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Review

Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation

Trisha Radia [a], Nia Williams [a], Pankaj Agrawal [a], Katharine Harman [b], Jonathan Weale [c], James Cook [b], Atul Gupta [b,d,*]

[a] Department of Paediatric Medicine, King's College Hospital, London, United Kingdom
[b] Department of Paediatric Respiratory Medicine, King's College Hospital, London, United Kingdom
[c] Department of Anaesthesia, Royal Brompton Hospital, London, United Kingdom
[d] Institute for Women's and Children's Health, King's College London, London, United Kingdom

Educational aims

The reader will be able to:

- Develop an understanding of the clinical presentation of patients with MIS-C
- Understand that severity of illness and acuity is high in patients presenting with MIS-C

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ABSTRACT

Multisystem Inflammatory Syndrome in Children (MIS-C) is a new phenomenon reported worldwide with temporal association with Covid-19. The objective of this paper is to evaluate reported cases in children and adolescents. From 1726 papers, 35 documented papers related to MIS-C cases identified 783 individual cases of MIS-C between March-June 2020; with 55% being male ($n = 435$) and a median age of 8.6 years (IQR, 7–10 years; range 3 months–20 years). Patients with MIS-C were noted to have a high frequency of gastrointestinal symptoms (71%) including abdominal pain (34%) and diarrhea (27%). Cough and respiratory distress were reported in 4.5% and 9.6% cases respectively. Blood parameters showed neutrophilia in 345/418 (83%) of cases and a high CRP in 587/626 (94%). 362/619 (59%) cases were SARS-CoV-2 infection positive (serology or PCR) however only 41% demonstrated pulmonary changes on chest imaging. Severity of illness was high with 68% cases requiring intensive care admission; 63% requiring inotropic support; 244/783 (28%) cases needing some form of respiratory support (138 mechanically ventilated), and 31 required extra-corporeal membrane oxygenation. Treatment strategies included intravenous immunoglobulin (63%) and intravenous steroids (44%). 29 cases received Infliximab, 47 received IL1 (interleukin) receptor antagonist, and 47 received IL6-receptor antagonist. 12/783 (1.5%) children died. In summary, a higher incidence of gastrointestinal symptoms were noted in MIS-C. In contrast to acute Covid-19 infection in children, MIS-C appears to be a condition of higher severity with 68% of cases having required critical care support.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread rapidly through human populations, presenting across a continuum of severity from asymptomatic carriage to multi-organ failure and death [1]. In comparison to adults, acute coronavirus disease (COVID-19) appears mild in children, comprising approximately 1% of admissions to hospital [2,3]. However, severe acute disease has been described, and is frequently associated with co-morbidities [4].

During early May reports emerged from the UK of children requiring admission to intensive care units due to an unexplained multisystem inflammatory syndrome with features of Kawasaki

* Corresponding author: Department of Paediatric Respiratory Medicine, King's College Hospital, London, United Kingdom
E-mail address: atul.gupta@kcl.ac.uk (A. Gupta).

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disease and toxic shock syndrome [5]. Similar cases were subsequently reported across Europe and the US, associated temporally and geographically with COVID-19 outbreaks [6–8]. The majority of children affected were RT-PCR negative for SARS-CoV-2 virus, but were antibody positive, indicating past infection. The cause of the clinical syndrome was postulated to be a post-infectious inflammatory response following SARS-CoV-2 infection.

Similar preliminary case definitions pertaining to this novel syndrome have been published in the UK, the US, and by the World Health Organisation (WHO) [9]. The WHO use the term multisystem inflammatory syndrome in children and adolescents temporarily related to covid-19 (MIS-C) to describe the disease; the defining features of which are presented in Box 1.

We present a systematic review of reported cases fulfilling the WHO criteria of MIS-C, with the aim of better characterising the clinical, biochemical, radiological and microbiological features of this novel syndrome.

METHODS

The study protocol was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Search strategy and data sources

A systematic search of the MEDLINE electronic database from December 1st 2019 to 31st May 2020 using the search terms "Covid 19 OR coronavirus OR sars-cov-2 AND children OR adolescents OR neonate OR infant" was performed to identify studies reporting clinical features of children who presented with an inflammatory syndrome related to COVID-19. The reference lists of identified studies were examined to identify further reports of interest. The search was extended from 31st May to 30th June using the search terms "COVID 19 or coronavirus or sars-cov2 AND children OR adolescents OR neonates or infant" to capture a rapid escalation in relevant publications following circulation of the WHO case definition of MIS-C.

Study selection

Three reviewers independently screened titles and abstracts of all citations for eligibility, and retrieved those that met the inclusion criteria. If insufficient information was available in the abstract to decide on eligibility, the whole article was retrieved for review. Discrepancies were resolved by consensus and utilisation of a fourth reviewer when necessary. Manuscripts reporting information on both children and adults were included only if paediatric data could be retrieved. Manuscripts were excluded if the full-text article was not available, original data was not reported (e.g. review articles), or if other coronavirus serotypes were identified as the infective agent.

Data extraction

A structured data extraction form was employed to standardise the identification and retrieval of data from manuscripts. Each manuscript was examined by two reviewers in duplicate. Where manuscripts reported physiological and laboratory results as absolute values, results were compared with internationally recognised normal ranges to determine normality. Where parameters were reported as normal or abnormal, and no values were presented, results were recorded as described.

RESULTS

1726 articles were retrieved from the initial search. A further 40 articles were identified following extension of the search to 30th June. 35 manuscripts were assessed as appropriate for data extraction. Described within the 35 manuscripts were 791 cases fulfilling the criteria of MIS-C. 8 cases were reported in two separate manuscripts, resulting in 783 identified cases.

Demographic details

The median age of CYP identified was 8.6 years (IQR,7–10 years; range, 3 months–20 years). 435/783 (56%) of CYP were male.

Past medical history

Comorbidities were reported in a minority of cases 156/783 (20%) with obesity as the most frequent co-morbidity described 60/783 (7.7%),

Symptoms

Gastrointestinal symptoms were reported in 553/783 (71%) of cases encompassing; abdominal pain in 285/783 (36%), diarrhoea in 214/783 (27%), and vomiting in 196/783 (25%). Rashes of varying description were reported in 330/783 (42%) cases. Respiratory tract symptoms were infrequently described; 35/783 (4.5%) of cases had symptoms of a cough and 32/783 (4%) cases a sore throat (Table 1).

Fever, a key criteria in the definition of MIS-C, was presumed present in all the 783 cases. Although, fever was documented in 779/783 case reports. The remaining 4 cases were described by authors as having met the case definition for MIS-C and describe fever as 'presenting symptom' [10] or 'clinical presentation of fever' [11]. We presumed fever occurred during the course of the illness for these 4 cases.

Physiological parameters and level of care

The majority of cases 531/783 (68%) exhibited severe physiological impairment necessitating admission to an intensive care unit [Table 2].

Cardiovascular dysfunction was the most frequently described physiological abnormality. 212/259 (82%) of cases were tachycardic and 255/420 (61%) were hypotensive. Cardiovascular support (fluid resuscitation and/or ionotropic support) was required in 531/688 (77%) and was the predominant reason for intensive care support.

Respiratory dysfunction was less frequently reported, 75/783 (9.6%). In cases where mechanical ventilation was required, 138/783 (18%), the predominant reason was for cardiovascular support. However, respiratory failure was also documented; 22/783 (3%) required high flow humidified oxygen therapy, 87/783 (11%) required non-invasive ventilation. 31/783 (4%) required extracorporeal membranous oxygenation.

Laboratory and radiological investigations

Varying laboratory and radiological investigations were reported in the included manuscripts. Evidence of current or past SARS-CoV-2 infection (RT-PCR or serology) was documented in 362/619 (58%) of cases.

Inflammatory markers were raised in the majority of cases, with 345/418 (83%) demonstrating a neutrophilia, and 587/626 (94%) a raised C-reactive protein (CRP). 391/783 (50%) of cases had a lymphopenia.

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Table 1
Clinical symptoms in children with MIS-C.

First Author	Country	Total Number (N)	Age in years (range)	Male (N)	Clinical symptoms (N)
Dolinger [6]	USA	1	14	1	Fever, abdominal symptoms
Verdoni [7]	Italy	10	7.5 (2.9–16)	7	Fever (10), diarrhoea (6)
Chiotos [8]	USA	6	7.5 (5–14)	1	Fever (6), diarrhoea (4), vomiting (5), abdominal pain (5)
Belhadjer [12]	France/Switzerland	35	10 (2–16)	18	Fever (35), respiratory distress (1), diarrhoea (28), fatigue (35)
Rauf [13]	India	1	5	1	Fever, diarrhoea, abdominal pain
Licciardi [14]	Italy	2	12, 7	1	Fever (2), diarrhoea (2), abdominal pain (2)
Dallan [15]	Switzerland	3	12, 10, 10	1	Fever (3), cough (2), dyspnoea (2), sore throat (2(, vomiting (2), abdominal pain (2)
Balasubramanian [16]	India	1	8	1	Fever, cough, sore throat
Jones [17]	USA	1	0.5	0	Fever, runny nose
Deza Leon [18]	USA	1	6	0	Fever, sore throat
Riphagan [5]	UK	8	8.9 (4–14)	5	Fever (8), diarrhoea (7), vomiting (4)
Labe [19]	France	1	3	1	Fever, fatigue
Acharrya [20]	India	1	0.3	1	Fever
Rivera-Figueroa [21]	USA	1	5	1	Fever, diarrhoea, abdominal pain
Toubiana [22]	France	21	7.9 (3.7–16.6)	9	Fever (21), cough (9), runny nose (9), diarrhoea (21), vomiting (21), abdominal pain (21)
Whittaker [23]	UK	58	9 (5.7–14)	25	Fever (58), cough (12), sore throat (6), runny nose (12), diarrhoea (30), vomiting (26), abdominal pain (31)
Ramcharan [24]	UK	15	8.8 (6.4–11.2)	11	Fever (15), GI symptoms (13), fatigue (4)
Cheung [25]	USA	17	8 (1.8–16)	8	Fever (17), dyspnoea (7), vomiting (15), abdominal pain (15)
Peres-Toledo [26]	UK	8	9 (7–14)	5	Fever (8), GI symptoms (8)
Blondiaux [27]	France	4	9 (6–12)	1	Fever (4), diarrhoea (2), vomiting (2), abdominal pain (4), fatigue (1)
Riollano-Cruz [28]	USA	15	12 (3–20)	11	Fever (15), cough (3), sore throat (2), dyspnoea (1), diarrhoea (6), vomiting (12), abdominal pain (9), fatigue (1), gI symptoms (13)
Miller [29]	USA	44	7.3 (0.6–20)	20	Fever (44), dyspnoea (11), diarrhoea (18), vomiting (25), abdominal pain (33)
Belot [30]	France	108	8 (5–11)	53	
Schupper [31]	Germany	1	5	1	Fever (1), cough (1), abdominal pain (1)
Pouletty [32]	France	16	10 (4.7–12.5)	8	Fever (16), dyspnoea (2), GI symptoms (13)
Hameed [11]	UK	35	11	27	Fever (33), diarrhoea (11), vomiting (4), abdominal pain (19)
Grimaud [33]	France	20	10 (2.9–15)	10	Fever (20), vomiting (20), abdominal pain (20)
Meredith [34]	UK	1	10	0	Fever (1), diarrhoea (1), abdominal pain (1)
Capone [35]	USA	33	8.6 (5.5–12.6)	20	Fever (33), cough dyspnoea, or sore throat (17), diarrhoea (32), vomiting (32), abdominal pain (32)
Greene [36]	USA	1	11	0	Fever (1), sore throat (1), abdominal pain (1), fatigue (1)
Yozgat [37]	Turkey	1	3	0	Fever (1)
Ng [38]	UK	3	16, 17, 13	2	Fever (3), sore throat (3), dyspnoea (2), diarrhoea (3), vomiting (3), abdominal pain (3)
Kaushik [10]	USA	33	10 (6–13)	20	Fever (31), dyspnoea (11), diarrhoea (16), vomiting (23), abdominal pain (21)
Feldstein [39]	USA	186	8.3 (3.3–12.5)	115	Fever (186), cough, GI symptoms (171)
Dufort [40]	USA	99	(0–20)	53	Fever (99), sore throat (16), dyspnoea (19), runny nose (22), diarrhoea (49), vomiting (57), abdominal pain (69)

Cardiac involvement was evident in the majority of cases where cardiac investigations were performed. 308/454 (68%) had a raised Troponin-T and 378/490 (77%) a raised proBNP [Brain Natriuretic Peptide]. Abnormalities were also detected on the majority of echocardiograms 369/628 (59%) when performed and included coronary aneurysms and pericardial effusions.

Radiographic changes were present in 130/316 (41%) on imaging of the lung parenchyma.

Treatment

A variety of anti-inflammatory treatments were reported with the majority having received intravenous immunoglobulin (IVIG), 493/783 (63%). 347/783 (44%) received intravenous steroids, 29/783 (4%) received Infliximab, 47/783 (6%), received Anakinra and 47/783 (6%) received IL6 inhibitors (Tociluzimab or Siltuximab).

Outcome

12/783 (1.5%) were reported to have died [Table 3]. The cause of death was not stated for most patients: 2 died following a stroke and 7 died despite ECMO treatment although the cause for each is not known.

DISCUSSION

Main findings

This is the first systematic review of cases meeting the diagnostic criteria MIS-C. The data presented show that the syndrome is rare, it predominantly affects children in later childhood, and is frequently associated with gastrointestinal symptoms and severe cardiovascular dysfunction.

Interpretation

Although a causal link between COVID-19 and the syndrome of MIS-C is yet to be confirmed the temporal, geographic and epidemiological features of MIS-C are strongly suggestive. Fortunately, MIS-C appears to be a rare phenomenon. We identified 783 cases in the context of an estimated 15 million cases of SARS-CoV-2 (all ages) reported worldwide.

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Table 2
Clinical, biochemical markers, co-morbidities & outcome in children with MIS-C.

First Author	Total Number (N)	Fever/Tachycardia/ Hypotension F/T/H (N)	High CRP (N)	High Ferritin (N)	High D-dimer (N)	High Trop-T (N)	High pro-BNP (N)	Positive SARS-CoV-2 PCR (N)	Positive COVID-19 Ab (N)	Co-morbidities (N)	Intensive care (N)	Inotropes (N)	Ventilation (MV/NIV/HFNC) (N)	Mortality (N)
Dolinger [6]	1	F (1), T (1), H (1)	1	1	1			1		1	0	0	0	0
Verdoni [7]	10	F (10), H (5)	1	5		5	10	2	8		2	2		0
Chiotos [8]	6	F (6), H (6)	6	6		4	5	3	5	0	6	5	MV 3, NIV 2	1 UK
Belhadjer [12]	35	F (35), H (28)	35		20			31	30	10	35	28	MV 22, NIV 11	0
Rauf [13]	1	F (1), T (1), H (1)	1	1		1	1	0		0	0	1	HFNC	0
Licciardi [14]	2	F (2)	2	2	1	1	1	0		0	0		NIV 1	0
Dallan [15]	3	F (3), T (3), H (3)						1		2	3	1	MV 1, NIV 1	0
Balasubramanian [16]	1	F (1), T (1), H (!)	1	1				1			1		HFNC	0
Jones [17]	1	F (1), T (1)	1					1		0	0			0
Deza Leon [18]	1	F (1), T (1), H (1)	1	1	1	1		1		0	1	1		0
Riphagan [5]	8	F (8), T (8), H (8)	8	8			5	2		6	8	8	MV 4, NIV 2, HF 1	1
Labe [19]	1	F (1)	1					0		0	0			0
Acharrya [20]	1	F (1)	1					1		0	0			0
Rivera-Figueroa [21]	1	F (1), H (1)	1	1		1		1		0	1		HFNC	0
Toubiana [22]	21	F (21), T (16), H (12)	21		19	17	14	8	19		17	14	MV 11	0
Whittaker [23]	58	F (58), H (27)	58	58	53	34	24	15	40	7	25	29	MV 25	1
Ramcharan [24]	15	F (15), H (10)	15	15	15	15	15	2	not done	NR	4	10	MV 4	0
Cheung [25]	17	F (17), H (13)	17	17	17	14	15	8	9	0	NR	10	0	0
Peres-Toledo [26]	8	F (8), H (7)	8	8							6	6		0
Blondiaux [27]	4	F (4),	4			4	4	0			4	3	MV 1	0
Riollano-Cruz [28]	15	F (15), T (12), H (13)	15	15	14	11	15	15	31		14	8	MV 2, NIV 5	1
Miller [29]	44	F (44)						0		16	NR			0
Belot [30]	108	F (108)						0			72	82		1
Schupper [31]	1	F (1)						0	1	0	NR	1		1
Pouletty [32]	16	F (16), T (11), H (11)	16	12/14			16	11		6	7	6	MV 2, NIV 3	0
Hameed [11]	35	F (33), T (21), H (21)	35	35	35	35		0			24	20		1
Grimaud [33]	20	F (20), T (20), H (20)	20			20	20	19	15		20	19	MV 8, NIV 11, HFNC 1	0
Meredith [34]	1	F (1)	1	1	1			0		1	NR			0
Capone [35]	33	F (33), T (16), H (16)	33				33	33		4	26	25	MV 6	0
Greene [36]	1	F (1), H (1)	1		1	1	1	1			1	1		0
Yozgat [37]	1	F (1), T (1), H (1)	1	1	1	1		0		0	0			0
Ng [38]	3	F (3), T (3), H (3)	3			3	3	1		1	3	2	MV 1, HFNC 1	0
Kaushik [10]	33	F (31), H (21)	33	33	33		33	11	27	16	32	17	MV 5, NIV 12	1
Feldstein [39]	186	F (186)	156	100		77/153	94/128	131	58	50	148	90	MV 37, NIV 32	4
Dufort [40]	99	F (99), T (96), H (32)	98/98	86/94		63/89	74/82	64		36	79	61	MV 10, NIV 7, HFNC 16	2

*NR = not reported.
UK = Unknown, N = Number, MV = Mechanical Ventilation, NIV = Non Invasive Ventilation, HFNC = High Flow Nasal Cannula; CRP = C Reactive Protein, Trop T = Troponin T, pro-BNP = B type Natriuretic Peptide.

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Table 3
Summary of all the findings.

	Number of cases (%)
Total no. of cases	783
Median age (interquartile range) years	8.6 years (IQR, 7–10 years; range 3 months-20 years)
Sex (%) male	435 (56%)
Presenting symptoms	
Fever (%)	784 (100%)
Gastro Intestinal symptoms (%)	553 (71%)
SARS CoV2 +ve (%)	362/619 (59%)
COVID-19 Antibody +ve (%)	243
High CRP	587/626 (94%)
High Troponin-T/pro-BNP	Trop-T 308/454 (68%) pro BNP 378/490 (77%)
Cardiac involvement	
Use of inotropes	436/688 (63%)
Abnormal echocardiogram	369/628 (59%)
Treatment given	
IVIG	493/783 (63%)
Intravenous steroids	347/783 (44%)
Other	Infliximab 29/783 (4%) Anakinra 47/783 (6%) Tocilizumab 47/783 (6%)
Intensive care management (%)	531/783 (68%)
Ventilation (MV/NIV/HHFNC*) (%)	Total 244/783 (31%) MV = 138/783 (18%) NIV = 87/783 (11%) HHFNC = 22/783 (3%)
ECMO (%)	31/783 (4%)
Mortality (%)	12/783 (1.5%)

Hypothesised to be a post-infectious inflammatory response following SARS-CoV-2 infection, MIS-C appears to have distinct epidemiological and clinical features when compared to features of acute severe COVID-19 infection in children. Indeed, acute severe COVID-19 infection in children is associated with young age, a history of co-morbidity, respiratory symptoms and respiratory dysfunction [4]. In contrast, the cases of MIS-C presented are older, did not frequently have co-morbidities, and the majority presented with gastrointestinal symptoms and significant cardiovascular dysfunction. These clinical features are similar to those recognised in the largest and most comprehensive MIS-C case series published to date ($n = 99$) [40]. Dufort et al. found that the majority of children diagnosed were aged between 6 and 12 years, 80% reported gastrointestinal symptoms, and 63% had cardiovascular compromise requiring inotropic support. A minority reported a cough (31%) or a co-morbidity (31%).

Despite its rarity MIS-C is of significant concern due to the severity of the illness, with the majority of children requiring intensive care treatment and the death of 12 children. Cardiovascular dysfunction was a striking feature commonly resulting in hypotension and echocardiographic abnormalities.

There is significant overlap of MIS-C and other hyper-inflammatory syndromes in children such as Kawasaki disease, HLH, MAS and toxic shock [40]. Indeed, this overlap may be expected as despite different aetiologies, activation and dysregulation of common inflammatory pathways result in clinical disease. Thus, although multiple non-specific markers of inflammation have been reported in MIS-C none as yet are sensitive or specific for this syndrome. Treatment strategies used in other hyper-inflammatory syndromes have been employed to modulate the dysregulated hyper-inflammation apparent in MIS-C. There is no evidence of efficacy of the immunomodulatory treatment strategies employed thus far although no adverse side effects have been reported. The long-term implications of cardiac involvement in MIS-C are unknown but may be important as in comparable hyper-inflammatory diseases such as Kawasaki disease [41].

Limitations

This study has several limitations. The research occurred over a brief 2 months period shortly after recognition of the syndrome. It is possible that cases may not have been recognised or reported and that acute severe cases of COVID 19 may have been reported as MIS-C. Furthermore, in the cases analysed there was heterogeneity in reporting of symptoms, clinical and laboratory test results making data extraction and analysis challenging. Almost all the articles came from Europe & US, as Asian and African studies in children with MIS-C were not available. We were unable to comment on the role of ethnicity & socioeconomic status as a potential risk factor for disease.

CONCLUSIONS

In this systematic review of cases fulfilling the WHO criteria of MIS-C, we have characterised important clinical, biochemical and radiological features of this novel syndrome. Higher incidence of gastrointestinal symptoms was noted in MIS-C. In contrast to acute Covid-19 infection in children, MIS-C appears to be a condition of higher severity with 68% of cases having required critical care support. Familiarity with the presenting features, and a particular recognition of the severe cardiovascular impact of this disease we hope will be of support to teams caring children affected.

DIRECTIONS FOR FUTURE RESEARCH

- Exploration of biochemical markers with a high specificity and sensitivity to aid early and accurate diagnosis of MIS-C.
- Study of treatment protocols for standardisation in the management of MIS-C.
- Explore the role of ethnicity & socioeconomic status as a potential risk factor for MIS-C.
- Further studies are required to better understand the pathogenesis and to identify possible preventive and therapeutic strategies

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Box 1 Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 [38] Preliminary case definition [a]

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 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).

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.

Conflict of interest

No conflict of interest.

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