BAPIO Publications

The Physician
Journal of The British Association of Physicians of Indian Origin

Black and minority ethnic children most at risk of developing Multisystem Inflammatory Syndrome - Temporally associated with COVID-19

Key points:

In the current climate, it is essential that all professionals dealing with children are aware of Multisystem Inflammatory Syndrome. The children may present in primary care, emergency department or to Paediatrics with a variety of symptoms. Majority of the children have mild or moderate symptoms, though the small minority may deteriorate quickly.

1. Early recognition and diagnosis of Multisystem Inflammatory Syndrome are essential to ensure early treatment and reduce morbidity and the risk of long-term complications particularly coronary artery aneurysms.
2. Children from BAME backgrounds appear to be more commonly affected. The reasons for this are likely to be multifactorial including socio-economic factors[3], health care seeking behaviour, but possible genetic influences on susceptibility[15] also need researching. Preliminary signals must be explored urgently[16]. Data collection on ethnicity should be included in all future studies.
3. Children with mild to moderate disease require only supportive care. For more severe cases particularly if they have comorbidities and or are from BAME group, the involvement of specialists and referral to Paediatric intensive care should be considered early.

Sahana Rao MBBS FRCPCH[1] & Bhupinder Sandhu OBE DSc(hon) MD FRCP FRCPCH[2]

[1] Consultant Paediatrician, Oxford University Hospitals NHS Trust, Oxford, UK; Sahana.Rao@ouh.nhs.uk

[2] Consultant and Professor in Paediatric Gastroenterology and Nutrition(hon), Bristol Royal Hospital for Children, Bristol UK; profbksandhu@gmail.com

Article Information

Submitted	22 May 2020
Pre-print	24 May 2020
Revised	13 June 2020

Cite as: Rao, S. & Sandhu, B. (2020) BAME children are most at risk of developing Multisystem Inflammatory Syndrome – Temporally Associated with COVID-19; Yet children are much less affected by COVID-19. *The Physician*, 6(1). DOI: 10.38192/1.6.1.13

Full Text

On 31 December 2019, a cluster of pneumonia cases of unknown aetiology was reported in Wuhan, Hubei Province, China. On 9 January 2020, China Centre for Disease Prevention (CDC) reported a novel coronavirus as the causative agent of this outbreak, coronavirus disease 2019 (COVID-19).

COVID-19 is caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease rapidly spread to other countries with devastating results. The World Health Organization declared Covid-19 infection a Public Health Emergency of International Concern on 30 January, and a pandemic on 11 March.[1]

Epidemiological studies have found that compared to adults children are far less affected by COVID-19. European Centre for Disease Prevention and Control (ECDC) found that children (aged 0-14years) accounted for only 2.1% of all confirmed COVID-19 cases[2]. Data from Kings College Hospital London on their COVID-19 admissions from 25 Feb 2020 to 28 April 2020 documented 2288 adult admissions and 12 paediatric admissions which is only 0.5 %

of the total[3].The disease also appears to take a milder course in children than adults with most infected children presenting with mild symptoms with very few developing life-threatening disease. CDC data from the USA reports that a high proportion of cases needing hospital admission had at least one comorbidity, most commonly respiratory.

A systemic review of 18 studies involving 1065 children (444 <10yrs and 553 aged10-19 yrs.) documented that commonest reported symptoms are fever dry cough and followed by runny nose, feeding difficulties, drowsiness, nausea or vomiting , abdominal pain, headache, sore throat and rash (3%)[4]. Coronavirus in Paediatric Emergency Departments (CONFIDENCE) study involving a cohort of 100 Italian children (<18yrs) with nasal or nasopharyngeal swab confirmed Covid-19 found 21% to be asymptomatic, 58% had mild disease,19% moderate and only 1% were in critical condition[5]. 43%were female and 57% male. 38%were admitted to hospital and there were no deaths. In summary most children are asymptomatic or exhibit mild symptoms.

However recently it has been noted that during the Covid-19 pandemic a very small number of children have presented with a Kawasaki-like syndrome. On 7th May 2020 doctors from the South Thames Retrieval Service in London, published a cluster of 8 children presenting over 10 days in mid-April 2020 with hyperinflammatory shock, showing features similar to atypical Kawasaki disease (KD), Kawasaki disease shock syndrome or toxic shock syndrome[6]. Normal incidence of Kawasaki in their setting has been 1- 2 per week. All children were previously well, 4 had known exposure to COVID-19. All tested negative for SARS-CoV-2 on bronchoalveolar lavage or nasopharyngeal aspirates but 2 were positive on later testing. No other pathogens were identified except for Adeno and enterovirus in one case. Clinical presentation was similar with multisystem involvement with unrelenting fever (38-40C), variable rash, conjunctivitis, peripheral oedema, generalised extremity pain, diarrhoea, vomiting and abdominal pain. Other findings included ventricular dysfunction, dilated coronaries, ascites, pleural effusions and in 1 case ileitis, gall bladder oedema and dilated biliary tree. All developed warm vasoplegic shock, refractory to fluid resuscitation requiring noradrenaline and milrinone for haemodynamic support. Most had no significant respiratory involvement although 7 required mechanical ventilation for cardiovascular stabilisation. All children required intensive care for 3-7 days. All were given Intravenous immunoglobulin in first 24 hrs, antibiotic cover and 6 have been given aspirin . One child (male age 14 yrs.) died on day 6 of cerebrovascular infarct [6]. This paper received a lot of publicity and led to concern among doctors and a lot of parents. What was not highlighted was that all 8 children in this study came from a BAME background (6 Afro-Caribbean,1 Middle Eastern and 1 Asian). A more recent paper published by Whittaker et al in JAMA on June 8th describes clinical characteristics of 58 children with Inflammatory Multisystem Syndrome temporally associated with SARS- Cov-2 from 8 hospitals in England who were hospitalised between 23rd March and 6th May. Forty (69%) of these children were from BAME groups. The median age was 9 years (range 3 months to 17 years) 33 were girls (57%).[7]

Is Ethnicity linked to incidence and outcomes of COVID-19?

Concerns about a possible association between ethnicity and outcome were raised after the first 10 doctors in the UK to die from COVID-19 were identified as being from Black Asian and Minority Ethnic (BAME) background[8] and confirmed by data from National Audit and Research Centre[9] showed that over a third of patients admitted to critical care units were from ethnic minorities. Ethnic minority groups have also been over affected in the US[10].

A recent (26th May 2020) prospective observational study from Paris confirms the emergence of Kawasaki-like multisystem inflammatory syndrome in children during the COVID-19 pandemic[11]. It describes 21 children (median age 7.9 yrs. (range 3.7-16.6) admitted to hospital ,12 (57%) with features of Kawasaki disease shock syndrome and 16 (76%) with myocarditis over a 15-day period (27 April- 11 May) .19 (90%) had evidence of recent SRS-CoV-2 infection, 17 (81%) required intensive care. All had gastrointestinal symptoms and high levels of inflammatory markers. 5(24%) had moderate coronary artery dilatation. All patients were discharged home after median 8 days (range 5-17) in hospital. 15 of the 21 (71%) children came from a BAME background 12 (57%) Afro-Caribbean ,2 (9.5%) Asian, 1 (5%) Middle Eastern. Only 6 (29%) were European. Both of these studies suggest that being BAME is a significant risk factor for Kawasaki-like multisystem inflammatory syndrome associated with COVID-19 .

Although hospitalisation for COVID-19 is rare in children, data from Kings College Hospital, London published in the Lancet 28th May 2020 by Harman et al concluded that ethnicity and the presence of pre-existing comorbidities might be independent risk factors for severe disease[3]. They prospectively identified 12 children with confirmed COVID -19 who required admission to hospital during 25 Feb to 28 April. 2020. 5 out of 12 had pre-existing comorbidities which included cerebral palsy, prematurity, Wilson's disease and dilated cardiomyopathy. The mean age of these children was 7.1yrs (range 0.2-15.3), 2 were less than 1 yr. and 2 were male. The most common symptom on admission was fever (60%) and tachypnoea (60%). Respiratory support was required in 3 (60%) of which 2 needed mechanical ventilation in the intensive care unit. 4 out of these patients (80%) were from BAME group. In the 7 non- comorbidity patients 5 out of 7 were also from BAME (64%). The numbers are small but provide further support for the suspicion that a child from BAME group may have at increased risk of adverse outcome from COVID-19.

An observational cohort study describing an outbreak of severe Kawasaki-like disease at the Italian epicentre of SARS-CoV-2 epidemic, Bergamo province, was published in the Lancet on 6th June by Verdani and colleagues[12]. They reported 10 children (7 boys, 3 girls aged 7.5yrs (SD 3.5) diagnosed between Feb 18 and April 20 with Kawasaki-like disease and 8 (80%)) had antibodies against SARS-CoV-2. They compared these to 19 children (7boys,12 girls aged 3 yrs. (SD 2.5) diagnosed with Kawasaki disease in the previous 5 years. The analysis showed that children diagnosed after the COVID-19 epidemic were older, had a higher rate of cardiac involvement and feature of macrophage activation and the disease was more severe. There was a 30-fold increase in incidence. No ethnicity data was published.

Kawasaki Disease (KD)

Kawasaki disease is a medium vessel vasculitis of childhood and most commonly occurs in children aged 6 months to 5 years but can occur at any age. American Heart Association criteria (2017) defined it as fever for ≥5 days plus four or more clinical criteria, including bilateral bulbar non-exudative conjunctivitis, changes of lips or oral cavity, polymorphic rash, non-suppurative cervical lymphadenopathy (with at least one node ≥ 1.5 cm in diameter), and changes in the hands or feet (erythema, oedema, induration, desquamation). Incomplete types include fever for ≥5 days plus two or three of clinical criteria and raised erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)[13]. Blood tests may reveal presence of anaemia, leucocytosis, thrombocytosis (week 2 of fever), hypoalbuminaemia, and raised transaminases. Echocardiogram may show coronary aneurysms or cardiac dysfunction. Complications of KD include aneurysms of mid-sized arteries, giant

coronary artery aneurysms, pericarditis and myocarditis. There are no diagnostic tests for KD. There is a large list of viral pathogens which have been associated with it including coronavirus so diagnosis is on clinical criteria. It is very important to recognise it early as treatment with aspirin and intravenous Immunoglobulin in the early phase decreases the risk of significant coronary artery aneurysm. Even with treatment aneurysms can occur in up to a fifth of the cases. It is estimated to be the commonest cause of acquired heart disease in children in Western countries.

The relationship of SARS-CoV-2 and this condition is not understood. Royal College of Paediatrics and Child Health (RCPCH), Public Health England and British Paediatric Surveillance Unit (BPSU) have started a prospective national study asking paediatricians to report all cases which have features of the multisystem inflammation. They will also be asked to report cases of Kawasaki disease and toxic shock syndrome to assess whether their incidence has increased compared to recent BPSU estimates for both conditions- and to determine any role of COVID-19. The study will run from March 2020 to March 2021.It should include data on ethnicity.

There have been attempts by various organisations to define multisystem inflammatory syndrome. On My 15th World Health Organisation (WHO) agreed a definition of Multisystem Inflammatory Syndrome in Children temporally related to COVID-19 (Scientific brief 15th May 2020) which is as follows. Although terminology may vary, it is basically concordant with that used by RCPCH in UK[14] and Centre for Disease control in America (who also noted that adult Ethnic minority groups have been over affected by COVID-19 in the US [15].

Guidelines

Clinical Guidelines for investigation and treatment of Multisystem Inflammatory Syndrome are available in most countries. In the UK these can be found on the Paediatric Critical Care society and on the RCPCH websites.12

RCPCH at https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501

Case definition of multisystem inflammatory syndrome in children and adolescents temporally associated with COVID-19.

Children and adolescents 0–19 years of age with fever > 3 days

AND

Two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous 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).

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

References

1. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020". World Health Organization. 11 March 2020.
2. European Centre for Disease Prevention and Control. Paediatric inflammatory multisystem syndrome and SARS-CoV-2 infection in children – 14 May 2020. ECDC: Stockholm; 2020.
3. Harman, K., A. Verma, J. Cook, T. Radia, M. Zuckerman, A. Deep, A. Dhawan and A. Gupta (2020). "Ethnicity and COVID-19 in children with comorbidities." Lancet Child Adolesc Health. Published on line May 28th 2020.
4. Castagnoli R, Votto M, Licari A et al. Acute Respiratory Syndrome Coronavirus 2 (SAR. S-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA pediatr 2020.doi:10.101001/jamapediatrics. ,2020.1467 .
5. Parri N, Lenge M, Buonsenso D. Children with Covid-19 in Pediatric Emergency Departments in Italy. NEJM.org 2020.
6. Riphagen S Gomez X, Gonzalez-Martinez C et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet ,23-29 May 2020;395:1607-8. Published online 2020 May 7. doi: 10.1016/S0140-6736(20)31094-1
7. Siddique H.UK government asked to investigate coronavirus deaths of BAME doctors..Guardian 2020 Apr 10. http://theguardian.comsociety/2020/apr/10/uk-coronavirus-deaths-bame-doctors-bma
8. Intensive Care National Audit and research Centre.Covid-19 study case mix programme.2020.
9. Resnick A ,Galea S, Sivashanker K.Covid-19 :the painful price of ignoring health

inequalities. BMJ Opinion,18 March 2020.https://biogs.bmj.com/bmj/2020/03/18/covid-19

10. Toubiana J, Poirault C, Corcia A et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris: prospective observational study. BMJ 2020:369:m2094. http://dx.doi.org/10.1136 bmj.m2094

11. Verdani L, Mazza A, Gervasoni A et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study.thelancet.com Vol 395 June 6, 2020

12. American Heart Association. Kawasaki didease.www.heart.org

13. RCPCH https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf .

14. MMWR Morbidity and mortality weekly report. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. 2020;69(14):422-6

15. Nguyen A, David JK, Maden SK et al. Human leucocyte antigen susceptibility map for SARS-CoV-2.J Virol 2020; published online April17.DOI:10.1128/JVI.00510-20

16. Khunti K, Singh AK , Parek M. Is ethnicity linked to incidence or outcomes of covid-19?BMJ 2020;369:m1548 doi:10.1136/bmj.m1548 (published 20 April 2020).

Conflict of interest : None

Further Reading - Hyperinflammatory shock in children during COVID-19 pandemic. Shelley Riphagen,a Xabier Gomez,a Carmen Gonzalez-Martinez,b Nick Wilkinson,b and Paraskevi Theocharisb Lancet. 2020 23-29 May; 395(10237): 1607–1608. doi: 10.1016/S0140-6736(20)31094-1