Over several decades, Kawasaki disease (KD) has been the leading cause of acquired heart disease in children. It is an acute systemic inflammatory illness and a multisystem vasculitis in young children with varied presentations. An undefined infectious trigger in a genetically predisposed individual is generally known to result in the disease. A genetic predisposition is suspected on the basis of clinical and epidemiological features. In addition, it is characterized by immune activation and increased cytokine production. Although intravenous immunoglobulin (IVIG) has changed its prognosis significantly, KD continues to be associated with the development of coronary artery aneurysms (CAAs) in a small percentage of children with coronary artery abnormalities. The disorder can be difficult to diagnose, and no diagnostic laboratory test has been developed yet. Prompt treatment with IVIG has been shown to treat all manifestations of KD and to significantly decrease the risk for development of CAA.

The difficulties in diagnosing incomplete KD lead to potential delays in treatment and higher risks of coronary artery abnormalities. Previous studies suggested that infants aged <12 months and older children are more likely to present with an incomplete clinical feature and that incomplete KD is associated with longer interval between symptom onset and treatment. Several scoring systems have been developed to identify children at the highest risk of coronary artery abnormalities. Tewelde et al. developed a risk score to determine the risk of future coronary aneurysms when a child presents with KD. Some studies, including the study by Newburger et al., have tried to predict children who will be unresponsive to IVIG treatment (a risk factor for the development of CAA). Nowadays, none of the models are completely accurate in predicting the development of CAA. The common pattern appears to be that children with evidence for the most severe inflammation in any population are at highest risk for developing CAA and for lack of response to IVIG. Most scores have low specificity.

KD is characterized by marked immune activation associated with cytotoxic anti-endothelial cell antibodies and increased cytokine production. This could contribute to endothelial cell damage. The early stages in the formation and development of arteritis in KD have been well studied morphologically. The media of affected vessels demonstrate edematous dissociation...
of the smooth muscle cells, which is most obvious toward the exterior. An influx of neutrophils is found in the early stages, with a rapid transition to large mononuclear cells in concert with lymphocytes (predominantly CD8+ T cells) and immunoglobulin A plasma cells. Destruction of the internal elastic lamina and, eventually, fibroblastic proliferation occurs at this stage. Active inflammation is replaced over several weeks to months by progressive fibrosis, with scar formation.

Pathological examination of KD would reveal that small arteries, larger arteries, capillaries, and veins are also affected to a lesser extent. Endothelial cells undergo histological changes consistent with both endothelial cell activation and damage. These morphological features include enlarged endothelial cells with increased synthetic organelles, increased replication of endothelial cells, and a marked increase in the adhesion of leukocytes to the endothelial wall, endothelial cell necrosis, and extracellular fibrin deposition.

The levels of various inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 are increased in serum during acute KD. Peripheral blood mononuclear cells from patients spontaneously secrete high levels of TNF-α and IL-1. The percentage of TNF-positive cases was higher in KD patients with than in those without coronary involvement.

The mode of action of IVIG in KD is not fully understood, although several mutually non-exclusive mechanisms have been proposed as follows: they involve the effects on endothelial cells, macrophages and monocytes, neutrophils and T and B cells, the expressions of adhesion molecules, and cytokine production.

Although great strides have been made in the treatment of KD and in understanding the natural history of the disease, major questions remain unanswered. The extent to which the disease may eventually contribute to the burden of adult cardiovascular disease is a growing concern. In the future, studies on KD should focus on early patterns of gene expression and search for potential early associations with subsequent coronary arterial aneurysm formation and IVIG resistance.

REFERENCES

