EDITORIAL

Biomarkers for Diagnosis of Kawasaki Disease

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Kawasaki disease is an enigmatic condition characterized by vasculitis of medium-sized arteries, especially the coronaries. Majority of children with Kawasaki disease are below five years of age. The etiology of Kawasaki disease is still an enigma even though it was recognized almost 50 years ago [1]. If not diagnosed in time and not treated appropriately, approximately 15-25% of children afflicted with Kawasaki disease can develop coronary artery abnormalities. The diagnosis of Kawasaki disease is based on a set of clinical criteria, and there is no pathognomonic laboratory test for this condition. The clinical presentation of children with Kawasaki disease can be very variable and can test the clinical acumen of even the most astute pediatrician. Several children can present with incomplete and atypical forms of Kawasaki disease thereby further confounding the clinical differentiation between this disease and other febrile illnesses of childhood.

In recent years, considerable progress has been made in identifying disease susceptibility genes for Kawasaki disease, based on genome wide linkage and association studies [2,3]. Another set of studies have focused on the dysregulated cytokine networks in Kawasaki disease. Levels of several inflammatory cytokines and chemokines are found to be elevated during the acute phase of the disease. Wang, *et al*. [4] studied Th1 and Th2 cytokines in patients with Kawasaki disease. Levels of interleukin 6, interleukin 20, tumor necrosis factor-α (TNF-α) and interferon-γ were found to be elevated during the acute phase and showed a prompt decline following administration of intravenous immunoglobulin (IVIg). Further, the levels of TNF-α continued to remain elevated in patients who were resistant to IVIg or those with coronary artery abnormalities.

Interleukin 17 (IL-17) is a pro-inflammatory cytokine produced by a distinct subset of helper T cells known as T helper type 17 (Th17) cells. Th17 cells, and IL-17 produced by them, have a profound inflammatory action through upregulation of other cytokines and involvement of matrix metalloproteinases. Th17 cells have been incriminated in a host of autoimmune and allergic disorders. A derangement in relative proportions of Th17 and regulatory T cells (Treg) in patients with Kawasaki disease has been reported during the acute phase [5]. The proportion of Th17 cells was elevated whereas that of Treg was decreased during the acute phase. Th17 cell numbers were significantly higher in patients with Kawasaki disease resistant to IVIg compared to those who responded to immunoglobulin therapy [5].

Natriuretic peptides such as brain natriuretic peptides are synthesized by the ventricular myocytes in response to myocardial stress and injury in a wide variety of disorders such as congestive heart failure, acute coronary syndromes, and following major surgeries. Brain natriuretic peptide (BNP) is synthesized in a precursor form, PreproBNP, from the cardiac myocytes. It is first cleaved in the liver to form ProBNP which is further cleaved by an endopeptidase in the blood to form BNP and N-terminal pro-BNP (NTpro-BNP). NTpro-BNP is an inactive cleavage product which has a longer half-life in circulation than pro-BNP. Some previous studies have evaluated the diagnostic utility and the predictive value of NT-pro-BNP in Kawasaki disease [6,7]. The results from these studies have also been analyzed further in a recent systematic review and meta-analysis [8].

In this issue of *Indian Pediatrics*, Wu, *et al.* [9] have evaluated the diagnostic utility of NT-proBNP and IL-17 to differentiate incomplete Kawasaki disease from other febrile infectious illnesses of childhood. IL-17 and NT-proBNP levels were estimated in 291 patients with complete Kawasaki disease, 74 patients with incomplete Kawasaki disease and 401 febrile infectious illnesses of unknown etiology. Combined with clinical criteria, when the cut-offs for IL-17 and NT-proBNP were set at 11.55 pg/mL and 225.5 pg/dL respectively, the sensitivity and specificity of differentiating incomplete Kawasaki disease from infectious illnesses reached as high as 86.5% and 94.8%, respectively.

Elevated levels of NT-proBNP are by no means specific for Kawasaki disease. The levels of NT-proBNP rise significantly in several heart ailments like congestive

heart failure, acute coronary syndromes and congenital heart diseases. NT-proBNP levels are also dependent upon age. Infants less than 1 month of age tend to have higher levels than older children. Overall, it seems that the concurrent estimation of the biomarker NT-proBNP and IL-17 may serve as a useful adjunct for differentiation of Kawasaki disease, especially in its incomplete form, from other confounding infectious diseases of children.

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REFERENCES

1. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph-node syndrome (MLNS) prevailing in Japan. Pediatrics. 1974;54:271-6.
2. Onouchi Y, Ozaki K, Burns JC, Shimizu C, Terai M, Hamada H, *et al.* A genome-wide association study identifies three new risk loci for Kawasaki disease. Nat Genet. 2012;44:517-21.
3. Lee YC, Kuo HC, Chang JS, Chang LY, Huang LM, Chen MR. Two new susceptibility loci for Kawasaki disease identified through genome-wide association analysis. Nat Genet. 2012;44:522-5.
4. Wang Y, Wang W, Gong F, Fu S, Zhang Q, Hu J, *et al.* Evaluation of intravenous immunoglobulin resistance and coronary artery lesions in relation to Th1/Th2 cytokine profiles in patients with Kawasaki disease. Arthr Rheum. 2013;65:805-14.
5. Jia S, Li C, Wang G, Yang J, Zu Y. The T helper type 17/regulatory T cell imbalance in patients with acute Kawasaki disease. Clin Exp Immunol. 2010;162:131-7.
6. Dahdah N, Siles A, Fournier A, Cousineau J, Delvin E, Saint-Cyr C. Natriuretic peptide as an adjunctive diagnostic test in the acute phase of Kawasaki disease. Pediatr Cardiol. 2009;30:810-7.
7. Kawamura T, Wago M, Kawaguchi H, Tahara M, Yuge M. Plasma brain natriuretic peptide concentrations in patients with Kawasaki disease. Pediatr Int. 2000;42:241-8.
8. Lin KH, Chang SS, Yu CW, Lin SC, Liu SC, Chao HY, *et al.* Usefulness of natriuretic peptide for the diagnosis of Kawasaki disease: A systematic review and meta-analysis. BMJ Open. 2015;5:e006703.
9. Wu L, Chen Y, Zhong S, Li Y, Dai X, Di Y. Blood N-terminal pro-brain natriuretic peptide and interleukin-17 for distinguishing incomplete Kawasaki disease from infectious diseases. Indian Pediatr. 2015;52:477-80.