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ACTA PÆDIATRICA NURTURING THE CHILD WILEY

BRIEF REPORT

Kawasaki disease or Kawasaki-like disease: Influence of SARS-CoV-2 infections in Japan

The coronavirus disease 2019 (COVID-19) pandemic witnessed several clusters of children with fever and multisystem inflammation resembling Kawasaki disease (KD). Due to the evidence of a preceding severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in most of these patients, post-viral immunological reactions were thought to play an important role in the pathogenesis.[1,2] The condition, called 'pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS)', has thus far been reported mainly from Europe and the United States,[1,2] and no cases have been diagnosed in Asia. We herein analysed the clinical data on patients in whom KD were diagnosed during a local COVID-19 epidemic to investigate the relationship between KD and SARS-CoV-2 infections in Japan, which has the highest KD incidence in the world.

The present retrospective observational study was conducted at Tokyo Metropolitan Children's Medical Center (Tokyo, Japan), one of the largest paediatric referral centres in the nation. Children who received a KD diagnosis and were treated at our hospital between December 1, 2019, and May 31, 2020, were included. KD was diagnosed using the Japanese diagnostic criteria. Patients who were treated for KD elsewhere before being transferred to our hospital were excluded. To compare the clinical presentations before and during the local COVID-19 epidemic, the patients were divided into two groups, period 1 and period 2, based on whether the diagnosis was made before or after March 1, 2020. The patients' data were extracted from their medical records. Levels of anti-SARS-CoV-2 IgM and IgG in the sera were measured by chemiluminescent microparticle immunoassay using the iFlash 3000 chemiluminescent immune analyser (YHLO Biotechnology Co., Ltd., Shenzhen, China) with a cut-off value of 10 AU/mL for IgM and IgG. Cryopreserved sera obtained before and one week after the initial intravenous immunoglobulin (IVIG) treatment were analysed. To evaluate the possible effect of IVIG on post-treatment serum anti-SARS-CoV-2 antibody levels, the anti-SARS-CoV-2 antibody levels in the IVIG preparations used for treatment were measured. The study was approved by our institutional review board (2020b-26).

In total, 44 patients with KD were analysed; 30 were from period 1, and 14 were from period 2 (Table S1). The median age was 2 years. No patients presented signs of shock. There was no significant difference in the clinical or laboratory characteristics of the two groups except for platelet count. Coronary artery aneurysms were observed in two (5%) patients at one month after the primary treatment.

Two patients were positive for the anti-SARS-CoV-2 antibody (Table S2). Patient 1 was also positive for the anti-*Mycoplasma pneumoniae* antibody on particle agglutination test. Patient 2 was hospitalised for SARS-CoV-2 infection at our hospital one month before KD diagnosis; KD onset occurred 56 days after COVID-19 onset.

Although the anti-SARS-CoV-2 IgG level in all the IVIG preparations was below the cut-off, it was higher than that in the patients' serum.

Our study revealed that most patients with KD at our hospital had clinical characteristics more compatible with classical KD than with PIMS-TS. Their demographic, clinical and laboratory features differed from those of patients with PIMS-TS, who are typically older and have a higher incidence of hemodynamic instability and gastrointestinal symptoms and a lower platelet count.[1] No dramatic increase in KD incidence or changes in its clinical features were observed during the local COVID-19 epidemic, unlike in other countries where PIMS-TS is endemic. Only one (2%) patient was positive for anti-SARS-CoV-2 IgG in contrast to around 80% of patients with PIMS-TS in Europe.[1]

There was an apparent drop in KD cases from period 1 to period 2. However, the number of patients with KD treated at our hospital in the previous year during the period corresponding to periods 1 and 2 was 32 and 19, respectively, showing a similar trend with the present subjects. Considering that the incidence of KD is lower in spring than in winter,[3] this drop was assumed merely to reflect the normal seasonality of KD rather than any effect of COVID-19.

Several reasons may explain the lack of PIMS-TS reports in Asia. First, patients with COVID-19 have thus far been much fewer in Asia than in Europe, leading to fewer children having the disease. Second, PIMS-TS apparently shows a predilection for individuals of black or Hispanic descent,[1,2] suggesting that genetic factors may contribute to its uneven distribution. The same trend was observed in Kawasaki shock syndrome, a severe form of KD characterised by clinical presentations very similar to those of PIMS-TS.[4] These ethnic groups may have some genetic factors that make them more susceptible to hyperinflammatory states. Our study incidentally revealed a higher anti-SARS-CoV-2 IgG level in IVIG preparations than in the patients' serum, indicating potential cross-reactivity between SARS-CoV-2 and common human coronaviruses, as previously demonstrated

in a study analysing human sera collected prior to the COVID-19 pandemic.[5]

According to recent reports from Europe and the United States, more than half of patients with PIMS-TS are known to present without Kawasaki-like symptoms.[1,2] Because the current study focused only on patients with KD, the exact epidemiology of PIMS-TS was not analysed. Furthermore, the present report was based on a small, retrospective study at a single institution; nationwide studies are needed to clarify the actual state of PIMS-TS in Japan.

In summary, our study revealed that most patients who received a diagnosis of KD during the COVID-19 epidemic in our catchment area had classical KD rather than PIMS-TS with Kawasaki-like presentations. The effect of COVID-19 on patients with KD in Japan seems to be small. Since a second COVID-19 wave is imminent, a prospective, nationwide study should be planned to establish the precise epidemiology of PIMS-TS in Asia.

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CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose. The intravenous immune globulin preparations used in this study were provided by Japan Blood Products Organization.

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SUPPORTING INFORMATION

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