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Original Article

Clinico-etiological profile of raised aminotransferases in hospitalized children with liver disease and correlation with their severity level

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ABSTRACT

Objective: The aim of this study was to analyze the clinico-etiological profile of raised aminotransferases in children with their severity level. **Materials and Methods:** We retrospectively analyzed 65 admitted children aged 1 month to 18 years with raised aminotransferases levels from January 2015 to July 2015. We divided them into three groups based on more liver specific, alanine aminotransferase (ALT) levels as mild (1-3 times of normal), moderate (3-20 times of normal), and severe if ALT ≥20 times. **Results:** Total 65 children were retrospectively studied with a mean age of 72±52 months (range 1 month - 18 years), and male: Female ratio of 1.5/1. These patients were divided into three groups on the basis of their maximum ALT levels. Average levels of deranged ALT (mean±standard deviation) in mild, moderate, and severe groups were 78.8±27, 289±153, and 1938±861 IU/L, respectively. Out of 65 children, the clinical presentation was acute hepatitis in 35 (53%), acute liver failure in 15 (23%), acute on chronic liver failure in 7, and chronic liver disease in 8 patients. The etiologies were acute infective hepatitis in 41% (27) followed by metabolic in 15% (10), extra hepatic obstruction (7), autoimmune hepatitis (5), ischemic causes (7), neonatal hepatitis (2), hemophagocytic lymphohistiocytosis (HLH) (2), drug induced (2), cryptogenic (2), and diabetic ketoacidosis (1). Mild elevation of aminotransferases (n=17) was most commonly seen in metabolic liver disease (35%) followed by biliary tract obstruction (28%). Moderate elevation of aminotransferases levels (n=24) was seen in acute infective (29%) followed by metabolic liver disease (16%). In patients with severe elevations (n=24), the most common etiological diagnosis was acute infective hepatitis in (70%) followed by ischemic hepatitis (20%). The most common cause of acute infective hepatitis was acute viral hepatitis A. **Conclusion:** On the correlation of raised ALT with etiology, we suggest that severity grading of deranged aminotransferases can guide toward etiological diagnosis and narrow down the specific investigation required. Thus, it may help in early diagnosis and cost-effective management.

Key words: *Aminotransferases, Hepatitis, Hypertransaminasemia, Serum glutamic oxaloacetic transaminase, Serum glutamate pyruvate transaminase*

Pediatric liver disorders constitute a major burden of hospital admissions. Liver function tests are one of the common routine biochemical evaluations done in patients with suspicion of liver disease. Among these, the aminotransferases (formerly transaminases) are the most sensitive biomarkers of hepatocyte integrity. Aminotransferases are intracellular enzymes produced mainly by the hepatocytes. They are normally present in serum at low levels and increase in their levelss suggests liver injury [1,2]. Aspartate aminotransferase (AST), previously known as serum glutamic oxaloacetic transaminase is widely distributed throughout the body. Besides liver, it is also present in cardiac and skeletal muscles, kidney, brain, pancreas, lung, leukocytes and erythrocytes, and in decreasing order of concentration. Alanine aminotransferase (ALT) or serum glutamate pyruvate transaminase is mainly present in liver thus more specific to liver disease [3,4]. While AST is present in both the mitochondria and cytosol of hepatocytes as two separate isoenzymes, ALT is localized to the cytosol [2-4].

Normal values of aminotransferases used in children vary among laboratories as reference pediatric standards have not been fully established. England et al. have proposed ALT centiles for age and sex based on a study in healthy European population [5]. They proposed an ALT upper limit of normal (ULN) of 60 IU/L in boys and 55 IU/L in girls during the first 18 months of life and 40 IU/L in boys and 35 IU/L in girls after the age of 18 months [5]. The screening ALT for elevation in Today's Youth (SAFETY) study conducted on a population of North American patients aged between 12 and 17 years shows that the ULN used by the most laboratories for ALT is too high to detect chronic liver disease [6].

Complete assessment of enzyme abnormalities involves careful evaluation of the predominant pattern of enzyme alteration, the magnitude alteration in aminotransferases, the

rate of change and the nature of the course of alteration [4]. The magnitude of enzyme elevation has been arbitrarily divided into mild (1-3 times ULN), moderate (3-20 times ULN), and severe (>20 times ULN, >1000 U/ml) types [3]. However, this classification is arbitrary as no standard definition exists. There are only a few studies on the approach to hypertransaminasemia in children with liver disease; especially, in a hospital setting. Through this study, we tried to analyze the data of hospitalized children with raised aminotransferases; thereby, understanding their spectrum of clinical presentation and correlate etiology with their severity level.

MATERIALS AND METHODS

This study was an observational retrospective study conducted in the Department of Paediatric Medicine, SMS Medical College, Jaipur. The study was conducted on 65 admitted children of age group, 1 month to 18 years with raised aminotransferase levels during 1st January 2015-31st July 2015. The hospital records of these patients were reviewed. All the detailed history, blood investigations, and radiological findings were noted. Full liver function test with prothrombin time (PT) international normalized ratio (INR) was analyzed. On the basis ALT levels, these patients were divided into three groups as mild (1-3 times of normal), moderate (3-20 times of normal), and severe if ALT ≥20 times [3]. The normal level of AST and ALT of our institute laboratory is 0-37 IU/L and 0-42 IU/L, respectively.

Based on the clinical picture and liver function tests, patients were divided into various groups such as acute hepatitis, acute liver failure, and chronic liver disease. Acute liver failure and acute on chronic liver failure were defined as per the following definitions.

Acute liver failure: (1) No evidence of a known chronic liver disease, (2) hepatic-based coagulopathy that is not corrected by parenteral administration of vitamin K, (3) hepatic encephalopathy must be present if the uncorrected PT or INR was between 15 and 19.9 s or 1.5-1.9, respectively; and (4) hepatic encephalopathy was not required if the PT or INR was ≥20s or 2.0, respectively [7].

Acute on chronic liver failure (Asian Pacific Association for the Study of the Liver Guidelines): Acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dl [85 μmol/l]) and coagulopathy (INR ≥1.5 or prothrombin activity <40%), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease [8].

The etiological diagnoses of these patients were noted. To ascertain the etiology in these patients our institutional protocol was as follows. We conduct infective workup and ultrasonography (USG) abdomen in each patient. Infective workup includes viral markers (hepatitis B surface antigen, hepatitis C virus antibody, hepatitis E virus immunoglobulin M [IgM], and hepatitis A virus IgM), malaria antigen, widal, and blood culture. USG abdomen with Doppler is performed to see the liver echotexture, signs of portal hypertension, biliary tract obstruction, and vascular obstructions.

Other specific investigations such as autoimmune workup (immunoglobulin G levels, Antinuclear antibody, anti-liver kidney microsomal antibodies, SMS antibody, etc., with liver histopathology), Wilson's disease workup (serum ceruloplasmin, 24 h urinary copper, slit lamp examination for Kayser-Fleischer Ring), and metabololic workup (blood gas analysis, tandem mass spectroscopy, serum lactate levels, urine reducing substance, urine succinylacetone, and histopathology of liver) are done according to the clinical scenario and standard practice guidelines to ascertain the etiology as and when required. Computerized tomography (CT) triphasic angio abdomen is done in suspected patients of Budd-Chiari syndrome. Magnetic resonance cholangiopancreatography is done in suspected cases of choledochal cyst. Diagnosis of extrahepatic biliary atresia is made on the basis of clinical presentation, USG abdomen, hepatobiliary iminodiacetic acid scan, and liver biopsy.

Compilation of data was done in Microsoft Excel 2010 spreadsheet, and percentage analysis was performed. The OpenEpi software was used for statistical analysis [9]. The correlation of the severity level with the etiology was done using simple statistical methods. Data were analyzed using descriptive statistics. $p<0.05$ was considered significant.

RESULTS

Total number of patients studied was 65, out of which 39 were male. The mean age was 72±52 months (range 1 month - 18 years). Out of 65 children, 35 (53%) had acute hepatitis, 15 (23%) acute liver failure, 7 (10%) acute on chronic liver failure, and 8 (12%) patients had chronic liver disease. Their etiological diagnosis based on appropriate investigations is noted and presented in Table 1. Their ALT levels were raised in the range of 50-3489 IU/L (normal range 0-42 IU/L). Mild elevation of ALT was seen in 17 (26%) patients with mean levels of 78.8±27 IU/L (range 50-117 IU/L). The etiologies for mild elevation were metabolic (6), extrahepatic obstruction (4), infective hepatitis (3), autoimmune hepatitis (2), diabetic ketoacidosis (1), and cryptogenic (1). The extrahepatic obstruction was due to extrahepatic biliary atresia (EHBA) in 3 and choledochal cyst in 1 case (Table 2).

Moderate elevation of ALT was seen in 24 (37%) patients with mean levels of 289±153 IU/L (range 124-686 IU/L). Moderate elevation was due to following etiologies: Infective hepatitis (7), metabolic (4), EHBA (3), neonatal hepatitis (2), ischemic (2), autoimmune hepatitis (2), HLH (2), cryptogenic (1), and drug-induced (1). The infective causes were due to viral hepatitis (2), sepsis (2), enteric fever (2), and malaria (1). Ischemic causes were due to congestive cardiac failure (1) and Budd-Chiari syndrome (1). Severe elevation of ALT was seen in 24 (37%) patients with mean levels of 1938±861 IU/L (range - 840-3489 IU/L). The most common etiological diagnosis was infective hepatitis in 17 (70%), followed by ischemic (5), autoimmune hepatitis (1), and drug-induced (1). Infective hepatitis was due to viral hepatitis

(13), sepsis (3), and falciparum malaria (1). Ischemic causes were due to shock (4) and Budd-Chiari syndrome (1) (Table 2).

Out of 27 acute infective hepatitis patients, 19 (70.4%) had viral hepatitis, 2 (7.4%) had severe falciparum malaria, 2 (7.4%) patients had enteric fever, and sepsis was present in 4 patients (14.81%). Out of 10 metabolic liver disease, 4 (40%) were Wilson disease, 3(30%) were hereditary tyrosinemia Type 1, and 1 (10%) were glycogen storage disease, and 2 (20%) cases were of suspected mitochondrial disease (Table 1).

Acute infective hepatitis had the most severe degree of enzyme elevation seen in 63% (17) of these patients while mild to moderate elevation was seen in 37% (10) of this group, ($p<0.05$).

Table 1: Clinico-etiological profile of study population (n=65)

Etiological diagnosis	Number of patients
Acute infective hepatitis (n=27)	
Acute viral hepatitis	19
Sepsis	4
Falciparum malaria	2
Enteric hepatitis	2
Metabolic liver disease (n=10)	
WD	4
Hereditary tyrosinemia type 1	3
Glycogen storage disease	1
Suspected mitochondrial disease	2
Biliary tract obstruction (n=7)	
Extrahepatic biliary atresia	6
Choledochal cyst	1
Ischemic (n=7)	
Septic shock	4
Acute Budd-Chiari syndrome	2
Cardiogenic shock	1
Autoimmune hepatitis	5
Neonatal hepatitis	2
HLH	2
Drug induced	2
Cryptogenic	2
Diabetic ketoacidosis	1

WD: Wilson disease, HLH: Hemophagocytic lymphohistiocytosis

All the patients of metabolic liver disease and extrahepatic biliary obstruction had only mild to moderate elevation of aminotransferases ($p<0.001$), (Table 3). Of the 15 cases presenting with acute liver failure, the most common cause was hepatitis A. AST/ALT ratio was calculated for different etiology. We found that 60% of autoimmune hepatitis, 50% of acute viral hepatitis, and 50% EHBA had AST/ALT <1. The ratio was more than two for 42% of ischemic hepatitis, and 50% of drug-induced hepatitis. Patients with Wilson disease (WD) who presented in acute liver failure had AST/ALT >4.

DISCUSSION

Liver diseases in children represent a significant problem with a major impact on public health. No data are available on the prevalence of liver diseases in children; especially, in developing countries. In unites states, about 15,000 children are admitted each year with liver diseases [10]. In our study, the most common presentation of hepatobiliary disease was acute hepatitis in 54% of the patients while the chronic liver disease was seen in 12.3% patients. A similar study by Yachha et al. has reported acute hepatitis in 28% and chronic liver disease in 36% of admitted children in North India [11]. Very few studies are available from this region of the world to shed light on the prevalence of chronic liver disease. The prevalence of chronic liver disease in our study was 23.1% including the acute on chronic liver disease; which is slightly less than the prevalence (36%) reported previously [11]. Metabolic liver disease was seen in 15.4% of our patients, which was similar to the figure of 16% in other North Indian hospital setting [11].

Alterations in liver enzyme levels that are encountered vary by the geographical location of the hospitals and the ethnicity of the patients. 60% of the cases of elevated hepatic AST levels in developed countries can be attributed to ischemic or toxic liver injury [12], whereas oro-fecal transmittable hepatitis viruses are the major cause (>60%) of sporadic acute and fulminant hepatitis in the developing countries [13-15]. Among the infective causes, hepatitis A was the most common cause of acute hepatitis in children in our study (41%).

Table 2: Etiological profile of deranged aminotransferases according to severity level

Mild elevation (1-3 times), (n=17)		Moderate elevation (3-20 times), (n=24)		Marked elevations (>20 times), (n=24)	
EHBA	3	Infective hepatitis	7	Acute viral hepatitis	13
Choledochal cyst	1	Autoimmune hepatitis	2	Ischemic	5
Infective hepatitis	3	EHBA	3	Sepsis	3
Hereditary tyrosinemia	3	Neonatal hepatitis	2	Falciparum malaria	1
Autoimmune hepatitis	2	WD	2	Autoimmune hepatitis	1
GSD type III	1	Ischemic	2	Drug induced	1
WD	2	Suspected mitochondrial liver disease	2		
Diabetic ketoacidosis	1	HLH	2		
Cryptogenic	1	Drug induced	1		
		Cryptogenic	1		

WD: Wilson disease, EHBA: Extrahepatic biliary atresia, GSD: Glycogen storage disease, HLH: Hemophagocytic lymphohistiocytosis

Table 3: Correlation of etiology with severity level of aminotransferases (mild to moderate vs. severe)

Etiological diagnosis	Total number	Mild to moderate elevation	Severe elevation	p-value
Acute Infective hepatitis	27	10	17	<0.05
Ischemic	7	2	5	0.07
Metabolic	10	10	0	<0.001
Extrahepatic obstruction	7	7	0	<0.001

Patients with a marked increase in aminotransferase levels more than 10 times the upper reference limits typically have an acute hepatic injury. The degree of elevation varies during the course of injury and depends on when the enzyme levels were tested. Patients with acute viral or ischemic or toxic liver injury reach the highest aminotransferase levels [4]. Similarly, our study showed that the most common cause of marked elevation of aminotransferases was acute viral hepatitis (70%) followed by ischemic injury (20%). Very high aminotransferase levels of more than >75 times the upper reference limits indicate ischemic or toxic liver injury in more than 90% of cases of acute hepatic injury, whereas they are less commonly observed with acute viral hepatitis [4]. Autoimmune hepatitis may present with a mild to marked increase in aminotransferase levels [4,16]. In our study, 40% of autoimmune hepatitis showed mild elevation, while 60% showed moderate to severe elevation of aminotransferases.

ALT exceeds AST in viral hepatitis, autoimmune hepatitis, chronic active hepatitis, and cholestatic hepatitis [3]. In our study, 60% of the autoimmune hepatitis, 50% of acute viral hepatitis, 50% EHBA had AST/ALT ratio less than one. In ischemic or toxic liver injury, AST levels usually peak before those of ALT because of the enzyme's peculiar intralobular distribution [17]. Zone three of the acinus is more vulnerable to both hypoxic (hepatocytes are exposed to an already oxygen-poor milieu) and toxic (hepatocytes are richer in microsomal enzymes) damage. Ischemic and hypoxic acute liver damage is more likely in patients with concomitant clinical conditions such as sepsis or low-flow hemodynamic state [12,17,18]. Our study showed 42% of ischemic hepatitis and 50% of drug-induced hepatitis with AST/ALT >2.

WD is a leading cause of metabolic and chronic liver disease in children [19]. The ratio of AST to ALT of more than two is usually observed in WD [20]. In acute liver failure due to WD, the serum AST level may be higher than the serum ALT level, potentially reflecting mitochondrial damage, but this finding is not sufficiently invariable to be diagnostic [19,20]. In our study, two patients of WD presented with acute liver failure with AST/ALT ratio more than two.

Only a few studies have documented the results of a thorough evaluation of patients with mildly elevated aminotransferases levels in children. Fatty liver, resulting either from alcohol use or from nonalcoholic fatty liver disease, is the major cause of mildly elevated aminotransferases in adults [4]. In our study, the metabolic liver disease was most common cause of mild elevation followed by extrahepatic obstruction. Nonalcoholic steatohepatitis and celiac disease are one of the common causes of mild elevation of ALT levels [3,4], which were not found in our study probably because the study was conducted only in admitted patients.

There were few limitations in this study. The study was a retrospective study conducted on admitted patients only; outpatients were not included in this study. The management and outcome of patients were not included.

CONCLUSIONS

Alterations in liver enzyme levels are one of the most common problems encountered in everyday clinical practice. These are a sensitive indicator of hepatocyte damage and are thus particularly useful in the early detection of viral hepatitis and in monitoring its progress. The pattern of enzyme abnormality, interpreted in the context of the patient's characteristics, can aid in directing the subsequent diagnostic workup. Awareness of the prevalence of determined liver disease in specific populations and of possible hepatic involvement during systemic illnesses or drug therapies may help the clinician identify the cause of alterations efficiently.

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