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CASE REPORT

# Kawasaki disease with G6PD deficiency—Report of one case and literature review

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Kawasaki disease (KD) is a systemic vasculitis primarily affecting children who are younger than 5 years. The most serious complications are coronary artery aneurysms and sequelae of vasculitis with the subsequent development of coronary artery aneurysm. According to the literature, intravenous immunoglobulin (IVIG) plus high-dose aspirin (acetylsalicylic acid) were standard treatment for KD, whereas low-dose aspirin (3-5 mg/kg/day) was used for thrombocytosis in KD via antiplatelet effect. However, aspirin has been reported to have hemolytic potential in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. We report a child with G6PD-deficiency who has KD, and review the literature.


## Introduction

Kawasaki disease (KD) is an acute febrile vasculitis of unknown etiology first described by Tomisaki Kawasaki.[1] KD occurs worldwide and primarily affects young children (younger than 5 years). The clinical characteristics of KD are prolonged fever, conjunctivitis, diffuse mucosal inflammation, polymorphous skin rashes, indurative edema of the

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hands and feet associated with subsequent peeling of the skin of the fingertips, and nonsuppurative cervical lymphadenopathy.[2,3] In some countries where newborn babies receive Bacillus Calmette-Guérin (BCG) vaccination, KD has been associated with erythematous induration or even ulceration of the BCG scars in one-third of affected patients.[4]

The most serious complications are coronary artery aneurysms and sequelae of vasculitis, with coronary artery aneurysms developing in 20-25% of untreated children.[2,3,5] In developed countries, KD is currently the leading cause of acquired heart diseases in children.[2,6–8] A United States multicenter study group established that a single high dose of 2 g/kg intravenous immunoglobulin (IVIG) plus aspirin could lower the incidence of aneurysms to 3-5%.[9] The treatment profile also had the effect of shortening the duration of fever.[8,9] Because coronary artery lesions (CAL) occur at a mean of 9.5 days after the onset of illness, it is important to diminish the severity of inflammation and vasculitis as soon as possible to prevent progression to CAL.[10] However, because some children were intolerant to high-dose aspirin, low-dose aspirin for antiplatelet effect after acute stage KD was prescribed in these patients as previously reported by Hsieh et al.[11]

Since the discovery that primaquine-induced hemolytic anemia is attributable to glucose-6-phosphate dehydrogenase (G6PD) deficiency, many other drugs, including aspirin, have been reported to have hemolytic potential in individuals with this enzyme abnormality.[12] There are currently no English-language articles discussing KD with associated G6PD deficiency. We report a case of a G6PD-deficient child with KD, and review the literature focusing on KD, aspirin, and G6PD deficiency.

## Case report

A 10-month-old boy (weight: 11.3 kg (90th to 97th percentile for age; height: 80 cm) had been well until admission, when fever, lethargy, irritability, rhinorrhea, and intermittent vomiting developed, and oral intake decreased after 3 days of fever. The patient was born full-term and was delivered vaginally; the Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. The results of routine newborn metabolic screening tests performed in Taiwan revealed G6PD deficiency, and the G6PD quantity was 0.44 U/g hemoglobin (class II G6PD deficiency in World Health Organization classification). He had been well otherwise, reaching normal growth and development milestones. His childhood immunization schedule reportedly was up to date, and he had no known allergies to drugs or foods. He did not attend a day care center and did not have a known history of travel or toxin exposure.

The vital signs on Day 4 of fever were: temperature 38.2°C, blood pressure 90/48 mmHg, heart rate 142 beats/minute and respiratory rate 27 breaths/minute. His conjunctivae were injected and nonicteric, his throat was injected (swelling and redness over throat), and he had two engorged lymph nodes in the anterior triangle of the left side of his neck on Day 4 of fever onset. The initial blood investigations were: white blood cell count, 13,100 cells/μL; segment/lymphocyte, 55/33%; hemoglobin, 9.6 g/dL; platelet count, 339,000 cells/L; carbon dioxide, 16.2 mEq/L; aspartate transaminase, 25 U/L; alanine aminotransferase, 13 U/L; albumin, 3.6 g/dL; and C-reactive protein, 133.2 mg/L. Urinalysis was normal without pyuria. Strawberry tongue with reddish lips, polymorphous skin rashes over the trunk and limbs, and erythematous palms were found on Day 5 after fever onset, symptoms compatible with the diagnosis of KD. Due to the possible risk of acute hemolytic anemia, high-dose aspirin was not prescribed for this G6PD-deficient patient. The fever declined within 12 hours after initial IVIG administration (2 gm/kg in 12 hours). A cardiac echogram (on Day 4 before IVIG) revealed mild dilatation of the left coronary artery (2.65 mm). He was discharged on Day 8 and dipyridamole (3 mg/kg/day) instead of low-dose aspirin was prescribed to prevent thrombocytosis. We prescribed neither high-dose nor low-dose aspirin for this patient during his treatment course; however, he experienced good recovery from CAL (2.17 mm) at 6-week follow-up examination.

## Discussion

Aspirin has been used in the treatment of KD for many years, even earlier than the use of IVIG in KD. Although aspirin has important anti-inflammatory (at high dose) and antiplatelet (at low dose) activity, it does not appear to lower the frequency of the development of coronary abnormalities.[6,11] During the acute phase of illness, aspirin is administered at 80 to 100 mg/kg per day in four doses. High-dose aspirin and IVIG appear to possess an additive anti-inflammatory effect. Practices regarding the duration of high-dose aspirin administration vary across institutions (from 30-50 to 80-100 mg/kg/day),[11] and many centers reduce the aspirin dose after the child has been afebrile for 48 to 72 hours. Other clinicians continue high-dose aspirin until Day 14 of illness and 48 to 72 hours after fever cessation.[8,11] When high-dose aspirin is discontinued, a low-dose aspirin regimen (3-5 mg/kg/day) is begun and maintained until the patient shows no evidence of coronary changes by 6 to 8 weeks after the onset of illness.[8] For children who develop coronary abnormalities, aspirin may be continued indefinitely.[8,13] However, Reye syndrome is a risk in children who take salicylates while they are experiencing active infection with varicella or influenza, and has been reported in patients taking high-dose aspirin for a prolonged period after KD.[14] Hsieh et al[11] reported that nonaspirin treatment of acute KD had no effect on the response rate of IVIG therapy, duration of fever, or incidence of CAL when children were treated with high-dose IVIG as a single infusion. It seems unnecessary to expose children with acute KD to high-dose aspirin, especially those with G6PD deficiency. However, in the literature, low-dose aspirin has been prescribed for at least 6-8 weeks to prevent thrombocytosis in patients with KD because of the antiplatelet effect.[8] If patients had an allergic reaction or intolerance to a particular drug, clinicians must discontinue its use and look for alternatives. Aspirin was used, often in conjunction with dipyridamole, in most patients. Dipyridamole has been used to treat patients with a coronary aneurysm resulting from KD.[15,16]

The relationship between aspirin therapy and hemolytic disorder in G6PD- deficient patients is unclear. Also, there is no literature discussing the use of low-dose aspirin and outcome of KD. G6PD deficiency, an X-linked disorder, is

the most common enzymatic disorder of red blood cells in humans. The clinical expression of G6PD deficiency encompasses a spectrum of hemolytic syndromes. Although affected patients are usually asymptomatic, some have episodic anemia whereas a few have chronic hemolysis. With the most prevalent G6PD variants (G6PD A- and G6PD Mediterranean), severe hemolysis is induced by the sudden destruction of older, more deficient erythrocytes after exposure to drugs with a high redox potential or to fava beans, selected infections, or metabolic abnormalities. The likelihood of developing hemolysis and the severity of disease are determined by the magnitude of the enzyme deficiency, which in turn is determined by biochemical characteristics of the G6PD variant. The World Health Organization has classified the different G6PD variants according to the magnitude of the enzyme deficiency and the severity of hemolysis.[17] Class I variants are characterized by severe enzyme deficiency (less than 10% of normal) and are associated with chronic hemolytic anemia. Class II variants also are associated with severe enzyme deficiency, but are usually only intermittently associated with hemolysis. Class III variants are associated with moderate enzyme deficiency (10 to 60% of normal) with intermittent hemolysis usually associated with infection or drugs. Class IV variants have no enzyme deficiency or hemolysis. Class V variants have increased enzyme activity. Classes IV and V are of no clinical significance. The incidence of hemolysis development in patients with G6PD deficiency after taking aspirin is related to dosage.[18] G6PD deficiency is commonly considered a contraindication to aspirin intake. However, a few studies[12] have suggested that aspirin can be safely administered in therapeutic doses to G6PD-deficient patients without nonspherocytic hemolytic anemia. Antiplatelet therapy is most commonly used to prevent thrombotic events in adults with atherosclerotic vascular disease, and for certain types of congenital heart disease in children, stroke, and KD.[19] Unfortunately, very few data on the efficacy and safety of antiplatelet therapy for pediatric patients, and even patients with G6PD, are available. No prospective data exist to guide clinicians in choosing an optimal regimen. Therapeutic regimens used in patients with KD depend on the severity of CAL and include antiplatelet therapy with aspirin, with or without dipyridamole or clopidogrel; anticoagulant therapy with warfarin or low-molecular-weight heparin; or a combination of anticoagulant and antiplatelet therapy.[8]

A few articles have reported G6PD-deficient patients with sustained KD.[20] However, the question of whether aspirin is suitable for KD patients with G6PD deficiency remains unanswered. Because aspirin has hemolytic potential in patients with G6PD deficiency, and because of its controversial role in the acute phase of KD, we did not prescribe aspirin for this patient. The fever subsided after single high-dose IVIG treatment with a good disease outcome (neither IVIG resistance nor CAL formation), which may support the necessary role of high-dose aspirin in the treatment of KD in the acute phase.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

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