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Analysis of hyperbilirubinemia in patients with Kawasaki disease

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Abstract

The present study attempted to analyze the clinical characteristics and pathogenesis of Kawasaki disease (KD) in children with hyperbilirubinemia.

A total of 390 children with KD hospitalized in our hospital from September 2018 to July 2019 were selected and divided into control (270 cases) and hyperbilirubinemia (120 cases) groups based on the total, direct, and indirect bilirubin values after admission. Clinical data of the inflammatory index and fever process of the 2 groups were analyzed and compared.

The difference in sex and age between the 2 groups was statistically nonsignificant ($P > .05$). In the hyperbilirubinemia group, the white blood cell count, C-reactive protein, hemoglobin, platelet count, erythrocyte sedimentation rate, alanine aminotransferase, aspartate aminotransferase, albumin, and routine urine leucocyte; and incidence of coronary artery expansion, heart injury, and unreactive gamma globulin treatment were higher than those in the control group and the differences were statistically significant ($P < .05$). In the hyperbilirubinemia group, the mean fever duration before admission was shorter than that in the control group, whereas the fever duration after gamma globulin treatment was longer than that in the control group; these differences were statistically significant ($P < .05$).

Hyperbilirubinemia incidence in children with KD was approximately 30.77% (120 cases), of which increased direct bilirubin was observed in 70.83% (85 cases) and increased indirect bilirubin in 29.17% (35 cases). Children with KD combined with hyperbilirubinemia exhibited a strong inflammatory reaction, which may be due to liver damage or biliary block.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase CRP: C-reactive protein, ESR = erythrocyte sedimentation rate, Hb = hemoglobin, KD = Kawasaki disease, PLT = platelet, WBC = white blood cell.

Keywords: children, hyperurticemia, inflammatory response, Kawasaki disease

1. Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is an immune-mediated systemic vasculitis that mainly affects the small arteries of the various systems in the body, causing arteritis in many organs. The disease has unknown etiology. KD can cause damage in multiple organs such as the coronary arteries, heart, joints, liver, central nervous system, muscles, and kidneys. The occurrence of hyperbilirubinemia in children with KD is due to abnormal bilirubin metabolism caused by various enzymes in the liver, direct liver injury, or abnormal bile metabolism.[1] KD complicated with hyperbilirubinemia has been rarely reported in China and other countries, with cases in children being rarer. The purpose of this study was to investigate the incidence and clinical features of KD associated with hyperbilirubinemia and to further explore the related pathogenesis. Our findings would contribute to the early identification of severe KD cases.

2. Materials and methods

This study was approved by the ethic committee of Xingtai People's Hospital. Written informed consent was obtained from the children's parents.

2.1. Research objects

A total of 390 children in the age group of 0 to 14 years with KD hospitalized in the Xingtai People's Hospital in the Hebei Province (China) from September 2018 to July 2019 were included in the study. The inclusion criteria were children aged between 0 and 14 years with KD diagnosed upon discharge according to the diagnostic criteria revised by the American Heart Association in 2004[2]; and children received complete treatment without the administration of gamma globulin and aspirin. The exclusion criteria were children treated with gamma globulin,

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The datasets used and analyzed during the current study are available from the corresponding author on request.

The authors declare that they have no conflict of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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aspirin, or hepatoprotective drugs before admission; children with primary or genetic metabolic diseases associated with liver function damage or hepatitis, kidney disease, and bilirubin rise identified before onset of KD; or incomplete case data.

2.2. Research objects

The data on their clinical symptoms and laboratory examination were collected. On the basis of the serum bilirubin levels, the patients were divided into the hyperbilirubinemia group (120 cases) and the control group (270 cases) based on their fasting blood test results. Patients with total bilirubin > 23 μmol/L, direct bilirubin > 8.0 μmol/L, and indirect bilirubin > 18 μmol were categorized into the hyperbilirubinemia group. Upon diagnosis, the children were orally administered enteric-coated aspirin at a dose of 30 to 50 mg/(kg/day) 3 times daily, which was adjusted to 3 to 5 mg/(kg/day) after 3 days after the fever had subsided. Large doses of gamma globulin 2 g/kg were administered by one intravenous infusion from days 5 to 10 of the disease course, and the duration of intravenous infusion was longer than 12 hours.

2.3. Clinical data

Demographic data of the children were collected. The time of fever onset before admission, the duration of fever after admission, and the time when the body temperature dropped to normal after treatment with gamma globulin were recorded. Laboratory analyses such as white blood cell (WBC) count, hemoglobin (Hb), platelet (PLT) count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (propagated), routine urine examination, total bilirubin, direct bilirubin, indirect bilirubin, and myocardial enzymes (including 2 exceptions) were performed, and test data were collected after admission. Echocardiography (atrioventricular diameter enlargement, coronary artery dilatation) was also performed and data analyzed.

2.4. Standard of instrument and coronary artery dilatation

Color Doppler echocardiography was used to select the probe frequency of 2.5 to 7.5 mHz. The following diagnostic criteria for coronary artery disease were applied[3]: coronary artery diameter of >3 mm in children <5 years and >4 mm in children ≥ 5 years; significantly enlarged inner diameter of coronary artery in the adjacent area (≥1.5 times); and the *z*-value of the inner diameter of coronary artery ≥2 mm. The dilated coronary arteries might be narrowed or occluded by thrombosis or thickening of the lining.

2.5. Statistical analysis

SPSS 18.0 (SPSS Inc., Chicago, IL) was used for statistical analysis of data. The data with normal distribution were described as means ± standard deviations. Independent sample *t* test or rank-sum test were performed to compare the data between the 2 groups. Quantitative data were expressed as numbers and percentages, and the Chi-square test was conducted. $P < .05$ was considered statistically significant.

3. Results

3.1. General information

Of the 390 children with KD, 120 (30.77%) had hyperbilirubinemia, of whom 85 children had increased direct bilirubin and 35 had increased indirect bilirubin. In the latter, the highest total bilirubin values reached 203 μmol/L. In this study, 85 children were administered amoxicillin or cephalosporins before admission, whereas 15 were administered roxithromycin or azithromycin for 3 to 5 days. A total of 102 patients were treated by Chinese patent medicine for 5 to 9 days, whereas 67 patients were treated with ribavirin for 3 to 5 days. Ibuprofen or paracetamol were administered as antipyretics to attenuate fever for a time duration ranging from 3 to 9 days (average time duration, 3.5 days). Dexamethasone was administered in 20 patients with fever; however, only 2 patients had isolated hyperbilirubinemia with no involvement of other organs such as heart and kidney. No liver function damage was observed, and hyperbilirubinemia was due to the earlier use of drugs before admission to the hospital.

The mean age of the 270 children in the control group comprising 176 males and 94 females was 2.98 ± 1.03 years, whereas that of the 120 children in the hyperbilirubinemia group comprising 86 males and 34 females was 2.77 ± 1.13 years. The difference in the sex and age between the 2 groups was statistically nonsignificant (Chi-square = 1.853, $t = 0.54$, Chi-square = 1.778, $P > .05$).

3.2. Comparison of laboratory data

The WBC count, PLT count, CRP, ESR, Hb, ALT, AST, albumin, routine urine WBCs, myocardial enzyme levels, expansion of coronary artery, heart injury incidence, and gamma globulin treatment without reaction rates were higher in the hyperbilirubinemia group than those in the control group, and these differences were statistically significant ($P < .05$) (Table 1). A total of 5 cases of aseptic meningitis, 15 cases of pericardial effusion, 1 case of coronary artery aneurysm with myocardial infarction, and 1 case of KD shock syndrome occurred in the hyperbilirubinemia group.

3.3. Comparison of clinical symptoms

In the hyperbilirubinemia group, the mean fever duration before admission was shorter than that in the control group, whereas the fever duration after the gamma globulin treatment was longer than that in the control group, and these differences were statistically significant ($P < .05$; Table 2).

In the hyperbilirubinemia group, the incidence of unresponsiveness to the first treatment with gamma globulin was higher than that in the control group, and the difference was statistically significant ($P < .05$). However, no significant difference was observed in the incidence of unresponsive gamma globulin treatment after the second dose ($P > .05$) (Table 3).

4. Discussion

Here, we studied children with KD and hyperbilirubinemia in an attempt to analyze the clinical characteristics and pathogenesis of KD in children with hyperbilirubinemia. A total of 120 children with a combination of KD and hyperbilirubinemia were included, with an incidence rate of 30.77%. Before admission, some of the patients had used antibiotics, Chinese patent medicines, and antipyretic drugs with different ingredients. Therefore, these drugs might have affected the concentration of serum bilirubin in the studied children, increasing the incidence of hyperbilirubinemia. However, Lena et al[4] conducted a statistical analysis on

Table 1

Comparison between the laboratory results of the 2 groups.

Indicators	The control group (n = 270)	The hyperbilirubinemia group (n = 120)	Statistical parameters	P
WBC $\times 10^9$/L, mean ± SD	13.8 ± 3.4	14.3 ± 4.4	$t = 0.06$	.875
Hb, g/L, mean ± SD	112.3 ± 10.3	85.4 ± 6.4	$t = 0.13$	.046
PLT $\times 10^9$/L, mean ± SD	110.3 ± 11.3	357.3 ± 26.4	$t = 0.31$	.039
CRP, mg/L, M (P_{25}–P_{75})	43.7 (34.2–87.7)	97.6 (34.2–87.7)	$Z = 4.15$	.020
ESR, mm/h, M (P_{25}–P_{75})	40.2 (23.2–65.3)	87.4 (34.2–120.7)	$Z = 1.12$	.010
ALT, U/L, M (P_{25}–P_{75})	43.8 (6.2–63.3)	103.5 (34.2–200.7)	$Z = 5.15$	.019
AST, U/L, M (P_{25}–P_{75})	37.2 (15.4–59.3)	50.5 (14.2–83.7)	$Z = 0.25$	.779
ALB, g/L, M (P_{25}–P_{75})	28.2 (25.4–40.3)	20.5 (12.2–32.8)	$Z = 5.05$	.048
Neutrophils, /μL, M (P_{25}–P_{75})	4.02 (0.0–15.3)	10.5 (5.2–30.0)	$Z = 4.21$	.379
CK-MB, U/L, M (P_{25}–P_{75})	34.2 (15.4–60.3)	60.5 (33.2–102.7)	$Z = 4.62$	.371

ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CK-MB = creatine kinase-MB, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, Hb = hemoglobin, PLT = platelet, SD = standard deviation, WBC = white blood cells.

Table 2

Comparison between the post-treatment responses of the 2 groups.

Indicators	The control group (n = 270)	The hyperbilirubinemia group (n = 120)	Statistical parameters	P
No response to the first dose of gamma globulin treatment, n (%)	15 (5.6)	13 (8.3)	$\chi^2 = 4.33$	.039
Coronary artery injury during hospitalization, n (%)	18 (6.6)	15 (12.5)	$\chi^2 = 5.14$	<.001
Coronary artery injury during convalescence, n (%)	13 (4.8)	6 (5.0)	$\chi^2 = 0.07$	.735
Fever duration before admission, d	4.3 ± 2.3	1.9 ± 1.5	$t = 2.23$	.034
Fever duration after the first dose of gamma globulin treatment, h	16.0 ± 7.5	30.6 ± 8.3	$t = 2.85$	.020

1692 infants with hyperbilirubinemia and observed that the etiology of hyperbilirubinemia was mainly caused by various infections. The authors established that antibiotics and antipyretic drugs did not contribute to the increase in serum bilirubin. In addition, antibiotics, proprietary Chinese medicine, antipyretics, and other drugs were used only for a short time before admission; thus, their influence was negligible. Foreign scholars have proposed that an elevated bilirubin level almost always indicates the presence of underlying diseases.[5]

The inflammatory indicators, WBC count, PLT count, the CRP, and ESR, were higher in the hyperbilirubinemia group than the control group.[6] In KD, the liver is stimulated by the inflammatory transmitter interleukin-6 to synthesize and secrete CRP, which activates the complement and increases the phagocytosis of WBCs. Simultaneously, the body has an acute inflammatory reaction, which causes platelet aggregation and activation of granulocytes and monocytes, resulting in increased vascular permeability, neutrophil extravasation, and vascular inflammatory reaction.[7] Therefore, we speculated that the inflammatory response of KD in children with hyperbilirubinemia was stronger.

Hyperbilirubinemia is mainly caused by the lysis of hepatocytes, which prevents the conversion of bilirubin into bile, or cholestasis. In addition, hemolysis significantly elevates bilirubin production levels, resulting in hyperbilirubinemia.

In KD, long-term fever increases hemolysis and decreases hemoglobin.[8] An earlier study observed that the hemolysis in KD was associated with the activities of anti-A and anti-B IgM antibodies, and anti-Rh IgG antibodies.[9] On the basis of the diagnostic criteria in other countries, the degree of anemia is positively correlated with the duration of active inflammation in KD.[10–14] Krause et al[15] described the presence of a peptide known as "hepcidin" in KD. This peptide is considered to block duodenal absorption, macrophage release, hepatocytic mobilization to store iron, and all functions associated with inflammatory anemia.[16,17] Therefore, serum bilirubin and hemoglobin are crucial indices of the inflammatory response in KD. In this disorder, hemolysis and the severe inflammatory reactions of various enzymes that activate the synthesis of red blood cells are hindered, resulting in hyperbilirubinemia.

ALT and AST are indices of liver function damage. KD is characterized by elevated ALT and AST; decreased serum albumin; probable association with hepatovascular inflammation leading to liver cell damage, or acute interleukins, interleukin-6, interleukin-1, tumor necrosis factor-α, and adhesion factor

Table 3

Comparison between the treatment responses of the second dose of gamma globulin treatment of the 2 groups.

Groups	The control group (n = 270)	The hyperbilirubinemia group (n = 120)	χ^2	P
No response to the second dose of gamma globulin treatment, n (%)	5 (1.9)	2 (1.9)	1.23	.830
Fever duration after the second dose of gamma globulin treatment, h	10.0 ± 5.5	9.6 ± 6.0	1.17	.779

increasing immune injury.[18] The hepcidin expression induced by high fat diet and the fatty degeneration and liver cell iron accumulation about.[17] Cholestasis was found in KD by foreign scholars, and the increased activity of gamma-glutamyltransferase and alkaline phosphatase further supported this explanation.[1] In addition, patients with KD often have Gilbert syndrome, which contribute to hyperbilirubinemia. This phenomenon was also observed in our patients.[1] Nonetheless, the relationship between these 2 conditions needs further research to be better understood. Furthermore, foreign scholars have reported that abnormal liver function can be considered an inflammatory indicator of the inflammatory response of KD.[19] Therefore, children with KD associated with hyperbilirubinemia have a stronger inflammatory response, and the liver injury caused by various factors is one of the causes of hyperbilirubinemia in KD.

In a previous examination, children with KD were in a hypercoagulable state, and B-mode renal ultrasound exhibited renal enlargement and enhanced renal cortical echo in the acute stage of KD.[20] Therefore, the kidney may suffer from acute hemodynamic changes in KD, resulting in renal capillary injury and renal vasculitis, leading to aseptic hyperleukuria. Research conducted in Iran revealed that coronary artery aneurysms in most children with KD were associated with aseptic hyperleukuria, but with no statistical difference.[21]

Heart injury is the most common complication of KD, and coronary artery injury is its most serious complication. In this study, the incidence of coronary artery injury in 390 children with KD was 31.2%, with 15.5% in the control group and 66.7% in the hyperbilirubinemia group. The difference between the 2 groups was statistically significant, suggesting that bilirubin and other indicators must be considered in the clinical treatment of KD. Most of the children receiving their final treatment with gamma globulin and enteric-coated aspirin tablets had good prognosis. However, the difference in fever duration after treatment and the (lack of) response to the first dose of gamma globulin between the 2 groups was statistically significant. However, no significant difference was observed in the incidence of lack of response to gamma globulin treatment after the second dose. Hyperbilirubinemia in KD has implications for the therapeutic effect.

Thus, hyperbilirubinemia has a higher incidence rate in KD, which may be because of hemolysis, whereas liver injury and cholestasis lead to obstructed transportation and excretion of bilirubin. The incidence of complications in the hyperbilirubinemia group in KD was higher than that in the control group. In addition, we found that the treatment effect in the hyperbilirubinemia group was longer relative to the control, and the incidence of nonresponse to gamma globulin in this group was higher than that in the control group. Hyperbilirubinemia was spontaneously attenuated with the improvement of KD, but the long-term prognosis of KD and the risk of adult coronary syndrome are still unknown. Therefore, more attention must be paid to bilirubin levels of children with KD in future research work. Furthermore, a complete follow-up mechanism should be identified.

Author contributions

Conceptualization: Fang Cheng.
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