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Paediatric Inflammatory Multisystem Syndrome associated with Covid-19 infection (PIMS-TS): Guidance for Oral Healthcare practitioners

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ABSTRACT

Paediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) has been reported globally since the outbreak of the coronavirus disease. The syndrome shares similarities with Kawasaki disease (KD). The manifestation of oral changes in both PIMS-TS and KD warrants that the oral health practitioner has an awareness of these conditions to facilitate timely management.

Introduction

The outbreak of the coronavirus disease 2019 (Covid-19) was an unprecedented global public health disaster which led to significant morbidity and mortality worldwide. Elderly patients infected with SARS-CoV-2 have been reported to be at higher risk of complications and death[1] than children who have contracted the severe acute respiratory syndrome. In rare cases, children – even with mild or asymptomatic Covid-19 infection – have developed severe disease, including Multisystem Inflammatory Syndrome in Children associated with Coronavirus Disease 2019 (MIS-C), also known as Covid-19 associated Paediatric Multisystem Inflammatory Syndrome or Paediatric Inflammatory Multisystem Syndrome temporally associated to SARS-CoV-2 infection (PMIS-TS).These disease presentations share similarities with Kawasaki Disease (KD).[2,3,4]

MIS-C emerged towards the end of 2020 as a serious paediatric manifestation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has now been described globally.[5] Affected children may require extensive care by a multidisciplinary team of experts in paediatric critical care, rheumatology and infectious disease practitioners.

The aim of this review is to describe the clinical manifestations of KD and MIS-C in the paediatric population and to create awareness among oral healthcare practitioners of the oral manifestations these children might present with.

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Kawasaki disease

Kawasaki disease (KD) was first described by Tomisaku Kawasaki in Japan. KD is a rare, acute, febrile and usually self-limiting vasculitis of medium-calibre vessels affecting predominantly healthy children under the age of five years.[6] Males are affected slightly more than females with a ratio of 1.5:1.[7] Though reported globally, the highest relative risk is in Asian children, especially of Japanese ancestry.[8]

The aetiology of KD remains unknown, although it is probably multifactorial. The frequent association of KD with an infectious pathogen has led to the hypothesis that it is an atypical response of the immune system to one or more unidentified pathogens in genetically predisposed individuals.[9,10]

KD, also referred to as mucocutaneous lymph node syndrome, classically presents with fever, mucocutaneous changes and cardiac involvement. The vasculitis which is characteristic of KD demonstrates a predilection for coronary arteries with coronary artery aneurysms being its main complication.[8] In developed countries it is the principal cause of acquired heart disease in children, accounting for 50% of cases in individuals of <2 years of age and 80% in those <5 years of age.[11]

There is no diagnostic test for KD given its multifactorial aetiopathologies; hence, its diagnosis relies entirely on clinical features and laboratory findings indicative of inflammation and positive echocardiography. It can thus be challenging to diagnose considering the wide spectrum of clinical presentations that overlap with many common paediatric febrile illnesses. Principal clinical findings and the descriptions thereof have shaped diagnostic criteria for KD.[12]

Diagnostic criteria include: fever, conjunctivitis (bilateral, bulbar, conjunctival injection without exudate), cervical lymphadenopathy (usually unilateral), rash (maculopapular, diffuse erythema or erythema multiforme), changes to lips and oral mucosa (red cracked lips, "strawberry" tongue or diffuse erythema of the oropharynx) and changes to the extremities (erythema and oedema of palms and soles in acute phase and periungual desquamation in subacute

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phase). A fever of five or more days along with any four or five of the other diagnostic criteria is required for a diagnosis of KD. However, KD may be diagnosed with fewer than four of these criteria if coronary artery abnormalities are detected. Should erythema and oedema of the hands and feet be present as one of four or more of the principle features, then KD may be diagnosed even if there is only a four-day history of fever. A thorough history of the clinical presentation is essential to the diagnosis since principle features may have been present, but could have resolved by the time a clinical examination is performed. The non-specificity of principal clinical findings warrants the consideration of other viral infections that may include rubeola, adenovirus, respiratory syncytial virus, coronavirus and influenza.[13-16]

Intravenous immunoglobulin therapy together with acetylsalicylic acid (ASA) forms the backbone of primary treatment. These drugs aim to reduce inflammation and arterial damage and to prevent thrombosis in patients with coronary artery abnormalities. Primary adjunctive therapy is advocated for patients at high risk for the development of coronary artery aneurysms.[12]

Due to the fact that PIMS-TS may present with features of classic or incomplete (atypical) KD, with or without cardiac involvement, the Royal College of Paediatrics and Child Health (RCPCH), the CDC and World Health Organization provide case definitions of this syndrome in children.

Children with PIMS-TS, according to the RCPCH case definition, may present with persistent fever, inflammation and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional clinical features. These additional clinical features include abdominal pain, confusion, conjunctivitis, cough, diarrhoea, headache, lymphadenopathy, mucous membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hands and feet, syncope and vomiting.

Although the clinical presentation of PIMS-TS patients shares similarities with KD, there are several differences. Patients with PIMS-TS, by definition, lack microbial confirmation of a staphylococcal or streptococcal infection. Compared to classical KD, patients with PIMS-TS more often present with prominent gastrointestinal and neurologic symptoms, and the incidence of cardiac involvement is higher in PIMS-TS patients. More than 50% of children with PIMS-TS develop some sort of cardiac involvement, defined by elevation of cardiac biomarkers, systolic or diastolic myocardial dysfunction or even cardiac shock.

The median age range of patients with PIMS-TS is between 2 and 16 years of age compared to that of classic KD in which most patients present younger than 5 years old.[18] Unlike KD which affects predominantly healthy children, a third of patients diagnosed with PIMS-TS have been reported to have asthma and obesity as comorbidities.[18]

Some studies have reported on the oral manifestations associated with PIMS-TS. Lips and mucosal changes were detected in 87%, 53%, 50% and 29% of the reported cases in France, US, Italy and UK respectively.[19-22] Oral mucosal changes can present as cheilitis, dryness, fissuring, peeling, vertical cracking and bleeding of the lips and glossitis (otherwise described as “strawberry tongue”) with prominent fungiform papillae, or diffuse erythema of the oral and pharyngeal mucosa with no focal lesions, ulcerations or exudates.[12] Patients with PIMS-TS may also demonstrate sore throat and lip swelling which rarely are evident in KD.[23] It is worth noting that oral changes are the only symptoms to be recognised with equal frequency in both typical KD and KD with atypical features.[24] In most instances, these oral manifestations in KD patients are self-limiting and require only supportive management; healing takes place without sequelae.

PIMS-TS might characterise a post-infectious inflammatory syndrome, which may be antibody or immune-complex mediated. If it is antibody mediated, it may explain why some children become severely ill while others are asymptomatic.[25] Children diagnosed with PIMS-TS have been reported to present with a cytokine storm different from acute Covid-19 infection and other hyperinflammatory conditions.[26] PIMS-TS patients who present with systemic/cardiac shock generally show laboratory abnormalities that are significantly more abnormal compared to KD shock. Patients with PIMS-TS who go on to develop shock have elevated C-reactive protein and ferritin levels. Other laboratory features of note are lymphopaenia, thrombocytopenia and low albumin levels. The platelet counts normalise after the acute phase is over. The most significant clinical feature in PIMS-TS is myocardial involvement causing significant myocardial dysfunction with laboratory markers of raised Troponin and Brain Naturetic Peptide (BNP).

Although different treatment guidelines for PIMS-TS are followed in different settings, most treatment protocols will use immunomodulatory treatment. The most commonly used medication includes the administration of intravenous immunoglobulin (IVIG and methylprednisolone). In patients who are refractory to IVIG, additional treatment may include the use of recombinant IL-1 receptor antagonist.

CONCLUSION

Following the guidance provided by the RCPCH, CDC and WHO, it is important for clinicians to note the presentation of paediatric multisystem inflammatory syndrome temporally associated with Covid-19 with clinical manifestations of fever, evidence of inflammation and evidence of single or multisystem organ injury.

The different presentation of PIMS-TS to classic KD warrants an understanding of the pathophysiology of this emerging phenomenon to ensure prompt and aggressive management. The complex nature of this disease warrants multidisciplinary collaboration, inclusive of oral healthcare practitioners, given that oral findings can be seen in this subset of patients.

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