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Paraclinical Evolutions Regarding Liver and Renal Abnormalities of Kawasaki Disease in the Southeast of Iran

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Background: Kawasaki disease (KD) is a vasculitis affecting multi-organ systems including liver and kidneys. KD is diagnosed by some clinical criteria including sterile pyuria, microscopic hematuria, proteinuria due to renal involvement, liver abnormalities manifesting as abnormal liver function tests, gallbladder hydrops, and hypoalbuminemia.

Objectives: The aim of the study was to determine the frequency of liver and renal abnormalities in patients with KD, hospitalized in Ali-Ebne-Abitaleb Hospital of Zahedan during 2006 - 2013.

Materials and Methods: Paraclinical findings including serum and urine tests as well as gallbladder ultrasonography of 47 patients with KD hospitalized in Ali-Ebne-Abitaleb Hospital of Zahedan during 2006 - 2013 were reviewed retrospectively.

Results: Liver abnormalities were found in 22 (46.8%) cases and impaired liver function tests were more common than other liver abnormalities in this cross-sectional study. The incidence of abnormal liver function tests in this study was about 42%. Gallbladder hydrops were found in 6 (12.7%) patients and 18 (38.3%) had renal involvement. Sterile pyuria was the most common urine abnormality with incidence of 36.2%. Microscopic hematuria and proteinuria were rarely found; in addition, serum urea nitrogen and creatinine had normal levels in all patients.

Conclusions: The possibility of KD should be considered in any infants or children with abnormal results in liver or renal function tests. Paraclinical findings of liver and renal involvements of all patients were partly similar to the previous studies.

Keywords: Kawasaki Disease; Hydrops; Renal Failure

1. Background

Mucocutaneous lymph node syndrome or Kawasaki disease (KD) is an acute febrile, multisystem illness associated with multiorgan medium-sized vessel vasculitis of unknown etiology. Kawasaki et al. reported this disease for the first time in 1967. KD occurs mainly in infants and children younger than 5 years and the peak incidence is at 9 to 11 months of age. Due to the unknown etiology and absence of diagnostic tests, specific clinical criteria and laboratory data are used for diagnosis of KD (1, 2). According to the American Heart Association (AHA) criteria, prolonged fever lasting longer than 5 days together with at least four of the five major clinical characteristics of KD including diffuse mucosal inflammation, bilateral nonpurulent conjunctivitis, dysmorphic skin rashes, indurative angioedema over the hands and feet, and cervical lymphadenopathy are required for diagnosis KD (Figure 1). In addition to the diagnostic criteria, there is a wide range of nonspecific clinical features, including irritability, uveitis, aseptic meningitis, cough, vomiting, diarrhea, abdominal pain, gallbladder hydrops, urethritis, arthralgia, arthritis, hypoalbuminemia, liver function impairment, and heart failure (3). The inflammatory process affects multiple organs such as liver and kidney; hepatic dysfunctions and hydrops of gallbladder have been reported in KD. Several studies have investigated selected liver function abnormalities (4). Gallbladder hydrops is not common in KD, occurring in 15% of patients (2). Findings pertaining to the inflammation of kidney are sterile pyuria, hematuria, and proteinuria. According to the previous works, the most common renal abnormality has been sterile pyuria, observed in 33% - 63% of patients with KD (5, 6).

2. Objectives

In this study, we considered the frequency of children with impairment of liver and renal function test and compared them together.

Implication for health policy/practice/research/medical education:
Kawasaki disease should be considered in any infants or children with abnormal liver or renal function tests. This project evaluated liver and renal involvement of the patients.

3. Materials and Methods

In this cross-sectional study, all patients with KD hospitalized in Ali-Ebne-Abitaleb Hospital of Zahedan from January 2006 to March 2013 were studied. All patients had the KD diagnosis criteria including fever ≥ 5 days and at least four of the five principal clinical features: polymorphous rash, nonpurulent conjunctivitis, cervical lymph node enlargement, changes of the extremities, and changes of the oral mucosa (Table 1). Data were extracted from the information forms containing liver and kidney parameters. Liver parameters included liver function tests (LFTs) (including ALT, AST, ALK-P, GGT, direct bilirubin, PT), serum albumin level, and enlargement of gallbladder (longitudinal and horizontal diameters greater than the average sizes without sludge or stone) in ultrasound imaging. Renal parameters were serum BUN and Cr in addition to WBC, RBC and protein in urine tests. These parameters were considered abnormal if any test results were at the upper limit of the reference value. Urine culture was used for assessment of sterile pyuria. Paraclinical data including serum and urine tests results were analyzed by SPSS software version 21 (SPSS Inc., Chicago, Illinois, USA).

4. Results

Of all 47 patients, 22 (46.8%) had liver abnormalities (Table 5 and Figure 2). Abnormal LFTs were the most common abnormalities in this study with incidence of 42.6%. Abnormal ALT was found in 14 (29.8%) and abnormal AST was observed in 19 (40.4%) patients. High GGT level was found in 31.9% and hypoalbuminemia in 31.9% of patients (Tables 2, 3, and Figure 3). Hydrops of gallbladder was less common in this study with incidence of 12.7% (Table 3 and Figure 4). High bilirubin levels were found in 14.9% of patients (Table 2). Renal abnormalities were found in 18 (38.3%) patients (Table 5 and Figure 5). Sterile pyuria was the most common abnormal renal function finding in our study, observed in 17 patients. Incidence of sterile pyuria was 36.2%; frequencies of hematuria and proteinuria were not high. Proteinuria was found in 7 (14.9%) and hematuria in 5 (10.6%) patients. Since serum levels of BUN and Cr were normal in all children, acute renal failure was not observed (Table 4).

5. Discussion

KD is a type of vasculitis that usually occurs in infant and children and affects multiple-organ systems (6, 7). Although KD occurs in all races, it is more common in the Asian race. The incidence of KD is increasing worldwide with an unknown etiology (8). The inflammatory process of this vasculitis affects multiple-organ systems such as liver and kidney. Liver involvement has been reported in KD (4). We studied liver and renal abnormalities in patients with KD hospitalized in Ali-Ebne-Abitaleb Hospital of Zahedan.

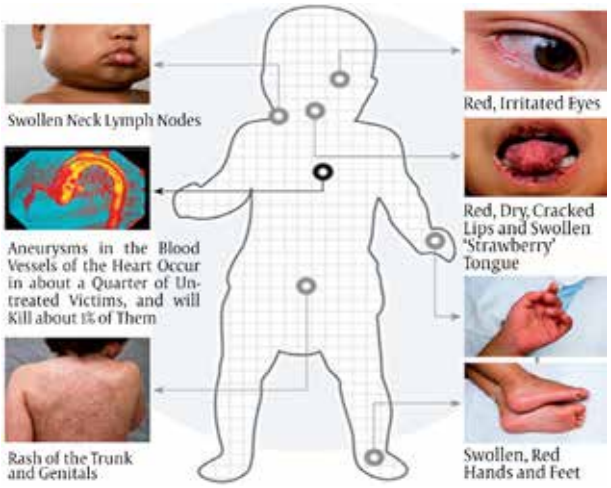

Figure 1. Anatomical Distribution of Clinical Manifestations of KD

Table 1. Diagnostic Criteria for Kawasaki Disease

Fever for 5 days or more, Presence of at least four of the five following conditions
Bilateral (nonpurulent) conjunctivitis
Skin rash
Changes in the lips and mouth
Redness, cracked lips
Strawberry tongue
Diffuse erythema of oral or pharyngeal mucosa
Changes in extremities
Erythema of palms or soles
Endurative edema of hand or feet
Desquamation of hands, feet and perianal skins
Cervical lymphadenopathy
More than 1.5 cm in diameter

Table 2. Frequency of Children With Impairment of Liver Function Tests

Liver Test	No. (%)
High ALT [a]	14 (29.8)
Low albumin	19 (40.4)
High ALK-P [a]	8 (14.9)
High bilirubin	7 (14.9)
High GGT [a]	15 (31.9)
Impaired PT [a]	3 (6.4)
Impaired LFT [a]	20 (42.6)

[a] Abbreviations: ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase;; PT, prothrombin time.

Table 3. Frequency of Children With Liver Involvement

Liver Parameters	No. (%)
Impaired LFT [a]	20 (42.6)
Hypoalbuminemia	15 (31.9)
Gallbladder hydrops	6 (12.7)

[a] Abbreviation: LFT, liver function test.

Table 4. Number of Children With Renal Involvement

Renal Parameters	No. (%)
Sterile pyuria	17 (36.2)
Proteinuria	7 (14.9)
Hematuria	5 (10.6)
High Cr [a], **BUN** [a]	0 (0)

[a] Abbreviations: Cr, creatinine; BUN, blood urea nitrogen.

Table 5. Number of Children With Liver and Renal Involvement

Parameters	No. (%)
Liver involvement	22 (46.8)
Renal involvement	18 (38.3)

Figure 2. Liver Involvement

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Figure 3. Hypoalbuminemia

Figure 4. Gallbladder Hydrops

Figure 5. Renal Involvement

Liver involvement had a wide range of hepatic symptoms including asymptomatic increase in liver enzymes, gallbladder hydrops, and cholestatic hepatitis. Increasing liver enzyme is often mild to moderate in KD. Liver disease is not a cause of morbidity and mortality in patients with KD, but subclinical liver involvement is common. Liver involvement ranges from mild asymptomatic increase in the liver enzymes to sever cholestatic hepatitis and/or hydrops of gallbladder. The mechanism of LFT impairments in KD is not clear. Hydrops of gallbladder is supposed to be secondary to the inflammatory process in the gallbladder wall. Lymph node enlargement and obstruction of the cystic duct were previously reported. In our study, 42% of patients developed elevation of one or both liver transaminases (ALT, AST) and 31.9% had elevated GGT. The incidence of elevated transaminase and GGT in our study was similar to the previous reports. In our patients, elevation of the liver enzymes was mild. Hypoalbuminemia is a usual finding in KD with likely multifactorial mechanism and was found in 40% of our patients. The diagnosis of KD is based on clinical criteria; however, none of the clinical features are pathognomonic. In addition to these clinical criteria, there are numerous nonspecific symptoms. Different conditions are considered in the differential diagnoses of KD; therefore, exclusion of other diseases that mimic clinical features of KD is required for its diagnosis. For example, streptococcal and staphylococcal

toxin-mediated illnesses, adenovirus, enterovirus, measles, and systemic allergic reactions mimic clinical features of KD (4). Sterile pyuria is the most common renal manifestation of KD and usually occurs in the acute phase. It is found in 33% - 63% of patients with KD. In this study, sterile pyuria was seen in 36.8% of patients, which was similar to other studies; moreover, it was the most common renal finding, which was in accordance with other studies (5, 6).

Several studies on liver and renal abnormalities in KD were performed in different countries including Iran (8, 9). Liver involvement, gallbladder hydrops and renal involvement in KD were reported in most of them; however, none of them were performed in Zahedan city, southeast of Iran. Therefore, we compared the frequency of abnormalities of liver and kidney as following:

Hydrops < hypoalbuminemia < impaired LFT

Renal failure < hematuria < proteinuria < sterile pyuria

According to our results, liver and renal abnormalities were common in KD. Therefore, KD should be considered in any children with any liver or renal abnormalities. Liver and renal abnormalities in our study were similar to other similar researches. According to the medical literature, complications of KD such as coronary artery aneurysm are common in KD patients with sterile pyuria; hence, with the diagnosis of KD in the initial phase, we can reduce the mortality and morbidity rates resulting from coronary events.

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Authors' Contribution

Gholamreza Soleimani and Simin Sadeghi Bojd: concepts, design, literature search, clinical studies, data acquisition, data analysis. Somayeh Rashidi, Elham Shafighi Shahri: statistical analysis, concepts, manuscript preparation. Mahsa Tajik: manuscript editing, manuscript review, data acquisition.

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