The decrease of Kawasaki syndrome during the second COVID-19 wave: a potential, unexpected effect of social distancing

Sirs,

The Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS CoV-2 infection (PIMS-TS) currently represents the main complication of COVID-19 in children. PIMS-TS, characterised by an immune-mediated pathogenesis, leads to a cytokine storm resulting in a hyperinflammatory state and a multiorgan failure. These patients may present rapid progressive shock, heart failure, coronary ectasia and arrhythmia, urgently requiring intensive care support (1).

In the early stages of its appearance at the end of March 2020, PIMS-TS has been associated with Kawasaki syndrome (KS). However, several features suggest that PIMS-TS represents a distinct clinical entity: the remarkable frequency in African and Caribbean ethnic groups, the higher median age of onset, the presence of abdominal symptoms. Cardiac involvement has also peculiar characteristics since it is more often associated with myocardial damage and ventricular dysfunction rather than coronary abnormalities (Table I) (1).

Table I. Comparing and contrasting features of PIMS-TS and KS.

	PIMS-TS	KS
Age	Infants to teen	<5 years old
Ethnic group	Hispanic and Afro Caribbean	Asian
Conjunctival infection, mucositis, rash, swollen and/or erythematous hands and feet, cervical lymphadenopathy	Typical clinical signs	Typical clinical signs
Gastrointestinal and neurological symptoms	More prominent	Less frequent
Main cardiac signs	Myocardial dysfunction and arrhythmias in older children, coronary artery ectasia/aneurisms in young children	Coronary artery ectasia/aneurisms, rarely myocardial dysfunction (<10% of KS)
Platelet count at onset	Normal or low	High
Lymphocyte count	Low, generally <10% of WBC count	Normal
CRP value	Remarkably high	Moderately high

PIMS-TS: Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS CoV-2 infection, KS: Kawasaki syndrome, WBC: white blood cells count, CRP:C-reactive protein.

During the first pandemic wave, Tuscany reported the fifth highest number of Italian COVID-19 cases in Italy, even if this prevalence was lower if compared to other high-prevalence regions in the North of Italy. Since the COVID-19 pandemic in Italy, the Paediatric Tuscany Network worked out the COVASAKI survey to report the incidence of Paediatric multisystem inflammatory syndrome temporally associated with SARS CoV-2 infection (PIMS-TS) and compare its characteristics with Kawasaki syndrome (KS) (1). During the first six-month period (February-July 2020), no PIMS-TS cases were observed while the KS incidence in Tuscany was identical to what was reported in the previous 5 years and in the corresponding months of the last 5 years (2).

However, since September 2020, the Tuscan situation has deeply changed with a significant increase of SARS CoV-2 positive cases, currently standing 225,000 (3).

As expected, this epidemiological shift has evidenced its effect also on COVASAKI survey.

In the six-month period between November 2020 and April 2021, 14 PIMS-TS children were admitted to 5 Paediatric Units (incidence 2.3/month), 10 boys and 4 girls with a mean age of 9.6 years (interquartile range [IQR] 8.8–12) (Supplementary Table S1). Eleven out 14 patients required intensive care unit admission: 10 needed amines and 3 underwent mechanical ventilation. Echocardiography revealed a reduced left ventricular ejection fraction in 8/14. A diffuse coronary artery ectasia was found in 1. All children completely recovered with a timely immunomodulatory treatment with intravenous immunoglobulins, steroids and, in case of severe cardiac involvement, anakinra. Nasopharyngeal swabs and serological test for SARS CoV-2 resulted positive in 5/13 and 14/14 respectively.

The PIMS-TS incidence rate, adjusted for the 5,170 children hospitalised, resulted 0.27% and represented the 13.9 % of paediatric COVID 19-related hospital admissions in Tuscany.

Conversely, the number of observed KS significantly reduced comparing to the first six months of COVASAKI survey: 3 cases, 0.5 incidence/month *versus* 11 cases, 1.8 incidence/month ($p<0.03$, RR 0.27, 95% CI 0.0–0.92).

Comparing the 2.7 incidence/month of the 165 diagnosed KS from 1 January 2015 to 31 January 2020, a statistically significant difference has been detected ($p<0.0005$, RR 0.24, 95% CI 0.07– 0.59). The same result has been found limiting the analysis to the 92 children with KS diagnosed during the same corresponding 6 months of the last 5 years: 3.0 *versus* 0.7 incidence/month ($p<0.0002$, RR 0.21, 95% CI 0.06–0.53).

Our results seem in accordance with the hypothesis of an infectious trigger in KS pathogenesis (4). Indeed, the stay-home imposed by pandemic and the extensive adoption of barrier protection devices have concomitantly reduced the incidence of respiratory infections among general and paediatric population. At this regard, the massive drop in the number of influenza virus infections during the winter months results emblematic (5). Influenza data reported to the World Health Organisation's FluNet platform from three Southern Hemisphere countries showed a very low influenza activity during June-August 2020, the typical Southern Hemisphere influenza season months. Moreover, 98% decrease in influenza activity, measured by percentage of submitted specimens testing positive, was reported in the United States (6).

Considering the paediatric population, Kuitunen *et al*. observed that, during the nationwide lockdown in Finland, the influenza season was shorter and the weekly rate of new cases among children decreased faster compared with the previous 4 influenza seasons. A similar decrease was also seen in Respiratory Syncytial Virus cases (7).

In this perspective, the observed decrease of KS cases could go hand in hand in hand with the significant reduction in the spread of airborne viral infections. From this point of view, it could be hypothesised that, in contrast to what had been previously reported in the early stages of its outbreak, the SARS CoV-2 pandemic could lead to a reduction rather than a substantial increase in the number of KS cases. Although indirectly, the behavioural measures adopted to contain the contagion or maybe further mechanisms not yet identified might be the reason.

M.V. Mastrolia[1], *MD*
R. Agostiniani[2], *MD*
C. Azzari[3], *MD*
R. Bernardini[4], *MD*
U. Bottone[5], *MD*
G.B. Calabri[6], *MD*
F. Civitelli[7], *MD*
R. Consolini[8], *MD*
R. Danieli[9], *MD*
R. Di Silvio[10], *MD*
S. Falorni[11], *MD*
L. Gagliardi[12], *MD*
S. Grosso[13], *MD*
G. Indolfi[14], *MD*
M. L'Erario[15], *MD*
M. Martini[16], *MD*
G. Memmini[17], *MD*
D. Peroni [18], *MD*
M. Pezzati[1], *MD*
G. Suriano[20], *MD*
L. Tafi[21], *MD*
S. Trapani[22], *MD*
A. Vaccaro[23], *MD*
P.L. Vasarri[24], *MD*
G. Simonini[25], *MD*
on behalf of the Paediatric Tuscany Network.

[1]*Rheumatology Unit, Meyer Children's University Hospital, Florence;*
[2]*Paediatric Unit, San Jacopo Hospital, Pistoia;*
[3]*Paediatric Immunology Unit, Department of Health Sciences, Meyer Children's University Hospital, Florence;*
[4]*Paediatric Unit, San Giuseppe Hospital, Empoli;*
[5]*Division of Neonatology and Paediatrics, Lotti Hospital, Pontedera, AUSL Toscana Nord Ovest, Pisa;*
[6]*Cardiologic Unit, Meyer Children's University Hospital, Florence;*
[7]*Division of Neonatology and Paediatrics, Montepulciano Hospital, AUSL Sud Est Toscana, Siena;*
[8]*Section of Clinical and Laboratory Immunology, Department of Clinical and Experimental Medicine, University of Pisa;*
[9]*Division of Neonatology and Paediatrics, Spedali Riuniti di Livorno, AUSL Toscana Nord Ovest, Pisa;*
[10]*Paediatric Unit, Mugello Hospital, Borgo San Lorenzo, Florence;*
[11]*Paediatric Unit, Misericordia Hospital, Grosseto;*
[12]*Division of Neonatology and Paediatrics, Ospedale Versilia Hospital, Viareggio, AUSL Toscana Nord Ovest, Pisa;*
[13]*Clinical Paediatrics, Department of Molecular Medicine and Development, University of Siena;*
[14]*Paediatric Unit, Meyer Children's University Hospital, NEUROFARBA Department, University of Florence;*
[15]*Paediatric Intensive Care Unit, Meyer Children's University Hospital, Florence;*
[16]*Paediatric Unit, San Donato Hospital, Arezzo;*
[17]*Division of Neonatology and Paediatrics, Apuane Hospital, Massa Carrara, AUSL Toscana Nord Ovest, Pisa;*
[18]*Department of Clinical and Experimental Medicine, Section of Paediatrics, University of Pisa;*
[19]*Paediatric Unit, Santa Maria Annunziata Hospital, Bagno a Ripoli, Firenze;*
[20]*Division of Neonatology and Pediatrics, Cecina Hospital, Cecina, AUSL Toscana Nord Ovest, Pisa;*
[21]*Paediatric and Neonatal Unit, Valdarno Hospital, Montevarchi, Arezzo;*
[22]*Pediatric Unit, Meyer Children's University Hospital, Department of Health Sciences, University of Florence, Firenze;*
[23]*Division of Neonatology and Pediatrics, San Luca Hospital, Lucca, AUSL Toscana Nord Ovest, Pisa;*
[24]*Paediatric and Neonatologic Unit, Santo Stefano Hospital, Prato;*
[25]*Rheumatology Unit, Meyer Children's University Hospital, Florence; NEUROFARBA Department, University of Florence, Italy.*

Please address correspondence to:
Maria Vincenza Mastrolia,
Reumatologia,
Azienda Ospedaliero-Universitaria Meyer,
Viale Gaetano Pieraccini 24,
50139 Firenze, Italy.
E-mail: maria.mastrolia@unifi.it

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