Another compelling evidence suggesting infectious diseases as the cause of Kawasaki disease?

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Kawasaki disease (KD) has been the most common cause of pediatric acquired heart disease in the developed countries and has been reported from >60 countries in the world.[1] The etiology remains unclear since Dr. Tomisaku Kawasaki proposed the disease about 50 years ago. The high incidence of KD in Asian children, even their residence in the United States living a Western lifestyle, strongly supports that genetic susceptibility plays an important role.[2] Besides, an infectious trigger is highly suspected because KD shared many similar clinical characteristics with some common childhood infections (systemic presentations, peak in young children, generally no recurring in nature, rarity of KD before 3 months of age because of protective maternal antibody, geographic and temporal clustering, seasonality shown in high incidence countries, such as peak incidence in January in Japan).[3,4] Multiple viral pathogens have been proposed with their associations with KD. Turnier et al[5] found half of all KD patients had one or more concurrent respiratory virus detected by polymerase chain reaction (PCR), with 4.7% cases positive with adenovirus. Jaggi et al[6] reported that 8.8% of typical KD and 25% of incomplete KD children had adenovirus. However, they also found that culture negative, significant lower viral burden of adenovirus was detected in the typical KD group (adenovirus species C, especially serotypes 1, 2, and 5) than that in active adenovirus disease group, in which adenovirus B or E predominated and grew easily in culture.[6,7] Therefore, detection of adenovirus by PCR in the nasopharynx does not definitely include or exclude the diagnosis of KD. The etiological role of the low-level persistence of adenovirus and specific adenovirus species in KD is still ill-defined. The identification of adenovirus in KD patients, therefore, should always be interpreted with caution. For example, one study argued against the role of adenovirus infection in KD because gene microarray assays of the blood samples showed different distinct patterns between KD and adenovirus-infected patients.[8]

In this original article, Huang et al[9] investigated the association between adenovirus infection and subsequent risk of KD from a large national population-based database. They found that significantly higher KD risk was noted in children with previous adenovirus infection than those without such infections (adjusted hazard ratio [HR] = 5.29, $p < 0.001$). The risk was particularly higher in children aged 3 to 5 years, in females, in those with a low urbanization level and allergic diseases. This study had the limitations of potentially less accurate diagnosis of adenovirus infection and KD by using *International Classification of Diseases* (Ninth Revision; ICD-9) coding in the national health insurance program data. For the diagnosis of KD, the authors tried to combine original database with the Registry for Catastrophic Illness Patient Database to enhance the validity of diagnosis. Consequently, the total case number from both groups (n = 49) could be greatly underestimated because some KD cases had never been registered.[10] Fortunately, it was a non-differential misclassification bias which could happen in both the case and control group and result in the strength of the association toward the null. Therefore, the strong association of the study results would still be valid. However, the diagnosis of adenovirus infections by ICD-9 coding rather than by culture reports, serum antibodies, or PCR assays was more problematic. Either overdiagnosis (if majority of cases were diagnosed solely on clinical judgement without objective evidences support) or underdiagnosis (if physicians did not type in the precise ICD-9 codes, which was quite common in everyday clinical practice) could happen. The latter bias (underdiagnosis of adenovirus) could lead to overestimation of the HR of KD due to underestimation of the denominator in the case group. In addition, the authors followed the KD event for several years after adenoviral infection. The existence of adenovirus could not be ascertained at the event of KD from this database and posed a big question mark whether there were other triggers at the moment of KD.

Another new evidence about the infectious disease as potential trigger comes to our attention this year as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads all over the world. Verdoni et al[11] reported an outbreak of severe Kawasaki-like disease in the epicenter of the SARS-CoV-2 epidemic in Italy. They found a 30-fold increased incidence and more severe presentations of Kawasaki disease shock syndrome (KDSS) and macrophage activation syndrome (MAS) during this outbreak. Similarly, Riphagen et al[12] demonstrated a clustering of Kawasaki-like disease in the United Kingdom, many of them had already been tested positive for COVID-19 antibody. Toubiana et al[13] underwent a prospective observational study and also found the strong relationship between Kawasaki-like disease and SARS-CoV-2 in Paris area in France. In 90% (19/21) of the cases, IgG antibodies for SARS-CoV-2 were detected; 52% of the patients fulfilled the complete criteria for KD. Although only six patients had recent history of an acute respiratory infection, all patients had gastrointestinal symptoms before the onset of

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KD symptoms. In addition, 57% of the patients were descendants from sub-Saharan Africa or Caribbean islands, and 14% from Asia, suggesting a possible genetic susceptibility. Finally, these patients showed a very strong immunologic response to SARS-CoV-2 with higher levels of pro-inflammatory markers than other cohorts. It is still not clear whether these clusters are KD with COVID-19 as the infectious trigger or an emerging complication with multiple organ inflammations caused by SARS-CoV-2.[14] Interestingly, currently it is not known that such clustering in Asian countries whose people are genetic is more susceptible to KD.

In conclusion, it seemed quite possible that diverse pathogens could be potential triggers of KD, which is caused by dysregulated immune response to these triggers in children with susceptible genetic background.[15] However, we should also keep in mind that KD is not the result with any infectious pathogen; otherwise, recurrence of KD should be quite common with subsequent infectious diseases.[15]

The study is the very first large population cohort study assessing the adenovirus infection and the subsequent risk of KD. The significant findings are still very informative. After all, identifying the cause of this mysterious disease is still the most important goal in the field to improve its diagnosis, treatment, and also its prevention in the future.

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