

Multisystem Inflammatory Syndrome in Children (MIS-C):

An Emerging Immune Mediated Syndrome in Children Associated with COVID-19

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Abstract

As the world came to terms with the current COVID-19 pandemic, children were initially thought to have milder disease than adults with significantly lower morbidity and mortality. The emergence of a multi-system inflammatory syndrome in children (MIS-C) associated with the SARS-CoV-2 virus was first recognized in Europe, and then across centers in the United States. Early and widespread data sharing among centers across the world was extremely helpful in early identification and treatment of these children, with a good prognosis in a majority of cases. Significant research is required to answer several questions that have been raised, including susceptibility, long-term effects, and pathogenesis and treatment options to name a few.

Initial Case

On April 12th, 2020, in the midst of the COVID-19 pandemic, a 14-year old multiracial (Caucasian and Hispanic) male presented to the emergency department with a four day history of fever, fatigue, and abdominal pain and subsequently developed fever, diarrhea and a rash. Polymerase Chain Reaction (PCR) for the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) was negative on admission. He was initially thought to have appendicitis, but work up for that was negative. On laboratory evaluation, he had very high levels of inflammatory markers including C-Reactive Protein and Erythrocyte Sedimentation rate. Brain Natriuretic Peptide, an indirect marker of cardiac function, was also elevated. Echocardiogram confirmed severely decreased heart function and mildly dilated coronary arteries. His clinical presentation had some overlapping features of Rheumatic Fever, Kawasaki Disease and Toxic Shock Syndrome, without meeting criteria for any one of them.^{1,2} His exact diagnosis was somewhat of a puzzle even to the multispecialty team treating him, including the intensivist, cardiologist, rheumatologist and infectious disease doctors.

He received intravenous fluids, vasopressors to support blood pressure, and milrinone and diuretics to support cardiac function. He was intubated and placed on mechanical ventilation. Due to the mild dilation of the coronary arteries, he was treated with intravenous immunoglobulin for possible Kawasaki disease, though he did not meet criteria even for the incomplete form.² He responded well to treatment, with resolution of presenting symptoms and markers of inflammation; and normalization of his cardiac function. He was discharged after 12 days in the hospital.

On April 24th, the National Health Service in the United Kingdom circulated a memo to health care providers, alerting them of an emerging Kawasaki-like syndrome in older children, with a predominance of gastrointestinal symptoms. On receiving that memo as a forward, on a social media app called WhatsApp, we sent antibody testing for the SARS-COV-2 immunoglobulin (SARS-COV-2 IgG) for our patient and he was confirmed to have what was initially known as

the pediatric multisystem inflammatory syndrome in children possibly associated with COVID-19 (PIMS), the first reported case in Delaware and one of the first in the United States.

COVID-19 in Children

In December 2019, an outbreak of a severe respiratory illness caused by a novel strain of coronavirus, SARS-CoV-2, was first identified in Wuhan, China.³ The World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 11 March.³ As the disease progressed through China, followed by Europe, the United States, and then the rest of the world, some solace was obtained from the data suggesting that severe illness in children was far less frequent than adults.⁴ A systematic review published in March 2020 came to the conclusion that COVID-19 was either rare in children or it had not been diagnosed that often because this age group remained asymptomatic.⁵ Children represented only approximately 1.2 to 5% of diagnosed cases.⁵ These low figures were consistent with the data from the Severe Acute Respiratory Syndrome (SARS) epidemic in 2003, when very few of the positive cases were children and none died.⁶ Several suggestions were put forward to explain the milder disease in children. Overall it seemed that children had a different immune system when compared to adults, and somehow that protected them from severe symptoms in this disease.

Evolution of the Multisystem Inflammatory Syndrome in Children (MIS-C):

In April, 2020, reports from the United Kingdom noted a number of children of all ages presenting with a multisystem inflammatory state requiring intensive care, presenting with abdominal complaints and cardiac inflammation. A possible correlation with COVID-19 was suggested with some of these children testing positive for SARS-COV-2 PCR, and some for related antibody tests. An international web-based meeting was hosted via Zoom, a cloud based online service, on May 2, 2020, including experts from Europe and the United States. They reported data from 38 cases identified between March 25 and April 1, ranging in age 1-15 years presenting with features of this syndrome. On May 4, 2020, the New York City Health Department issued an alert to health care providers in the United States after identifying 15 patients aged 2-15 years, who had been hospitalized from April 17 to May 1, 2020 with illnesses compatible with a multisystem inflammatory syndrome.⁷ Then on May 14, the Centers for Disease Control (CDC) put out a health advisory outlining diagnostic criteria for this syndrome, now called Multisystem Inflammation Syndrome in Children (MIS-C, Table 1).⁸ CDC required reporting of identified cases to state, local or territorial health departments. While the CDC did not provide guidance on treatment, intravenous immunoglobulin and supportive care were noted as common approaches to management. WHO followed on May 15, with a similar case definition (Table 2).⁹

Table 1: CDC Case Definition for MIS-C⁸

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| <ul style="list-style-type: none"> • Age \leq 21 years • Fever $>$ 38°C or subjective fever \geq 24 hours • Clinically severe illness requiring hospitalization with \geq2 organ involvement: <ul style="list-style-type: none"> cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological • Laboratory evidence of inflammation: |
|---|

Elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, LDH, IL-6, elevated neutrophils, reduced lymphocytes and low albumin

- No alternative plausible diagnoses
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

CDC: Center for Disease Control; MIS-C: Multisystem Inflammatory Syndrome in Children; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; LDH: lactic acid dehydrogenase; IL-6: Interleukin-6; RT-PCR: real time polymerase chain reaction; COVID-19: coronavirus disease 2019

Table 2: WHO Preliminary case definition for MIS-C⁹

- Age 0-19 years
- Fever > 3 days
- AND 2 of the following:
 - 1) Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet)
 - 2) Hypotension or shock
 - 3) Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP)
 - 4) Evidence of coagulopathy (by PT, PTT, elevated d-Dimers)
 - 5) Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).
- AND
 - Elevated markers of inflammation such as ESR, CRP, or procalcitonin
- AND
 - No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
- AND
 - Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19

WHO: World Health Organization; MIS-C: multisystem inflammatory syndrome in children; ECHO: echocardiogram ; PT: prothrombin time; PTT: partial prothrombin time; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NT-proBNP: N-Terminal prohormone brain natriuretic peptide; RT-PCR: real-time polymerase chain reaction; COVID-19: Coronavirus disease 2019

More cases were reported from Europe and Eastern states in the United States, with highest numbers from New York. As of early June, more than 250 cases were reported from more than 25 states in the United States, of which approximately six were from Delaware. A surge of cases was also noted from more than twelve countries in Europe. Interestingly, no definitive cases of MIS-C were identified in China. Castagnoli's et al. systematic review included data from 1065 children with COVID-19 infection in China with 444 cases in children aged younger than 10 years, and 553 children aged between 10 and 19 years.¹⁰ The authors reported that the children presented with symptoms similar to the presentations in adult populations e.g. fever, dry cough, fatigue, sore throat, headache, loss of taste and smell, and/or shaking chills. Chest x-ray findings reported bronchial thickening, ground-glass opacities, as well as inflammatory lung lesions.

None fit the criteria for an inflammatory post infectious syndrome. It has been speculated that there are different circulating strains of the SARS-CoV-2 virus, and that the Italian strain is more likely to result in MIS-C as opposed to the Wuhan strain. This would also explain the greater incidence of this syndrome on the Eastern coast of the United States which is in closer proximity to Europe, as opposed to the Western coast where the virus first originated from a traveler from China.

Role of Social Media and Internet Based Meeting Platforms

In this age, even prior to the current pandemic, social media platforms such as Twitter, Facebook, Instagram and WhatsApp have become primary sources of information for a vast majority of the population. They are also however vehicles for fake news and misinformation. Data shared on these sites is not required to be peer-reviewed or back by valid research. The strength of these platforms however lies in those very deficiencies. They are widely used and news can be shared even as the situation evolves, in real-time and from multiple sources.

Initial knowledge of this syndrome was distributed via Whatsapp and Facebook. The widespread availability and ease of setting up meetings using Zoom and WebEx allowed very early interchange of information between countries in Europe such as Italy, Spain and United Kingdom with several centers in the United States and around the world. Medical professionals were able to share data quickly, avoid the time lag and hurdles to publication, thus enabling early identification of these cases, and expedited development of management protocols.

Correlation with Kawasaki Disease

Due to the cardiac, especially coronary involvement in MIS-C, several comparisons were drawn to Kawasaki Disease. This mysterious illness was first described by Dr. Tomisaku Kawasaki of Japan who recently passed away on June 5, 2020 at the age of 95 (unrelated to COVID-19 related causes). In 1967, he published his full description of a child he encountered in 1961 with fever, rash and oral changes.¹¹ Kawasaki Disease was also independently recognized as a new and distinct condition in the early 1970s by pediatricians Marian Melish and Raquel Hicks at the University of Hawaii.¹¹ Several theories were put forth to explain the basis for near simultaneous recognition of this condition in distant parts of the world. Since that time Kawasaki Disease has become the leading cause of acquired heart disease among young children in North America, Japan and several other countries. The exact cause of this condition has remained an enigma, and baffled scientists and physicians around the world for the past 50 years. Some studies have suggested an infectious or post infectious etiology in a genetically susceptible population although a definite culprit has not yet been identified.¹² There is no specific diagnostic test for Kawasaki Disease, and diagnosis is made by a combination of clinical and laboratory findings.²

The suggested association of Kawasaki Disease with coronavirus infection is not a new one. Between 2002 and 2004, SARS was identified as a viral respiratory disease of zoonotic origin caused by severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1), the first-identified strain of the SARS coronavirus species. Fortunately, it was not as widespread as the current COVID-19 pandemic. Prior to that the human coronavirus was thought to only cause mild, self-limited respiratory illness. Then, in 2005, a small case-control study was published from New Haven Connecticut, suggesting an association between a novel coronavirus from New Haven (HCoV-NH) and KD.¹³ Subsequent studies, however, failed to identify an association of Kawasaki Disease with HCoV-NL63, a coronavirus thought to be highly similar to the

previously described HCoV-NH, thus contradicting previous claims by Esper and colleagues.¹⁴ The many controversies of Kawasaki Disease and mysteries of its etiology thus continued.

In the case of MIS-C and current COVID-19 pandemic, it is noteworthy that these cases were recognized four weeks after the initial surge in COVID-19 infection in the region in Europe and United States. These children were typically older than children presenting with Kawasaki Disease, with a median age of eight years. There was a slight male preponderance and a slight increased prevalence in the black and Hispanic populations in the United States. Prevalence in the Asian population was low, in stark contrast with previous data on Kawasaki Disease. Abdominal complaints were a very prominent feature. The heart was involved in approximately one third of these patients with the extent of myocardial dysfunction being much more than what is typically seen in patients with Kawasaki Disease. Vast majority of these children responded well to treatment with anti-inflammatory medications such as steroids, supportive therapy using medications to improve blood pressure, such as norepinephrine as well as intravenous immunoglobulin.

Need for further research and gaps in current knowledge

A pandemic of this nature has not been seen by anyone living at this time. The new emergence of a potentially severe inflammatory syndrome in children, contradicting previously noted mild nature of disease in this subpopulation has been unsettling. So how do we make sense of all this? Which children are most susceptible to MIS-C and which ones are protected? Many of these children noted to have MIS-C have antibody levels suggesting prior infection, but the primary infection itself was asymptomatic. What does the prevalence of MIS-C in Europe and Eastern United States, but absence of cases in China where the disease originated mean? Why the increased incidence in certain demographic groups? While thankfully, the number of cases worldwide remain small, how does MIS-C play into the discussion of reopening summer camps, daycare centers and schools?

Several national and international registries and databases have been formed for descriptive observational studies to further understand the basic clinical, epidemiological and genetic parameters associated with this emerging condition. CDC, European Center for Disease Control, and WHO are partnering with institutions to analyze some of the data. Further studies—such as prospective cohort studies, seroepidemiological investigations, and investigations of inflamed tissue for the presence of virus—are required to determine the precise role played by SARS-CoV-2 virus in the pathogenesis of MIS-C and to determine underlying predisposing factors. Biobanks are being created for blood and respiratory specimens to investigate a variety of parameters including antibody levels, other indicators of immune response, markers of inflammation, viral shedding and the effects of various treatments used for COVID-19; as well as conduct genetic studies looking for variations in DNA that either protect children from COVID-19 and/or MIS-C or make them more susceptible. There is also a lack of understanding with regard to the SARS-CoV-2-induced humoral and cellular immune responses; more details are needed, especially on the duration of those immune responses and how they may relate to MIS-C.

Many hope for a vaccine as the only reliable means of controlling the spread of COVID-19 infection. However considering that MIS-C is mediated by an immunological response to the virus, is it possible that it may be replicated by immune response to a vaccine? How long is long enough to ensure vaccine safety in children?

This current pandemic has completely changed the way we do things, from the mundane events of daily life, to national and international travel and meetings. Lessons that we learn today will define the new normal of tomorrow, for generations to come. It is a big responsibility, and not one to be taken lightly, for our sake and for the sake of our children!

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