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Guest Editorial

KAWASAKI DISEASE

Kawasaki disease (KD) is the most common cause of acquired heart disease in children in developed countries.[1] It is now being increasingly recognized even from developing countries like India and China.[2] KD is a medium vessel vasculitis predominantly affecting young children. If left untreated, it leads to development of coronary artery abnormalities (CAAs) in 15–25% of patients.[3] The exact etiology has remained a mystery even after 53 years from the time it was first described by Dr Tomisaku Kawasaki in 1967.[4]

KD has been reported across the world with highest incidence being in Japan ≈320/100,000 children under 5 years of age.[5] In Western countries, the incidence of KD varies between 9–25/100,000 children of <5 years.[5,6] While the incidence rates of KD continue to increase in Japan, Korea and Taiwan, the rates seem to have plateaued in the United States and European countries.[7] KD is more common in preschool children, but it is increasingly being reported in infants, older children, adolescents and adults.[8]

The pathogenesis of KD remains an enigma. It is believed to be due to aberrant immune response to one or more antigens in genetically predisposed individuals. There has been significant progress in our understanding of the genetic basis of KD. This is based on the results of linkage studies, genome-wide association studies and miRNA-based studies. A systematic review identified 16 gene polymorphisms (*ITPKC, PD1, ACE, SMAD3, HLA-E, MPO, CASP3, BLK, IL6, IL1A, FGβ, FCGR2A, CD40, CCL17, LTA* and *TNF* gene), which were associated with KD. Further, 10 gene polymorphisms (*ITPKC, IL10, BTNL2, GRIN3A, HLA-E, FGβ, FCGR2A, CASP3, FGF23,* and *TGFBR2*) have been associated with CAAs in KD.[9] Recently, *ORAI1* gene was also found to have significant association with KD.[10]

In recent years, researchers have tried to identify a triggering agent, if any, that can initiate the cytokine cascade of KD. Nagata et al. speculated that a heat shock protein (HSP60) produced by several gram +ve cocci, and even by some gram -ve bacilli, may be involved in the process. These heat shock proteins may act as superantigens and induce secretion of proinflammatory cytokines by mononuclear cells.[11]

The etiopathogenesis of KD has also been linked to tropospheric wind patterns over Japan and the United States. It was proposed that winds blowing from northeastern China may be carrying a putative fungal toxin that may trigger KD. The typical seasonal distribution of KD is considered to be associated with this pattern of wind.[12] A recent study in mouse model suggests that IL-ß may also have a significant role in pathophysiology of KD.[13]

Diagnosis of KD depends on clinical features, with no single clinical feature being considered as pathognomonic. Classic KD is defined as presence of fever duration ≥5 days with ≥4 of the 5 principal clinical features.[1]

It can be a difficult task to come to a diagnosis of KD when the typical clinical features are not present. So, need of the hour is to validate biomarkers to confirm the diagnosis. Unfortunately, the clinical utility of these biomarkers is still limited. At present, none of the biomarkers studied can be considered useful for confirmation of a clinical diagnosis of KD.[7]

Some patients with KD can present with shock due to severe myocarditis.[14] This is a newly recognized entity and has been given the name of Kawasaki disease shock syndrome (KDSS). Children with KDSS tend to be older and are more likely to develop CAAs and often require additional therapy in form of corticosteroids.[15] Occasionally, a patient of KD may also develop macrophage activation syndrome (MAS). The persistence of high spiking fever with thrombocytopenia, falling erythrocyte sedimentation rate, hyperferritinemia, hypertriglyceridemia and hypofibrinogenemia should raise the possibility of MAS in KD.[16]

The importance of KD has become more relevant in context of ongoing COVID-19 pandemic where a 'KD-like illness' has been recognized following COVID-19 infection. However, this new syndrome has some distinctive features. It has later age of onset as compared to KD. There is frequent and more severe myocarditis and involvement of gastrointestinal tract is also more common. It often presents as a cytokine storm with multisystem involvement. It is associated with high levels of C-reactive protein, serum ferritin and pro-inflammatory cytokines (e.g: IL-1, TNFα and IL-6).[17,18]

Serial 2D echocardiography is the imaging modality of choice for assessment of coronary arteries in a suspected case of KD. It is a useful technique that can be repeated as often as required. However, 2D echocardiography is not without limitations. It is difficult to visualize left circumflex artery and the distal segments of coronary arteries by 2D echocardiography. Sensitivity and specificity of echocardiography for identifying thrombi in coronary artery remains unclear. In addition, it is difficult to visualize coronary arteries in older children because of thick chest walls and a poor acoustic window. These limitations can be overcome with use of advanced imaging techniques such as dual-source computed tomographic coronary angiography (DSCT) or cardiac magnetic resonance imaging.[1] DSCT provides precise delineation of coronary arteries and is the preferred modality for assessment of thrombo-occlusive lesions.[19]

Intravenous immunoglobulins (IVIg) in a single infusion (2 g/kg) along with aspirin (30–50 mg/kg/day) remains the treatment of choice and can reduce the risk of development of CAAs from 15–25% to 3–5% of all patients with KD.[1] A recent meta-analysis showed no added advantage of higher (>30 mg/kg/day) doses as compared to lower (3 – 5 mg/kg/day) doses of aspirin in terms of prevention of CAAs, rate of reduction of IVIg resistance, fever duration, and adverse events.[20] Aspirin may, therefore, be given at lower doses even in acute stage of KD.

Approximately 10–15% of KD patients have IVIg resistance (as defined by persisting fever after 36 hours of completion of IVIg infusion). These patients were found to have an increased risk for development of CAAs.[1] Several risk scoring systems (e.g: Kobayashi, Egami, Sano) have been developed to identify children at risk of developing IVIg resistance.[21–23] Most of these scoring systems have been tried on Japanese children and have not been found to be useful in other populations.[24] Various treatment modalities have been suggested for treatment of IVIg-resistant KD. These include second dose of IVIg, corticosteroids, TNF-α blockers, and cyclosporine A. Corticosteroids (mainly, intravenous methylprednisolone 20–30 mg/kg/day for 3–5 days with or without subsequent tapering dose of oral prednisolone) or second dose of IVIg are now being increasingly used.[25] A study by Burns et al. showed infliximab (a TNF-α blocker) to be of comparable

efficacy to a second course of IVIg.[26] A phase-3 randomized, open-label trial from Japan showed significant reduction in duration of fever with higher defervescence rates in those who received infliximab.[27] Safety and effectiveness of infliximab for KD refractory patients was also proven in another recently published study from Japan.[28] A multicenter randomized controlled trial (KIDCARE) will provide more definitive answers on effectiveness and safety profile of infliximab as compared to a second IVIg dose in children with IVIg resistant KD.[29]

In a randomized controlled trial where etanercept was given along with first dose of IVIg, there was significant reduction in incidence of IVIg resistance, and a decrease in CAAs, as compared to those who received IVIg alone. This study was, however, restricted to children above 1 year.[30]

IL-1 seems to play a key part in pathogenesis of KD.[13] A retrospective study of anakinra (an IL- 1 receptor antagonist) in 11 patients with IVIg-resistant KD showed fever resolution in all patients and significant decrease of inflammatory markers.[31] An open-label, phase II study (KAWAKINRA) showed anakinra to be well tolerated with good efficacy in reducing the incidence of fever, inflammatory markers, and CAAs in KD patients resistant to IVIg.[32]

Polymorphisms of genes involved in calcium-calcineurin nuclear factor of activated T cells (NFAT) pathway (viz; *ITPKC* and *CASP3* genes) have also been associated with pathophysiology of KD.[33] A multicenter randomized controlled study in patients with KD who are predicted to have high risk of developing CAAs had 2 treatment arms: one group was given only IVIg, while the other received either IVIg along with cyclosporine (an immunosuppressant targeting NFAT pathway). It showed a significantly lower incidence of CAAs, shorter fever duration with no increase in incidence of adverse events in those who received IVIg and cyclosporine.[34]

Mortality is approximately 0.01% in Japan while it is 0.87% at Chandigarh.[35,36] The higher mortality in our study may be due to delays in diagnosis in our country, especially in infants where KD is often confused with infectious disease. Lack of awareness of KD amongst physicians as well as the laity also contributes to delays in diagnosis. Early and adequate treatment of KD is essential to prevent development of CAAs and other complications. Recurrence rates of KD are 3.5% in Japan and 0.98% from a study in India.[37,38]

KD is one of the commonest vasculitides in children, and can lead to serious cardiac complications. There is an urgent need for identification of a laboratory marker for diagnosis of KD. There is growing evidence for use of immunomodulatory and biologic agents for treatment of refractory cases of KD.

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