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

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Paediatric Multisystem Inflammatory Syndrome temporally associated with Covid-19 (PIMS-TS)

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's Disease (KD) and Toxic Shock Syndrome (TSS) (1–3). The median age of children with PIMS-TS is approximately eight 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 prior 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 (CRP) levels typically greater than 100mg/l as well as an elevated erythrocyte sedimentation rate, hyponatraemia, hypertriglyceridemia and elevated D-dimer and serum ferritin (1-3). Lymphopenia is common as are abnormal cardiac biomarkers such as elevated 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 (3,4). The longer term outcomes from PIMS-TS are unknown. Initial reports suggest that whilst most measures of cardiac function normalise within six months approximately half of children have ongoing fatigue and poor exercise tolerance (5). 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 pro-inflammatory 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 confers an increased risk to PIMS-TS remains 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 (10). Between 15% and 30% of children with PIMS-TS test positive for SARS-CoV-2 on nasopharyngeal PCR testing (1,9). 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 TNF-alpha, 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 TCR binding site, sharing structural similarity with the staphylococcal enterotoxin B (SEB) superantigen (9). Next generation sequencing of the T cell receptors (TCR) of PIMS-TS cases has identified enrichment of TRBV gene segments, and in particular TRBV11-2 gene enrichment has been associated with increased severity of PIMS-TS patients. In comparison adults with severe COVID-19 disease have also been shown to have an expansion of TRBV genes. The CDR3 gene, which encodes for the CDR3 loop of the T cell receptor, plays the most important role in determining specificity of T cell receptors. 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-MHC complex interacting with a T cell receptor in a conventional antigen specific manner. This TRBV11-2 gene expansion has been linked with HLA class I allele expansion, these being HLA-A02, B35, and C04 (9). To date the majority of PIMS-TS cases have been reported in Europe and the United States, 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 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 multi-omics. Detailed analyses of the cytokine profile has demonstrated similarities between PIMS-TS and KD such as the release of the pro-inflammatory cytokine IL-6, cytokines involved with Natural Killer and T-Cell recruitment (CXCL-10, CCL19, CXCL10, CCL21) 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 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 (13). Single cell RNA sequencing has shown that NK and Cytotoxic T Cells show increased expression of cytotoxic molecules (perforin, granzyme A and granzyme B) that are capable of increasing tissue damage and promoting ongoing inflammation (15).

Endothelial Inflammation

Post mortem studies of Kawasaki disease cases have found neutrophil infiltration of the tunica media, the smooth muscle lining of arterial vessels, with associated necrotizing arteritis (16). Similarly endothelial injury with cell necrosis and death is typical in PIMS-TS (10,12). 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 (DAMPs) including the production of endothelial specific Alarmins (S100A12) (13,15). These components of the innate immune system act as chemotactic agents recruiting neutrophils, monocytes and lymphocytes with prolonged inflammation and subsequent necrosis and have roles in other paediatric autoimmune diseases (17). Children with PIMS-TS produce autoantibodies to targets within the endothelium of blood vessels (endoglin, P2RX4, ECE1, and MMP14), and the gastrointestinal tract (MUC15, TSPAN13, and SH3BP1) (13,14). 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 have been encouraging, with several aspects of innate and adaptive immunity of interest identified. Figure 2 show 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 characterization 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.

Table 1: Diagnostic criteria for PIMS-TS

CHILD MUST MEET AT LEAST ONE CRITERIA FROM EACH ROW.

INFLAMMATION	Fever, Inflammation (neutrophilia, elevated CRP and lymphopaenia)
SINGLE OR MULTI-ORGAN FAILURE	Shock, cardiac, respiratory, renal, gastrointestinal disorder
EXCLUDE OTHER CAUSES	Bacterial sepsis, staphylococcal or streptococcal shock syndrome, infective myocarditis/endocarditis.
EVIDENCE OF SARS-COV-2 INFECTION	PCT testing may be positive or negative

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