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Short Communication

Is it all MIS-C? Unusual findings in a series of nine German patients with multi-system inflammatory syndrome in children after SARS-CoV-2 infection

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ABSTRACT

Objectives: Multi-system inflammatory syndrome in children (MIS-C) is a post-viral inflammatory vasculopathy of children and adolescents following Covid-19 infection. Since the incidence of SARS-CoV-2 infections has been increasing in Germany since October 2020, we observe an increasing number of children presenting with MIS-C.

Design: We present detailed clinical characteristics of a cohort of nine children with MIS-C admitted to a tertiary PICU at the University Hospital of Cologne between March 2020 and February 2021.

Results: The clinical signs and symptoms are largely in line with recent reports. All but one patient had positive SARS-CoV-2 antibodies. Latency from infection to MIS-C was 4–6 weeks. Two children presented with unusual findings: A girl had encephalomyelitis and a boy developed MIS-C side to side with acute leukemia.

Conclusion: MIS-C has been increasing in Germany parallel to SARS-CoV-2 infections. Rarely, unusual findings may be associated with MIS-C.

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Multi-system inflammatory syndrome in children (MIS-C) is a post-viral inflammatory vasculopathy of children and adolescents following coronavirus disease 2019 (COVID-19). Since its first description in May 2020 (Verdoni et al., 2020), specific diagnostic criteria have been issued by the Centers for Disease Control and Prevention (2020) and the World Health Organization (2020). Recently, case series have been reported from the UK (Davies et al., 2020) and Spain (Garcia-Salido et al., 2020), and a systematic review has summarized numerous cases of MIS-C from European, American and Asian countries (Radia et al., 2020). In Germany, the incidence of COVID-19 in Spring 2020 was low, with a peak of 6500 infections on 2 April 2020. Furthermore, the numbers were decreasing rapidly, with <2000 infections on 24 April 2020 (<https://corona.rki.de>). Consequently, patients with MIS-C were rare in Germany during the first wave of the pandemic. However, since then, there has been a marked increase in the number of children hospitalized with COVID-19 [1056 children up to February 2021 (<https://dgpi.de/covid-19-survey-update-2021>)],

and paediatric intensive care units (PICUs) in Germany have been confronted with increasing numbers of children with MIS-C (137 cases up to February 2021) (<https://dgpi.de/pims-survey-07-2020>).

We present detailed clinical characteristics of a cohort of nine children with MIS-C admitted to a single tertiary PICU at the University Hospital of Cologne, Germany between March 2020 and February 2021. Of note, only a single case of MIS-C occurred prior to September 2020. To rule out the possibility that previous patients with MIS-C may have gone unrecognized, PICU admissions from January to September 2020 were assessed retrospectively but no additional patients with MIS-C were identified. This is in line with a recent systematic review (Radia et al., 2020) which included numerous patients from the USA, France and the UK, but only one patient from Germany. Moreover, in a nationwide MIS-C survey in Germany and Austria, only 43 children with MIS-C were reported within the first 23 weeks of 2020, compared with 94 children within the following 11 weeks. Compared with 74 cases from Spain between 1 March and 15 June 2020 and 78 cases from the UK between 1 April and 10 May, the numbers from Germany were considerably lower.

Interestingly, all but one child came from families that had immigrated from Turkey, Syria, Iran, India and Eastern Europe.

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Table 1
Characteristics of children with multi-system inflammatory syndrome.

Hospital admission	Mar 2020	Jan 2021	Nov 2020	Dec 2020	Dec 2020	Sep 2020	Dec 2020	Nov 2020	Feb 2021
Gender	Female	Male	Female	Male	Male	Male	Female	Male	Male
Age (years)	1	14	6	14	15	15	12	16	16
Comorbidities	None	None	None	Obesity	None	Leukaemia	None	SLE	None
Documented SARS-CoV-2 infection	No	Yes	No	Yes	Yes	Yes	No	Yes	No
Latency SARS-CoV-2 infection – onset of symptoms	Unknown	Unknown	4 weeks	6 weeks	6 weeks	6 weeks	Unknown	1 week	5 weeks
SARS-CoV-2 PCR (nasopharyngeal swab)	Negative	Positive	Negative	Negative	Negative	Positive	Negative	Positive	Negative
SARS-CoV-2 spike protein antibody	IgA pos, IgG pos	ND	IgA pos, IgG pos2	IgA pos, IgG pos	IgA pos, IgG pos	IgA pos, IgG pos	IgA pos, IgG pos	IgA pos, IgG pos	IgA pos, IgG pos
Suspected diagnosis on admission	Encephalo-myelitis	Thrombosis	Gastro-enteritis	Gastro-enteritis	Septicaemia	Septicaemia	Gastro-enteritis	Nephrotic syndrome	Fever of unknown origin
Symptoms at hospitalization									
Fever	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gastrointestinal ^a	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes
Fatigue	No	No	Yes	Yes	Yes	No	Yes	No	No
Hypotension	No	No	Yes	Yes	Yes	No	Yes	No	No
Respiratory	No	No	Dyspnoea	No	No	No	No	Dyspnoea	No
Conjunctivitis	No	No	No	Yes	Yes	No	Yes	No	Yes
Rash	No	No	No	Yes	No	No	No	Yes	No
Other	Coma, cardiac arrest	Back pain	No	No	Headache	Sore throat, hip pain	Seizure	Oedema	Scrotal pain
Laboratory and imaging results									
Neutrophil count x1E9/L (admission, max)	24.5 (27.0)	17.3 (17.3)	8.5 (24.3)	16.3 (27.1)	15.8 (18.3)	8.8 (19.5)	16.0 (16.0)	17.5 (21.2)	8.2 (10.8)
Platelet count x1E9/L (admission, min)	254 (42)	184 (142)	150 (73)	236 (95)	134 (111)	59 (3)	210 (210)	297 (160)	210 (210)
CRP mg/L (admission, max)	<0.6 (217)	42 (165)	62 (173)	328 (333)	128 (128)	44 (376)	181 (181)	0.8 (185)	206 (206)
PCT µg/L (admission, max)	0.1 (96)	0.1 (0.2)	2.1 (2.6)	2.3 (2.3)	5.6 (6.9)	5.0 (17.8)	1.8 (1.8)	0.1 (16)	0.5 (0.5)
LDH (U/L) (admission, max)	964 (2714)	226 (317)	300 (449)	311 (311)	254 (263)	830 (4068)	193 (218)	281 (455)	410 (438)
Ferritin µg/L (admission, max)	ND	525 (525)	364 (364)	1281 (1341)	680 (680)	789 (32792)	654 (654)	ND (1014)	ND (110)
D-dimer mg/L (admission, max)	4.30 (4.30)	5.72 (5.72)	4.90 (10.20)	6.23 (6.23)	2.24 (2.24)	6.77 (7.64)	1.22 (2.27)	ND (8.40)	ND (1.72)
Troponin T µg/L (admission, max)	4.400 (10.900)	<0.003 (0.052)	ND (0.025)	0.129 (0.129)	0.095 (0.354)	ND	0.350 (0.410)	ND	ND (0.179)
Echocardiography	Pericardial effusion, FS 35%	Increased coronary flares	Normal	Pericardial effusion, increased coronary flares	Coronary aneurysm, FS 28%	Normal	Pericardial effusion, FS 15%	Pericardial effusion	
Chest X-ray	Pulmonary oedema	ND	ARDS	ARDS	Normal	ARDS	ND	Atelectasis	
CT	ND	Pulmonary embolism	ARDS	ND	ND	ARDS	ND	ARDS	
Drug therapy									
Intravenous immunoglobulin	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Steroids	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Aspirin	No	No	No	Yes	Yes	No	Yes	No	No
Anticoagulation	No	Yes therapeutic	Yes prophylactic	Yes prophylactic	Yes prophylactic	No	Yes prophylactic	Yes prophylactic	Yes prophylactic
Respiratory support									
HFNC	No	No	Yes	Yes	Yes	Yes	No	Yes	No
MV	Yes	No	Yes	No	No	Yes	No	Yes	No
ECMO	No	No	No	No	No	Yes (V-V)	No	No	No
Latency to transfer to PICU	Directly from ER	1 day	5 days	Directly from ER	Directly from ER	7 days	Directly from ER	17 days	No PICU
Infection with non-SARS-CoV-2 pathogen	Yes adenovirus	No	No	No	No	Yes candidaemia, aspergillosis	No	Yes CMV	No
Discharged healthy	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Discharged with sequelae	Yes (minimal conscious state)	No	Yes	No	No	No	No	Yes, fatigue	No
Died	Yes, 4 months after discharge (cause?)	No	Aneurysma left coronary	No	No	Yes aspergillosis	No	No	No

ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computer tomography; ECMO, extracorporeal membrane oxygenation; ER, emergency room; HFNC, high flow nasal cannula; Ig, immunoglobulin; LDH, lactate dehydrogenase; MV, mechanical ventilation; ND, not done; PCR, polymerase chain reaction; PCT, procalcitonin; PICU, paediatric intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; V-V, veno-venous ECMO.

^a Diarrhoea, vomiting, abdominal pain.

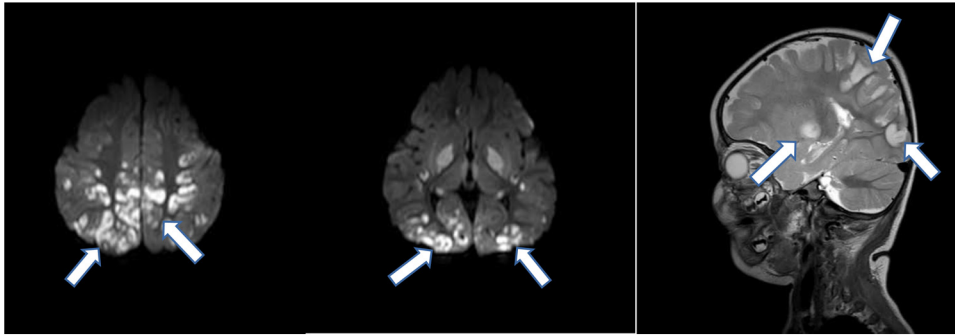


Figure 1. Cranial magnetic resonance imaging scan of Patient #1 diagnosed in March 2020 [diffusion weighted images (DWI) and T2-weighted image]. Arrows indicate multiple patchy lesions in the occipital, parietal and temporal lobes indicating an inflammatory process (lesions appear 'bright' in DWI and T2-weighted images).

Similar findings were reported previously in a small case series of three teenagers with MIS-C (Ng et al., 2020). Furthermore, a recent study from Norway demonstrated higher risk for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in immigrants, presumably caused by social disparity (Indseth et al., 2021).

Clinical signs and symptoms as well as laboratory findings for the patients in our case series are largely in line with recent reports (Table 1). All but one child had positive SARS-CoV-2 IgA and IgG antibodies, and three children had positive polymerase chain reaction tests. Of note, in our case series, latency between COVID-19 and MIS-C was 4–6 weeks in most patients. All patients had persistent high fever and signs of hyperinflammation, with markedly elevated levels of C-reactive protein and ferritin but less pronounced levels of procalcitonin. Gastrointestinal symptoms were common and were the cause of hospital admission in three patients. Additionally, cardiac involvement was observed frequently, indicated by increased levels of troponin T and abnormal echocardiographic findings, such as pericardial effusion, impaired fractional shortening or coronary anomalies.

Two children presented with unusual findings. A girl aged 11 months was admitted after cardiac arrest at home. She had no evidence of any previous illness except for self-limited diarrhoea a few days ago. A magnetic resonance imaging (MRI) scan of her brain showed distinct signs of encephalomyelitis (Figure 1), but cerebrospinal fluid analysis was unremarkable and failed to identify a pathogen. She was discharged in a minimal conscious state and passed away a few months later. Apart from the unusual pattern of her brain MRI scan, she had frequent episodes of generalized flush that were unresponsive to any medication but were self-limiting after 10–30 min. Neurological symptoms in MIS-C are wide-ranging (Lin et al., 2021) but mainly non-specific, such as headache and fatigue. Severe neurological complications such as coma, encephalopathy, ataxia and peripheral neuropathy were described in individual cases, but we did not find any reports highlighting MRI abnormalities comparable with our case. Although the majority of neurological symptoms in children were reported to improve, data on long-term neurodevelopment are elusive. Our case probably indicates that MIS-C may be associated with critical neurological sequelae in a small number of cases.

The second case was a 15-year-old boy who developed severe MIS-C while receiving chemotherapy for newly diagnosed acute myeloid leukaemia. Intriguingly, leukaemia was diagnosed only a few weeks after oligosymptomatic SARS-CoV-2 infection. After 2 days of induction chemotherapy with cytarabine, he developed sudden dyspnoea and was admitted to the PICU where he was treated with broad-spectrum antibiotics for suspected

septicaemia. No pathogen was identified but his respiratory function deteriorated, and he required mechanical ventilation for acute respiratory distress syndrome (ARDS). Following a steroid pulse, he was successfully weaned off mechanical ventilation after 3 days, but his pulmonary function deteriorated again after a few days of chemotherapy. This time he progressed rapidly to severe ARDS with haemorrhagic alveolitis. He was mechanically ventilated and started on rescue extracorporeal membrane oxygenation therapy for 25 days, and he continued on mechanical ventilation after tracheostomy. Although his respiratory function improved, he developed both cerebral and pulmonary aspergillosis treated with neurosurgery and a triple antifungal medication. Despite these efforts, he passed away after 2 months of intensive care treatment. While there is currently no evidence that infection with SARS-CoV-2 could trigger leukaemic malignancies, the observation that only short cytotoxic treatment was followed by severe MIS-C-associated organ failure is intriguing. Clinically, it appeared that MIS-C was triggered by chemotherapy, raising the question of whether the cytotoxic dose may need to be reconsidered carefully in patients with recent COVID-19.

Ethical approval

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Conflict of interests

None declared.

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