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Editorial

Challenges in early diagnosis and treatment of Kawasaki disease

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Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, was first reported by Kawasaki in Japan in 1967. Despite over 50 years of research, the understanding of this disease, particularly its etiology and long-term prognosis, remains incomplete, and there are gaps in its diagnosis and treatment protocols. In recent years, the incidence of incomplete Kawasaki disease (IKD) has been increasing in countries such as China and Japan, making it crucial to enhance the diagnosis and treatment of KD/IKD. One of the 2023 pediatric quality control improvement goals set by the National Health Commission in China is to "reduce the incidence of cardiac events and mortality associated with Kawasaki disease." The summary of this goal mentions that the level of KD diagnosis and treatment varies widely across the country, presenting a significant challenge for pediatric healthcare quality improvement. Although clinical research on KD has advanced in recent years, the number of studies remains limited. The diagnosis and treatment of KD face several challenging issues that require attention and in-depth research [1].

KD is primarily diagnosed based on clinical features and laboratory tests reflecting systemic vasculitis, lacking a gold standard and requiring the exclusion of other diseases. The diagnosis of classic KD is usually straightforward, but diagnosing IKD and severe KD requires high clinical vigilance.

IKD presents with fewer and less typical clinical symptoms, necessitating comprehensive judgment based on specific laboratory indicators and echocardiography. Sometimes, dynamic observation and comprehensive assessment during the disease course are needed for diagnosis. Special attention should be given to children with laboratory indicators such as elevated CRP, accelerated ESR, increased white blood cell count (mainly neutrophils), elevated platelet count, decreased hemoglobin, abnormal liver function, elevated total bilirubin, decreased albumin and serum sodium, sterile pyuria, and elevated levels of interleukins (IL-1, IL-6) and tumor necrosis

factor α. These laboratory abnormalities are common in IKD patients. Some researchers suggest using elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) as markers for diagnosing IKD, but sufficient clinical validation studies are lacking. Echocardiography is crucial for diagnosing IKD, particularly for observing coronary artery lesions (CAL) and evaluating myocardial function, valvular regurgitation, and pericardial effusion [2].

A small number of KD patients have severe forms, such as Kawasaki disease shock syndrome (KDSS) and KD with macrophage activation syndrome (MAS). Severe KD often involves hemodynamic instability, which can be life-threatening and requires early recognition and treatment. For KDSS, early anti-inflammatory treatment, correction of hypoalbuminemia, and maintenance of hemodynamic stability are key to successful treatment. This includes primary disease treatment, anti-shock therapy, and management of complications. First-line treatments include IVIG, aspirin, and corticosteroid pulse therapy. In critical cases, infliximab, anakinra, cyclosporine, or plasma exchange may be considered. MAS is a form of secondary hemophagocytic lymphohistiocytosis (HLH) and a potentially unrecognized complication of KD. Early recognition of MAS is challenging due to its lack of distinctive clinical and laboratory features and overlapping manifestations with KD. Risk factors for MAS in KD include persistent fever, liver dysfunction, hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia, pancytopenia, and frequent hemophagocytosis observed in bone marrow examination. Studies have found that KD patients with persistent fever, splenomegaly, elevated ferritin levels, and thrombocytopenia may have MAS [3].

The initial treatment for acute KD includes high-dose intravenous immunoglobulin (IVIG) and oral aspirin. In addition to concerns about aspirin allergy and potential side effects, several issues related to IVIG use need to be addressed.

IVIG resistance is defined as a body temperature higher than 38 ℃ 36–48 hours after receiving IVIG 2 g/kg and aspirin within 10 days of disease onset or recurrent fever within 2–7 days or even 2 weeks, along with at least one KD diagnostic criterion. The incidence of IVIG resistance is about 10%–20%, and it predicts a higher risk of CAL. The mechanisms of IVIG resistance in KD are unclear and may involve genetic factors, overactivation of immune cells, and inflammatory mediators. To accurately predict IVIG resistance and adjust treatment plans timely to reduce CAL risk, various risk factor scoring systems for IVIG resistance have been proposed by experts, but they exhibit significant racial and regional specificity, and their predictive accuracy and specificity are uncertain. Some researchers found that adding corticosteroids to IVIG may help reduce IVIG resistance, but large-scale prospective studies are needed [4].

The effective dose of IVIG for treating KD has been debated. Initially, IVIG was recommended at 400 mg/kg/day for 5 days, but some studies reported slower resolution of symptoms and suboptimal control of CAL at this dose. Comparisons of different IVIG doses have shown that higher doses (2 g/kg single infusion) result in better clinical and laboratory outcomes and lower rates of IVIG resistance and CAL.

Some researchers believe that CAL occurs at the peak of inflammation, making IVIG treatment within 10 days of fever onset crucial for preventing CAL. Delayed IVIG treatment (>10 days) is associated with higher CAL incidence. It is widely believed that IVIG should be administered within 10 days of KD onset, preferably within 7 days, as CAL may begin to appear around days 8–9. Some studies suggest that administering IVIG within 5 days of fever onset may increase IVIG resistance, with days 6–10 being the optimal window. This may be influenced by genetic, racial, regional, and environmental factors.

In conclusion, the diagnosis of IKD and severe KD requires significant clinical attention to avoid misdiagnosis and missed diagnosis. The factors contributing to IVIG resistance in KD are not fully understood, and the dosage and indications for IVIG use need further refinement. These issues warrant continued research to improve the treatment outcomes and prognosis of Kawasaki disease [5].

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare that they have no relevant conflicts of interest.

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Author contributions

JFY was involved in overall structure and elaboration of concepts for review. Manuscript writing was by PY. All authors contributed to editing of the manuscript.

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