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COVID-19 and Kawasaki Disease: Finding the Signal in the Noise

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Abbreviations: KD, Kawasaki Disease; TSS, Toxic Shock Syndrome

On April 7, 2020, *Hospital Pediatrics* published a case report describing an infant who was diagnosed and treated for Kawasaki disease (KD) and also happened to test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19.[1] Prior to this publication, we had been reading multiple reports of vascular and multisystem inflammatory involvement in adult patients with COVID-19. Although our journal does not traditionally publish case reports, we felt that this case could help spark awareness of a possible association and trigger further investigations in children. However, we were also cognizant that the COVID-19 positivity and the KD in the published case may have been "true, true and unrelated." We also recognized (as did the article authors) that the association, if true, had few if any clinical implications for the case in question.

Since then, attention over a possible association between COVID-19 and KD and other hyperinflammatory states has mounted. On April 26, an alert was sent to general practitioners in London advising them of rising numbers of cases of a multisystem inflammatory state in children with overlapping features of toxic shock syndrome (TSS) and atypical KD. These cases were subsequently described in a correspondence in the *Lancet* on May 7, 2020, which detailed 8 children with critical illness characterized by severe inflammation, though not all had confirmed COVID-19 infection or exposure.[2] In Bergamo, Italy, KD was diagnosed in 20 children over a short period, roughly equivalent to the total number of cases that region sees over 3 years.[3] The French health minister reported that around 15 children were hospitalized in Paris hospitals with symptoms of KD.[3]

On May 4, 2020, the New York City health department issued a health alert describing 15 cases of a multi-system inflammatory syndrome with features of KD or TSS.[4] Since then, media reports have increased dramatically in the New York City area and now include Detroit and

Chicago, though given the lack of details inherent to these types of reports, deciphering the exact nature and severity of the crop of cases remains challenging.

The COVID-19 pandemic has been characterized by unknowns and uncertainties. Enthusiasm for certain interventions such as chloroquine and early intubation has led to rapid adoption, with later realization that these interventions may have caused more harm than good. In the face of a serious pandemic, taking early action in the absence of solid data is understandable and often necessary.

With over a million documented cases in the United States alone, finding associations between COVID-19 infections and other conditions will not be hard. Apophenia is a term that refers to the pervasive human tendency to seek patterns in random information. Picking up patterns, in general, helps us more than it hurts, and may have evolutionary advantages. In medicine, pattern recognition is central to diagnostic acumen, and individual clinical expertise is an important component of Sackett's original conception of the term "evidence-based medicine."[5] However, because we are sometimes misled by these patterns, objective and thorough investigations are needed to confirm our observations.

In the case of an association between COVID-19 and KD and/or other related hyperinflammatory syndromes, there are 2 key questions. One, are the associations causal? Two, if they are in fact causal, to what extent do the associations inform care?

While it is still early, the emergence of patterns that appear to be quite similar across multiple cities certainly points towards a causal association. The alerts from Italy and France contain little data; publications are likely forthcoming. Most of the children in New York and England did not have evidence of acute infection with COVID-19, though the positive serologies in some patients

suggest that the syndrome could represent a delayed immune response. The dearth of reports of the syndrome in Chinese data and on the West coast of the United States is notable but may simply reflect lower overall incidence of COVID-19 in this areas. The fact that KD and TSS are relatively vague conditions without definitive diagnostic tests adds to the challenge of deciphering whether all of these cases reflect a true signal. Similarities in laboratory values such as C-reactive protein, D-Dimer, and ferritin may be clues to both diagnosis and pathogenesis but, unfortunately, these laboratory tests are non-specific.

Future investigations assessing the regional and national prevalence of KD (and possibly TSS) will be helpful. However, even large-scale observational studies will be challenging to interpret. KD has been associated with multiple viruses, and transmission of these viruses has undoubtedly decreased as a result of the disappearance of infectious reservoirs such as school and daycare. Additionally, families have been apprehensive about pursuing medical care for fear of contagious exposure in the healthcare setting. For both of these reasons, any contribution from COVID-19 to overall KD incidence might get diluted. Conversely, given that KD (particularly "atypical KD") can be an ambiguous diagnosis, heightened awareness from all of the recent media attention might trigger an increase in KD diagnoses in patients who previously would not have been diagnosed. These factors must be considered when evaluating potential associations.

If the association is in fact causal, then it matters for several reasons. There are proven therapies for KD, such that delays or failures to diagnose could lead to worse outcomes related to coronary aneurysms.[6] On the other hand, COVID-19 has been rare in children to date, and most of the larger published series reporting clinical characteristics do not describe features consistent with KD.[7-10] In one series, for example, fever >38° Celsius was present in only 41% of patients, and rash in only 3%.[9] Therefore, COVID-19 patients with prolonged fever and other features of KD

should still trigger consideration of the disease. The association could also matter if the manifestations, outcomes, and responses to treatment are different for COVID-associated KD as compared to other types of KD. Additionally, we may learn that acute COVID-19 infections are associated with KD just as other viruses have been (as in our journal's case report), but that there is a separate hyperinflammatory syndrome distinct from classic KD that occurs following recovery from the acute COVID-19 infection. Better characterization of the latter will be useful in defining optimal management approaches. The reported disease severity in some of these patients heightens the need for a concrete case definition, which in turn may help with earlier recognition and treatment.

On the other hand, we need to be aware of potential negative consequences of widespread dissemination of this possible association as well. Misdiagnosis of KD could drive overtreatment, and anchoring on this diagnosis could prevent practitioners from considering other hyperinflammatory or infectious conditions. A false inflation of the reported incidence could further heighten anxiety and perhaps lead to public health interventions of uncertain benefit such as continued school closures. Disassociating the syndrome from KD by giving it a separate name, such as "Pediatric Multisystem Inflammatory Syndrome" as has been proposed by some, could mitigate overtreatment concerns.

Pediatricians and public health experts in communities where this syndrome has been described are working to aggregate data and experiences in order to create an evidence base for diagnosis and treatment. Promoting awareness is crucial in order to learn more and foster collaborations. However, given the potential for misattributions of causality, we must tread carefully and objectively.

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