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COVID-19 Pandemic and Increased Frequency of Multisystem Inflammatory Syndromein Children/Benghazi 2020

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Abstract:
A flare-up of unidentified pneumonia in Wuhan has drawn an extraordinary consideration around the globe. Primary reports from Europe and the USA found an association between severe acute respiratory syndrome coronavirus 2 and multisystem inflammatory syndrome in children, This study assessed this association in children confirmed with COVID-19 in Benghazi. A series of 12 cases were described. All cases presented with fever, skin and mucous membrane manifestations, GIT symptoms. Three cases developed CNS involvement, three have lymphadenopathy, two cases with cardiac manifestations, and two with renal involvement. Laboratory data revealed elevated ESR and CRP, and lymphopenia. Management strategy included IV antibiotics, oral aspirin, and sandoglobulin. The overall prognosis of all cases is very good.
Keywords: Multisystem inflammatory syndrome, COVID-19, Paediatric.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronaviruses-2(SARS-CoV-2) are significant microorganisms for humans and vertebrates. They can affect numerous systems in the body including the respiratory, gastrointestinal, hepatic, and focal sensory system of human, animals, fowls, bat, mouse, and numerous other wild creatures.[1–3]

A flare-up of unidentified pneumonia in Wuhan since December 2019 has been developed which drew an extraordinary consideration around the globe. The causative operator of this secret pneumonia has been recognized as a novel Covid

virus (nCoV) by profound sequencing and etiological examinations by various autonomous research facilities of China. On 12 January 2020, The WHO named this new virus-like the 2019 novel coronavirus (2019-nCoV).On the 11th of February2020,the WHO named the disease caused by the(2019-nCoV)coronavirus disease (COVID-19).[4]

The impact of COVID-19which is caused by the novel coronavirus has been widespread, with a total detected cases (up to 29.09.2020) of 33758805 worldwide. since the virus was identified in January 2020.[5]
in Libya, according to the national center for disease control the total number of confirmed cases of COVID-19 up to 28/09/2020 was 34014, active cases 14572, and 540 deaths. In the Eastern region of Libya, the total confirmed cases 3024, with 2218 active cases, The vast majority of cases were from Benghazi as they accounted for 2123 total cases and 1725 active cases followed by Tobruk.[6]
In the beginning, the preliminary data have been focused on severe respiratory manifestations, which are seen mainly in adults, with a dearthof data on the burden of COVID-19 in children.[7] Later on, many studies have addressed the impact of COVID-19 in paediatric age groups.For instance, Dong et al reported that 4% of virologically confirmed cases of COVID-19 in children are asymptomatic, and this rate almost underestimatesthe true rate of asymptomatic infection becausemany asymptomatic children are unlikely to be tested.[8]

Among kids who were affected, 5% had dyspnea or hypoxemia (a significantly lower rate than what has been accounted for adults), and 0.6% advanced to intense respiratory distresssyndrome or multiorgan failure (a rate that is likewise lower than that found in adults). Preschool-aged children and infants were more likely than older children to have severe clinical manifestations[8]. Another study directed on hospitalized Norwegian kids identified COVID-19 in 10% of hospitalized kids with respiratory infections.[9]

In Pakistan, Children and adolescents younger than 20 years of age constituted 10.6% (24 625 out of 231 818) of the total reported confirmed cases of COVID-19 up to July 8, 2020, with a mortality of 0.3% for those aged 10 years or younger and 0.5% for those aged 11–20 years.[10]

Primary reports from Europe and the USA found an association betweencoronavirus infection in children and multisystem inflammatory syndrome in children(MIS-C), also known as paediatric inflammatory multisystem syndrome.[10, 11]

The affected children may be requiring admission to intensive care units with a multisystem inflammatory condition showing some features similar to those of Kawasaki disease and toxic shock syndrome. Some case reports even described a presentation of acute illness accompanied by a hyperinflammatory syndrome, leading to multiorgan failure and shock.[12,13]

Kawasaki disease (KD) is a rare acute febrile multisystem inflammatory vasculitis[14]. It is the leading cause of acquiredheart disease in children, affects children less than 5 years of age, and is triggered by some viral and bacterial infections.However; its exact etiology still unclear.[15]

The pathogenesis of hyper-inflammatory syndrome can be explained bya phase of elevated interleukin-6 (IL-6) causes "cytokine storm", an increased immune reaction of the infected child[16]. The clinical manifestations of this phase comprise multi-organ failure, shock, myocarditis, respiratory failure, and renal failure, somehow similar to hemophagocytic lymphohistiocytosis. Decreased T helper, cytotoxic lymphocytes, and regulatorylymphocytes, as well as increased inflammatory cytokinesand biomarkers, can be found in this stage.[17]

Clinically KD is characterized by prolonged fever lasting more than five days, with dysmorphic skin rashes and diffuse mucosal inflammation, bilateral nonpurulent conjunctivitis, indurative angioedema seen commonly in hands and feet, and cervical lymphadenopathy. Along with a broad range of nonspecific clinical features such as irritability, uveitis, aseptic meningitis, cough, vomiting, diarrhea, abdominal pain, urethritis, arthralgia, arthritis, hypoalbuminemia.[18]

WHO described the criteria to diagnose MIS-C as the following

Preliminary case definition: Children and adolescents 0–19 years of age with fever for three days and more

AND two of the following:

1. Rash or bilateral non-purulent conjunctivitis or mucocutaneous 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 (diarrhoea, vomiting, or abdominal pain).

In addition to all of the following

- Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.
- No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
- Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19

On the other hand, The Centers for Disease Control and Prevention (CDC) has defined the disease considering the following features:

- An individual aged less than 21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organs involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological).
- 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 four weeks before the onset of symptoms.
- Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours.

- Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

Presentation of (MIS-C) cases in the Eastern region of Libya:

A series of 12 casesdiagnosed by serology and clinical picture, all are Libyan, their age ranged between (2-14year), out of the nine males and three females, all are from Benghazi except four cases were from Elmarj, Derna, Tazerbo, and Jalo (black race), all of them presented with fever,lehtergy,GIT manifestations, in particular, vomiting, diarrhea and abdominal pain, 2-3 days after fever most of themdemonstratedmucocutaneous manifestations typical for KD (pic1,2) with perianal erythema in three cases(pic3) and another case developed palmer erythema. Three cases exhibited cervical lymph nodes enlargement, another three cases presented with conjunctivitis.Two cases presented with respiratory symptoms (cough, dyspnea, chest pain).One case presented with myocarditis while nephritis was evident in another case.

All of the cases were previously healthy and have no chronic illnessexcept a case known for bronchial asthma that presented with hands and feet swelling which occurred in further three cases. At the time of presentation, all of them have no focal site of infection.Meningeal signs were positive in three cases(table 1).

Table 1: Clinical manifestations of the cases

No	Age (Years)	Sex	Fever	Skin and MM*	Hands and feet swelling	L.A.P**	Respiratory	GIT	CVS	Renal	CNS
1	4	♂	+	+	+	+	-	+	-	-	+
2	5	♂	+	+	+	+	-	+	-	-	-
3	14	♀	+	+	-	-	-	+	-	-	-
4	5	♂	+	+	-	-	-	+	-	+	-
5	7	♂	+	+	+	-	-	+	-	-	-
6	2	♂	+	+	-	-	-	+	-	-	+
7	12	♂	+	-	-	-	++	+	-	-	-
8	2	♀	+	+	+	-	-	+	-	+	-
9	11	♂	+	+	-	+	+	+	+	-	-
10	2	♂	+	+	-	-	-	+	+	-	-
11	6	♀	+	+	+	-	-	+	-	-	+
12	9	♂	+	+	-	-	-	+	-	-	-

*L.A.P : lymphadenopathy ** M.M: Mucous Membrane

Laboratory investigations:

- All cases have been subjected to baseline laboratory investigations including CBC, ESR, CRP, RFT,LFT, urine analysis (routine and culture), CSFanalysis (routine and culture).
- The hall marks of all cases were: elevated ESR and CRP, and lymphopenia.

- ALL cases tested positive for COVID-19 IgG and one case positive for COVID-19 IgM and IgG, whereas four cases tested positive for both (RT.PCR and serology).
- There were elevated levels of D.Dimar in four cases, LDHin six cases, T.Troponine in five, and serum ferritin in six cases.
- Three cases have had thrombocytopenia which was as low as zero in one case with prolonged PT and APTT.

- Two cases showed renal involvement with elevated renal parameters in one of them while the other one showed abnormal urine routine tests with elevated WBC, RBS, and presence of RBSs casts.
- Four casesdemonstrated elevated liver enzymes(ASTand ALT) with low serum albumin levels.
- CSF analysis was normal for all cases.

Radiological assessment

Chest x-ray of two patients revealed that there is bilateral interstitial infiltration and another oneshowed significant opacity which has been confirmed as pleural effusion by ultrasound in addition to ascitis (Pic 4).
ECG was significant in only one case whichshowed the right bundle branch block.
ECHO in all cases was normal except one case with left ventricular diltation and mild aortic regurgitation and another case had dilatedcardiomyopathy.

picture (**1**) skin rash

picture (**2**) strawberry tongue with cracked lips

picture (**3**) perianal edema

picture (**4**)case 7 with pleural effusion

**** The photos have been published after the permission of each child`s family.**

Treatment

Ten Patients who presented with the moderate disease treated with I.V antibiotics,oral aspirin, I.V sandoglobulin,out of the three cases received I.V methylprednisolone.Two mild cases were treated only by oral aspirin. One casewas diagnosed late by serology and getting well without treatment.

Outcome

Duration of hospital admission of all cases ranged between 5-7 days, their clinical conditions showed signs of improvementwithin two days, none of them needed ICU admission, all have been discharged in a good healthon oral treatment and follow up guidance with the cardiologist.

Discussion

KD is an infection-induced vasculitis that influences medium-sized arteries, which primarily affects infants and children younger than 5 years.[19]The gender and age distribution as reported elsewhere suggested boys to be more commonly diagnosed, and the majority of cases occurring in children aged 5 years. In Japan, the peak incidence is at 11 months of age and 85% of cases occur in those aged 5 years.[20]It occurs with variable incidence all over the world its incidence in Arab countries of North Africa or Maghreb countries is not exactly known.However; it is reported to below.[21]

Since the beginning and spread of the ongoing pandemic of COVID-19, multiple reports have been published describing cases of the hyperinflammatory syndrome with multiorgan involvement in the paediatric age group. Some of these reports were about children with a clinical picture consistent with KD besides laboratory tests suggestive of current or past SARS-CoV-2 infection(ECDC).[2]
The current case series confirmed that since the time of the spread of COVID-19 in the city of Benghazi there was a raised incidence of KD among children. Although there are no documented figures of KD in Libya specifically the Eastern region, the paediatricians claimed that beforethe COVID-19 epidemic we have never received such a frequent case of KD and MIS-C in such frequency, which reached in some times to three cases a day. It is worth mentioning that this growth in KD incidence was reported in different countries and regarded as one of the common clinical presentations of COVID-19 in the paediatric age group despite that, no causal link has been established between MIS-C and COVID-19 in children [14]
Available literature pointed that viruses have an important role in human vasculitic disease. Several pathogens such as herpesvirus, novel human coronavirus, Epstein–Barrvirus, and parvovirus B19 have been suggested as possible agents in the pathogenesis of KD.[22]

COVID-19 affected the incidence and presentation of classic KD in paediatrics. The affected cases were of different age groups starting from two years and more frequently in older children. Some cases are aged 9 -14 years. Male children were the predominant victims just like the known gender difference of the disease. There is difference from the available knowledge of the classic KD prior to

COVID-19 epidemic which is known by the typical changes in the mucous membranes and with less frequency of GIT symptoms. Poor response to antibiotics is a feature of the disease .[23]

In Pakistan, a report published online in August 2020 documented two major presentations of KD induced by COVID-19, atypical or typical KD (6 of 8, 75%) and a more severe second one with shock or low cardiac output (2 of 8, 25%). Common presenting features were fever, body aches, and abdominal pain. The patient presented with altered consciousness and signs of meningism, and an initial diagnosis of meningoencephalitis was made.[17]

Classic KD was documented to be of seasonal variation in the incidence according to geographic area, Canada, Korea, Japan, and China the peak incidence in winter, while in Taiwan its peak during spring.In North Africa countries the peak was in spring with the secondary peak in winter in Algeria and summer in Tunisia which could be related to allergy and viral seasons in general as a relationship between KD and immunological dysregulation is suggested.[24] In the present series of MIS_C and classic KD there are accumulating cases in a dramatic excess started in August which is a dry and hot time in Libya as it is summer season. The peak of the disease might occur later and the rule of the seasonality of classic KD might be broken by the COVID-19 epidemic.

Conclusion

COVID-19 epidemic can be seen as a leading factor for MIS-C.twin epidemics of COVID-19 and MIS-C has been evident so far. Peadiatric age group was generally considered safe and they act as disease transmitters in the COVID-19 epidemic. However, COVID-19 is manifested as MIS-C which leads to the greater burden of the epidemic on the health sector and resulted in increased morbidity and hospital admission of children.

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