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Case Report

# Are Genetics Involved in the Development of Multisystem Inflammatory Syndromes in Children?

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## ABSTRACT

The relationship between Multisystem Inflammatory Syndrome in Children (MIS-C) and genetic predisposition is not well established. The aim of this article emphasize the presence of genetic predisposition in MIS-C by presenting two sibling cases from two separate families with a diagnosis of MIS-C. The patients applied with complaints of fever, abdominal pain, diarrhea and maculopapular rash. While the coronavirus disease-2019 (COVID-19) polymerase chain reaction test was negative in all cases, three had both IgM and IgG positivity, and the other case had only IgG positivity. Patients who did not define any other infection were diagnosed with MIS-C according to the Centers for Disease Control and Prevention criteria. The patients were discharged with full recovery. The fact that siblings share the same genetic background and the same environmental factors suggests that MIS-C syndrome occur in individuals with a genetic predisposition. Further genetic studies with a large MIS-C series are needed to determine which genotypic trait may cause the development of MIS-C in COVID-19 infection.

**Keywords:** Children, COVID-19, genetic, MIS-C, siblings

## INTRODUCTION

The severe global effects of the coronavirus disease-2019 (COVID-19) (severe acute respiratory syndrome-coronavirus 2) epidemic are still being experienced, with it officially being declared a pandemic by the World Health Organization (WHO) on March 11, 2020. At the end of April 2020, a novel syndrome-made appearance, and was understood to be linked to COVID-19; the findings were similar to that of Kawasaki disease (KD), toxic shock syndrome and macrophage activation disease, reported initially in case studies from the UK, then in the United States and Central Europe. This disease was first termed pediatric inflammatory multisystem syndrome temporarily by the Royal College of Pediatrics and Child Health and was associated with COVID-19; it was later called COVID-19-associated Multisystem Inflammatory Syndrome in Children (MIS-C) by the Centers for Disease Control and Prevention (CDC) and WHO. Although the immunopathogenesis of MIS-C is still unclear, it is classified as a hyperinflammatory condition that develops approximately 1-6 weeks after a COVID-19 infection.[1] The relationship between MIS-C development and genetic predisposition is not well established.

This article aimed to emphasize the presence of genetic predisposition in MIS-C by presenting two previously healthy siblings from two separate families, who were not consanguineous marriage and followed up with the diagnosis of MIS-C.

### Case 1

A nine-year-old girl with no prior complaints was admitted to our clinic with a fever and rash. The patient experienced fever (39 ºC), abdominal pain and headache for 4 days. The patient had a history of contact with his uncle, who previously had an active

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COVID-19 infection three months prior. During this time, COVID-19 symptoms were also present in the patient's parents, but they had not been tested. The patient's physical examination revealed maculopapular rashes on the extremities and torso. There was widespread abdominal tenderness present. COVID-19 testing showed that COVID-19 real time-polymerase chain reaction (PCR) was negative, COVID-19 IgM negative and COVID-19 IgG positive. Laboratory evaluation was as follows: C-reactive protein (CRP): 136 mg/L, sedimentation: 40 mm/hour, d-dimer: 2.43 mg/L, ferritin: 265 µg/L, procalcitonin: 0.33 µg/L, white blood cell (WBC): 10420/mm$^3$, neutrophil: 8640/mm$^3$, lymphocyte: 1080/mm$^3$, proBNP: 800 ng/L, fibrinogen: 631 mg/dL. Due to the presence of fever, skin lesions and hematological, gastrointestinal and cardiovascular involvement, the patient was diagnosed with MIS-C with respect to the CDC criteria. Low molecular-weight heparin and intravenous immunoglobulin were administered. The patient's clinical findings improved during the eight-day follow-up and she was discharged with full recovery.

**Case 2**

A seven-month-old male patient, who was the brother of the first case, presented with fever and restlessness that lasted for 3 days. The fever started about 10 days after her sister's symptoms first appeared. Physical examination showed widespread maculopapular rash and non-purulent conjunctivitis in the eyes. After further evaluation, COVID-19 PCR was found to be negative, but COVID-19 IgG and IgM were positive. Laboratory testing was as follows: d-dimer: 3.09 mg/L, fibrinogen: 163 mg/dL, CRP: 1.49 mg/L, procalsitonin: 0.12 ug/L, ferritin: 70 µg/L, proBNP: 525 ng/L, WBC: 11210/mm$^3$, neutrophil: 590/mm$^3$, lymphocyte: 9640/mm$^3$. Cardiovascular evaluation showed no signs of pathology other than a high-ProBNP level. Similar to his sister, the male patient was diagnosed with MIS-C according to CDC criteria and was administered low molecular-weight heparin and intravenous immunoglobulin. The patient's clinical findings improved in the follow-up and he was discharged with full recovery.

**Case 3**

A six-year-old male patient was admitted to the emergency department complaining of fever, abdominal pain and diarrhea. The patient's complaints had been present for 2 days. His mother and father had an active COVID-19 infection one week prior. On physical examination, the patient exhibited no findings other than abdominal tenderness. A few days prior, the family stated that the boy had red eyes and dry and cracked lips. The patient's COVID-19 evaluation revealed a negative PCR, but positive COVID-19 IgM and IgG. The patient's laboratory results were as follows: CRP: 253 mg/L, procalcitonin: 1.38 µg/L, d-dimer: 1.82 mg/L, WBC: 15830/mm$^3$, neutrophil: 12740/mm$^3$, lymphocyte: 1860/mm$^3$, proBNP: 218 ng/L, ferritin: 104 µg/L. During the follow-up, the patient's cultures exhibited no signs of microbial growth. The patient had positive COVID-19 serology and high proBNP as well as cardiovascular, hematological and gastrointestinal involvement. Since no other infective agent could reasonably explain these findings, the patient was diagnosed with MIS-C according to the CDC criteria. Low molecular-weight heparin and intravenous immunoglobulin were administered. The patient's clinical findings improved in the follow-up and he was discharged with full recovery.

**Case 4**

A 3-year-10-month-old male patient, who was the brother of case 3, presented to our outpatient clinic complaining of fever, abdominal pain and diarrhea that had been present for a day. Physical examination revealed no findings other than abdominal tenderness. The patient was found to have a negative COVID-19 PCR and positive COVID-19 IgM and IgG. Laboratory testing was as follows: CRP: 73.9 mg/L, procalcitonin: 0.90 µg/L, d-dimer: 1.50 mg/L, WBC: 15110/mm$^3$, neutrophil: 12200/mm$^3$, lymphocyte: 2120/mm$^3$, proBNP: 384 ng/L, sedimentation: 26 mm/hour, fibrinogen: 125 mg/dL, ferritin: 71 µg/L. All of the patient's culture results were negative. The patient exhibited cardiovascular, hematological and gastrointestinal involvement as well as positive COVID-19 serology and since no other infective agent could be considered, the patient was diagnosed with MIS-C with respect to CDC criteria, similar to his brother. Furthermore, the patient was administered low molecular-weight heparin and intravenous immunoglobulin. The clinical and laboratory characteristics of the patients are presented in Table 1.

## DISCUSSION

Our article is the first article in the literature to present two siblings (4 cases) from two different families diagnosed with MIS-C. The patients were diagnosed with MIS-C according to the CDC criteria. They all were administered intravenous immunoglobulin and low molecular-weight heparin. In a comprehensive seroconversion study, median seroconversion times of total antibody, IgM, and IgG were found to be 11, 12, and 14 days, and seroconversion rates were 93.1%, 82.7%, and 64.7%, respectively. Additionally, the study stated that the sensitivity of the test was 66.7% in the early stage of the disease (within 7 days after contact), however, this number increased upon the 8$^{th}$ day after the onset of symptoms and exceeded 90% on the 12$^{th}$ day. It was reported that the sensitivity for total antibody, IgM and IgG in samples taken in the days after were 100%, 94.3%, and 79.8%, respectively.[2] All of our cases were presented in the early period (the first 7 days after the onset of symptoms). While the COVID-19 PCR test was negative in all cases, three had both IgM and IgG positivity, and the other case had only IgG positivity. Due to the clinical and laboratory similarity between KD and MIS-C, understanding the etiology of can provide us with new information regarding the pathogenesis of MIS-C in COVID-19. For this purpose, data about families with KD were analysed; some infectious pathogens may trigger KD in familial cases, and it should be emphasized that these cases have a higher risk of KD development compared with the general population. Our case is the first in the literature in which familial MIS-C has been reported. These results suggest that in patients with a COVID-19 infection, genetic factors can affect the

**Table 1. The clinical and laboratory characteristics of the patients**

| | **Case 1** | **Case 2** | **Case 3** | **Case 4** |
|---|---|---|---|---|
| Age (month) | 104 | 7 | 77 | 46 |
| Sex | Female | Male | Male | Male |
| Relation | Case 2 | Case 1 | Case 4 | Case 3 |
| CDC diagnosis | | | | |
| 1. Fever ≥38° C or subjective for ≥24 hours | 4 day | 3 day | 2 day | 1 day |
| 2. Laboratory inflammation | | | | |
| CRP (mg/L) | 136 | 1.49 | 253 | 73.9 |
| Sedimentation (mm/hour) | 40 | | 12 | 26 |
| Procalsitonin (µg/L) | 0.33 | 0.12 | 1.38 | 0.9 |
| Fibrinogen (mgdL) | 631 | 163 | | 125 |
| D-dimer (mg/L) | 2·43 | 3.09 | 1.82 | 1.5 |
| Ferritin (µg/L) | 265 | 70 | 104 | 71 |
| Neutrophil (/mm$^3$) | 8640 | 590 | 12740 | 12200 |
| ProBNP (ng/L) | 800 | 525 | 218 | 384 |
| 3. Severe illness requires hospitalization | Yes | Yes | Yes | Yes |
| 4. ≥2 organ systems involved (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological and neurological) | Cardiac (ProBNP ↑) Hematological (D-dimer ↑) Dermatological (maculopapular rash) Gastrointestinal (abdominal pain, abdominal tenderness) | Cardiac (ProBNP ↑) Hematological (D-dimer ↑) Dermatological (maculopapuler rash) | Cardiac (ProBNP ↑) Hematological (D-dimer ↑) Gastrointestinal (abdominal pain, diarrhea) | Cardiac (ProBNP ↑) Hematological (D-dimer ↑) Gastrointestinal (abdominal pain, diarrhea) |
| No other plausible diagnosis | No | No | No | No |
| SARS-CoV-2 infection or exposure defined as | | | | |
| COVID-19 PCR | Negative | Negative | Negative | Negative |
| COVID-19 IgM | Negative | Positive | Positive | Positive |
| COVID-19 IgG | Positive | Positive | Positive | Positive |

CDC: Centers for Disease Control and Prevention, CRP: C-reactive protein, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction

severity of disease, characteristics of the symptoms and severity of the host immune response to this infection. In their studies on twins, Williams et al.[3] reported that 50% of the COVID-19 infection phenotype variance was caused by genetic factors. Additionally, they had previously expressed that the anosmia symptom showed 48%-inherited characteristics.[3] Hoffmann et al.[4] stated that the symptoms occurring in a COVID-19 infection may be linked to genes encoding angiotensin-converting enzyme-2 receptors, and that these genes may reflect the genotypic status in a COVID-19 infection as it is required for viral attachment. Although the immunopathogenesis of MIS-C is still not clearly understood, its good response to immunomodulation therapy may imply that the disease is due to immune dysregulation.[5] While the molecular similarity between COVID-19 antigens and body cells cannot be shown, autoimmune response with macrophage activation is another mechanism suggested to play a role in the development of cytokine storm. However, the genotypic features associated with MIS-C development are currently a mystery.

In conclusion, our patients are siblings who share the same genetic background, are exposed to the same environmental factors and the same viral strain, suggesting that MIS-C syndrome is an indicator of the excessive immune response that occurs in individuals with genetic predisposition after a COVID-19 infection. However, it is not known which genotypic trait may cause MIS-C development in COVID-19 infection. Therefore, genetic studies with large MIS-C series are required.

### Ethics

**Informed Consent:** The informed consent was obtained.

**Peer-reviewed:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: S.İ., U.U.G., Concept design: S.İ., Data Collection or Processing: U.U.G., Analysis or Interpretation: S.İ., Literature Search: S.İ., U.U.G., Writing: S.İ., U.U.G.

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