Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2

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Abstract

Objectives To know the clinical presentation and outcome of children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) at a pediatric tertiary care center in Chennai.

Methods Clinical and biochemical parameters of 65 children with PIMS-TS treated between July and October 2020 were studied. All children had their COVID RT-PCR and IgG COVID antibodies tests done.

Results Mean age of the study group was 5.65 ± 3.68 y. Fever with red eyes, rash, vomiting, abdominal pain, and shock were common presenting features. Sixty percent of the study group had Kawasaki/incomplete Kawasaki features. Sixty-seven percent of the study group had coronary dilatation, 41% presented with shock, and 25% had left ventricular dysfunction. Coronary aneurysms were documented in 58% of the study group (z score more than 2.5). Respiratory presentation with pneumonia was seen in 10%. Four children presented with acute abdomen. Acute kidney injury, acute liver failure, hemolysis, pancytopenia, macrophage activation syndrome, encephalopathy, and multiorgan dysfunction syndrome (MODS) were other features. Forty-three percent required noninvasive oxygen support and 15.4% required mechanical ventilation. Intravenous immunoglobulin (73.8%) and methylprednisolone (49.8%) were used for therapy. Mortality in the study was 6%, which was due to MODS.

Conclusions Acute febrile illness with mucocutaneous and gastrointestinal manifestations should have PIMS-TS as a possible differential diagnosis and needs evaluation with inflammatory markers and SARS-CoV-2 antibodies.

Keywords PIMS-TS · Kawasaki syndrome · Macrophage activation syndrome · COVID-19 · MIS-C

Introduction

Since the pandemic of coronavirus disease 2019 (COVID-19), many countries around the world have reported their data but data from India have been limited. Initial reports suggested that children were spared from severe disease [1]. However, currently there are increasing reports of pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS) also called the multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 and the multisystem inflammatory syndrome in children (MIS-C) [2, 3]. PIMS-TS is a spectrum of disease with phenotypes including Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome [4, 5]. The authors describe their experience of treating children with PIMS-TS from a pediatric tertiary care center in South India.

Material and Methods

This was a descriptive study undertaken at the pediatric tertiary care center at Chennai and all children with PIMS-TS admitted to the hospital between July and October 2020 were included. Their medical and laboratory data were analyzed and the symptomatology and outcome were reported. The criteria for diagnosis was based on Royal College of
Of the 65 children, 27 (41.5%) presented with shock at the present in 86% (56/65). Coronary aneurysm. SARS-CoV-2 IgG antibodies were COVID infection or presence of antibody, but had features 4 wk. Two children had no history of contact or previous of them were COVID-19 RT-PCR–positive in the previous of contact with individuals with COVID-19 infection and 2 these children were obese. Nine (6%) children had history between 5 and 12 y. Male to female ratio was 1.5:1. None of (29/65) were between 1 and 5 y, and 49.23% (32/65) were of 5 y, of which, 6.1% (4/65) were less than 12 mo, 44.6% (28/65) were between 1 and 5 y, and 49.23% (32/65) were between 5 and 12 y. Male to female ratio was 1.5:1. None of these children were obese. Nine (6%) children had history of contact with individuals with COVID-19 infection and 2 of them were COVID-19 RT-PCR–positive in the previous 4 wk. Two children had no history of contact or previous COVID infection or presence of antibody, but had features of coronary aneurysm. SARS-CoV-2 IgG antibodies were present in 86% (56/65).

The median duration of illness was 5 d (range 2–14 d). Of the 65 children, 27 (41.5%) presented with shock at the emergency room and 17 (26%) were hypotensive at admission to PICU. Thirty-three children required PICU care. Inotrope support was needed in 25/65 (38.5%) children. Twelve children required one inotrope, 9 required two inotropes, 3 children required three inotropes, and 1 child required four inotropes. Clinical features are summarized in Table 1. Differential diagnosis considered at admission included acute febrile illness, dengue, scrub typhus fever, and fever with thrombocytopenia, bronchopneumonia, and acute abdomen. Highest temperature recorded was 108 °F with a mean of 102.58 ± 1.72 °F. Respiratory involvement was in the form of breathlessness, pleural effusion 12% (8/65), consolidation in 9% (6/65), and ARDS in 1 child. Nearly half of the children [54% (38/65)] required respiratory support. Twenty-three needed non-rebreathing mask oxygen, 3 required high-flow humidified nasal cannula oxygen (HHFNC), 2 required BIPAP, and 10 required mechanical ventilation.

Of the 65 children, 35 had received either antibiotics or antiemetics or analgesics/antipyretics before presenting to the authors’ institute. Clinical presentation was predominantly acute febrile illness with mucocutaneous and gastrointestinal manifestations as shown in Table 1. Mucocutaneous features included skin rash, edema, conjunctival congestion, cracked lips, red lips, red tongue, and peeling of skin. Gastrointestinal manifestations included, nausea, vomiting, diarrhea, and pain in abdomen. Cardiac involvement included coronary artery abnormalities (68%, 44/65), tachycardia (60%, 39/65), shock (42%, 27/65), hypotension (26%, 17/65), and left ventricular dysfunction (25%, 16/65). Coronary artery abnormalities seen were nontapering coronaries, echogenic coronaries, coronary dilatation, and coronary aneurysm with a z score > 2.5. Coronary abnormalities were seen in 44 children. Eight had dilatation (z score 2–2.5), 34 had small aneurysm (z score 2.5–5), 1 had medium aneurysm (z score 5–10), and 1 had echogenic and tram tracking of coronaries. Figure 1 shows dilated coronaries in short

**Table 1 Clinical presentation (n = 65)**

| Presentation                | n (%) | Presentation            | n (%) |
|-----------------------------|-------|-------------------------|-------|
| Fever at admission          | 63 (96.9) | Nausea                  | 15 (23.08) |
| Vomiting                    | 47 (72.3) | Myalgia                 | 14 (21.54) |
| Conjunctivitis              | 45 (69.23) | Headache                | 8 (12.5) |
| Edema                       | 36 (55.38) | Sore throat              | 6 (9.28) |
| Rash                        | 35 (53.85) | Skin peeling            | 6 (9.23) |
| Diarrhea                    | 29 (44.62) | Bleeds                  | 3 (4.52) |
| Shortness of breath         | 21 (32.3) | Chest pain              | 2 (3.13) |
| Abdominal pain              | 29 (49.62) | Seizures                | 2 (3) |
| Red lips                    | 20 (30.7) |                         |       |
| Altered sensorium           | 19 (29.23) |                         |       |
| Reduced urine output        | 18 (27.69) |                         |       |
| Red tongue                  | 15 (29.23) |                         |       |
axis view. With respect to 43 children with coronary dilatation and aneurysm, factors like age, gender, clinical features, shock, AKI, MODS, HLH, and left ventricular dysfunction did not reveal significant difference in those without coronary dilatation. However, the group with coronary dilatation had significantly higher NLR ratio ($p = 0.014$).

Other ECHO findings included pericardial effusion (49.2%), mitral regurgitation (17/65), aortic regurgitation (2/65), and tricuspid regurgitation (3/65). One child had supraventricular tachycardia. Neurological features included encephalopathy in 6% (4/65), seizures in 3% (2/65), and stroke in 1 child. One child had refractory hypertension for weeks following diagnosis and is on antihypertensives. Acute abdomen (surgical presentation) was seen in 4 children. Three of them were operated and were later diagnosed as PIMS-TS. Associated comorbid conditions included febrile seizures (3/65), children known to have reactive airway disease (3/65), and acute lymphoblastic leukemia (2/65). Hematological abnormalities included anemia (78%, 51/65), neutrophilic leucocytosis (70.7%, 46/65), lymphopenia (72.3%, 47/65), high neutrophil lymphocyte ratio more than 3 (55%, 33/65), thrombocytopenia (55%, 33/65), thrombocytopenia (31.25%, 20/65), pancytopenia (29%, 19/65), and hemophagocytosis (6%, 4/65). Renal involvement with elevated urea was reported in 37% (24/65) of children. Renal complications (pRIFLE) included risk in 4 children, injury in 5, and failure in 3. Hepatic involvement included elevated SGOT (49%, 32/65), elevated SGPT (32%, 21/65), and hyperbilirubinemia (17%, 11/65), ascites in 15% (10/65), and acute liver cell failure in 7.7% (5/65). Other laboratory abnormalities included hyponatremia (84.62%, 55/65) and hypoalbuminemia (40%, 26/65). Thirty-eight children had LDH levels measured and all of them had elevated LDH and 81.6% (31/38) had anemia with elevated LDH levels.

Coinfections noted were dengue, scrub typhus, and typhoid in 1 child each, which were excluded from the study group. Overall, the clinical phenotypes were as follows: Kawasaki phenotype [51/65, (78.4%)], toxic shock syndrome phenotype [27/65, (41%)], and HLH phenotype [6/65, (9.23%)]. Nine children (13.8%) had no specific phenotype. Multigener failure was seen in 7 (10.7%) children. The laboratory findings are summarized in Table 2. Management of children with coronary dilatation was by 2 g/kg of intravenous immunoglobulin (IVIG) and aspirin with or without steroids. Children with LV dysfunction and those refractory to IVIG were on pulse methylprednisolone. Presence of myocardial dysfunction or hemodynamic compromise in the form of shock were considered as upfront indications to start on methylprednisolone along with IVIG. Therapy included IVIG and methylprednisolone in 36 children, IVIG alone in 12 children, methyl prednisolone alone in 6, dexamethasone in 3 children, tocilizumab in 4 children, and aspirin in 48 children. Overall mortality was 6% (4/65); among those who died, all 4 received IVIG and methyl prednisolone, and 1 received tocilizumab in addition. All the 4 children who died had shock, multigener dysfunction (MODS), encephalopathy, and macrophage activation syndrome (MAS). Three had Kawasaki-like features and 3 had acute kidney injury (AKI). High NLR ratio, AKI, MODS, shock, and HLH were identified to be associated with mortality with a $p$ value of 0.00002, 0.008, 0.0001, 0.013, and 0.0008, respectively (Table 3).

**Discussion**

PIMS-TS is a rare pediatric condition characterized by hyperinflammation and multigener dysfunction frequently following an infectious trigger by SARS-CoV-2. PIMS-TS was initially reported by pediatricians in UK. Subsequently, the US center for disease control and the WHO published the criteria and named it as multisystem inflammatory syndrome in children (MIS-C) and RCPCH defined it as PIMS-TS [2, 3]. This condition is typically seen 2–4 wk after an acute COVID-19 infection. However, in the present cohort, only 9 children reported history of COVID-19 infection or contact with COVID infection in the recent past. The median age group was similar to other published reports [5, 8, 9] and as described in other reports, a male preponderance was found in this study as well [10]. Data from the present study add to the evidence that a large proportion of children with PIMS-TS present with gastrointestinal manifestations [8, 11–15], thus highlighting that PIMS-TS should be considered in children presenting with fever and GI symptoms. Mucocutaneous features like red eye and rashes is another common presentation similar to the studies elsewhere [16, 17]. Median duration of illness was 5 d and
pain presenting as a surgical emergency has been previously reported in children with PIMS-TS [22, 23]. Similar to this, 3 of the children in the present study were also operated for appendicitis and later diagnosed as PIMS-TS. Clinical features of PIMS-TS often overlap with the clinical presentation of other infectious diseases, especially scrub typhus fever and dengue. Hence, it is imperative to consider and exclude other causes of acute febrile illness in children in tropical countries. Presence of lymphopenia, high neutrophil-to-lymphocyte ratio, raised ESR, hyponatremia, hypoalbuminemia along with either previous history of COVID-19 or contact with COVID-19 or a positive IgG antibody status would help clinicians differentiate PIMS-TS.

The limitation of this study is that COVID RT-PCR-positive children were treated in COVID-exclusive facility and could not be included. Overlap of Kawasaki disease in Kawasaki phenotype of MIS-C is possible. Likewise, being a tertiary care referral hospital, children with severe complications may have been received and mild cases of PIMS-TS could have been missed or not referred to. Being a new disease there is an urgent need for further research and long-term follow-up of these children. Future research

### Table 2: Laboratory parameters in PIMS-TS (n = 65)

| Parameter                  | Range (mean ± SD)               |
|----------------------------|---------------------------------|
| Total count (cells/cumm)   | 3200–42,000 (12,386 ± 6594.7)   |
| Hemoglobin (g/dL)          | 5–16 (9.92 ± 1.8)               |
| Ferritin (ng/mL)           | Initial 32–10,379 (965 ± 1567)  |
|                            | Highest 90–11,600 (1237 ± 2752) |
| Triglycerides (mg/dL)      | 44–509 (64.86 ± 70)             |
| Prothrombin time (second)  | 10.5–34.6 (16.42 ± 5.2)         |
| INR                         | 0.75–2.33 (1.244 ± 0.378)       |
| Sodium (mEq/L)             | 118–142 (131.2 ± 4.3)           |
| Potassium (mEq/L)          | 2.8–6.1 (4.40 ± 0.67)           |
| Urea (mg/dL)               | Initial 8–145 (32.92 ± 29.45)   |
|                            | Highest 8–210 (49 ± 49.5)       |
| Creatinine (mg/dL)         | Initial 0.2–2.6 (0.52 ± 0.37)   |
|                            | Highest 0.3–4.8 (0.695 ± 0.77)  |
| ESR (mm/h)                 | Initial 3–140 (61 ± 32.6)       |
|                            | Highest 12–171 (87 ± 33.3)      |
| CRP (mg/dL)                | Initial 2–307 (43.23 ± 65.23)   |
|                            | Highest 2–307 (64.86 ± 70)      |
| Platelet (lakhs/cumm)      | Initial 1.35–7.8 (2.2 ± 1.96)   |
|                            | Highest 3.4–14.53 (3.77 ± 2.95) |
|                            | Lowest 0.06–7.69 (1.77 ± 1.57)  |
| NLR 0.7–100 (6.17 ± 12.36) |                                  |
| SGOT (IU)                  | Initial 15–309 (62.8 ± 56.08)   |
|                            | Highest 15–755 (81.54 ± 121)    |
| SGPT (IU)                  | Initial 8–220 (49 ± 41.9)       |
|                            | Highest 9–521 (60.8 ± 85.65)    |
| Procalcitonin              | (N-0–0.5 ng/mL) 0.1–382 (29.5 ± 61.9) |
| Interleukin 6              | (N-0.1–7 pg/mL) 0.01–12.10 (177.64 ± 258.4) |
| Lymphocyte count (cells/cumm) | 0–11,970 (2646 ± 2080) |

### Table 3: Comparison between survivors and nonsurvivors

| AKI | MODS | Coagulopathy | MAS/HFH | KD | AKI | NLR (mean) |
|-----|------|--------------|---------|----|-----|-----------|
| N=61| N=4  | p value      |         |    |     |           |
| 23  | 4    | 0.013        |         |    |     |           |
| 3   | 4    | 0.001        |         |    |     |           |
| 8   | 3    | 0.059        |         |    |     |           |
| 3   | 3    | 0.000        |         |    |     |           |
| 48  | 3    | 0.862        |         |    |     |           |
| 2   | 3    | 0.000        |         |    |     |           |
| 30.1| 4.5  | 0.000        |         |    |     |           |

*AKI: Acute kidney injury; KD: Kawasaki disease; MAS: Macrophage activation syndrome; MODS: Multiorgan dysfunction*
should focus on identifying the variables that can prognosti-
cate which pediatric COVID-19 patients will develop MIS-C and which, if any, markers correlate with systemic outcomes.

Conclusions

Acute febrile illness with mucocutaneous and gastroin-
testinal manifestations should have evaluation with lab-
oratory markers, ECHO, and SARS-CoV-2 antibodies. PIMS-TS spectrum in children includes acute febrile illness with Kawasaki-like features with or without shock, and acute abdomen. Myocardial dysfunction, shock, leucopenia, thrombocytopenia, high neutrophil-to-lymphocyte ratio, hyponatraemia, and hypoalbuminemia are frequently encountered in KD phenotype PIMS-TS. Macrophage activation syndrome, encephalopathy, stroke, acute abdomen, hemolysis, and thrombotic microangiopathy are less common presentations of PIMS-TS in children. Therapy includes intravenous immunoglobulin, methylprednisolone, and immunomodulatory agents like tocilizumab. Outcome is good if recognized early and treated appropriately. High NLR ratio, AKI, MODS, shock, and HLH were identified to be associated with mortality with a p value of 0.000, 0.008, 0.0001, 0.013, 0.0008, respectively.

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Authors’ Contributions ES, PV were involved in concept development, data collection, analysis, and write up. PV, GK, GSV were involved in data collection, analysis, write up and review of literature. RSSJ was involved in concept development, analysis and review of literature. PV will act as the guarantor for this paper.

Declarations

Ethical Approval The study was approved by the Institutional Ethics Committee, Madras Medical College, Chennai.

Conflict of Interest None.

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