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Received 2020 August 22; Accepted 2020 August 22.

Abstract

COVID-19 as a viral infection is usually asymptomatic in children, but complication of this disease in children is not rare and may be fatal. Hyper inflammation of COVID-19 is a potential fatal in undiagnosed children. It is very similar to Kawasaki disease but with higher mortality and morbidity. Multisystem inflammatory syndrome in children (MIS-C) and multi-organ involvement was reported in hyper inflammation syndrome following COVID19. Herein we report our algorithmic approach to Kawasaki-like syndromes due to COVID-19 in our center. Based-on this approach we had no mortality during the last 5 months.

Keywords: COVID-19, Multisystem Inflammatory Syndrome in Children, Kawasaki Disease, Children

1. Background

The World Health Organization (WHO) declared coronavirus outbreak a global pandemic on 11th March 2020 (1). The first children’s coronavirus cases were reported in Wuhan, the epicenter of COVID-19, showing mild respiratory symptoms and fever with positive SARS-CoV-2 RNA in nasopharyngeal/throat swabs (2, 3). However, the first report from United Kingdom (UK) introduced shared clinical manifestations of the new syndrome with other critical syndromes, such as toxic shock syndrome (TSS), atypical Kawasaki disease (KD), Kawasaki disease shock syndrome (KDSS), and secondary hemophagocytic lymphohistiocytosis (HLH) with antibody SARS-CoV-2 positive (4). This was followed by reports from Italy (5) and Switzerland (6). Thus, on 14th May, the United States Centers for Disease Control and Prevention (CDC) named multisystem inflammatory syndrome in children (MIS-C) on these manifestations of SARS-CoV-2 in children (7).

Children have been associated with the early phase of the virus replication with positive SARS-CoV-2 RNA of nasopharyngeal involvement with mild symptoms and delayed phase of inflammation and immune dysregulation with seropositive SARS-CoV-2 due to MIS-C (4, 5, 8-10).

In Iran, especially at the second peak, several patients and consultations with KD and/or MIS-C, according to CDC criteria, were referred to our hospital. Hence, this kind of approach to patients with MIS-C in the Tehran Children’s Medical Center, (affiliated to Tehran University of Medical Sciences) is confirmed and advised by pediatric rheumatologists, pediatric infectious disease specialists, and pediatric cardiologists. According to this experience, we have some research and report on a different aspect of MIS-C recently (11, 12).

2. Kawasaki Disease and Kawasaki-Like Diseases

Kawasaki disease (KD) is an inflammatory disease that damages mucous membranes (eyes, lips and oral mucosa), skin (rashes), lymph nodes, and medium-sized vessels (vasculitis, specially coronary arteries) (13). Nowadays, similar
clinical manifestations of KD and MIS-C have attracted the attention of clinicians to a higher prevalence of Asian vasculitis.

The seasonal incidence of viral infection and Kawasaki disease suggests the viral trigger factor of the immune system to be involved in KD.

The seasonal incidence of viral infection and KD led to the speculation that viral infection may be a trigger factor of the immune system in KD (14). The association of SARS-CoV1 and KD was described (15). However, this theory has not been accepted by subsequent studies. A 30-fold increased incidence of KD after the COVID-19 pandemic compared to the same period in the last five years in the Italian literature may confirm the triggering role of SARS-CoV-2 in KD patients with higher affinity than SARS-CoV1 (5). Thus, the first complete KD with positive SARS-CoV-2 RNA-PCR was reported with a significant response to intravenous immunoglobulin (IVIg) treatment without MIS-C presentations (16).

Kawasaki disease shock syndrome (KDSS) is one of the severe manifestations of KD (1% - 5%) with decreased ejection fraction (EF), thrombocytopenia, anemia, and increased inflammatory laboratory data (ESR, CRP). KDSS patients were older, with more coronary involvement and IVIg resistance (17).

In the acute phase of KD as a hyper-inflammatory condition, the levels of cytokines, such as TNF, IL6, IL1β, IL17, and GCS-F are increased. In IVIg-resistant KD patients, IL6 and IL10 levels are higher with more coronary involvement than IVIg-responsive KD patients (18) Thus, increased levels of IL6, IL10, and interferon-gamma (IFN-γ) were reported in IVIg-resistant KDSS patients (17). Hence, MIS-C patients may be resistant to IVIg treatment.

IVIg is prepared from the serum of 1000 - 15000 blood donors. IVIg targets both innate and adaptive immune systems. The endocytosis of macrophages and dendritic cells is inhibited by blocking the activation of the immune complex. Thus, it would be helpful in the early phase of the inflammatory cascade. In contrast, due to high concentrations and increased plasma viscosity should be dealt with the volume overload and thrombotic events, especially in cardiogenic shock (CS) and hyper-coagulative states, such as KDSS and MIS-C (19).

To the best of our knowledge, there are two aspects of COVID-19 KD in childhood nowadays:

First, at a younger age (less than five years old), the results of the SARS-CoV-2 PCR-RNA become more positive than antibody test in patients with complete or incomplete KD (according to AHA criteria) and this group is responder to IVIg treatment (IVIg-responsive patients).

Second, at an older age (older than five years), patients with incomplete KD criteria or Kawasaki-like disease resembling KDSS exhibit higher coronary and valvular involvement. In this group, antibodies become more positive than SARS-CoV-2 PCR-RNA and do not respond to IVIg treatment (non-IVIg-responsive patients) (8, 9).

3. Cytokine Storm and MIS-C

Macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (HLH) is a cytokine storm phenomenon arising from malignancies, rheumatic disorders, or viral infections. The dysregulation of NK cells and cytolytic CD8 T cells (CTL) lead to inherited or acquired antigen-presenting activation and INF-γ. TNFα secretion, on the other hand, causes the recruitment of other inflammatory cells, such as neutrophils and lymphocytes, leading to increased secretion of cytokines and activation of macrophages, along with the production of pro-inflammatory cytokines, TNF-α, IL-6, IL-1, IL-18, and hemostatic tissue factor (TF). The activated macrophages exhibit HLH and hyperferritinemia. This cycle continues until a cytokine storm occurs ultimately (20).

The same pathway may be taken in a cytokine storm, or MIS-C phenomenon of SARS-CoV-2 as a secondary HLH triggered by a viral infection with antibody-mediated stimulation (21, 22). Secondary HLH, like the primary HLH, may occur with a fundamental role of a genetic disorder (23). Therefore, it may be a response to the question why the first MIS-C reports were from European children of specific races as opposed to Asian children with higher susceptibility to KD and the source of SARS-CoV-2 from this population.

MAS is a life-threatening condition, which requires prompt evaluation and treatment. Due to the highly increased cytokines, the antagonists of key cytokines, such as anti-IL1, anti-IL6, and INF, were administered and evaluated in the treatment of the cytokine storm phenomena (24). Although there is no consensus and evidence on efficacy of pulsed intravenous methylprednisolone (IVMP), rapid resolution of hypercoagulable state and critical response to MAS with suppression of activated macrophages lead to administration of IV pulses of methylprednisolone in one to three doses (25-27). Indeed, the economic state and availability of medicine in the immediate therapeutic intervention should be noticed.

In the recent pandemic state, corticosteroids in patients with MIS-C are prescribed and yield good results (8, 9, 11, 12, 28). Therefore, the majority of MIS-C patients are SARS-CoV-2 PCR-RNA negative accompanied by SARS-CoV-2 antibody positive with delayed presentation, leading to conducting clinical trials to suppress the inflammatory response process rather than virus suppression.
Tehran Children’s Medical Center, Pediatrics Center of Excellence in Iran as a tertiary pediatric referral center has been encountered with more than 50 MIS-C cases during 3 months. So, all relative departments including rheumatology, infectious disease, intensive care, cardiology and emergency departments were involved in designing an algorithmic approach for diagnosis and treatment of children suspicious to MIS-C and Kawasaki like disease following COVID-19. This approach is presented in this report. Based on this approach we diagnosed all patients as soon as possible and treated all suspected children without any mortality or morbidity (Figures 1-5).

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Footnotes

Authors’ Contribution: Vahid Ziaee designed an algorithmic approach based on the consensus of all members. Raheleh Assari prepared the first draft of the paper. All authors approved the final version of the manuscript.

Conflict of Interests: There is no conflict of interest.

Funding/Support: It is not declared by the authors.

References


Algorithm 1: Approach to children with fever and rash <19 years old

Age<19 + fever and rash
History of closed contact with COVID-19 or highly suggestive of COVID-19

YES

Algorithm 4

NO

Clinical manifestations of Complete and Incomplete Kawasaki disease with non-confirmed laboratory data

Algorithm 4

Incomplete Kawasaki disease criteria with confirmed laboratory data

Algorithm 3

Complete Kawasaki disease criteria with confirmed laboratory data

Algorithm 2

*According to American Heart Association 2017 diagnostic criteria for complete and incomplete Kawasaki disease.

**Algorithm 1:** Approach to Kawasaki-like syndromes in pandemic COVID-19: The Tehran Children's Medical Center Protocol (algorithm 1); designed by Pediatric Rheumatology Department confirmed by Pediatric Infectious Diseases, Pediatric Intensive Care, Pediatric Cardiology, and Pediatric Emergency Departments.
Algorithm 2: Complete Kawasaki with confirmed laboratory data

Fever more than 4 days and 4 of five criteria:
- Polymorphous skin rashes
- Bilateral non-purulent conjunctival injection
- Mucosal changes: cracked lips, strawberry tongue, mucosal erythema
- Extremity changes: hands and feet edema or palmar erythema
- Unilateral cervical lymphadenopathy > 1.5 cm

Laboratory data

Confirmed laboratory data:
- ESR > 40
- CRP > 30
- WBC > 15000
- Platelet in upper limit or thrombocytosis
- ALT elevation
- Normal ferritin or < 450

No other organ involvements explained in algorithm 4

Treatment with ASA 3-5 mg/kg/d continued + Echocardiography (after 10-14 day and 2 months later)

Response to treatment (fever resolved)

The classic Kawasaki treatment:
IVIG 2 gr/kg + ASA 30-50 mg/kg/d + Echocardiography

No response to treatment (Fever not resolved)

Abnormal Echocardiography

Referred to Pediatric Rheumatologist

Recommend to SARS-COV2 serology in sub-acute phase for all Kawasaki patients in COVID19 Pandemic

Figure 2. Approach to Kawasaki-like syndromes in pandemic COVID-19: The Tehran Children’s Medical Center Protocol (algorithm 2); designed by Pediatric Rheumatology Department confirmed by Pediatric Infectious Diseases, Pediatric Intensive Care, Pediatric Cardiology, and Pediatric Emergency Departments.
Algorithm 3: Incomplete Kawasaki according to American Heart Association criteria

Fever≥ 5 days plus two or three clinical criteria

- ESR, CRP*
  - ESR > 40
  - CRP > 30
  - ESR < 40
  - CRP < 30

3 from the following 6 laboratory tests positive:
- WBC > 15000
- Platelet > 450000
- Anemia (not appropriate for age)
- Increased ALT
- Albumin < 3g/dl
- Sterile pyuria (> 8-10 WBC) with negative urine culture

OR
- Abnormal echocardiography with coronary involvement
  - Ferritin normal or < 450
- No other organ involvements explained in algorithm 4

Patient follow up
Clinical and laboratory evaluated after 48 hours

- Fever resolved
- Peeling
- New clinical manifestation

No other follows up

Echocardiography and decision

Decision according new manifestations

Algorithm 4

Treatment according algorithm 2

BOX 1: Para-clinic evaluation for all suspicious patients:
- CBC, ESR, CRP, B/J, U/J, U/C
- Liver function test, PT, PTT, INR, serum albumin and serum Ferritin
- D-Dimer, BNP, II/S, Procalcitonin (if available)
- Pancreatic and Cardiac Enzymes (in selective patients)
- Abdominal ultrasonography
- Echocardiography
- COVID-19 confirmation*:
  - SARS-COV2 RT-PCR
  - Serology
- Diagnostic complementary evaluations (for patients suspicious to other infectious disease)
  - based on pediatric infectious disease consultation
* If negative, recheck (both PCR and serology) after 7-10 days

Figure 3. Approach to Kawasaki-like syndromes in pandemic COVID-19: The Tehran Children’s Medical Center Protocol (algorithm 3); designed by Pediatric Rheumatology Department confirmed by Pediatric Infectious Diseases, Pediatric Intensive Care, Pediatric Cardiology, and Pediatric Emergency Departments.
Algorithm 4: Kawasaki-like syndrome or multisystem inflammatory syndrome in children (MIS-C) caused by SARS-COV2

Complete or incomplete Kawasaki criteria with ≥ 1 unusual clinical criteria or laboratory results and Closed contact with COVID-19 or high suspicion to COVID-19

Box 2: Unusual clinical manifestations in KD:
- Shock or low blood pressure
- Cardiac failure, Carditis
- Acute abdominal presentations
  - Acute gastroenteritis
  - Ascites or edema of intestinal wall
- Hepatic failure
- Pancreas involvement
- Splenomegaly
- Clinical icterus
- Clinical manifestations of coagulopathy (thrombosis, bleeding,...)
- CNS involvements (seizure, loss of consciousness, cranial nerve involvement)

Box 3: Unusual laboratory results in KD:
- Hematologic involvement:
  - Leukopenia (WBC <4000)
  - Thrombocytopenia (platelets <150000)
  - Lymphopenia (according to age)
- Acute phase reactants:
  - ESR <30 with highly elevated CRP
  - Ferritin >450 ng/ml
  - IL-6 >100 pg/mL
  - Procalcitonin >1 ng/mL
  - BNP >100 pg/mL
- Hypercoagulopathy state:
  - Increased PT, PTT
  - Decreased fibrinogen <500
  - D-Dimer >1000
- Hepatic dysfunction:
  - Increased ALT >2 times

Box 4: Imaging evaluations in CT scan and ultrasonography
- Pulmonary involvements according to COVID-19
- Free fluid in abdominal cavity
- Edema of intestinal wall
- Thrombosis suspicions in imaging
- Ejection fraction <45%

Box 5: Diagnostic criteria
- Suspicious to KD according to clinical criteria (algorithm 2, 3)
- Two of the 3 following criteria:
  - At least one clinical criterion (box 2)
  - At least two laboratory criteria (box 3)
  - One imaging criteria (box 4)
- In shock state, fever for one day would be accepted

Figure 4. Approach to Kawasaki-like syndromes in pandemic COVID-19: The Tehran Children’s Medical Center Protocol (algorithm 4); designed by Pediatric Rheumatology Department confirmed by Pediatric Infectious Diseases, Pediatric Intensive Care, Pediatric Cardiology, and Pediatric Emergency Departments.
**Algorithm 5**: Therapeutic approach to Kawasaki-like syndrome or multisystem inflammatory syndrome in children (MIS-C) by SARS-COV2

**Box 6: Treatment of cytokine storm***:
- Treatment with methylprednisolone pulses (20-30 mg/kg/day) for 3 consecutive days.
- Treatment with IVIG 2gr/kg single dose after the first MTP (if coronary arteries involved)
- Enoxaparin in critical patients (admitted in ICU) 0.5 mg/kg/dose every 12 hours
- Aspirin 3-5 mg/kg
IVIg should be infused with blood pressure and pulse rate monitoring in a prolonged time of about 18-24 hours with complete hydration
* Consult pediatric rheumatologist

**Box 7: Suspicious to infectious disease***:
- Antibiotic therapy (if necessary)
- Anti viral therapy (if necessary)
- Hydroxychloroquine treatment
- Treatment of other symptoms
* The above mentioned approaches should be performed parallel cytokine storm treatment with pediatric infectious disease consultation

**List of Abbreviations**:
- IVIg: Intravenous Immunoglobulin
- ASA: Acetylsalicylic Acid
- ESR: Erythrocyte Sedimentation Rate
- CRP: C-Reactive Protein (mg/L)
- KD: Kawasaki Disease
- IL-6: Interleukine-6
- BNP: Brain natriuretic peptide
- CNS: Central Nervous System
- PT: Prothrombin Time
- PTT: Partial thromboplastin time
- ALT: Alanine Aminotransferase

**Figure 5.** Approach to Kawasaki-like syndromes in pandemic COVID-19: The Tehran Children’s Medical Center Protocol (algorithm 5); designed by Pediatric Rheumatology Department confirmed by Pediatric Infectious Diseases, Pediatric Intensive Care, Pediatric Cardiology, and Pediatric Emergency Departments.

Fever not resolved
- Consider biologic drugs based on expert pediatric rheumatologist consult

Fever resolved
- Echocardiography (after 7, 14 days and 2 months) and Aspirin (3-5 mg/kg/day) until complete recovery with 3 normal echocardiography and normal platelet count (at least 2 months)