Review and future directions for PIMS-TS (MIS-C)

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PAEDIATRIC MULTISYSTEM INFLAMMATORY SYNDROME TEMPORALLY ASSOCIATED WITH COVID-19

Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS), also known as multisystem inflammatory syndrome in children (MIS-C), is a novel hyperinflammatory condition that shares features with Kawasaki disease (KD) and toxic shock syndrome (TSS).1–3 The median age of children with PIMS-TS is approximately 8 years with male sex, obesity and black or Asian ethnicity associated with an increased risk.1,2 Children with PIMS-TS typically have a history of SARS-CoV-2 infection in the weeks preceding presentation.1–2 The clinical phenotype varies and includes fever, gastrointestinal symptoms, cardiac manifestations, conjunctivitis, polymorphous rashes and respiratory failure.1–3 Figure 1 and table 1 report the diagnostic criteria for PIMS-TS and the common features seen in children with the disease. Children with PIMS-TS often resemble children with KD/TSS. Many appear very unwell and require admission to the paediatric intensive care unit.1,2 Initial investigations universally demonstrate evidence of hyperinflammation with C reactive protein levels typically greater than 100 mg/L as well as an elevated erythrocyte sedimentation rate, hypotension, hypertriglyceridaemia, and elevated D-dimer and serum ferritin.1–3 Lymphopenia is common as are abnormal cardiac biomarkers such as elevated brain natriuretic peptide (BNP) and troponin.1–3

The principles of management of PIMS-TS include immunomodulation (typically with intravenous immunoglobulins and steroids), supportive care, management of cardiac complications and thromboprophylaxis.1–4 The longer term outcomes from PIMS-TS are unknown. Initial reports suggest that while most measures of cardiac function normalise within 6 months, approximately half of children have ongoing fatigue and poor exercise tolerance.1 Very few children with COVID-19 infection develop PIMS-TS suggesting that PIMS-TS occurs by a combination of a genetic predisposition and an aberrant immune response to an infective trigger and prolonged endothelial inflammation.

Genetic predisposition

It is known that siblings of children with KD are at a significantly greater risk of KD than the wider population with several genes linked to an increased susceptibility to KD (ITPKC, CASP3, CD40 and ORAI1).6 Whole-exome sequencing of a small number of children with PIMS-TS has indicated that some children have an underlying genetic predisposition towards a proinflammatory immune response to infection. These include mutations in the intracellular signalling proteins DOCK8, X-linked inhibitors of apoptosis as well as cytochrome b-245 subunits.7 The exact mechanisms by which these mutations confer an increased risk to PIMS-TS remain unclear.7,8

Infective trigger

Ongoing viral replication, whether in the nasopharynx, gut or elsewhere, has been suggested to be involved in PIMS-TS pathogenesis.9 Between 15% and 30% of children with PIMS-TS test positive for SARS-CoV-2 on nasopharyngeal (NP) PCR testing.10 On an immunological level, however, a positive NP swab does not indicate that the SARS-CoV-2 virus is replicating in the airway epithelium as fragmented viral RNA may be amplified by PCR. Increasingly, evidence points away from PIMS-TS representing chronic SARS-CoV-2 infection.

The more plausible mechanism is that in susceptible individuals, a SARS-CoV-2 superantigen binds to T cells in a non-specific manner causing excessive T cell activation and the inappropriate release of proinflammatory cytokines. Superantigens can bind to beta chain variable (βV) of T cells in a non-specific manner, leading to T cell activation and an inappropriate release of proinflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin (IL)-6 and interferon gamma. In silico analysis has identified a motif near the cleavage site on spike protein of SARS-CoV-2 between its S1 and S2 subunits as the most likely superantigenic T cell receptor (TCR) binding site, sharing structural similarity with the staphylococcal enterotoxin B superantigen.10 Next-generation sequencing of the TCRs of PIMS-TS cases has identified enrichment of TRBV gene segments, and in particular TRBV11-2 gene enrichment has been associated with increased severity.

Conjunctivitis (53%)

Gastrointestinal signs and symptoms
• Abdominal pain (52%)
• Vomiting (50%)
• Diarrhoea (48%)

Cardiac signs and complications
• Tachycardia (57%)
• Hypotension (40%)
• Reduced left ventricular ejection fraction (34%)
• Coronary artery aneurysms (13%)

Laboratory abnormalities
• CRP > 100
• Raised Ferritin
• Lymphopenia
• Thrombocytopenia
• Neutropenia
• Raised Troponin, BNP and D-Dimer

Other signs and symptoms
• Fever (98%)
• Rash (56%)
• Cough (24%)

Figure 1 Clinical features of PIMS-TS. CRP, C reactive protein; PIMS-TS, paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Brain natriuretic peptide (BNP), C-reactive protein (CRP)

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of patients with PIMS-TS. In comparison, adults with severe COVID-19 have also been shown to have an expansion of TRBV genes. The CDR3 gene, which encodes for the CDR3 loop of the TCR, plays the most important role in determining specificity of TCRs. Its diversity is maintained in PIMS-TS cases, further supporting a response to superantigen-driving inflammation, as this indicates that T cells are not being activated following a peptide-major histocompatibility complex (MHC) interacting with a TCR in a conventional antigen-specific manner. This TRBV11-2 gene expansion has been linked with human leukocyte antigen (HLA) class I allele expansion, these being HLA-A02, B35 and C04.10 To date, the majority of PIMS-TS cases have been reported in Europe and the USA, with cases also reported in South America, South Asia and the Middle East. Interestingly, very few cases have been reported in the Far East, despite the high incidence of KD in this area.11 This may be due to a number of factors, including lower rates of COVID-19 in this area, reduced reporting of PIMS-TS or genetic differences in the populations. One hypothesis for this distribution is that a mutation of the SARS-CoV-2 spike protein (D839Y/N/E), found predominantly in Europe, results in greater superantigenic stimulation of T cells.12

Aberrant immune response
Several studies have investigated the immune phenotype of children with PIMS-TS using multiomics. Detailed analyses of the cytokine profile have demonstrated similarities between PIMS-TS and KD such as the release of the proinflammatory cytokine IL-6, cytokines involved with natural killer (NK) and T cell recruitment (CXCL10, CCL19, CCL10, CD26), and the downregulation of TWEAK, a cytokine that helps to regulate the cytotoxic Th1-type immune response and angiogenesis.13 14 There are, however, notable differences between PIMS-TS and KD including lower levels of IL-17A, a cytokine that links T cell activation and neutrophil migration, in children with PIMS-TS compared with KD.13 Children with PIMS-TS also demonstrate a different cytokine profile to children with acute COVID-19 infection with higher levels of IL-17A, IL-6 and CD40 in those with

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**Figure 2** Immune mechanisms of PIMS-TS. IFNγ, interferon gamma; IL, interleukin; PIMS-TS, paediatric multisystem inflammatory syndrome temporally associated with COVID-19, tumour necrosis factor (TNF), granulocyte macrophage colony stimulating factor (GM-CSF).

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**Table 1** Diagnostic criteria for PIMS-TS
Child must meet at least one criteria from each row.

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Inflammation</td>
<td>Fever, inflammation (neutrophilia, elevated CRP and lymphopaenia)</td>
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<tr>
<td>Single or multiorgan failure</td>
<td>Shock, cardiac, respiratory, renal, gastrointestinal disorder</td>
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<tr>
<td>Exclude other causes</td>
<td>Bacterial sepsis, staphylococcal or streptococcal shock syndrome, infective myocarditis/endocarditis</td>
</tr>
<tr>
<td>Evidence of SARS-CoV-2 infection</td>
<td>Polymerase chain reaction (PCR) testing may be positive or negative</td>
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CRP, C reactive protein; PIMS-TS, paediatric multisystem inflammatory syndrome temporally associated with COVID-19.
PIMS-TS. Flow cytometry has demonstrated a reduction in total T cell counts and reduced cytotoxic T cells in children with PIMS-TS when compared with healthy controls and children with acute COVID-19 infection. Single-cell RNA sequencing has shown that NK and cytotoxic T cells show increased expression of cytotoxic molecules (perforin, granzyme A and granzyme H) that are capable of increasing tissue damage and promoting ongoing inflammation.

Endothelial inflammation

Postmortem studies of KD cases have found neutrophil infiltration of the tunica media, the smooth muscle lining of arterial vessels, with associated necrotising arteritis. Similarly, endothelial injury with cell necrosis and death is typical in PIMS-TS. The mechanism by which this occurs is complicated and poorly understood. Initial evidence suggests that the cytokine storm described above results in injury to the endothelial and upregulation of damage-associated molecular patterns including the production of endothelial-specific alarmins (S100A12). These components of the innate immune system act as a chemotactic agent recruiting neutrophils, monocytes and lymphocytes with prolonged inflammation and subsequent necrosis and have roles in other paediatric autoimmune diseases. Children with PIMS-TS produce autoantibodies to targets within the endothelium of blood vessels (endoglin, P2R×4, EC1E1 and MMP14), and the gastrointestinal tract (MUC15, TSPAN13 and SH3BPI). Whether autoantibodies are the primary drivers of inflammation in PIMS-TS or arise secondary to tissue damage remains to be established.

Summary

Although still a relatively novel condition, the clinical course of PIMS-TS has been well documented, and the initial research into the immune mechanisms underlying the disease has been encouraging, with several aspects of innate and adaptive immunity of interest identified. Figure 2 shows a summary of the possible mechanisms. Identification of genetic factors associated with PIMS-TS will require a concerted, large-scale profiling of the genomes of PIMS-TS cases from different countries. That infection with SARS-CoV-2 provides a trigger for an inappropriate release of inflammatory cytokines, with T cell involvement driving systemic inflammation, with a superantigen possibly the cause of this appears plausible. The role of autoantibodies in this inflammation needs further investigation. Better characterisation of the cellular mechanisms leading to the observed acute cardiac dysfunction may uncover new therapeutic targets. The long-term implications of the condition are still being established, and to this end all data on the clinical and immunological profiles of these children after discharge are of value. Future research on these and other areas will hopefully provide us with a clear hypothesis as to the pathogenesis of the disease, and ideally will lead to improved clinical diagnosis and management of the condition.

REFERENCES