea that an infection or exposure to an infectious agent (eg, a virus, bacteria, or fungus) can cause symptoms similar to those observed in children with KD. During the COVID-19 pandemic, old theories on KD’s viral origin come to life again, bringing back to the spotlight past studies that found associations even between human coronaviruses and KD.

There are different ways by which research on the so-called epidemiological or disease mimicry can be performed in the case of KD: through comparison of the prevalence of the agent in children with KD vs healthy children (or those with a different disease), through an evaluation of the type of agent, given their pathway of transmission (if so, as in the case of an infection or by separating among modes of transmission, direct, oral, vector, droplet, or airborne), or through comparison of the differences in the immune responses the disease elicits in children with KD when exposed to similar agents. Recent advances on the latter recently postulate the role of gut microbiota in KD pathogenesis through an imbalance caused between T-helper 17 cells and regulatory T cells associated with aberrant immune responses in KD. This dysbiosis, defined as changes in the composition of the gut microbiota, is beginning to be associated with various other inflammatory diseases.

On the origins of KD, controversy remains, and the list of alleged microbial agents widens, including Epstein-Barr virus, human herpesvirus, HIV, human adenovirus, human coronavirus, retrovirus, human parvovirus B19, human bocavirus, Staphylococcus aureus, Streptococcus pyogenes, Yersinia pseudotuberculosis, Bacillus cereus, Mycoplasma pneumoniae, Mycobacterium species, Bartonella henselae, Coxiella burnetii, and Candida species. This list is yet incomplete.

In the study by Hara and colleagues, the authors take nearly real-time data from 6 hospitals around Fukuoka, Japan, and cross-compare the evolution in the incidence of KD and other types of diseases of known transmission patterns. Through this assessment, Hara et al aim to provide...
evidence to support or disprove hypotheses on the way the agents responsible for the autoimmune trigger of KD spread, counterbalancing the propagation via droplet, oral, or direct contact through fomites with an airborne mode of transmission and with these agents spreading embedded in aerosolized particles. The use of face masks and other protective barriers to adhere to SARS-CoV-2 transmission reduction efforts has proven effective against influenza in 2020 and has remained so in 2021, with the near absence of wintertime influenza epidemics so typical in the temperate regions of the Northern and Southern Hemispheres. This illustrates the decreased risk of spreading infectious pathogens reliant on close-contact transmission. This is further manifested in the study by Hara and colleagues, with admissions in Fukuoka hospitals owing to respiratory tract and gastrointestinal infections being greatly reduced during the pandemic.

At the same time, KD admissions in the same area have only slightly decreased compared with previous years, leading to a compelling increase in the ratio of KD incidence to contact- or droplet-mediated infections. Were these patterns to be consistent, it would suggest that the role of contact- or droplet-transmitted infectious agents as a major route for KD development was unlikely and point to a more relevant role of airborne-carried agents, as proposed elsewhere.

The approach by Hara et al is a stimulating and intriguing experiment that sets the stage for other more populated initiatives with larger sample sizes, longer temporal spans, and a wider categorization of diseases and transmission pathways, which should provide more robust support for the direction the conclusions by Hara et al suggest. It is time now to continue testing in this unprecedented natural scenario the pandemic has prepared for us. If the environmental cause or modulating factor of KD is linked to a mixture of air pollution effects and microbial components eliciting the immune response typically seen in KD, the scene is now set for a different, more ambitious experimental scenario, one in which the array of potential sources of some of these agents and pollutants, including local, regional, or remote, can be selectively controlled for and their relative weights properly elucidated. Let us take advantage of this unique collective opportunity.

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