CASE REPORT

Kawasaki disease in siblings and a review of drug treatment

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Abstract

We have managed two anonymized siblings with Kawasaki disease (KD). The occurrence of KD in the elder brother alerted us to the occurrence of incomplete KD in the younger brother. Both siblings were treated with intravenous immunoglobulin and a high dose of dipyridamole with resolution of the coronary artery aneurysm. Dipyridamole was used instead of aspirin because both siblings were glucose-6-phosphate dehydrogenase deficient for which aspirin was contraindicated. To prevent damage to the coronary arteries, treatment should be started as soon as the diagnosis is made. There have been a lot of advances in medical therapy in recent years, which are reviewed together with conventional proven therapy for KD. Early diagnosis and prompt treatment are therefore critical to achieve optimal treatment outcome in KD. Family history of KD among siblings enables clinicians for an earlier diagnosis so as to prevent the disease complications particularly in patients with incomplete features.

Keywords: COVID-19, dipyridamole, intravenous immunoglobulin, Kawasaki disease, siblings.

Citation

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Introduction

Kawasaki disease (KD) is an acute systemic vasculitis that predominantly affects medium-sized arteries, with a predilection for coronary arteries, and occurs mostly in children between 6 months and 5 years of age.1,2 Early diagnosis and timely treatment are therefore critical to achieve optimal treatment outcome.3 This article describes the management of two siblings with KD followed by a short review. Joint CUHK-NTEC CREC approval was obtained to review mortality and morbidity of patients admitted to the Department of Pediatrics. We have de-identified details such that the identity of the patients may not be ascertained in any way.

Case 1

The elder brother, an ethnic Chinese with glucose-6-phosphate dehydrogenase (G6PD) deficiency, presented at 4 months of age with fever for 5 days up to 39°C. On physical examination, he had bilateral conjunctival injection without exudate and congested throat with bright red tongue and lips. Besides, he also had a diffuse maculopapular eruption over the face, trunk, and limbs and swelling with erythema over both hands and feet. Investigations on admission revealed an elevated erythrocyte sedimentation rate (ESR) of 70 mm/hour, C-reactive protein (CRP) of 21.8 mg/L, normal hemoglobin, and normal white blood cell count (WBC). Platelet count was elevated at 443 x 10^9/L. Serum sodium, albumin, and transaminases were all unremarkable. Urinalysis showed no sterile pyuria. Viral panels including influenza, parainfluenza, parvovirus, measles, and Epstein-Barr virus were negative. Blood, nasopharyngeal aspirate, and urine cultures were unremarkable. Echocardiography showed dilated left coronary artery and right coronary artery with normal cardiac structure and function. He was treated as a case of classic KD with intravenous immunoglobulin (IVIG) 2 g/kg and, in view of his background of G6PD deficiency, oral dipyridamole at 5 mg/kg in three divided doses daily was given on Day 5 of the fever. The fever subsided 1 day after treatment with IVIG and oral dipyridamole. Serial echocardiogram 7 months after the acute episode showed resolution of the dilated left coronary artery and right coronary artery and oral dipyridamole was stopped.
Case 2

The younger brother of the patient in Case 1, also an ethnic Chinese with G6PD deficiency, presented at 6 months of age with a more complicated picture. He presented with fever for 6 days with a maximum temperature of 39.4°C, left cervical lymphadenopathy with abscess formation, and a faint maculopapular eruption over trunk sparing the extremities. He did not have conjunctival and mucosal changes suggestive of KD. Laboratory findings on presentation were as follows: hemoglobin 8.8 g/dL, WBC 3.5 x 10⁹/L with an absolute neutrophil count of 0.17 x10⁹/L, normal platelet count, ESR 82 mm/hour, CRP 44.2 mg/L, serum sodium 132 mmol/L, serum albumin 31 g/L, and normal serum transaminases. Urinalysis showed no sterile pyuria. Computed tomography (CT) scan showed a 4 cm x 1.5 cm x 1.6 cm abscess over the left lower jugular region. Incision and drainage of the cervical abscess were performed. Culture of the pus drained revealed methicillin-sensitive Staphylococcus aureus (MSSA). Acid-fast bacilli stain and culture of the pus drained were negative for mycobacteria. Chest X-ray, ultrasound abdomen, viral panels, bacterial and fungal culture for blood, nasopharyngeal aspirate, and urine revealed no other significant septic foci. The patient was treated initially with empirical intravenous piperacillin/tazobactam and subsequently with intravenous cloxacillin according to the sensitivity result. Granulocyte-colony stimulating factor (G-CSF) was started with only transient improvement of the neutropenia. The neutrophil count dropped 2 days after stopping the G-CSF infusion. Further workups of the neutropenia including anti-neutrophil antibody, neutrophil function test and neutrophil elastase gene (ELANE) mutation screening were all unremarkable. The fever persisted despite broad spectrum antibiotic and adequate drainage of the abscess as shown in the repeated CT scan. In view of history of KD in his elder brother, an echocardiography was performed, which revealed a 4 mm pericardial effusion with increased echogenicity over both coronary arteries and a small proximal left coronary artery aneurysm. IVIG, 2 g/kg, and, in view of his background of G6PD deficiency, oral dipyridamole at 5 mg/kg in three divided doses daily was started on Day 11 of fever. The fever subsided 1 day after the IVIG infusion and dipyridamole. Echocardiography 2 months later showed normal carotid arteries and cardiac function, and oral dipyridamole was stopped.

Discussion

Summary of findings

The elder brother had classic KD at 4 months of age while the younger brother presented with incomplete KD at 6 months of age. In the case of the younger brother, in view of the positive family history of KD and a high index of suspicion, an echocardiography was performed during the febrile episode, which revealed a coronary artery aneurysm. The occurrence of KD in the elder brother alerted us to the occurrence of incomplete KD in the younger brother. Both siblings were treated with IVIG and high dose of dipyridamole (5 mg/kg in three divided doses daily) with resolution of the coronary artery aneurysm. Dipyridamole was used instead of aspirin because both siblings were G6PD deficient for which aspirin was contraindicated.

KD in siblings

The exact etiology of KD is unknown and is likely multifactorial. There is a genetic predisposition as the incidence of KD is much higher in Japan and Japanese children living in other parts of the world and among siblings and offspring/parents of an index case. Dergun and colleagues reported the largest series of familial occurrence of KD in North America. These authors reported nine families with two affected siblings and nine families with KD in two generations or multiple affected family members. There was only one family with two affected members under 6 months of age (5.5 months and 5.8 months, respectively). Sufficient to say, KD is uncommon in the first few months of life. This is especially so for the familial occurrence in siblings of such a young age. Our report is unique in that one sibling had classic KD while the other sibling had incomplete KD.

Infections and KD

In a multicenter review on the epidemiology of respiratory syncytial virus infection and its effect on children with heart disease in Hong Kong, KD is noted to be a complication. In a recent pandemic of coronavirus infection, severe Kawasaki-like disease is associated. Pediatric multisystem inflammatory syndrome (PMIS), or multisystem-inflammatory syndrome-in-children (MIS-C), or pediatric inflammatory multisystem syndrome-temporally associated with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (PIM-TS) are newly coined acronyms representing a systemic disease involving persistent fever, inflammation, and organ dysfunction following exposure to SARS-CoV-2, the virus responsible for coronavirus disease 2019 (COVID-19). This syndrome is recently considered to resemble KD and systemic inflammatory response syndrome (SIRS). This apparent link could also be due to the similarities in clinical presentation between COVID-19 and all the other sepsis syndromes, including SIRS, toxic shock syndrome, KD shock syndrome, and MODS. Common respiratory viruses including adenovirus, enterovirus, rhinovirus, coronavirus, and respiratory syncytial virus RSV have long been reported to be associated with KD. Hence, SARS-CoV-2 is just one of the many respiratory viruses that can cause MIS-C or PIMS-TS or KD.

Neutropenia and KD

Both siblings had normal neutrophil counts on follow-up. Neutropenia associated with KD has been rarely reported. The presence of an autoantibody to a novel antigen on immature myeloid cells or neutrophils is the likely cause of severe neutropenia.
**Classic versus incomplete KD**

The diagnosis of classic KD is based on clinical criteria established by the American Heart Association. Patients who have a fever for five or more days and only three major clinical features can also be diagnosed as having classic KD when coronary artery disease is detected by two-dimensional (2-D) echocardiography or coronary angiography.

Supportive laboratory findings include marked elevation of acute phase reactants, such as ESR (≥40 mm/hr) and CRP (≥3 mg/L), leukocytosis (WBC ≥15 x 10^9/L) with left shift, normocytic, normochromic anemia (hemoglobin ≥2 standard deviations below the mean for age), thrombocytosis (platelet count ≥ 450,000/mm^3), hyponatremia (serum sodium <135 mmol/L), hypoalbuminemia (serum albumin ≤3 g/dL), elevated serum transaminases, and sterile pyuria (≥10 WBC/high power field). Incomplete KD occurs most frequently in young infants (<6 months) and children >9 years of age. Patients with fever for 5 or more days plus 2–3 major clinical features are considered to have incomplete KD. Incomplete KD should not be regarded as mild KD because the risk of coronary artery abnormalities is comparable, if not higher, than classic KD. It is important to remember that what appears to be “incomplete” at a given point in time might not be so as some of the clinical features might have already subsided and other features may evolve.

**KD treatment**

Children with KD should be hospitalized. To prevent damage to the coronary arteries, treatment should be started as soon as the diagnosis is made. There have been a lot of advances in medical therapy in recent years. These will be described together with convention proven therapy for KD.

1. IVIG is the standard treatment for KD and is administered in high doses with marked improvement usually noted within 24 hours. If the fever does not respond, an additional dose may have to be considered. IVIG given within the first 10 days of the disease reduces the risk of damage to the coronary arteries in children, without serious adverse effects.

2. Salicylate therapy remains an important part of the treatment, but salicylates alone are not as effective as IVIG. Aspirin therapy is started at high doses until the fever subsides, and then is continued at a low dose when the patient returns home, usually for 2 months to prevent blood clots from forming. High-dose aspirin is associated with anemia and does not confer benefit to disease outcomes. Approximately 15–20% of children following the initial IVIG infusion show persistent or recurrent fever and are classified as IVIG-resistant. Children with KD will be taking aspirin for up to several months. Vaccination against varicella and influenza is required, as these infections are associated with Reye syndrome.

3. Corticosteroids have also been used, especially when other treatments fail or symptoms recur, but in a randomized controlled trial, the addition of corticosteroid to immunoglobulin and aspirin did not improve outcome. A 2017 Cochrane Review found the use of corticosteroids in the acute phase of KD was associated with improved coronary artery abnormalities, shorter hospital stays, a decreased duration of clinical symptoms, and reduced inflammatory marker levels. Patient populations based in Asia, people with higher risk scores, and those receiving longer steroid treatment may have greater benefit from steroid use.

4. Our experience is the first report of familial KD with coronary artery abnormalities that resolved with IVIG and oral dipyridamole (5 mg/kg in three divided doses daily). Experience in using dipyridamole in KD was limited. Dipyridamole has been used in combination with aspirin for patients with coronary artery aneurysm. The medication has been shown to have vasodilatory effect on peripheral coronary arterioles but not on the proximal part, leading to an increase in coronary blood flow. With its antithrombotic effect, dipyridamole might be considered in the treatment of patients with a coronary aneurysm in whom high-dose aspirin is contraindicated. There is generally insufficient evidence for the effectiveness of antithrombotic or antiplatelet therapy for KD.

5. Second-line therapy in IVIG-refractory KD has recently been reviewed. It is concluded that infliximab monotherapy should be considered in patients, who fail to respond to initial IVIG, based on a systematic review of the literature with pooled outcome data analysis suggesting infliximab is more effective in fever resolution compared to a second IVIG dose and intravenous methylprednisolone. According to a 2019 Cochrane review, tumor necrotic factor (TNF) alpha blockers (TNF-α) may reduce treatment resistance and the infusion reaction of IVIG after treatment initiation; further research is, however, needed. Subcutaneous etanercept with IVIG for acute KD was studied in a randomized controlled trial. Etanercept appeared to ameliorate coronary dilation in patients >1 year of age. In the cases just mentioned, the younger brother had parapharyngeal abscess with MSSA. It was unclear whether MSSA played a superantigen role in KD or just a coincidental finding. Surgical interventions like incision and drainage might have been needed in case the lymphadenitis did not respond to IVIG and antibiotics.

**Conclusion**

Early diagnosis and prompt treatment are important to achieve optimal treatment outcome in KD. Family history of KD among siblings enables clinicians for an earlier diagnosis so as to prevent the disease complications, particularly, in patients with incomplete features.
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