Script for MIS-C slides

Slide 1

NB: We shall be discussing the spectrum of Multisystem Inflammatory Syndrome in children temporally related to COVID-19. Dr Satya Prakash will be presenting the topic.

Slide 2

We will cover the epidemiology, pathogenesis, clinical features and the differential diagnoses and finally sketch a diagnostic algorithm for multisystem inflammatory syndrome.

Slide 3

As we learnt in the early days of COVID-19 pandemic, children were noted to have a relatively mild disease compared to adults. However, amidst April 2020, there was an eruption of some severe cases in children with an epidemiological link to COVID-19 following which, NHS, England issued a warning against such cases. This entity was defined as Multisystem Inflammatory Syndrome in children and adolescents temporally related to COVID-19 by WHO, Multisystem Inflammatory Syndrome in Children (MIS-C) by CDC, and Pediatric multisystem inflammatory syndrome temporally associated with COVID-19 by RCPCH.

Slide 4

As on July 31′ 2020, over 700 cases have been reported from the world over, with a majority of these from USA and Europe, but reports from Asia have also started erupting.

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From the reported cases, it is clear that this disease predominantly affects previously normal children with evidence of current or past COVID infection, and has prominent gastrointestinal and cardiac manifestations.

Slide 5

WHO case definition for Multisystem Inflammatory Syndrome in children and adolescents temporally related to COVID-19 requires all six of the following criteria to be fulfilled:

Age up to 19 years, presence of fever for at least 3 days, clinical signs suggestive of multisystem involvement, with presence of at least 2 of the following five: Rash, bilateral non-purulent conjunctivitis or mucocutaneous inflammation, Hypotension or shock, cardiac involvement in the form of cardiac dysfunction, pericarditis, valvulitis or coronary abnormalities, on echocardiography or elevated cardiac biomarkers, Evidence of coagulopathy in the form of deranged PT, PTT or d-dimer and acute gastrointestinal symptoms, such as vomiting, diarrhea or abdominal pain.

Additionally, there must be elevated inflammatory markers like ESR, CRP or procalcitonin, with no other obvious microbial cause of inflammation. And there must be an evidence of SARS-CoV-2 infection in the form of a positive RT-PCR, antibody test, antigen test or even a contact with a positive case.

The CDC criteria is similar but has come subtle differences compared to the WHO criteria, such as it includes age up to 21 years, it defines exposure to a contact to have been occurred 4 weeks prior to the presentation, and it has a mandatory criteria that the disease must be a “severe illness requiring hospitalization”.

Slide 6: skip to the next slide in a few seconds

Slide 7

Here we have mentioned a few of the published reports on multisystem inflammatory syndrome. What is noticeable is this data is the frequent involvement of gastrointestinal and cardiac systems, as highlighted previously, with many patients also having mucocutaneous involvement akin to Kawasaki disease. Around two thirds of the patients test negative for RTPCR for COVID, but 50-90% demonstrate a positive antibody test. Because of multisystem involvement, these children need close monitoring and may require intensive case support. Immunosuppressants and immunomodulators are the mainstay of treatment, intravenous immunoglobulin and steroids are most commonly used. The overall mortality is less than 5%.

Slide 8

Looking at the epidemiological data related to COVID-19 from March to May 2020 from USA, we see that the peak of COVID-19 test positivity rate was reached in April 2020, but the number of reported cases of MIS-C started rising later.

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There was a gap of around 3-6 weeks between the peak of COVID-19 infection and a noticeable surge in MIS-C cases. Similar findings were reported from Europe.

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As on 3rd June 2020, only two cases of MIS-C were published. However, there are several more unpublished cases to our knowledge.

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There studies had a similar presentation and outcomes as the ones reported from West. But considering the delayed peak of COVID-19 in India, a surge in cases of MIS-C cases may be seen from India, especially as clinicians become more familiar with the presentation of the disease and more cases are picked up.

Slide 10

Coming to the pathogenesis of MIS-C, several aspects are unclear and are still evolving. What is relatively more certain is that the terminal point of the pathogenesis is cytokine storm. Yet poorly understood, the postulated mechanisms include the following.

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The most widely accepted theory is that after a SARS-CoV-2 infection, *click* there is formation of antibodies against the virus by the body followed by clearance of virus from the system. *click* Subsequently, there is an IgG mediated enhancement of the immune response leading to a hyperimmune response, *click* causing a cytokine storm. *click* This in turn causes the characteristic multisystem involvement. *click* This hypothesis is supported by the observation that most patients test negative by RTPCR for COVID, but have a positive antibody test. In addition, the lag of 3-6 weeks between the peak of COVID infection and peak of MIS-C cases further compound this hypothesis. *click* The second hypothesis predicts that after a COVID-19 infection with a heavy viral load, there is a blockade of the interferon responses, as has been seen with other coronaviruses. *click* Subsequently, there is a delayed response to the active infection in the form

of an exaggerated cytokine surge causing MIS. *click* The third hypothesis states that instead of directly leading to a cytokine storm, SARS-CoV-2 may be acting as an intermediate primer or a co-stimulatory agent or just providing a portal of entry to an as yet unknown trigger which is *click* causing the immune response and causing MIS-C. *click**click**click*

Why this phenomenon is occurring predominantly in children and why certain systems are more commonly affected is not definitively known.

Slide 11

Coming to the clinical features, fever is a universal symptom and is a necessary criterion for diagnosis of MIS-C. Gastrointestinal symptoms have been reported in 60-100% of the published cases and include abdominal pain, vomiting, diarrhea. Patients have even presented with an acute abdomen requiring explorative laparotomy in a few cases. Cardiac involvement, especially as left ventricular dysfunction is seen in over 50% of the cases. Similarly, shock is a commonly seen feature, seen in 50-80% of the cases, and in most series has been seen to be clinically warm type of shock.

Slide 12

MIS has several features which may mimic those seen in Kawasaki disease. In fact, the criteria for Kawasaki Disease may be met in around 40% of the cases. These features include rash which is usually polymorphous and may be seen on the trunk or extremities. Similarly, these children may have bilateral non-purulent conjunctivitis, mucous membrane involvement in the form on mucosal erythema and strawberry tongue and swelling over hands and feet. In addition, coronary artery abnormalities have been reported in 8-48% of the patients, but long-term data about the progression of these abnormalities is not known.

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This image shows the typical erythematous maculopapular rash seen on the extremities and trunk. Targetoid rashes have also been described.

Slide 13

Other clinical features include neurocognitive symptoms, which can manifest as headache, lethargy, confusion or irritability in a younger child. As opposed to COVID-19 in infection typically seen in adults, respiratory symptoms are usually not a prominent symptom of MIS-C, and may be seen in 20-60% cases. Serositis in the form of pericarditis and pericardial effusion, pleural effusion and ascites may be seen in a minority of patients. In many cases, patients may develop multi-organ dysfunction in the form of respiratory failure, acute renal failure and less commonly, acute liver failure.

Slide 14

Let us now discuss a few differential diagnoses that may mimic MIS-C. Kawasaki disease is a close differential with several overlapping features. However, some differences have been noted between the two conditions. In MIS-C, the children are typically older, usually 8 to 10 years of age, while Kawasaki disease is seen mainly in children below 5 years of age. Gastrointestinal symptoms, myocardial dysfunction and shock are much more common in MIS-C. Inflammatory markers have been seen to much more highly elevated in MIS-C as compared to Kawasaki disease, and thrombocytopenia is a relatively common feature of MIS-C, but is rare in Kawasaki disease.

Toxic shock syndrome is another close differential, because of the presence of multiorgan involvement along with fever. However, a microbiological evidence of Staphylococcus or

Streptococcus is necessary for the diagnosis of TSS. Bacterial sepsis and septic shock can not be ruled out in most severe cases of MIS-c at presentation, and needs work-up. However, certain features like coronary artery abnormalities are not seen in sepsis. Lastly, in endemic countries like India, dengue and dengue-related secondary hemophagocytic lymphohistiocytosis has to be kept in mind, especially in the monsoon season, and dengue infection must be ruled in suspected cases of MIS-C.

Slide 15

Multisystem inflammatory syndrome requires a thorough investigations not only to establish the diagnosis, but to exclude other important differentials and find out the extent of organ involvement.

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Complete blood count with differential count is necessary and may reveal lymphopenia and neutrophilia, along with mild anemia and thrombocytopenia.

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Levels of inflammatory markers like ESR, CRP, procalcitonin, interleukin 6 are determined and are seen to be universally elevated.

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In addition, other markers of secondary HLH and macrophage activation syndrome like ferritin, fibrinogen, triglycerides and LDH are often elevated.

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Cardiac markers like troponin, NT-Pro BNP are elevated in 68-100% cases and indicate myocardial involvement.

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Liver function tests often reveal mild derangement of liver enzymes and hypoalbuminemia.

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Renal function tests are done to look for renal involvement. Blood gas analysis is necessary for management of respiratory failure and shock.

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Coagulation defects are sometimes seen in MIS; hence coagulation studies, including PT/INR, aPTT and d-dimer levels need to be done.

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ECG is done which may reveal ST-T changes and arrhythmia in myocarditis and electrolyte abnormalities, and low voltage waves in case of pericardial effusion.

Slide 16

As discussed previously, sepsis is a close mimicker of MIS-C. Hence, in all suspected cases of MIS-C, efforts to find an infective cause must be made. These include blood cultures, urine analysis and urine culture, and work-up for malaria and dengue. Additionally, other tests to rule out infectious etiologies such as scrub typhus, leptospirosis, disseminated viral infections may be done when clinically indicated.

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As you would recollect, the case definition of MIS-C requires a link with COVID-19 to be established. This is established by the presence of any of the following: a positive RTPCR for SARS-CoV-2 in a nasopharyngeal or lower respiratory tract sample, a positive antibody test, which may either be IgM or IgG, a positive antigen test for SARS-CoV-2, or even a recent exposure to a confirmed case of COVID-19.

click

As discussed previously, based on the published case series, around 50-90% cases of MIS-C have a positive antibody test. RTPCR is negative in over two-thirds of the cases.

Slide 18

Imaging studies are necessary in patients with MIS-C. The most important of these is an echocardiogram, which is recommended in all cases at presentation. Echo may reveal depressed LV function in 31-58% patients. Coronary artery abnormalities may also be seen in 8-48% cases, and must be quantified using z-scores to classify the dilatation. The z-score calculators are easily available online. Pericardial effusion and valvular dysfunction may be noted on echo. In addition, a follow-up echo is also recommended at 7-14 days and 4-6 weeks of illness to look for residual cardiac abnormalities, including coronary artery abnormalities. Chest X ray and CT scan may be done in cases with prominent respiratory symptoms, and may reveal cardiomegaly, pleural and pericardial effusion and ground glass opacities. Ultrasound abdomen is necessary for cases with severe gastrointestinal symptoms, and may show ascites and inflammation of the bowel and mesentery.

Slide 19

Having learnt about the features of MIS-C, we propose the following diagnostic algorithm.

The first step is to determine if the child has all of the following features suggestive of MIS-C-, such as fever, gastrointestinal symptoms, rash, conjunctivitis, oral mucosal changes, confusion, palmar erythema, and an epidemiological association with COVID-19. If these symptoms are not present, the child is unlikely to have MIS-C, and further evaluation for other conditions is done as clinically indicated.

If the child has these symptoms, we need to look for features of shock or cardiac failure. The presence of these features makes the possibility of MIS-C very likely, and these children need to undergo a thorough evaluation. This includes a basic battery of investigations, including RTPCR for SARS-CoV-2, as well as more specialised tests, such as tests for cardiac function and levels of inflammatory markers like ferritin.

If the child doesn't have upfront features of shock of cardiac failure, initially only the initial investigations needs to be done. If these investigations are suggestive of a diagnosis of MIS-C as described previously, then the further more specialized tests need to be done. If the initial investigations are not compatible with a diagnosis of MIS-C, then other conditions need to be looked for, while monitoring carefully for evolution of new symptoms.

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To summarise, here is a pictorial representation of the features of MIS-C. Children have fever, along with conjunctivitis, rash, swelling of palms and soles. They often have nausea, vomiting, abdominal pain and diarrhea with mildly elevated liver enzymes. Cardiac involvement in prominent with

elevated cardiac biomarkers and echo abnormalities. There may be headache, meningismus and lethargy. Respiratory involvement in the form of hypoxemia, and pulmonary infiltrates may be seen. Blood tests reveal thrombocytopenia, neutrophilia and lymphopenia, and elevated inflammatory markers. And importantly, there is a lab evidence or current of past SARS-CoV-2 infection or a history of exposure to COVID-19. The management aspects of MIS-C will be covered next. Thank you.

NB: Thank you Satya for a nice presentation. The house is open for any questions and comments.