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Abnormal Liver Panel in Acute Kawasaki Disease

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Abstract

Background and Aims—Abnormalities of liver panel (liver function test [LFT]) are frequently documented in patients with Kawasaki disease (KD). We sought to define the spectrum of abnormalities in liver panel tests in children with KD. We studied the characteristics of KD patients who presented with an abnormal liver panel and their response to treatment.

Methods—We retrospectively reviewed the medical records of all KD patients admitted between 2004 and 2009 with one or more LFTs done at presentation and compared patients with and without at least 1 abnormal liver panel test including alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, and bilirubin. These patients were divided into 2 groups: those with normal LFTs (normal LFT group) and those with at least one abnormal LFT at presentation (abnormal LFT group).

Results—Of 259 patients, 240 (92.7%) patients with KD reviewed had one or more LFTs performed. One hundred nine (45.4%) had at least 1 abnormal liver panel test. Patients in the abnormal LFT group presented earlier ($P = 0.01$) and were more likely to have intravenous immunoglobulin (IVIG) resistant disease ($P = 0.01$). There was no significant difference between groups in development of coronary artery abnormalities or aneurysms. Multivariate analysis identified C-reactive protein and total bilirubin at admission as significant predictors for IVIG resistant disease.

Conclusion—We report the largest US single center study of the spectrum of liver panel abnormalities in children with acute KD. Abnormalities of LFTs are frequently found in patients with acute KD and children with abnormal LFTs were at higher risk for IVIG resistance.

Keywords

Kawasaki disease; liver function tests; IVIG resistance

Kawasaki disease (KD) is a multisystem inflammatory disease of childhood with vasculitis involving medium sized arteries.¹ The inflammatory lesions develop not only in coronary arteries but also in abdominal arteries.^{2,3} Hepatic dysfunction and hydrops of the gall bladder have been reported in KD.^{3–9} Several studies have reported on selected liver function abnormalities.^{7,8} To our knowledge, this is the first study that reports and compares clinical and laboratory characteristics and response to therapy in KD patients with and without abnormalities in liver function tests (LFTs).

METHODS

All patients with suspected KD admitted to The Children's Hospital in metropolitan Denver, Colorado, were evaluated by a pediatric infectious disease physician. Patients with a diagnosis of KD were entered in a KD database maintained by the pediatric infectious diseases department. We retrospectively reviewed the database for KD patients admitted between 2004 and 2009 and their medical records were reviewed. Demographic, clinical, and laboratory data were collected. Liver panel tests were considered abnormal if any test was above the maximum reference values for age on admission. Prothrombin time was not included in this analysis since very few patients had this index tested. Because of the potential multifactorial nature of hypoalbuminemia we decided to exclude albumin as a marker of liver dysfunction. Patients with KD that had at least one or more LFTs (bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], or gamma glutamyl transferase [GGT]) measured were included for analysis. The first day of illness was defined as the first day of fever. Intravenous immunoglobulin (IVIG) resistance was defined as persistent or recrudescence fever at least 36 hours, but not longer than 7 days, after completion of the first IVIG infusion. Definitions of coronary artery abnormalities and coronary artery aneurysms were based on echocardiographic measurement of internal diameters of the vessels adjusted for body surface area. A z-score of greater than 2.5 was considered abnormal.

For analysis, patients were divided into 2 groups for comparison purposes based on the presence or absence of any abnormalities of LFTs. The first group of KD patients had no abnormalities of LFTs (normal LFT group). The second group of patients had one or more abnormal LFTs (abnormal LFT group). We compared the demographic, laboratory characteristics, and outcomes of these 2 groups of patients. For categorical variables, the percentages of patients in each category were calculated. Wilcoxon rank sum test was used for continuous variables and Fisher exact test or the χ^2 test for dichotomous variables. Factors that had a significant association ($P < 0.05$) having any abnormal LFTs were put into a full model for multiple logistic regression analyses. A backward selection method was performed for model fitting and predictors with the highest P value were taken out from the model one at a time until achievement of the most parsimonious model. All analyses for this study were performed with SAS software, version 9.2 or SPSS software. This study was approved by the Colorado Multi-institutional Review Board.

RESULTS

A total of 259 patients with KD were admitted between January 1, 2004 and December 31, 2009. Of these 259 patients, 240 (92.7%) patients had one or more LFTs done on presentation and these patients were included in the analysis. Of the cases in the analysis group, 163 of 240 (67%) patients had complete LFTs done at admission including AST $\pm$ ALT, GGT, and bilirubin, 76/240 had all LFTs performed except a GGT, and 1 of 240 had only a GGT. The spectrum of LFT abnormalities in the 240 patients is shown in Table 1. Of 240 patients, 109 (45.4%) had at least 1 abnormality at presentation, and 131 of 240 (54.5%) had no LFT abnormalities.

Table 2 shows a summary of the demographic, clinical, and laboratory data and outcomes comparing the abnormal LFT and normal LFT groups. The median age of the abnormal LFT group was significantly older than the normal LFT group ($P = 0.01$). Patients in the abnormal LFT group were admitted significantly earlier ($P < 0.001$) and treated a median of 2 days earlier ($P < 0.001$) than patients in the normal LFT group. As expected, patients in the abnormal LFT group had higher median ALT, AST, GGT, and bilirubins. Patients in the abnormal LFT group were more likely to have more than 65% segmented neutrophils on

their complete blood count differential than the comparator group ($P < 0.001$). Median serum albumin, ESR, and C-reactive protein (CRP) were not significantly different. Twenty-two percent of patients in the abnormal LFT group had IVIG resistant disease versus 9% of patients in the normal LFT group ($P = 0.007$).

To assess which LFT values had the most significant effect on the outcome of IVIG resistant disease, we conducted a multivariate analysis using IVIG resistance as the outcome variable. Multivariate logistic regression analysis using continuous variables identified 2 statistically significant risk factors for development of IVIG resistant disease. These included high CRP (odds ratio = 1.1, 95% confidence interval = 1.02–1.1) and elevated bilirubin (odds ratio = 1.6, 95% confidence interval = 1.2–2.1).

We also did a subset analysis of the 163 children who had complete LFTs at presentation (AST $\pm$ ALT, GGT, and bilirubin). Figure 1 shows the spectrum of LFT abnormalities in this subset of patients and the proportion with overlapping abnormalities. We compared the 78 of 163 (47.8%) patients with abnormal LFTs with the 85 of 163 (52.2%) patients with normal LFTs. The results were not different from the 240 patients included in the primary analysis reported previously.

DISCUSSION

We report the spectrum of liver panel abnormalities in a consecutive series of 259 children with KD presented at a single institution. At least 1 abnormal LFT was detected in almost half of our patients. Of patients in this study, 37% presented with elevation of one or both liver transaminases (ALT, AST) and 41% had elevation of GGT. The prevalence of elevated transaminases and GGT in this study is similar to previous reports.^{3,7,8} However, in each of these reports, only a single LFT was the main focus of the paper. In the current study, we reported and analyzed a more comprehensive set of liver panel tests in a large population of patients with KD.

Hepatic disease is not a significant cause of morbidity or mortality in patients with KD, but subclinical liver involvement is common. Liver involvement ranges from mild asymptomatic increase in liver enzymes to a severe cholestatic hepatitis and/or hydrops of the gallbladder.^{3–10} In this study, most patients with elevated transaminases had only mild elevation, less than twice the upper limit of normal. Two patients, however, had transaminase elevations more than 10 times the upper limit of normal, and both of these patients presented with a picture of clinical hepatitis with jaundice. This presentation resulted in initial diagnostic confusion and delayed the diagnosis of KD and initiation of IVIG treatment. Both patients had complete resolution of their liver dysfunction shortly after receiving IVIG, and neither developed coronary artery abnormalities.

As the mechanism of hypoalbuminemia in KD is incompletely understood and likely multifactorial, we elected not to include it as an element in our definition of abnormal LFTs. This is supported by the observation that the median serum albumin was low but not significantly different between the LFT groups. Hypoalbuminemia is commonly observed in patients with KD, and several mechanisms to explain why it occurs have been proposed.^{11–13} Inflammatory processes have been associated with hypoalbuminemia and appear to be mediated, at least in part, by inflammatory cytokines directing protein synthesis toward increased production of acute phase proteins (ie, CRP), with a subsequent decrease in production of other proteins such as albumin.¹¹ Also, during acute inflammation, there may be increased albumin escape across inflamed vessels, often referred to as capillary leak. Increased capillary permeability may occur as a result of hormonal-mediated, nerve-mediated, or cytokine-mediated (especially IL-2, interferon- α , and IL-6) increases in the

movement of albumin from the intravascular compartment into interstitial fluid.¹² Finally, alterations in the interstitial gel matrix associated with an acute phase response may allow for additional interstitial space.¹³

The mechanism of abnormalities of LFTs in KD has not been established. Hypotheses include generalized inflammation, vasculitis of small and medium sized vessels, congestive heart failure secondary to myocarditis, nonsteroidal anti-inflammatory antipyretics, toxin-mediated effects, or a combination of these events.^{8,14–17} Hydrops of the gallbladder has traditionally been thought to be secondary to a vasculitic process in the gallbladder wall, although enlarged lymph nodes surrounding and potentially obstructing the cystic duct have also been reported.¹⁸ In support of vasculitis as a potential cause of liver function abnormalities in KD, vasculitis was demonstrated in the liver of 6 of 37 KD patients autopsied.² Other pathologic findings described in KD patients with hepatic presentation or in autopsies are inflammatory cell infiltration (predominantly polymorphonuclear leukocytes and eosinophils) in sinusoids and portal areas (usually localizing in the lumen of bile ducts), proliferation and/or swelling of Kupffer cells, fatty degeneration, and severe congestion.^{19–21} Giant mitochondria were seen by electron microscopy of a liver biopsy in a patient with KD who presented with cholestasis.²⁰ As giant mitochondria possibly result from impaired fission because of oxidative damage to mitochondrial DNA, membranes, and proteins, it is possible that oxidant stress that is reported in acute KD may play a role in the pathogenesis of liver function abnormalities.^{22,23} An acute rise in serum concentration of total bile acids during the acute phase of KD that gradually normalized after IVIG treatment has also been reported. These investigators postulated that the rise in total bile acids may be explained by increased bile acid synthesis from cholesterol or damage to the bile duct cells of the biliary system by cytokine activation.²⁴

In this study, IVIG resistant disease was significantly more common in the abnormal LFT group. Multivariate analysis identified high CRP and high bilirubin at presentation to be significant predictors for IVIG resistant disease. Two previous reports have also identified CRP and bilirubin as predictors for IVIG resistance, however, these 2 studies also identified transaminase elevation as a risk factor.^{17,25} One of these studies was performed in a Korean population and the other in a Japanese population. In addition, a US study identified GGT >60 IU/L as a predictor for IVIG resistance.²⁶ In our study, looking at GGT as a continuous variable, we did not find it to be a significant risk factor for IVIG resistance.

Although the association between IVIG resistant disease and coronary artery abnormalities has been reported previously, there was no difference in our study in the prevalence of coronary artery abnormalities between patients with and without LFT abnormalities.^{27,28} However, in the subset of the 163 patients who had complete LFTs obtained, there was a trend toward patients with abnormal LFTs to have a higher percentage of coronary artery abnormalities (31% vs. 19%, $P = 0.07$).

There are a few limitations to our study. First, not all of the patients included in our study had a complete set of LFTs performed. In particular, several patients did not have a GGT obtained. To control for this potential bias, we conducted a separate analysis of the 163 patients who had complete LFTs. The results from this analysis did not change any of the study conclusions (data not shown). A second possible limitation to our study is that our sample size may have been too small to detect significant differences in coronary artery abnormalities between groups.

The present study demonstrates that abnormal liver panel tests are frequently found in patients with acute KD and are associated with IVIG resistant disease. In particular, elevated bilirubin or CRP is an independent risk factor for IVIG resistant disease.

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FIGURE 1.

Overlap of LFT abnormalities in the subset of 163 KD patients with complete LFTs. One hundred sixty-three patients had complete LFTs obtained and 78 (47.8%) had abnormal values which are depicted here.

TABLE 1**Spectrum of Liver Function Test Abnormalities in KD Patients**

Test Result	ALT or AST N = 239	Bilirubin N = 239	GGT N = 164
Normal test	150 (62.8%)	207 (86.6%)	103 (62.7%)
Abnormal test	89 (37.2%)	32 (13.4%)	61 (37.3%)
>Normal but <2 times upper limit of normal	41 (17.1%)	16 (6.7%)	29 (17.7%)
≥2 times but <5 times upper limit of normal	37 (15.5%)	14 (5.9%)	26 (15.9%)
≥5 times upper limit of normal	11 (4.6%)	2 (0.9%)	6 (3.7%)

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

TABLE 2

Demographics, Laboratory Values, Clinical Characteristics, and Outcomes of Patients With Kawasaki Disease Presenting With and Without Abnormal Liver Function Tests (LFTs)

	Normal LFT Group N = 131 Median (Range)	Abnormal LFT Group N = 109 Median (Range)	P*
Demographics			
Male number; no. (%)	79 (60%)	63 (58%)	0.79 [†]
Age in months	29.5 (16–52.5)	40 (20–66)	0.01
Hepatobiliary laboratory tests			
ALT (U/L)	29 (5–65)	98 (23–530)	<0.001
AST (U/L)	28 (6–98)	51 (6–319)	<0.001
GGT (U/L)	18 (5–72)	96 (10–395)	<0.001
Bilirubin (mg/dL)	0.3 (0.1–4.0)	0.6 (0.1–7.0)	<0.001
Albumin (g/dL)	3.2 (1.8–4.5)	3.2 (1.9–4.3)	0.8
Other laboratory values			
CRP at admission (mg/dL)	9.2 (0.2–56.7)	9.8 (0.2–56)	0.16
CRP ≥10 mg/dL; no. (%)	59 (45%)	53 (49%)	0.61 [†]
ESR (mm/h)	58 (1–139)	59 (1–145)	0.96
Hemoglobin (g/dL)	11.5 (7.9–14.9)	11.9 (8.2–14.3)	0.04
WBC (10 ³ /uL)	12.8 (2.0–34.4)	13.4 (3.5–27.4)	0.66
Platelets (10 ³ /uL)	414 (73–1308)	383 (82–635)	0.24
PMNs ≥65%; no. (%)	40 (31%)	63 (58%)	<0.001 [†]
Bands ≥10%; no. (%)	31 (24%)	32 (29%)	0.38 [†]
Clinical course			
Days from onset to admission	6 (1–23)	5 (1–34)	<0.001
Days from start of illness to treatment	7 (1–23)	5 (1–34)	<0.001
Outcomes			
Length of stay, (d)	3 (1–14)	3 (1–18)	0.19
Admission to PICU; no. (%)	7 (5%)	6 (6%)	1 [†]
IVIG resistant; no. (%)	12 (9%)	24 (22%)	0.01 [†]
CAA; no. (%)	23 (18%)	26 (24%)	0.26 [†]
Aneurysm; no. (%)	13 (10%)	11 (10%)	1 [†]

* Wilcoxon sum rank test.

[†] Fisher exact test.

LFT indicates liver function test; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells; PMN, polymorphonuclear leukocytes; PICU, pediatric intensive care unit; IVIG, intravenous immunoglobulin; CAA, coronary artery abnormality.