Clinical study of 135 cases of Kawasaki disease

Abstract

Objective: To analyze 135 cases of complete kawasaki disease (cKD) and incomplete Kawasaki disease (iKD) in terms of clinical characteristics, laboratory examination, diagnosis and treatment, coronary artery injury and other risk factors, and to provide reference for clinical diagnosis and treatment.

Methods: Clinical data of 135 pediatric patients admitted to our hospital from August 1999 to January 2022 were retrospectively analyzed. 41 cases were less than 1 year old (30.4%), 51 cases were between 1 and 3 years old (37.8%), 26 cases were between 3 and 5 years old (19.2%), and 17 cases were over 5 years old (12.6%). Among them, 93 cases were male (68.9%), 42 cases were female (31.1%), male: female (2.2:1), and the age ranged from 15 days to 8 months. Results Among 135 children with KD, 87 cases with cKD (64.4%), 48 cases with iKD (35.6%), 37 cases with coronary artery disease (CAL), including cKD (19.5%, 17/87) and iKD (41.7%, 20/48). There was no significant difference in gender between cKD and iKD, and iKD was more common in infants in age characteristics. There was no significant difference in esR and C-reactive protein between cKD and iKD, and the probability of kawasaki red in iKD children was higher than that in cKD children. iKD is associated with higher coronary artery disease (CAL).

Conclusion: Incomplete KD has atypical clinical manifestations and is easy to be misdiagnosed and missed. In infants with fever of unknown cause for more than 5 days, the diagnostic conditions of Kawasaki disease are insufficient, so iKD should be considered in the examination of echocardiography and other examinations should be actively improved. High-dose intravenous injection of human immunoglobulin and aspirin should be given in the acute phase to relieve inflammatory response and reduce the occurrence of CAL.

Key words: mucodermal lymph node syndrome, diagnosis, treatment, comprehensive.

Introduction

Kawasaki disease (KD), also known as mucosa-cutaneous lymph node syndrome, is a common autoimmune vasculitis in infants and young children, mainly occurring in children under 5 years old. KD was first reported in 1967 by Japanese pediatrician Dr. Tomisaku Kawasaki through clinical findings in 50 children. At the time, it was unclear whether KD involved the heart, and there was no effective treatment. Later, autopsy was performed on the children who died of KD, and

coronary aneurysm and thrombosis were found, and the cardiac complications of KD became clear. KD has been reported in children of almost all ethnic groups since Dr Kawasaki first reported it, and has been increasing in recent years. Undiagnosed and untreated KD in children can affect health care delivery systems in developing countries over the long term. KD is easy to invade small and medium-sized vessels in the whole body, especially coronary arteries. The incidence of coronary artery injury in children without treatment or early treatment of KD is as high as 20%~25% [1]. At present, the specific pathogenesis of KD is not completely clear, and most views at home and abroad support the hypothesis that immune-mediated superantigen and/or ordinary antigen co-cause disease [2]. KD can be divided into cKD and iKD according to whether the clinical manifestations are typical. The clinical diagnosis of children with cKD is relatively easy, while the clinical diagnosis of children with iKD is often missed and misdiagnosed, resulting in a poor prognosis. This article reviews the diagnosis and research progress of iKD.

1. Diagnostic criteria for Kawasaki disease

Diagnosis criteria for cKD: fever for more than 5 days with ≥ 4 of the following five major clinical features can be diagnosed as cKD. (1) Changes of limbs: palmoplantar erythema, hand and foot induration in acute stage, membranous peeling of the toe in subacute stage; (2) rash; (3) Ocular adhesion membrane hyperemia, no secretion; (4) lips congestion chapped, oral mucosa diffuse congestion, strawberry tongue; (5) Acute non-suppurative cervical lymph node enlargement, usually directly > 1.5cm [3]. The definition and diagnostic criteria of iKD are relative to cKD, which refers to fever ≥5 days and 2 to 3 of the following main clinical manifestations of cKD: ① Bulbous membrane hyperemia without purulent secretions; (2) lips congestion chapped, tongue nipple bulging congestion, strawberry tongue; ③ In acute stage, scleroma of hands and feet, erythema of palms and toes; Recovery period finger (toe) end membranous desquamate; ④ Pleomorphic erythema and rash, perianal redness and peeling; ⑤ Cervical lymph nodes are enlarged, mostly unilateral, with a diameter often ≥1.5 cm. IKD can also be diagnosed when the above clinical manifestations do not meet the four criteria but coronary artery injury is found on echocardiography. When clinically diagnosing iKD, fever and rash diseases, such as measles, systemic lupus erythematosus and scarlet fever, should be excluded first [4]. Some studies have pointed out that iKD should be considered when children have fever of unknown cause ≥5 days and have any of the clinical manifestations of KD. IKD should be considered when the fever duration is ≥7 d and the prolonged fever cannot be explained by other reasons. When the child has any of the above conditions, laboratory examination should be performed [5-6]. When c-reactive protein (CRP) ≥30 mg/L and erythrocyte sedimentation rate (ESR) ≥40 mm/h, other laboratory indicators were further detected: ① hemoglobin; ② Platelet ≥450× 109/L after 7d of disease course; ③ Albumin ≤30 g/L; ④ Alanine aminotransferase increased; ⑤ White blood cell count ≥15 × 1012

/ L; ⑥ Urine white blood cell > 10 / high magnification field of 3 of the 6 items can be diagnosed, when have any of the above and echocardiography positive results can also be diagnosed. The positive results of echocardiography included: ① Z value ≥ 2.5 of left anterior descending branch (LAD) or right coronary pulse (RCA); ② Coronary aneurysm; ③ Patients with ≥3 of the following conditions: decreased left ventricular function, mitral regurgitation, pericardial effusion, LAD or RCAZ value of 2.0-2.5. When CRP < 30 mg/L and ESR < 40 mm/h, if fever persists, bedside manifestations should be observed again and laboratory examinations should be performed. Echocardiography should be performed to further assist diagnosis if typical membranous descaling occurs during the course of the disease.

2.The characteristics of the iKD

According to information and material statistics, iKD accounts for 10% ~ 36% of the total number of KD children, and with the continuous improvement of people's awareness in recent years, the incidence of iKD has been increasing year by year [7-8]. Compared with cKD, iKD has its own characteristics. The onset age of iKD children is younger than that of cKD children [9-10], but there is no significant difference in gender ratio between iKD and cKD children. A number of studies have analyzed a large amount of clinical data, indicating that the age of onset of iKD in children is significantly younger than that in children with cKD [6, 9-10]. For this reason, children with iKD are at a higher risk of coronary artery injury because of their younger age of onset and relatively immature cardiovascular system, which makes them more vulnerable to immune injury. Furthermore, iKD children have a higher incidence of carscal red than cKD children, which is conducive to early clinical diagnosis, especially children 3 months to 3 years after BCG vaccination are more likely to have this important manifestation [11]. Clinical attention should be paid to iKD in young infants, especially those less than 6 months of age, whose clinical manifestations are more atypical, even with recurrent fever. Such children are more prone to coronary artery injury and poor prognosis. Therefore, for patients with recurrent fever and unknown etiology, especially for small infants, relevant auxiliary examinations should be improved as soon as possible to assist diagnosis. When ESR and CRP are significantly increased, echocardiography should be improved to understand whether coronary arteries are damaged.

3. treatment of iKD

3.1 Intravenous infusion of human immunoglobulin (IVIG) has been widely proven in practice. Timely administration of IVIG at the early stage of iKD is beneficial to reduce the occurrence of coronary artery injury and improve the prognosis of children. For dosage, 2 g /kg intravenous infusion is currently recommended, and the infusion is completed within 10 to 12 hours. The optimal timing of medication is within 5 to 10 days after the onset of the disease. Premature or late medication is not conducive to the recovery of the disease, and early medication will increase the possibility of no response to IVIG, while

late medication will increase the risk of coronary artery injury, so it is very important to accurately grasp the timing of medication [12]. However, the mechanism of IVIG reducing iKD coronary artery injury is still unclear. Meanwhile, for single dose, some scholars believe that 1 g /kg is the most economical and effective single dose of IVIG. If a single dose cannot effectively reduce fever, it can be applied again the next day [13-14].

Clinically, some KD children, especially iKD children, were diagnosed relatively late due to atypical clinical manifestations. For children with KD diagnosed after 10 days, IVIG infusion should be given when CRP > 30 mg /L or ESR increased with fever or coronary aneurysm Z value ≥ 2.5. If the body temperature of the child has returned to normal, inflammatory indicators are reduced to normal, and the coronary artery is not damaged, IVIG can not be used [5]. If the child with KD receives standard treatment with IVIG within 10 days of onset and the body temperature is still > 38℃ 48 hours after the onset, or fever occurs again within 2-7 days or 14 days after sufficient medication and at least one clinical manifestation of KD, it is called IVIG non-response. After adequate IVIG treatment, if the temperature of the child continues to relapse or inflammatory indicators continue to rise, IVIG 2 g /kg can be given again [5]. Some studies have indicated that children with iKD are more likely to develop IVIG nonresponse than children with cKD [15,21], so attention should be paid in clinical practice.

3.2Aspirin has become a routine drug for children with KD. High-dose application in acute stage has anti-inflammatory effect, and low-dose application in post-acute stage has anticoagulant effect. However, there is no unified standard for specific application scheme. According to the latest studies, the recommended dose of aspirin in iKD acute phase is 30-50 mg /(kg.d), which is maintained at a low dose of 3-5 mg /(kg ·d) after 48-72 h or 2 weeks of disease course after normal body temperature, and discontinued after 6-8 weeks [4,16].

3. 3 Glucocorticoids Currently, the use of glucocorticoids in children with iKD is still controversial. In the past, it was believed that glucocorticoids could increase the risk of coronary artery injury in children with iKD, so for a long period of time, it has been contraindicated for children with KD. Later, with the deepening of research, it was found that the combination of glucocorticoid and IVIG was effective for the treatment of KD children with IVIG resistance [17-18].

3.4 Infliximab Infliximab (IFX) is a tumor necrosis factor -α antagonist (TNF-A). Anti-tnf-a therapy has become an important choice for refractory KD. In most studies, the dosage of IFX is 5.0-6.6mg/ kg-d and is administered only once. Current studies show that the effect of infliximab in the treatment of KD has not exceeded

that of IVIG. But foreign studies have shown that children with KD children with interferon treatment can shorten the thermal process, decreased significantly with blood CRP inflammatory indexes such as, especially in the IVIG in children with no response, the drug can be used as a candidate for the treatment, generally with the tolerance is better, so far no serious adverse reaction (19-21).

Discussion

KD is a mucosa-cutaneous lymph node syndrome, usually occurring in children under 5 years old, with more boys than girls affected, which may be related to male specific FCGR2A susceptibility gene [22]. The most serious and common complication of KD is coronary artery disease, and the incidence of coronary artery disease in untreated KD patients is 20%-25%[23]. Coronary artery dilatation and coronary artery aneurysm are both coronary artery lesions and aneurysms are severe coronary artery dilatation. In acute stage, the incidence of coronary artery injury was significantly reduced after high dose intravenous injection of human immunoglobulin (IVIG) for KD treatment. In 1993, a survey of kawasaki disease children at 652 hospitals in Japan found that children who received IVIG nine days after onset had a higher risk of cardiac sequelae [24], a view confirmed by continuing studies [25]. The 2017 American Heart Association guidelines recommend that IVIG should be actively used to treat KD within 10 days of the course of disease [26]. From the onset age, children aged 1 to 3 years were significantly higher than other age groups. 135 children with KD complicated with coronary artery damage, accounting for 27.4% of the total. Although the incidence of coronary artery injury was significantly reduced after the application of IVIG in KD acute stage, the occurrence of coronary artery aneurysm would affect children's physical and mental health to varying degrees. Early detection of coronary artery injury risk factors in KD acute stage will help to prevent coronary aneurysms. Therefore, timely diagnosis and treatment of KD is one of the important means to reduce the occurrence of coronary artery damage. In conclusion, medical staff should enhance the awareness of KD, improve the diagnostic procedure of KD, and perform cardiac ultrasound examination to determine the coronary artery status as soon as possible. Special attention should be paid to early recognition and treatment of iKD, which is one of the important means to reduce the occurrence of coronary artery damage. A large sample, multi-center, long-term follow-up clinical study is expected.

Conclusion and Future aspect

KD is an acute vasculitis disease, and the incidence of KD has increased significantly in recent 10 to 20 years [27]. CAL is still the most common and one of the most serious complications of KD. Therefore, early recognition and timely treatment are crucial to improve the prognosis. Due to the atypical clinical manifestations of iKD, it is difficult to diagnose iKD at an early stage, which requires clinicians to carefully inquire the medical history and conduct comprehensive evaluation and judgment combined with the results of

auxiliary examination. It is noteworthy that iKD can also cause myocarditis, pericarditis leading to ventricular systolic dysfunction, valvular regurgitation, arrhythmias, and even KD shock syndrome during acute inflammation. Therefore, in addition to assessing coronary artery diameter and appearance, attention should be paid to assessing left ventricular and valve function. Treatment options such as infliximab may be considered in patients who do not respond to IVIG. In addition, traditional Chinese medicine has some curative effect on this disease. With the continuous development of medical technology, there will be more breakthroughs in the diagnosis and treatment of iKD.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

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