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Editorial

Laboratory Markers Helpful in Diagnosing Kawasaki Disease in Febrile Infant: Role of Age-adjusted Z-values of Blood Cells

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▸ See the article "Significance of Differential Characteristics in Infantile Kawasaki Disease" in volume 49 on page 755.

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Kawasaki disease (KD) is an acute febrile illness of young children that causes systemic vasculitis, especially attack coronary arteries. Coronary vasculitis leads to coronary artery aneurysms in less than 5% of treated cases with intravenous immunoglobulin (IVIG). Presently, KD is the leading cause of acquired heart disease in children in developed countries with the potential for coronary artery abnormalities (CAA) that may result in long-term cardiac disease into adulthood.[1] Prompt diagnosis and timely initiation of IVIG is crucial in reducing the incidence of CAA in KD.

The diagnosis of KD depends on the principal clinical findings in febrile children. Patients who have sufficient clinical criteria are said to have complete Kawasaki disease (cKD). They who lack the sufficient clinical findings may be diagnosed incomplete Kawasaki disease (iKD).

In the absence of specific diagnostic test, other clinical, laboratory, and echocardiographic findings can support the diagnosis of iKD. Latest recommendation is that patients with KD should be treated with IVIG within 10 days of illness onset but as early as possible after diagnosis. Some KD patients, especially infants, can develop CAA despite apparent clinical response to IVIG treatment given in the first 10 days of illness.[1]

Therefore, early detection and timely initiation of IVIG is more important in infantile KD.

But, infants have tendency lacking sufficient clinical findings, especially <6 months old, are at high risk of delayed diagnosis and late treatment and developing CAA. As infants, the AHA recommendations defined incomplete KD with fever for 7 days without other explanation.

In the meta-analysis including 4,504 cases and 32,519 controls, the pooled results indicated that iKD was associated with an increased risk of CAA. Subgroup analyses demonstrated higher associations in patients younger than 12 months.[2]

Infants <6 months and children >5 years were highest risk for CAA in the latest Japanese survey.

Acute cardiac lesions were more prevalent among age <1 year. Giant coronary aneurysm risk factors were similar to CAA risk factors: age <1 year, later presentation to hospital, atypical definite cases, and resistance to initial IVIG therapy.[3]

Therefore, many studies have been making to define the better laboratory markers that support diagnosis of KD.

Elevation of inflammatory markers is characteristic in KD. Leukocytosis is typical during the acute stage, with a predominance of granulocytes. Normochromic and normocytic anemia occurs commonly, and resolves with resolution of inflammation. Elevation of acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) is nearly universal. Thrombocytosis is a characteristic feature of KD in subacute stage.[4]

Mild to moderate elevations in serum transaminases or gammaglutamyl transpeptidase occur in 40% to 60% of patients, and mild hyperbilirubinemia occurs in around 10%. Hypoalbuminemia is common and associated with more severe and more prolonged acute disease. Urinalysis may show pyuria in up to 80% of children. N-terminal pro B-type natriuretic peptide (NT-proBNP), likely indicative of myocardial involvement, may be elevated in some patients with KD.[1]

One study used age-adjusted Z-values of cell counts to define laboratory marker profiles typical of iKD during illness, especially with respect to the presence of CAA. They concluded that the iKD patients shared KD-specific laboratory marker profiles in terms of complete blood cell counts and acute phase reactant levels with cKD patients. However, the factors predicting coronary dilation differed according to the phenotype; lower acute and subacute age-adjusted hemoglobin levels predicted coronary dilation only in iKD patients.[5]

Kwak et al.[6] compared age-adjusted Z-values of white and red blood cells in infants with KD with those in non-infants with KD. They concluded that infants with iKD could be more easily differentiated from infants with simple febrile illness using pre-IVIG Z-hemoglobin and CRP values.[6]

In another study, iKD was much more common in infants than in children (65% vs. 31.8%). The serum levels of platelet after 1 week, CRP, and NT-proBNP were all significantly higher in the infants group. Comparing the infants with KD versus the other acute febrile diseases, there were significantly higher serum levels of ESR, CRP, and NT-proBNP for the infants with KD group.[7]

In recent China study, peripheral blood neutrophil-to-lymphocyte ratio (NLR) was increased significantly in IVIG-resistant children compared to the IVIG responders. A cut-off value of NLR of 2.51 in KD patients younger than 1-year old yielded a sensitivity of 0.545 and specificity of 0.840, respectively. Their conclusion was that the peripheral blood NLR ≥2.51 was useful to predict the IVIG resistance in KD patients younger than 1-year old.[8]

The diagnosis of iKD should be considered in any infant with prolonged unexplained fever, fewer than 4 of the principal clinical criteria, and compatible laboratory or echocardiographic findings. Continuing consistent efforts to find better laboratory markers in diagnosing KD in febrile infant will support prompt diagnosis and timely management and eventually contribute to decrease CAA.

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