Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Cardiovascular magnetic resonance imaging in children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 and heart dysfunction

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To the Editor,

The coronavirus disease 2019 (COVID-19) appears to affect proportionally fewer children than adults and with a less severe clinical presentation. However, during the COVID-19 pandemic, a new childhood disorder has emerged worldwide characterized by fever, elevated inflammatory markers, and organ dysfunction [1,2]. A case definition was published in April 2020 by The Royal College of Paediatrics and Child Health in the United Kingdom, and was named "pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)", or PIMS-TS. World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (CDC) have subsequently also published their own case definitions.

We describe the recent experience with five patients affected by this condition from April 28 to May 11, 2020. All were previously healthy children, with a median age of 7 years old, [interquartile range (IQR), 5-12 years]. They presented at admission with fever, tachycardia and hypotension. The median white cell count was 9100 cells/mm3 (IQR: 7700-9660) and the median lymphocytes count was 1700 cells/mm3 (IQR: 610-1760). Other ancillary tests revealed elevated cardiac biomarkers [median troponin T was 66.6 ng/l (IQR: 3.2-75.2) and NT-proBNP of 14,407 pg/ml (IQR: 3988–16,150)], and markedly increased inflammatory biomarkers like C-reactive protein and procalcitonin [10.2 mg/dl (IQR: 9.4-26.9) and 10.5 ng/ml (IQR: 3.4-14.8), respectively]. The median ferritin was 421 μg/l (IQR: 369-639) and the median interleukin 6 was 63.5 pg/ml (IQR: 27.2-216.2). The echocardiography revealed mild to moderate heart dysfunction in all of the patients (Table 1). All of them had a positive serology against SARS-CoV-2 (Ig anti receptor-binding domain) and met criteria for PIMS-TS according to UK, WHO and CDC definitions.

They received IGIV, and in three cases steroids were added because of persistent fever 48 hours after IVIG administration. They were discharged home with total recovery of the heart function.

The exact mechanisms of how SARS-CoV-2 causes this transient myocardial dysfunction in children with PIMS-TS are not well understood. During the last decade, cardiovascular magnetic resonance imaging (CMRI) has become the diagnostic tool of choice for patients with evidence for acute nonischemic myocardial injury, including myocarditis. The largest pediatric study assessing the role of CMRI in myocarditis included 143 children and young adults up to 21 years old. CMRI abnormalities were identified most commonly with late gadolinium enhancement. Based on CMRI features 117 children (82%) were interpreted as positive for myocarditis, 18 as negative (13%) and equivocal in 7 (5%) [3].

CMRI allows for targeting several features of myocardial injury: inflammatory hyperemia and edema, necrosis/scar, contractile dysfunction and pericardial effusion. CMRI is also a predictor of

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Table 1
Demographic, clinical characteristics, ancillary tests, treatmenta and outcomes of children with PIMS-TS and heart dysfunction

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics and epidemiology					
Age (years)	6	9	5	7	12
Sex	Male	Male	Female	Female	Male
Ethnicity	Sub-Saharan African	Arabic	Hispanic	Caucasian	Caucasian
Medical history	Healthy	Psoriasis	Healthy	Healthy	Tonsillectomy
Family cluster of SARS-CoV-2 infection	No	Yes	Yes	Yes	Yes
Signs and symptoms at admission					
Temperature (°C)	40.3	38.5	40.2	39.3	40.7
Days of fever before admission (>38°C)	5	7	5	6	5
Rash	Yes	Yes	Yes	No	Yes
Distribution of the rash	Thorax, arms and legs	Hands and feet	Palms, thorax and legs		Palms
Conjunctivitis	Yes	Yes	Yes	Yes	No
Lymphadenitis	No	No	No	No	No
Lips	Normal	Cracked lips	Normal	Normal	Normal
Tongue	Normal	Normal	Normal	Normal	Normal
Abdominal pain	Yes	Yes	Yes	Yes	Yes
Diarrhea	No	Yes	Yes	Yes	Yes
Cough	No	No	No	No	Yes
Oxygen saturation (%)	87	97	95	98	95
Heart rate (bpm)	125	182	130	116	112
Blood pressure (mmHg)	86/44	75/42	88/46	90/50	87/38
Image and heart evaluation					
Chest X-rays	Mild left pulmonary infiltrate	Normal	Normal	Normal	Normal
Echocardiography (at admission	• Mild systolic disfunction (LVEF 52%) • Diastolic dysfunction • Normal coronary arteries: LCA 2,4mm (z score -1.6) and RCA 2,3mm (z score -1).	• Moderate systolic disfunction (LVEF 40%) • Diastolic dysfunction • Normal coronary arteries: LCA 2,8mm (z score 0), LAD 2,8mm (z score: +1.5) and RCA 2.5mm (z score 0).	• Moderate systolic disfunction (LVEF:40%) • Diastolic dysfunction • Severe mitral regurgitation and moderate tricuspid regurgitation • Normal coronary arteries: LCA 2,9mm (z score +1.4), LAD 2,2mm (z score +1), RCA 2,7mm (z score +1.5).	• Moderate systolic disfunction (LVEF: 40%) • Normal coronary arteries: LCA 2.7mm (z score +0.2) and RCA 2.5mm (z score +0.4).	• Mild systolic disfunction (LVEF 50%) • Normal coronary arteries: LCA: 3,8mm (z score +0.6), RCA: 3,4mm (z score +0.5).
Electrocardiogram	• Normal	• Repolarization abnormalities	• Normal	• Repolarization abnormalities	• Normal
Treatment	Dopamine Norepinephrine Ceftriaxone IVIG (2 gr/kg) Steroids (2 mg/kg) Hydroxychloroquine Azithromycin	Dopamine Cefotaxime IVIG (2 gr/kg)	Ceftriaxone Clindamycin IVIG (2gr/kg)	Ceftriaxone IVIG (2gr/kg) Steroids (2 mg/kg)	Norepinephrine Amoxicillin-clavulanate IVIG (2gr/kg) Steroids (2 mg/kg)
PICU admission	Yes	Yes	Yes	No	Yes
Respiratory support/ oxygen therapy	BiPAP	Nasal cannula	Nasal cannula		Nasal cannula
Outcome					
Echocardiography	Complete resolution of abnormalities on day 7 of admission. LVEF 70%. Normal coronary arteries.	Complete resolution of abnormalities on day 5 of admission. LVEF 55%. Normal coronary arteries.	Evaluation on day 6 of admission. Mild tricuspid regurgitation. Resolution of mitral regurgitation. LVEF 60%. Normal coronary arteries	Complete resolution of abnormalities on day 5 of admission. LVEF 70%. Normal coronary arteries	Complete resolution of abnormalities on day 8 of admission. LVEF 70%. Normal coronary arteries
Cardiovascular Magnetic Resonance	LVEF 60% (EDV 76 ml/m2)	LVEF 65% (EDV 78 ml/m2) RVEF 69% (EDV 83 ml/m2)	LVEF 57% (EDV 70 ml/m2)	LVEF 66% (EDV 64 ml/m2)	LVEF 66% (EDV 64 ml/m2)

(*continued on next page*)

Table 1 (*continued*)

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
	RVEF 57% (EDV 84 ml/m2) No myocardial edema or enhancement abnormalities	No myocardial edema or enhancement abnormalities	RVEF 57% (EDV 73 ml/m2). Mild trycuspid regurgitation. No myocardial edema or enhancement abnormalities	RVEF 67% (EDV 63 ml/m2) No myocardial edema or enhancement abnormalities	RVEF 67% (EDV 63 ml/m2) No myocardial edema or enhancement abnormalities

BiPAP, Bilevel Positive Airway Pressure; LAD, Left Anterior Descending; EDV, End-Diastolic Volume; IVIG, Intravenous Immunoglobulin; LCA: Left Coronary Artery; LVEF, Left Ventricular Ejection Fraction; ND, not done; PICU, Pediatric Intensive Care Unit;; RCA: Right Coronary Artery; RVEF: Right Ventricular Ejection Fraction.
Z-score for coronary artery diameters was assessed according to: Dallaire F, Dahdah N. New equations and a critical appraisal of coronary artery Z scores in healthy children. J Am Soc Echocardiogr. 2011 Jan; 24:60-74. https://doi.org/10.1016/j.echo.2010.10.004.

functional and clinical recovery. In summary, on the basis of available research, CMRI allows for a robust assessment of the extent of injury and dysfunction in clinically acute scenarios of myocardial injury [4]. However, the diagnostic value of echocardiography for myocardial injury is limited by the fact that many patients with less severe disease have a normal echocardiogram and the highly variable echocardiographic findings lack specificity.

A cardiovascular magnetic resonance imaging (CMRI) was performed after discharge [median day after admission: +16, (9-17)]. The protocol performed included steady-state free precession cine 2D sequences (short axis, 4, 3 and 2 Chamber views); study of edema (Inversion Recovery sequence in short axis), hyperemia and capillary leak (early gadolinium enhancement) and myocyte necrosis and fibrosis (late gadolinium enhancement). Both ventricles had normal function and no edema or abnormalities in early and late gadolinium enhancement were observed in any cases.

CMRI did not show any myocardial damage in this series. CMRI is considered a highly sensitive technique to evaluate myocardial injury. Although the number of patients in this series was small, heart dysfunction did not seem secondary to myocardial viral injury in these children. An alternative hypothesis is that the exaggerated inflammatory response observed in these children with PIMS-TS could be the cause of the heart dysfunction [5]. The rapid recovery of the heart function after immunomodulatory treatment and the absence of myocardial abnormalities in CMRI support this hypothesis. Studies to further elucidate the cause of myocardial dysfunction in children with multisystem inflammatory syndrome related to COVID-19 are warranted.

Author contributions

LP, DB, AL, DC and BT had full access to all of the data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. ALL authors contributed equally in writing the paper and approved the final manuscript as submitted.

Transparency declaration

Potential conflicts of interest

No conflicts of interest.

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