

Severe Jaundice in Two Children with Kawasaki Disease: A Possible Association with Gilbert Syndrome

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Kawasaki disease is a systemic vasculitis, mainly encountered in children. It may affect any organ. Acute cholestasis and severe obstructive jaundice is an atypical manifestation of the disease. We herein present two children with Kawasaki disease and severe direct hyperbilirubinemia who also were homozygous and heterozygous respectively for the (TA)₇ promoter polymorphism of Gilbert syndrome. Intravenous immunoglobulin was administered to both patients at the acute phase of the disease and the fever remitted within 24 hr following the immunoglobulin administration. Furthermore oral aspirin at a dose of 80-100 mg/kg/24 hr was also given. The first child did not develop any coronary ectasia or aneurysm, whereas dilation of the right coronary artery was identified in the second child, one month after the disease onset. We discuss the possible contribution of Gilbert syndrome to the development of jaundice in our patients.

Key Words: Kawasaki Disease; Gilbert Syndrome; Jaundice; Acute Cholestasis

INTRODUCTION

Kawasaki disease (KD) was first described in 1974 (1). Since then, a series of children diagnosed on the basis of certain clinical features, have been reported and the disease has become the leading cause of acquired heart disease in children (2). Apart from the specific diagnostic criteria, there are several other early or late features of the disease (2, 3). Jaundice is a rather uncommon clinical finding, attributed mainly to direct hyperbilirubinemia due to liver dysfunction or cholestasis (4). Elevated bilirubin and increased CRP, LDH, γ GT were associated with unresponsiveness to treatment with intravenous immunoglobulin (IVIG) (5).

We, herein, report two children with KD and severe direct hyperbilirubinemia who were either homozygous or heterozygous for the (TA)₇ promoter polymorphism of Gilbert syndrome. This syndrome is a well known cause of indirect hyperbilirubinemia under certain circumstances (6). We discuss the possible contribution of Gilbert syndrome to the development of jaundice in our patients.

CASE DESCRIPTION

Case 1

A 7-yr-old previously healthy boy was admitted to the hospital, in 2008, with abdominal pain, fever and rash. Physical examina-

tion revealed generalized rash, small palpable axillary lymph nodes and marginally palpable liver. Later, he developed jaundice due to direct hyperbilirubinemia accompanied with elevated aminotransferases. Abdominal ultrasound and MRCP were performed which were normal. The patient was initially given penicilline which was changed to cefotaxime upon clinical suspicion of infection. The 3rd day of the disease he developed oedema of the hands and feet, conjunctivitis and cheilitis. The 5th day he was still febrile and IVIG at a dose of 2 g/kg plus aspirin at a dose of 80 mg/kg/24 hr were administered with the presumptive diagnosis of KD. Since then, the child remained afebrile, icterus gradually remitted and transaminases returned to the normal range. A cardiologic evaluation with triplex ultrasound examination was performed on the 5th and the 10th day of the disease as well as six weeks later without revealing any ectasia or aneurysm formation of the coronary arteries. Desquamation of fingers and toes developed on the 10th day.

On admission, the laboratory investigation showed white blood cells 11,920/ μ L with a shift to the left (neutrophils 89%, lymphocytes 4% and monocytes 7%), Hb 13.7 g/dL, Ht 40.2%, platelets 264,000/ μ L, CRP 80 mg/L. It is of note that hemoglobin gradually decreased to 8.2 g/dL and on the 10th day of the disease it returned to 9.6 g/dL. The blood cultures were sterile and PCR for pneumococcus, haemophilus, staphylococcus, meningococcus, listeria and pseudomonas were negative. A strept-

test was also negative and pharyngeal culture revealed normal flora.

When jaundice was developed, bilirubin was as high as 7.45 mg/dL with a direct component 4.86 mg/dL. It gradually decreased and on the 10th day of the disease it was 1.35 mg/dL, with a direct component of 0.74 mg/dL. SGOT was 84 U/L and SGPT 138 U/L on the 2nd day of the disease and gradually returned to the normal range. PT and aPTT were within normal range, whereas γ GT and alkaline phosphatase were elevated (134 U/L, 316 U/L respectively). As jaundice has been considered an atypical presentation of KD, serological analysis for several hepatotropic viruses as well as for rickettsia and leptospira was performed. It revealed only antiHBs which were positive due to previous immunization. Because of the severity of jaundice the child was examined genotypically for Gilbert syndrome and Wilson's disease. DNA analysis for Gilbert syndrome revealed homozygosity for the (TA)₇ promoter polymorphism.

Case 2

A 3.5-yr-old girl was admitted to the hospital, in 2003, with high spiking fever of 4 days duration and generalized rash. She also developed jaundice and conjunctivitis 24 hr prior to admission. On clinical examination, she was in compromised general condition, with erythema and swelling involving the upper and lower extremities, cheilitis, erythema of the genitals and hepatosplenomegaly. At the clinical suspicion of a bacterial infection, cefotaxime and vancomycin were administered.

On admission, the laboratory investigation revealed leukocytosis (white blood cells 31,400/ μ L, neutrophils 85% lymphocytes 4%, monocytes 11%). Hb was 11 g/dL, Ht 32.4%, platelet count 346,000/ μ L, CRP 247 mg/L and bilirubin 15.1 mg/dL with direct component of 12.5 mg/dL. The third day of hospitalization, Hb decreased to 7.4 g/dL and it returned gradually to 12.2 g/dL in a month time. Bilirubin decreased to 2.7 mg/dL on the third day after admission with direct bilirubin being 1.8 mg/dL. On admission, liver function tests were as following: SGOT 41 U/L, SGPT 124 U/L, alkaline phosphatase 186 U/L, γ GT 56 U/L. She also had hypokalemia and hyponatremia which were corrected by the administration of the appropriate fluids. The remaining biochemistry findings were within the normal range. Chest X-ray finding was normal and abdominal ultrasound revealed mild hepatomegaly with normal liver echogenicity. Serological tests to several viruses, leptospira and rickettsia were all negative whereas anti-Hbs were positive due to prior immunization. The 6th day of the disease and while the patient was still febrile, IVIG was administered at a dose of 2 g/kg and oral aspirin (100 mg/kg/day) with the suspicion of KD.

She remained afebrile the 8th day of the disease and the same day she also developed desquamation of fingers and toes and small palpable cervical lymph nodes. Echocardiograms performed on the 5th, the 10th and the 15th day of the disease were

all normal. However, one month later, the follow-up echocardiogram revealed dilation of the right coronary artery. Because of the jaundice, DNA analysis for Gilbert syndrome was performed which revealed that the child was heterozygous for (TA)₇ promoter polymorphism.

DISCUSSION

Kawasaki disease is characterized by acute systemic vasculitis which can affect almost any organ (3). Jaundice, due to direct hyperbilirubinemia, is a rare clinical feature of the disease (4). However, hydrops of gallbladder and acute cholestasis were described not only as clinical features of the disease but also as atypical presenting manifestations (3). Pathophysiology of jaundice during KD is attributed to cholestasis, an explanation further supported by elevated γ -glutamyltransferase and alkaline phosphatase activities (4). Taking into consideration the elevated values of bilirubin, a finding rather uncommon in KD, we investigated many different factors of jaundice among which Gilbert syndrome.

Gilbert syndrome was first described in 1901 by Gilbert and Lereboulle (6). In patients with Gilbert syndrome, hepatic glucuronidating activity is reduced to about 30% of normal (6). Indeed, in 1995 Bosma et al. (7) showed the reduced expression of bilirubin UDP-glucuronosyltransferase 1, due to an abnormality in the promoter region of the gene for this enzyme. More specifically, individuals with Gilbert's syndrome were homozygous for two extra bases (TA) in the TATAA element of the 5 promoter region of the gene (7). Gilbert syndrome is common in Caucasians (11%-16%) (7). It is characterized by elevated levels of unconjugated bilirubin and 30% elevation of bilirubin monoglucuronide excreted in the bile, which is less water soluble than the normal diglucuronide (6). Therefore, Gilbert syndrome may contribute to the cholestasis induced by KD. Furthermore, one third of individuals with Gilbert syndrome have minor abnormalities in plasma clearance of bromsulfophthalein and indocyanine green, dyes which were considered as indicators for hepatic clearance (8). These abnormalities imply that a defect in hepatic uptake, intracellular transport or excretion of bilirubin may also exist.

Gilbert syndrome plays a role in the pathophysiology of jaundice coexisting with other inducing agents such as drugs, breast feeding, pyelonephritis or coinherited disorders mainly G-6PD deficiency, β -thalassemia and hereditary spherocytosis (6). The contribution of Gilbert's syndrome to gallbladder stone formation even in patients without hemolytic conditions is also known (9). More recently, an association of Gilbert syndrome with EBV induced cholestasis which was also reported in children with acute acalculous cholecystitis due to EBV infection (10). It is therefore evident that although Gilbert syndrome is an innocent condition, it can exaggerate the clinical manifestations of indirect

hyperbilirubinemia as well as cholestasis of other clinical disorders.

In conclusion, Gilbert syndrome contributed to some extent to the hyperbilirubinemia of KD in our patients. Gilbert syndrome should therefore be considered in the etiology of jaundice in children with KD. It may also be considered as a risk factor for the KD severity as elevated bilirubin is a predictive factor for coronary artery abnormalities.

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