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MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) ASSOCIATED WITH COVID-19

Developed by Mia Voyatzis and Dr. Lillian Lim for PedsCases.com.
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Introduction:

Hello, my name is Mia Voyatzis, a second-year medical student at the University of Alberta. With the guidance of Dr. Lillian Lim, an Assistant Professor in Pediatric Rheumatology at the Stollery Children's Hospital of the University of Alberta, this podcast was developed to discuss an overview and approach to multisystem inflammatory syndrome in children associated with SARS-CoV-2 infection in COVID-19, also known as [MIS-C].

This podcast will review the following learning objectives:

1. Review the clinical presentation of MIS-C and understand how it presents on a variable spectrum.
2. Explore the basic pathophysiology of MIS-C.
3. Identify the key investigations to consider when a patient is suspected to have MIS-C.
4. Develop general management principles for treating a child who is diagnosed with MIS-C.
5. Discuss the importance of follow-up in pediatric MIS-C patients.

Let's consider a clinical case. You are a PGY-1 resident working in the pediatric emergency department. A worried mother presents with her 5-year-old daughter Mila who has had three days of a high fever (39ºC) and fatigue. Mila looks acutely unwell and has developed a diffuse maculopapular erythematous rash along the trunk of her body and is holding her stomach in severe pain. Upon obtaining a stat CBC and differential, it is noted that Mila's inflammatory markers were extremely elevated (CRP > 70 mg/L).

When reviewing the history, Mila's mother mentions that about 4 weeks ago, both she and Mila's father tested positive for COVID-19 but did not test Mila as she seemed to be asymptomatic. Mila was well and behaving normally until the last 72 hours.

Mila's mother asks you if her daughter is going to be OK? She also wonders if Mila has COVID-19 right now, or if this is some other condition or infection?

The description of Mila's presentation is an example of one way that multisystem inflammatory syndrome in children associated with COVID-19 (also known as MIS-C) can acutely present in children who have been previously infected or exposed to the SARS-CoV-2 virus.

For this podcast, we are going to specifically focus on exploring the clinical features, pathophysiology, and management of MIS-C. If you would like more information on COVID-19 infection specifically in children, feel free to check out the wonderful PedsCases podcast written by Dr. Guari Shah titled "Management of COVID-19 in Children".

Epidemiology:

While the incidence of MIS-C is uncertain, it appears to be a relatively rare complication of COVID-19 in children, occurring in less than 1 percent of children with confirmed SARS-CoV-2 infection. The average age of presentation of MIS-C is between 7 to 9 years old, though children much younger (such as infants) and older (including teenagers) have been affected.[1] Of note, Afro-American, Afro-Caribbean, and Hispanic children have been disproportionally negatively affected by MIS-C.[1]

Pathophysiology:

Although the exact pathophysiology is still being studied for MIS-C, it is suggested that this syndrome is a result of a dysregulated immune response to a recent infection, leading to a post-infectious hyperinflammatory syndrome that is often associated with myocardial injury.[2] MIS-C has been deemed to be similar and likely on the same spectrum as Kawasaki Disease (KD), Macrophage Activation Syndrome (MAS), and cytokine release syndrome, all of which are due to severe immune dysregulation.[2] MAS for example, is most commonly charactered by persistent fever, rash, lymphadenopathy, and hepatosplenomegaly that is a result of activation and expansion of T-cells, hemophagocytic macrophages, and increased levels of proinflammatory cytokines such as IL-1, IL-6, and IFN-gamma.[3]

Clinical Presentation:

Typically, pediatric patients present with MIS-C anywhere between 2 to 6 weeks post-infection or exposure to COVID-19.[1] One of the most critical aspects of MIS-C to understand is that it presents on a spectrum.[2] Some patients may present with an isolated fever and biochemical evidence of hyperinflammation; others may present with a Kawasaki disease-like presentation; and more rarely, some may present with toxic shock syndrome-like symptoms. Although there are no distinct pathognomonic features of MIS-C, a common hallmark of the disease is a high and persistent fever that has

lasted for at least 3 days.[2] Clinicians should have a high index of suspicion for MIS-C in pediatric patients who present with high fever and a temporal association of a recent COVID-19 infection or exposure, associated with elevated inflammatory markers.

According to case studies from hospitals around the world, most MIS-C patients were found to have gastrointestinal findings and mucocutaneous findings.[2] Gastrointestinal features of MIS-C included most commonly abdominal pain, vomiting and diarrhea.[2] Mucocutaneous features of MIS-C resembled oral mucosal and skin changes seen in Kawasaki Disease.[2] Most commonly seen were erythema of the oral and pharyngeal mucosa, erythema of the hands and feet, strawberry tongue, non-exudative conjunctivitis, as well as an erythematous maculopapular rash. Other features seen in MIS-C can involve neurological signs and symptoms like headache, stiff neck, altered mentation, and lethargy.[2] Renal involvement may occur in some patients when treatment is delayed.

Of particular note, many cases of MIS-C have cardiac involvement and it is critical to diagnose and manage cardiac issues urgently to prevent progression to severe manifestations such as severe hypotension and shock.[2] While MIS-C appears to be rare in children, pediatric patients have a propensity to deteriorate quickly and therefore we need to maintain a high degree of suspicion for the diagnosis if we know that this child has been previously infected or exposed to COVID-19.

Typical clinical signs of cardiac involvement include tachycardia and hypotension, other manifestations of cardiac dysfunction can include: heart failure, a new murmur, gallop rhythm, elevated troponin, ECG abnormalities, and/or cardiomegaly on a chest X-ray.[1] Similar to patients with Kawasaki disease, MIS-C patients are at an increased risk for developing coronary artery aneurysms and abnormalities.[1]

Investigations:

One of the issues in diagnosing MIS-C with laboratory testing is that there are no standardized evidence-based recommendations about when we should be ordering tests for patients who present with unexplained fever.[1] A detailed history, including infection exposure, is critical to help direct investigations.

Biochemical assays: All patients with suspected MIS-C are recommended to have a CBC and differential, CRP, ferritin (which can be elevated in hyperinflammatory states), renal, and liver function tests, and acute-phase reactants like D-dimer. Coagulation markers should be considered depending on clinical severity. Patients with persistent inflammation may develop cytopenias due to the cytokine storm and the hemophagocytic macrophages that may be involved.[1] Labs initially suggestive of MIS-C include an elevated CRP plus one out of five other lab tests: elevated ferritin, diminished platelets, lymphopenia, neutrophilia, and hypoalbuminemia.

It is also important to obtain PCR and serology tests for SARS-CoV-2 prior to the start of any treatment.[2] Care must also be taken to rule out any other viral or bacterial infections, especially sepsis, given that MIS-C patients may present with similar features such as fever and hypotension. Hence completing a full viral panel and blood cultures is recommended.

Children with suspected MIS-C should be promptly examined and investigated for any signs of cardiac dysfunction; this may often involve ordering an EKG.[2] Those with overt features of cardiac involvement such as tachycardia and hypotension often warrant other urgent cardiac investigations, primarily an echocardiogram.

Management:

Most patients with MIS-C will present to the local emergency department. A critical aspect of care is full involvement of a multidisciplinary team which includes but is not limited to: general pediatrics, infectious diseases, rheumatology, ICU, cardiology, and hematology and thrombosis services.[4] Involve these services to obtain more details and advice about specific dosing regimens.

Most MIS-C patients will require intravenous immunoglobulins (IVIG), as well as high dose corticosteroids for a short period of time.[4] Those who are critically ill (such as those presenting with hypotension or shock) may require pulse intravenous doses of methylprednisolone for 1 to 3 days. Please consult your friendly neighborhood rheumatologists for more advice. In some rare situations, patients who do not respond to IVIG and steroids may require biologic therapy, in consultation with rheumatology.[4]

Management of any cardiac dysfunction should be done in consultation with cardiology, and patients with thromboses should receive anticoagulation as per the thrombosis team.[4] It is advisable to perform an echocardiogram prior to administering IVIG, to better assess cardiac function and to help determine the risk for fluid overload and need for diuretics with the IVIG infusion.[4]

Follow-up:

Most MIS-C patients improve rapidly within a few days of immunosuppressive treatment.[4] Post-hospital follow up is still critical, done in combination by a multidisciplinary team which may include cardiologists, rheumatologists, and general pediatricians. Patients who were treated with corticosteroids or biologics often require 2 weeks or more of therapy, with tapering of medications based on improvement of laboratory markers, as well as follow up ECG and echocardiograms as an outpatient.[4]

Case Wrap-Up:

Mila had a normal echocardiogram at presentation. She was admitted to hospital and received IVIG and high dose steroids for a few days and made a rapid recovery. She

was seen in follow up by her pediatrician and rheumatology and cardiology, with weekly labs done, while her oral steroids were tapered over two weeks

Key Take-Home Points:

1. Take a good history and consider MIS-C in patients who have been exposed to or had COVID-19 in the last 2-6 weeks who present with fever.
2. MIS-C likely exists on a spectrum of hyperinflammation with other conditions like MAS and Kawasaki disease. Therefore, patients may have a wide range of clinical presentation from mild symptoms to being acutely unwell.
3. Urgent investigations and management are critical, especially in those with suspected cardiac dysfunction. Get a prompt echocardiogram at presentation.
4. Most MIS-C patients will require IVIG and corticosteroids, and should be managed in consultation with ID, Rheumatology, Cardiology, Thrombosis, and ICU as needed.

References:

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