Title: Multisystem Inflammatory Syndrome (MIS-C) in an Adolescent Nigerian Girl with COVID-19: A call for vigilance in Africa

Chizaram Onyeghala[1,4], *[*]Datonye Alasia*[1,4,5], *Orezioghene Eyaru*[2,4], *Paul Nsirim*[2,4,5], *Omosivie Maduka*[3,4,5], *Nosa Osemwengie*[1,4,]*Nkem Ugwueze*[2], *Collins Ordu*[1,4] , *Ebitei Igbosi*[1,4], *Mary Irabor*[2,4], *Emeka Eyidia*[4].

Affiliations: Departments of Internal Medicine[1], Peadiatrics[2], Public Health[3], COVID-19 response Team[4], University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria. [5] Faculty of Clinical Sciences, University of Port Harcourt

Correspondence: *datonye.alasia@uniport.edu.ng

Note: This is a preprint that has been submitted to the International Journal of Infectious Diseases

Abstract:

Majority of reports of Multisystem Inflammatory Syndrome (MIS-C) associated with COVID-19 have come from Europe and North America, with a paucity of cases in the Asia-Pacific region and Africa. The paucity of reports in Africa is in contrast with the demographics of the series in New York, Paris and UK which reported that children of African ancestry accounted for 40%, 57% and 75%, respectively of all cases of MIS-C. With the global trend of higher prevalence of MIS-C in children of African ancestry, enhanced surveillance and awareness for this syndrome in children with COVID-19 in Africa is therefore important as the previous and current observations of Kawasaki Disease (KD) and MIS-C as a rarity in Africa may be due to under-reporting, a poor index of suspicion and missed diagnosis. A case report of a 12-year old Nigerian girl with MIS-C is presented in line with the WHO call for urgent reporting and global surveillance especially in areas were MIS-C is considered a rarity. This case report stimulates a call for vigilance and expanded effort at surveillance to promote early recognition and diagnosis of MIS-C in Africa; using current case definitions which promote the recognition of MIS-C in areas of resource limitation. The favourable outcome and experience from this case will create awareness, expand knowledge, and support clinicians on the African continent in their approach to other potential cases.

Keywords: SARS-COV2; COVID-19; MIS-C; Kawasaki; Africa.

Highlights:

- MIS-C is a new syndrome that is temporarily related to previous exposure to the SARS-COV2.
- This hyper-inflammatory syndrome with dermatologic, mucocutaneous, and gastrointestinal manifestations is associated with cardiac dysfunction.
- MIS-C shares similarity with atypical Kawasaki disease but prominent clinical signs are largely different.

- There is an established active global surveillance to describe hospitalized patients with the syndrome especially in communities with higher levels of SARS-COV-2 transmission.
- Reports of cases of MIS-C in Europe and North America have revealed a higher prevalence among children of African ancestry, while reports from Africa on MIS-C and KD are rare.
- This is first case report of MIS-C in Nigeria and probably from Africa during the COVID-19 pandemic.
- On the background of higher prevalence of MIS-C in Europe and North America in children of African ancestry and the rarity of MIS-C in Africa, this report provokes a call for vigilance and enhanced surveillance for MIS-C on the African continent.
- The favourable outcome of this case which corresponds with outcomes in Europe and North America provides learning points for physicians in Africa.

Introduction

The COVID-19 pandemic caused by the novel SARS COV2 has been associated with unique and evolving clinical presentations including severe disease associated with intense inflammatory response. [1] In the initial progress of the pandemic it was observed that SARS COV-2 infection was less prevalent in children with a 2% prevalence for people aged ≤ 19 years among a Chinese cohort of 72314 cases. [2] Children were also reported to have lower risk for severe COVID-19 disease requiring critical care in North America. [3] As the pandemic progressed, reports from European and North American countries highlighted the occurrence of a hyper, multisystem inflammatory process in children that had features like Kawasaki disease (KD). [4-7]

Verdoni et al in Italy, [6] reported a 30-fold increase in the incidence of Kawasaki-like disease with evidence of immune response to SARS COV-2 over a 30 day period, while Toubiana et al from Paris also reported a KD like syndrome in a cohort of children with COVID-19. [7] Dufort et al, in New York also reported 95 confirmed cases with multisystem inflammatory syndrome in children (MIS-C) as of May 10, 2020. [4] The KD like syndrome associated with COVID-19 in children has been described as atypical KD and a possible distinct clinical entity.[8] This syndrome therefore been described as paediatric multisystem inflammatory syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C).[8] These distinctions in the clinical manifestations have thus prompted the development of case definitions and diagnostic criteria by the World Health Organisation (WHO), [5] Center for disease control (CDC) [9] and the Royal College of Paediatric and Child Health (RCPCH).[10] In addition this condition has been designated as an urgent reportable condition by the

WHO emphasizing the importance of global epidemiology surveillance and case reporting for this condition, especially in places where it is considered a rarity.

Majority of reports of MIS-C associated with COVID-19 have come from Europe and North America, with a paucity of cases in the Asia-Pacific region and Africa [11]. The paucity of reports in Africa is in contrast with the demographics of the series in New York [6] and Paris [7] and UK [12] which reported that children of African ancestry accounted for 40%, 57% and 75%, respectively of all cases of MIS-C. It has been previously observed, that very few cases of KD have been reported from Nigeria, with four separate reports documenting only 10 cases since 2010. [13,14,15,16] The low reporting and largely unknown prevalence of KD has been attributed to a poor index of suspicion, late presentation and missed diagnosis by Animashaun et al. [13] With the global trend of higher prevalence of MIS-C in children of African ancestry, enhanced surveillance and awareness for this syndrome in children with COVID-19 in Africa is therefore important. This first report of a case of MIS-C in a Nigerian female child, is expected to promote awareness of this syndrome and improve care of children with severe COVID-19 disease in Nigeria and Africa.

Methods

The case records of a 12-year-old female diagnosed with severe COVID-19 and MIS-C and a review of the literature was utilised. Ethical considerations such as confidentiality, identity protection and consent were adhered to. Key words in literature search of google, Medline, PubMed databases were Kawasaki Disease, MIS-C, SAR-COV-2, COVID-19 and Africa.

Case Report

A 12-year-old girl presented on referral to the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria, COVID-19 treatment centre on the 3rd of June 2020, with high grade intermittent fever for 10 days; progressively worsening breathlessness for 4 days; skin rashes, mucosal excoriations, conjunctivitis and diarrhoea for 3 days respectively. (Clinical features are presented in Table 1). Her immunization status was up to date according to the Nigerian national guideline. On admission, clinical signs comprised body weight of 50Kg, temperature of 39ºC, respiratory rate of 64 per minute, pulse rate of 135 per minute and blood pressure of 90/50mmHg. Oxygen saturation (SP02) was 76% in room air, modified early warning systems (MEWS) score [17] and the African emergency medicine (AFEM) COVID-19 severity scoring tool [18] which were used in monitoring severity and clinical progression revealed scores of 12 and 15 respectively indicative of critical care. Other physical examinations findings are presented in Table 1.

Laboratory and ancillary investigations showed leucocytosis with neutrophilia, lymphopenia, thrombocytopenia, anaemia; and elevated Erythrocyte sedimentation rate (ESR). Chest radiograph

revealed bilateral background tiny nodular lesions in both lungs. RT-PCR for SARS-COV-2 was positive. Laboratory and ancillary results are shown in Table 2. Based on her symptoms and laboratory findings, she was diagnosed with Severe COVID-19 disease in line with the Nigerian case guidelines [19] with MIS-C in accordance with the WHO preliminary case definition [5].

The treatment regimen comprised of initial high flow oxygen at 10 litres per minute via non-rebreather mask, blood transfusion with intravenous (IV) frusemide to prevent fluid overload, IV ceftriaxone 1g daily for superimposed bacterial infection, IV hydrocortisone 200mg daily, prophylaxis anticoagulation with subcutaneous (SC) enoxaparin 40mg daily, tablets Azithromycin 500mg daily, tabs Paracetamol 1g tds, tablets Hydroxychloroquine 200mg BD for 24hrs then 100mg BD for 4 days, vitamin A capsules 200,000iu on days 1,2, and 4 and vitamin C tablets at 500mg daily. On day 5 of hospitalization, her clinical symptoms improved remarkably with normal vital signs, MEWs and AFEM score of 4 and 5 respectively, prompting ICU discharge on the day 6. The patient was discharged 14 days after hospitalization following a negative SARS COV-2 test result and normalised clinical and laboratory parameters as shown in tables 1. She was seen two weeks post-discharge at the clinic with no symptoms, with a long term follow up plan and echocardiography request for cardiac evaluation.

Discussion

The global reports of MIS-C associated with the COVID-19 pandemic from Europe and North America documented high prevalence in children of African ancestry, in contrast to the rarity on the African continent [4-7]. To the best of our knowledge, this is the first case of MIS-C in Nigeria and probably in Africa since the onset of the COVID-19 pandemic. The diagnosis of MIS-C in this case; which was centred on the clinical presentation and basic laboratory evaluation, also demonstrates the utility of the WHO preliminary case definition, as a tool which is applicable to all settings irrespective of resource capacity.

The diagnostic criteria in the index case in accordance with the WHO preliminary case definition were; Age of 0–19 years with fever > 3 days, rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet); Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain); elevated markers of inflammation such as ESR and evidence of COVID-19 with positive RT-PCR test. The criteria as earlier stated is easily applicable for diagnosis of MIS-C in developing and low resource settings, to the extent that limitations in the performance of elevated Troponin/NT-proBNP, echocardiography, CRP and procalcitonin did not limit the capacity for diagnosis in this case.

Intravenous steroids with other adjunctive therapy was applied in our patient, as part of our severe COVID-19 treatment protocol, with a favourable outcome and rapid resolution of symptoms. The

favourable outcome and ICU stay of 6 days in this case, is similar to the outcome of other reported series by Riphagen et al in the UK [12], Verdoni et al in Italy [6] and Toubiana et al in France [12]. Despite non-use of intravenous immune globulins (IVIG) for our patient, response to treatment was still good. This shows that favourable outcome is expected in most patients with MIS-C with early recognition and therapy which targets hyper-inflammation through anti-inflammatory effects. The outcome of this case also justifies the role of steroids in the management of these cases either alone or in combination with IVIG as implemented by Riphagen et al [12] for cases in the UK.

The diagnosis of MIS-C in this Nigerian child, therefore, reinforces the need for physicians and health care systems in Africa to be more vigilant in the assessment of children with severe COVID-19 disease. The observations of higher prevalence of MIS-C in children of African ancestry in Europe and North America, may suggest a racial and genetic susceptibility which puts African children at higher risk [7] and supporting the claims that KD may be more common in sub Saharan Africa (SSA) than previously thought [12]. The increased surveillance for MIS-C in Africa, might also reveal a contrasting lower prevalence among children in the African continent compared to what is reported among children of African ancestry outside Africa. Therefore, as the global cases of COVID-19 and infections with SARS-COV-2 continue to increase across all age grades, more vigilance is required for cases of MIS-C across Africa.

In conclusion, we report a rare case of MIS-C in Nigerian child and recommend vigilance among physicians and expanded effort at surveillance to promote early recognition and diagnosis of MIS-C in Africa. All the current case definitions of MIS-C by the CDC, [9] RCPCH [10] and WHO [5] are all easy to use with the WHO preliminary case definition [5] particularly promoting the recognition of MIS-C in areas of resource limitation. [5] The management of MIS-C was successful in this case in correspondence with outcomes from other countries, while long term follow-up of the patient is ongoing. It is expected that increase surveillance will provide required evidence for understanding of the geographic and racial factors which influence the prevalence of MIS-C and KD. The experience from the case will create awareness, expand knowledge, and support clinicians on the African continent in the approach to other potential cases.

Table 1: Clinical presentation of the patient

Symptoms	Duration (Days)	Description	Day 5 status	Day 14 status
Fever	10	high grade and intermittent		
Breathlessness	4	Progressive worsening		
rashes	4	face, upper limbs, and trunks, pruritic		
Flaking of lips	4	peeling of the upper lips and mucous membranes of the mouth		
Redness of eyes	3	cream coloured sticky discharge		
Diarrhoea	3	Stools were loose, greenish, non-bloody, about 3 to 4 bowel		
Clinical Signs	Values			
Temperature (^{O}C)	39		37	36.5
Respiratory Rate/minute	64		32	28
Pulse /minute	130		90	84
Blood Pressure (mmHg)	90/50		90/50	90/60
SPO_2 (room air) %	80		98	99
MEWs Score	12		4	1
AFEM score	15		5	2
Eyes		bilateral conjunctival injection		

Mouth and mucosa		dried peeled lips and hyperaemic oral mucosa		
Skin		Diffuse maculopapular rashes were found on the face and upper limbs		
Legs		pedal oedema		
Chest		bibasilar crackles		
Abdomen		Tender hepatomegaly		

Table 2: Laboratory Parameters of the patient

Parameters	Result	Normal ranges	Interpretation
Haemoglobin (g/dl)	8.95	11.5-13.5	Anaemia
White blood count ($x10^9$/L)	21.20$x10^9$/L	4.5-13.5	Leucocytosis
Neutrophils %	85.19	40-75	Neutrophilia
Lymphocytes %	8.7	20-45	Lymphopenia
Neutrophils ($x10^9$/L)	18.06	1.50 – 8.50	Neutrophilia
Lymphocyte ($x10^9$/L)	0.85	1.00-6.5$x10^9$/L	Lymphopenia
Eosinophil ($x10^9$/L)	0.42	0.00-0.40	Marginal elevation
Monocytes ($x10^9$/L)	0.77	0.00-1.00	Normal
Platelet (x 10^9/L)	84.3	150-450	Thrombocytopenia
ESR (mm/hr)	70mm/hr	0.00-4	Elevated
Sodium (mmol/L)	135mmol/L	135-145	Normal
Potassium (mmol/L)	3.4mmol/L	3.5-5.5	Hypokalemia
Bicarbonate (mmol/L)	29mmol/L	24-30	Normal
Urea (mmol/L)	2.9mmol/L	2.4-6.2	Normal
Creatinine (umol/L)	130mmol/L	60-120	Azotemia
Random Blood Sugar (mmol/l)	5.6	4.0 – 10.0	Normal
HIV Screening	Seronegative		
GFR (mls/min/BSA) (MDRD)	70.87		Evidence of AKI

RT-PCR for SARS-COV-2 (3/6/2020)	Positive	RT-PCR for SARS-COV-2 (24/6/2020)	Negative
Chest Radiograph	Dense lung fields with bilateral background tiny nodular lesions		Atypical Interstitial pneumonia

References:

1. WHO-China Joint mission. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), February 2020. Available online - https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf- Accessed 20th March 2020.
2. Wu Z, MacGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323(13):1239-1242.
3. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, Heidemann SM, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian paediatric intensive care units. JAMA Pediatr. Published online May 11, 2020. doi:10.1001/jamapediatrics.2020.1948
4. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, Barranco MA, et al. Multisystem inflammatory syndrome of children in New-York state. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med 2020; 383:347-358.DOI: 10.1056/NEJMoa2021756

5. WHO. Multisystem inflammatory of children and adolescents with covid-19. WHO- 2019-ncov/sci-brief/multisystem syndrome children/2020.1.
6. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020; 395:1771–1778. doi: 10.1016/S0140-6736(20)31103
7. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, Debray A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ, 2020; m2094 DOI: 10.1136/bmj.m2094
8. Kam K-Q, Ong JSM, Lee JH. Kawasaki disease in the COVID-19 era: a distinct clinical phenotype? The Lancet; Child and Adolescent health 2020.https://www.thelancet.com/pdfs/journals/lanchi/PIIS2352-4642(20)30207-8.pdf
9. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19).https://emergency.cdc.gov/han/2020/han00432.asp. Published 2020. Accessed June 20, 2020.
10. Royal College of Paediatric and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19.https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19. Published 2020. Accessed June 22, 2020.
11. Son MBF. Paediatric inflammatory syndrome temporally related to covid-19. BMJ, 2020; m2123 DOI: 10.1136/bmj.m2123
12. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; 395:1607-8. 10.1016/S0140-6736(20)31094-1 32386565
13. Animasahun AB, Adekunle MO, Kusimo OY, Fadipe C. The diagnosis of Kawasaki disease among Nigerian children: a nightmare for the caregivers and the doctors. Journal of Public Health and Emergency (JPHE), 2017; 1:69,6pages. doi: 10.21037/jphe.2017.06.06
14. Sotimehin SA, Ogunlesi TA, Adekanmbi AF, Fetuga MB, Odumuyiwa EA, Olowu OA. Kawasaki Disease in A Nigerian Child- a case report. Nigerian Medical Practitioner 2010;57(4):10-15.
15. Utuk EE, Akpan MU, Kawasaki Disease In A Two Year Old Nigerian Child; Full Recovery With Supportive Treatment. Ibom Medical Journal 2015;8(1):18-22.

16. Sani UM, Ahmed H. Kawasaki disease: an unusual presentation in a 14 year old boy, in Sokoto north western Nigeria. Niger J Paed 2013; 40(4): 422-425.
17. Kyriacos U, Jelsma J, James M, Jordan S. Monitoring Vital Signs: Development of a Modified Early Warning Scoring (Mews) System for General Wards in a Developing Country. PLoS ONE 9(1): e87073. doi:10.1371/journal.pone.0087073
18. African Federation for emergency medicine (AFEM). Covid-19 severity scoring tool. https://africacdc.instructure.com/courses/8/files/1501?module_item_id=1857. Accessed 19th March 2020
19. Nigerian Centre for Disease Control (NDCD). National Interim Guidelines for Clinical Management of COVID-19 Version 3,June 2020. https://covid19.ncdc.gov.ng/media/files/National_Interim_Guidelines_for_Clinical_Management_of_COVID-19_v3.pdf

Sources of funding: None

Conflict of Interest: None