



Distribution of Diseases Causing Liver Function Test Abnormality in Children and Natural Recovery Time of the Abnormal Liver Function

Mirinae Jang, Min Su Oh, Se-Cheol Oh, and Ki-Soo Kang

Department of Pediatrics, Jeju National University School of Medicine, Jeju, Korea

Received: 26 March 2016

Accepted: 24 July 2016

Address for Correspondence:

Ki-Soo Kang, MD

Department of Pediatrics, Jeju National University School of Medicine, 15 Aran 13-gil, Jeju 63241, Korea

E-mail: kskang@jeju.ac.kr

Although liver function test abnormality is frequently noted in children, there is no report about the distribution of the etiology and natural recovery time of the abnormal liver function. From March 2005 to February 2014, clinical information was retrospectively collected from 559 children who had abnormal liver function and were hospitalized or visited the outpatient clinic at the Jeju National University Hospital. The etiology of abnormal liver function was classified into groups and the natural recovery time of abnormal liver function was analyzed. The etiological groups of 559 patients included 'nonspecific hepatitis' in 42 (7.5%), 'infection' in 323 (57.8%), 'rheumatologic and autoimmune' in 66 (11.8%), 'nonalcoholic fatty liver disease' in 57 (10.2%), 'anatomic' in 12 (2.1%), 'toxic' in 13 (2.1%), 'metabolic' in 8 (1.4%), 'hematologic' in 7 (1.3%), 'hemodynamic' in 4 (0.7%), and 'others' in 27 (4.8%). Among the 'infection' group (57.8%), the 'viral infection in the respiratory tract' subgroup, which had 111 patients (19.8%), was the most common. The natural recovery time of the abnormal liver function was 27 days (median) in 'nonspecific hepatitis', 13 days (median) in 'viral respiratory tract disease', 16 days (median) in 'viral gastroenteritis', 42 days (median) in 'viral febrile illness', and 7 days (median) in "Kawasaki disease". The information on the natural recovery time of abnormal liver function may help the physician to perform good clinical consultation for patients and their parents.

Keywords: Liver Function Test; Children; Recovery

INTRODUCTION

In the pediatric ward of our hospital, we often encounter many children with abnormal liver function test (1). Most patients only have the elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in the blood chemistry. AST and ALT elevation indicate hepatic injury, which is a primary hepatic disease or secondary to extrahepatic diseases. A few patients have jaundice or liver dysfunction associated with hepatic failure. The causes of the abnormal liver function test in children are multiple and more variable than those in adults. An overview of the etiology and grouping of the abnormal liver function test can guide the physician to take a good diagnostic approach in the patients.

We often observe slow spontaneous resolution of the elevated AST and ALT levels in the patients after recovery from their acute illness. Resolution may take from several weeks to several months. The parents wonder when their child's abnormal liver function test result will be resolved.

Although liver function test abnormality is frequently noted in children, there is no report about the distribution of the etiol-

ogy and there is no report about the natural recovery time of the abnormal liver function in diseases which show a transient abnormality in the test.

MATERIALS AND METHODS

From March 2005 to February 2014, clinical information was retrospectively collected from 559 children. All patients had abnormal liver function and were hospitalized or visited the outpatient clinic at the Jeju National University Hospital. Liver function abnormality was basically defined as elevated AST and ALT higher than 50 IU/L, respectively. Liver function abnormality might occur in combination with or without an increased bilirubin level and/or prothrombin time prolongation and low level of serum albumin. All patients in this study were differentially diagnosed using liver battery, hepatotropic virus marker, muscle enzyme, serum ceruloplasmin level, viral markers in diseases suspecting systemic infection, and/or virus polymerase chain reaction (PCR) in diseases suspecting respiratory tract infection or gastroenteritis, radiologic examination, and et Cetra.

We classified the etiology of the abnormal liver function test

into 10 groups. These groups included 'nonspecific hepatitis,' 'infection,' 'rheumatologic and autoimmune,' 'nonalcoholic fatty liver disease (NAFLD),' 'anatomic,' 'toxic,' 'metabolic,' 'hematologic,' 'hemodynamic,' and 'others.' 'Nonspecific hepatitis' is a disease which is characterized by only elevated AST and ALT levels without any other clue for suspecting other disease group or specific disease. 'Infection' group was further classified into 9 subgroups. These nine subgroups were 'hepatotropic virus infection,' 'cytomegalovirus (CMV) infection,' 'epstein barr virus (EBV) infection,' 'enterovirus infection,' 'viral infection in the respiratory tract,' 'viral acute gastroenteritis (AGE),' 'r/o viral febrile illness,' 'other viral infection,' and 'nonviral infection.' We also analyzed the natural recovery time of abnormal liver function in the disease group or subgroup showing an acute illness combined with abnormal liver function during some part of the study period.

Statistical analyses

Statistical analysis was performed using the Anova, Post Hoc (Bonferroni) of SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Ethics statement

This study had been done under the institutional review board (IRB No. JNUH 2014-07-005-002) in the Jeju National University Hospital. No informed consent form from the patients was received, because the study was just a retrospective study collecting clinical information in the electronic medical chart.

RESULTS

The age of these 559 children was 3.6 ± 4.4 years (mean ± SD), and it ranged from 1 month to 16 years. There were 338 male patients (60.5%) and 221 female patients (39.5%). Among these

559 children, the distribution of etiologic disease groups was as follows: 'nonspecific hepatitis,' 42 patients (7.5%), 'infection,' 323 patients (57.8%), 'rheumatologic and autoimmune,' 66 patients (11.8%), 'nonalcoholic fatty liver disease,' 57 patients (10.2%), 'anatomic,' 12 patients (2.1%), 'toxic,' 13 patients (2.3%), 'metabolic,' 8 patients (1.4%), 'hematologic,' 7 patients (1.3%), 'hemodynamic,' 4 patients (0.7%), and 'others,' 27 patients (4.8%) (Fig. 1).

In the 'infection' (57.8%) group, the distribution of subgroups was as follows: 'hepatotropic virus infection,' 43 patients (7.7%), 'CMV infection,' 20 patients (3.6%), 'EBV infection,' 6 patients (1.1%), 'enterovirus infection,' 9 patients (1.6%), 'viral infection in the respiratory tract,' 111 patients (19.8%), 'viral AGE,' 59 patients (10.5%), 'r/o viral febrile illness,' 41 patients (7.3%), 'other viral infections,' 18 patients (3.2%), and 'nonviral infection,' 16 patients (2.9%) (Fig. 2).

The distribution of all diseases in each group is presented in Table 1. In the 'hepatotropic virus infection' subgroup, hepatitis B virus infection was the most common. The 'viral infections in the respiratory tract' included influenza, adenovirus infection, respiratory syncytial virus infection, rhinovirus infection, upper respiratory infection, pneumonia, and bronchiolitis. The 'viral AGE' subgroup consisted of rotavirus infection and nonrotavirus infection. The 'nonviral infection' included urinary tract infection, orbital cellulitis, and acute acalculous cholecystitis et cetera. In 'rheumatologic and autoimmune' group, Kawasaki disease was the most common. The 'anatomic' group included biliary atresia. The 'toxic' group included drug induced hepatitis and TPN induced hepatitis. The 'metabolic' group consisted of Wilson disease and glycogen storage disease. The 'hematologic' group included leukemia, lymphoma, secondary hemochromatosis, pancytopenia and hemophagocytic lymphohistiocytosis. The 'others' group included neonatal hepatitis, cervical lymphadenitis, fulminant hepatic failure, and muscular dys-

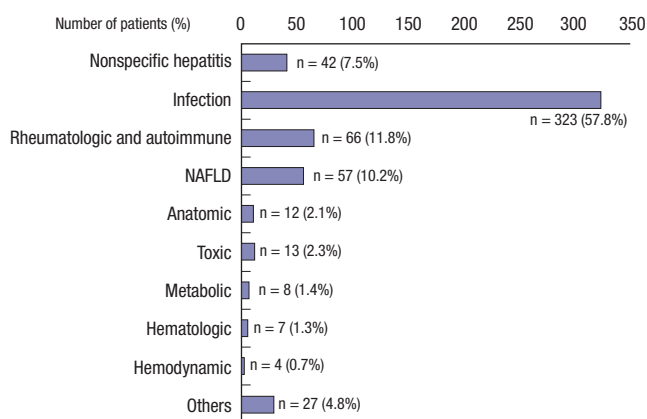


Fig. 1. The distribution of the etiologic disease groups causing abnormal liver test in 559 children. The 'Infection' group was the most common, followed by 'Rheumatologic and autoimmune,' 'NAFLD,' 'Nonspecific hepatitis,' 'Others,' 'Toxic,' and 'Anatomic' groups et cetera. NAFLD = non-alcoholic fatty liver disease.

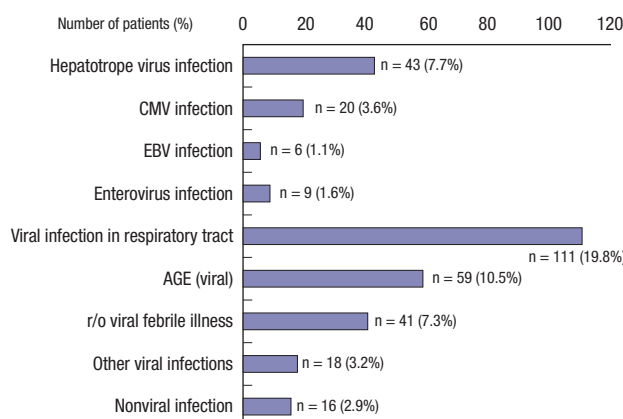


Fig. 2. The distribution of the etiologic disease subgroups in the 'Infection' group. The 'Viral infection in the respiratory tract' subgroup was the most common, followed by 'viral AGE,' 'hepatotropic virus infection,' 'r/o viral febrile illness,' 'CMV infection,' 'Other viral infection,' and 'Nonviral infection' subgroups et cetera. CMV = cytomegalovirus, EBV = Epstein barr virus, AGE = acute gastroenteritis.

Table 1. Distribution of all diseases in each group and subgroup of children with abnormal liver function test

Groups	Subgroups	Diseases	No. of patients (%)	Age, yr mean \pm SD
Nonspecific hepatitis			42 (7.5)	2.4 \pm 3.1
Infection	Hepatotropic virus infection	Hepatitis A virus infection	11	12.4 \pm 3.1
		Hepatitis B virus infection	31	7.0 \pm 5.5
		Hepatitis C virus infection	1	2.4 \pm 0.0
		Subtotal	43 (7.7)	8.2 \pm 5.6
	CMV infection		20 (3.6)	1.3 \pm 2.0
		EBV infection	6 (1.1)	4.5 \pm 2.7
	Enterovirus infection		9 (1.6)	0.9 \pm 0.5
		Viral infection in the respiratory tract	Influenza	6
	Adenovirus infection		13	1.1 \pm 0.5
	RSV infection		9	0.8 \pm 0.6
	Rhinovirus infection		2	0.9 \pm 0.1
	URI		24	1.3 \pm 1.1
	LRI (Pneumonia, bronchiolitis)		57	2.2 \pm 2.7
	Subtotal		111 (19.8)	1.7 \pm 2.2
	AGE (viral)		Rotavirus infection	26
		Non-Rota. AGE	33	2.5 \pm 3.5
		Subtotal	59 (10.5)	1.9 \pm 2.8
	r/o Viral febrile illness		41 (7.3)	1.1 \pm 1.8
	Other viral infections	Fever without a focus	16	2.4 \pm 3.9
		Herpetic gingivostomatitis	1	1.3
		Rubella infection	1	1.1
		Subtotal	18 (3.2)	2.3 \pm 3.7
		Non-viral infection	Urinary tract infection	3
	Orbital cellulitis		2	2.4 \pm 1.8
	Tonsillitis		2	1.1 \pm 0.2
	4S		1	1.7
	Acute otitis media		3	1.2 \pm 0.2
r/o Sepsis	2		0.7 \pm 0.7	
Scarlet fever	1		2.8	
Streptococcal pharyngitis	1		7.7	
Acute acalculous cholecystitis	1		13.9	
Subtotal	16 (2.9)		2.5 \pm 3.5	
Total			323 (57.8)	2.6 \pm 3.8
Rheumatologic, autoimmune	Kawasaki disease	63	2.3 \pm 1.7	
	JRA	1	5.0	
	Autoimmune hepatitis	1	13.1	
	Kikuchi disease	1	14.9	
	Subtotal	66 (11.8)	2.7 \pm 2.6	
NAFLD		57 (10.2)	11.1 \pm 2.6	
Anatomic	Biliary atresia	12 (2.1)	1.1 \pm 2.8	
Toxic	Drug induced hepatitis	10	2.6 \pm 3.2	
	TPN induced hepatitis	3	1.2 \pm 1.3	
	Subtotal	13 (2.3)	2.3 \pm 2.9	
Metabolic	Wilson disease	5	9.9 \pm 3.1	
	Glycogen storage disease	3	8.3 \pm 3.4	
	Subtotal	8 (1.4)	9.3 \pm 3.3	
Hematologic		7 (1.3)	3.2 \pm 3.2	
Hemodynamic (congestive heart failure)		4 (0.7)	0.3 \pm 0.5	
Others	Hereditary pancreatitis	1	5.6	
	Neonatal hepatitis	8	0.2 \pm 0.1	
	Fulminant hepatic failure	5	6.3 \pm 5.2	
	Cervical lymphadenitis	7	6.5 \pm 4.1	
	Diabetes Mellitus	1	13.4	
	Acute epididymitis	1	0.2	
	Idiopathic hepatosplenomegaly	1	10.4	
	Muscular dystrophy	3	2.2 \pm 1.2	
	Subtotal	27 (4.8)	3.9 \pm 4.6	
Total		559 (100)	3.6 \pm 4.4	

CMV = cytomegalovirus, EBV = Epstein Barr virus, RSV = respiratory syncytial virus, URI = upper respiratory tract infection, AGE = acute gastroenteritis, LRI = lower respiratory tract infection, 4S = staphylococcal scalded skin syndrome, JRA = juvenile rheumatoid arthritis, NAFLD = non-alcoholic fatty liver disease, TPN = total parenteral nutrition.

Table 2. Laboratory test results of etiologic groups in children with abnormal liver function test

Etiologies	ALP (U/L) (± SD)	AST (IU/L) (± SD)	ALT (IU/L) (± SD)	T.Bil (mg/dL) (± SD)	WBC (/uL) (± SD)	CRP (mg/dL) (± SD)
Nonspecific hepatitis	673 (± 285)	274 (± 438)	367 (± 659)	0.59 (± 0.98)	9,682 (± 4,387)	0.89 (± 1.88)
Infection	714 (± 338)	272 (± 481)	345 (± 519)	0.64 (± 1.22)	11,349 (± 5,645)	1.55 (± 2.60)
Rheumatologic and autoimmune	821 (± 388)	197 (± 311)	232 (± 256)	1.03 (± 1.24)	13,191 (± 4,622)	8.73 (± 6.93)
NAFLD	812 (± 254)	80 (± 48)	161 (± 99)	0.61 (± 0.48)	8,074 (± 2,071)	0.73 (± 1.25)
Anatomic	2,180 (± 1,136)	236 (± 103)	172 (± 76)	9.93 (± 3.38)	12,413 (± 6,103)	0.27 (± 0.20)
Toxic	1,014 (± 619)	443 (± 274)	391 (± 300)	1.66 (± 2.46)	10,283 (± 5,420)	2.40 (± 5.25)
Metabolic	647 (± 193)	228 (± 169)	261 (± 217)	0.43 (± 0.18)	8,763 (± 7,111)	2.47 (± 3.11)
Hematologic	684 (± 210)	411 (± 231)	310 (± 267)	4.41 (± 4.73)	81,186 (± 173,467)	3.29 (± 3.83)
Hemodynamic	714 (± 397)	371 (± 292)	182 (± 119)	2.65 (± 1.77)	13,854 (± 13,846)	0.12 (± 0.07)
Others	848 (± 587)	359 (± 525)	352 (± 345)	2.87 (± 3.17)	9,933 (± 4,971)	1.23 (± 1.40)

NAFLD = nonalcoholic fatty liver disease, ALP = alkaline phosphatase, AST = aspartate aminotransferase, ALT = alanine aminotransferase, T. Bil. = total bilirubin, CRP = C-reactive protein.

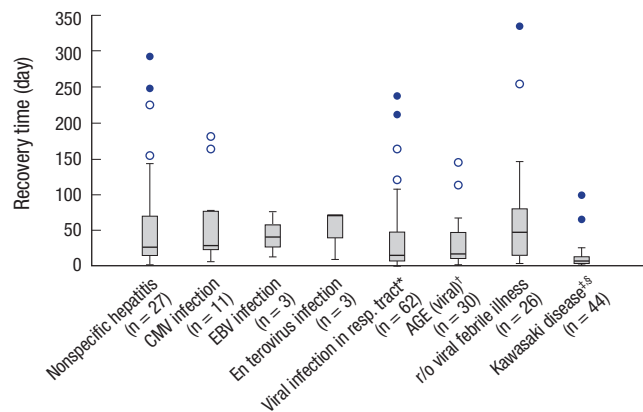


Fig. 3. Natural recovery time (median) of the abnormal liver function in etiologic disease subgroups, which had transient abnormal liver function test. The natural recovery time was analyzed in the patients of 8 etiologic subgroups who completed follow-up until recovery of abnormal liver function. The natural recovery time of 8 etiologic subgroups was 27 days (median) ranged from 2 days to 293 days in the 'nonspecific hepatitis' subgroup, 29 days (median) ranged from 7 days to 181 days in the 'CMV infection' subgroup, 40 days (median) ranged from 13 days to 76 days in the 'EBV infection' subgroup, 70 days (median) ranged from 9 days to 71 days in the 'enterovirus infection' subgroup, 13 days (median) ranged from 2 days to 238 days in the 'viral infection in the respiratory tract' subgroup, 16 days (median) ranged from 2 days to 145 days in the 'viral AGE' subgroup, 42 days (median) ranged from 4 days to 335 days in the 'r/o viral febrile illness' subgroup, and 7 days (median) ranged from 2 days to 99 days in the 'Kawasaki disease' subgroup. CMV = cytomegalovirus, EBV = epstein bar virus, AGE = acute gastroenteritis. *[†]Compared to the 'r/o viral febrile illness' subgroup: **P* = 0.008, [†]*P* = 0.020, [‡]*P* = 0.000; [§]Compared to the 'nonspecific hepatitis' subgroup: [§]*P* = 0.005 (ANOVA, Post Hoc analysis, Bonferroni).

trophy et cetera. Muscular dystrophy is a disorder mimicking abnormal liver function.

Laboratory test results for the etiologic disease groups are presented in Table 2. All groups showed variable AST and ALT

levels. The 'nonalcoholic fatty liver' group showed relatively low AST/ALT level. Total bilirubin level in the 'anatomic' group was 9.93 ± 3.38 (mean ± SD) mg/dL. The 'Anatomic' group had a markedly higher total bilirubin than the other groups.

Natural recovery time of the abnormal liver function in the etiologic disease groups, which had a transient abnormal liver function test, is presented in Fig. 3. The natural recovery time was analyzed in the patients who completed follow-up until recovery of abnormal liver function. The natural recovery time of 8 etiologic subgroups was 27 days (median) ranged from 2 days to 293 days in the 'nonspecific hepatitis' subgroup, 29 days (median) ranged from 7 days to 181 days in the 'CMV infection' subgroup, 40 days (median) ranged from 13 days to 76 days in the 'EBV infection' subgroup, 70 days (median) ranged from 9 days to 71 days in the 'enterovirus infection' subgroup, 13 days (median) ranged from 2 days to 238 days in the 'viral infection in the respiratory tract' subgroup, 16 days (median) ranged from 2 days to 145 days in the 'viral AGE' subgroup, 42 days (median) ranged from 4 days to 335 days in the 'r/o viral febrile illness' subgroup, and 7 days (median) ranged from 2 days to 99 days in the 'Kawasaki disease' subgroup.

DISCUSSION

Although liver function tests literally mean tests of hepatic synthetic function, liver function tests usually include hepatocellular enzymes, protein synthesis, bilirubin metabolism, and production of bile acids (2,3). This definition might be based on the fact that almost all diseases with liver dysfunction have abnormal levels of hepatocellular enzymes in the clinical field. The

elevation of AST and ALT indicates injury to the hepatocytes (4). Most patients with primary or secondary liver diseases show abnormal elevation of AST and ALT (5). All patients included in this study showed abnormal AST and ALT elevation. Small proportion of patients only had abnormal hepatic synthetic function or cholestatic processes in this study. Isolated elevation of AST and ALT may be either of hepatic origin or not, because the enzymes can also be derived from cardiac muscle, skeletal muscle, kidneys et cetera (3,6). Except for only a few patients with muscular dystrophy in this study, almost all patients had abnormal AST and ALT levels of hepatic origin.

This is the first report which reveals the distribution of diseases causing liver function test abnormality in children and natural recovery time of the abnormal liver function after acute illness in some diseases. Etiological groups included 'nonspecific hepatitis', 'infection', 'rheumatologic and autoimmune', 'nonalcoholic fatty liver disease', 'anatomic', 'toxic', 'metabolic', 'hematologic', 'hemodynamic', and 'others' (Fig. 1). The groups were modified from Yazigi's classification for hepatitis (7). The 'infection' group (57.8%) was the most common among the 10 groups, followed by 'rheumatologic and autoimmune' group (11.8%), NAFLD group (10.2%), 'nonspecific hepatitis' group (7.5%), 'toxic' group (2.3%), 'anatomic' group (biliary atresia, 2.1%), 'metabolic' group (1.4%) et cetera. The 'nonspecific hepatitis' is different from nonspecific reactive hepatitis. The 'nonspecific hepatitis' is a disease which is characterized by only elevated AST and ALT levels without any other clue for suspecting other disease group or specific disease. Nonspecific reactive hepatitis is just a pathological terminology, which indicates a nonspecific inflammatory process without any specific histologic findings suspecting a specific liver disease (8,9).

In the 'infection' group (57.8%), the 'viral infection in the respiratory tract' subgroup was the most common (19.8%), followed by 'viral acute gastroenteritis' subgroup (10.5%), 'hepatotropic virus infection' subgroup (7.7%), 'r/o viral febrile illness' subgroup (7.3%), 'cytomegalovirus infection' subgroup (3.6%), 'nonviral infection' subgroup (2.9%) et cetera (Fig. 2).

Spectrum and incidence of diseases causing liver function test abnormality greatly differ between children and adults. In adults, most of the abnormal liver function test includes acute and chronic hepatitis (10). Acute hepatitis is classified into several etiological groups, which include acute hepatotropic viral hepatitis, acute nonhepatotropic viral hepatitis, drug-induced acute hepatitis, cholestatic hepatitis, nonspecific reactive hepatitis, and diseases mimicking acute hepatitis (10). Chronic hepatitis is classified into the several etiological groups, which include chronic viral hepatitis, autoimmune hepatitis, drug-induced hepatitis, alcoholic liver disease, nonalcoholic fatty liver diseases and nonalcoholic steatohepatitis, metabolic diseases and other causes of chronic hepatitis, and diseases mimicking chronic hepatitis (10).

Fig. 3 shows distribution of natural recovery time data in 8 etiological disease groups or subgroups. The median natural recovery time in the 'Kawasaki disease' group was shortest. The 'viral infection in the respiratory tract' was most common in the etiological subgroups (Table 1) and had the natural recovery time with 13 days (median) ranged from 2 days to 238 days (Fig. 3).

The limitations of this study are as follows: the first, this study was a retrospective study. Although the work-up for differential diagnosis of hepatitis was performed in almost all patients, it was not done in a few patients. The interval of the follow-up liver function test, in the patients who have slow natural recovery of abnormal liver function after acute illness, was not always the same.

In conclusion, the 'Infection' group was most common among the etiological groups causing abnormal liver function in children. Among the subgroups, 'viral infection in the respiratory tract' subgroup was the most common, followed by Kawasaki disease, NAFLD, Viral AGE, hepatotropic virus, 'nonspecific hepatitis', 'r/o viral febrile illness' subgroups et cetera. Wilson disease was found in about 1% of all patients with liver function abnormality. The overview of the distribution causing liver function abnormality can make the diagnostic approach easier. The information about the natural recovery time will help the physician to perform good consultation for the patients and their parents, who have abnormal liver function tests in some disease subgroups.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Study design: Kang KS. Data collection and analysis: Jang M, Oh MS, Oh SC. Data interpretation: Kang KS. Writing: Jang M, Kang KS. Revision: Kang KS. Final approval of manuscript: all authors.

ORCID

Mirinae Jang <http://orcid.org/0000-0002-3466-1435>

Min Su Oh <http://orcid.org/0000-0001-5327-0934>

Se-Cheol Oh <http://orcid.org/0000-0003-1415-6543>

Ki-Soo Kang <http://orcid.org/0000-0001-6374-8356>

REFERENCES

1. Kang KS. Abnormality on liver function test. *Pediatr Gastroenterol Hepatol Nutr* 2013; 16: 225-32.
2. Pratt DS. Liver chemistry and function tests. In: Feldman M, Friedman LS, Brandt LJ, editors. *Sleisenger and Fordtran's Gastrointestinal and Liv-*

- er Disease. 9th ed. Philadelphia, PA: Elsevier Saunders, 2010, p1227-38.
3. O'Brien CB. The hospitalized patient with abnormal liver function tests. *Clin Liver Dis* 2009; 13: 179-92.
 4. Astegiano M, Sapone N, Demarchi B, Rossetti S, Bonardi R, Rizzetto M. Laboratory evaluation of the patient with liver disease. *Eur Rev Med Pharmacol Sci* 2004; 8: 3-9.
 5. McKenna JP, Moskovitz M, Cox JL. Abnormal liver function tests in asymptomatic patients. *Am Fam Physician* 1989; 39: 117-26.
 6. Johnson PJ. Role of the standard 'liver function tests' in current clinical practice. *Ann Clin Biochem* 1989; 26: 463-71.
 7. Yazigi N, Balistreri WF. Viral hepatitis. In: Kleigman RM, Stanton BF, St. Geme JW III, Schor NF, Behrman RE, editors. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Elsevier Saunders, 2011, p1393-403.
 8. Steigmann F, Szanto PB, Meister HP, Pamukcu F. Clinical significance of nonspecific (reactive) hepatitis. *Am J Gastroenterol* 1965; 44: 129-37.
 9. Schaffner F, Popper H. Nonspecific reactive hepatitis in aged and infirm people. *Am J Dig Dis* 1959; 4: 389-99.
 10. Suriawinata AA, Thung SN. Acute and chronic hepatitis. *Semin Diagn Pathol* 2006; 23: 132-48.