Original article

Effect of Acute Appendicitis on routine Liver Function Tests

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Background: Liver plays a central role in metabolism and host defense mechanism. It is the first organ to receive substances absorbed or microorganism translocated from gastro intestinal tract (GIT). The aim was to evaluate the effect of acute inflammation of appendix on routine liver function test.

Method: 50 cases with no history of hepatotoxic drug intake, non –alcoholic or alcoholic with AST (SGOT)/ALT (SGPT)<2,hepatitis B surface antigen (HBsAg) negative and no past history of jaundice with acute appendicitis were studied.

Result: Among 50 cases 49 cases were of acute appendicitis and its complications. Serum bilirubin was raised in 87.7% cases. It was mixed type in majority (84.6%) of the cases. The average level of serum bilirubin was 2.34 mg/dL. Serum Alanine Amino Transferase (ALT) was normal in 73.46% of the cases where as elevated in 26.54% of the case. Aspertate. Age and sex adjusted alkaline phosphatase (ALP) was normal in 51.2% of the cases where as it was elevated in 48.98% of the cases. Amino Transferase (AST) was normal in 61.22% cases whereas elevated in 38.77% of the cases

Conclusion: There was mixed type of hyperbilirubinemia and that was due to dysfunction rather than damage of the hepatocyte. This might be due to combined effect of depressed hepatocellular uptake of unconjugated bilirubin and excretion of the conjugated bilirubin by bacteria, their toxins or cytokines. The elevation of AST and ALP is of no diagnostic value where as elevation (≥1times) of ALT can be helpful to rule out acute inflammation of appendix at 95% level of confidence in clinically suspected cases of acute appendicitis.

Key Words: Acute Inflammation of Appendix, Acute appendicitis, Hyperbilirubinemia, Routine liver function tests.

Introduction

Liver performs an important role in extraordinary spectrum of functions. It helps to maintain homeostasis by detecting and altering components of both splanchnic and systemic blood. The organ regulates energy storages as well as catabolic and anabolic processes. It is ultimately involved in metabolism of bilirubin as well. Besides metabolic function, liver also plays a role in host defense. The defense mechanisms occur via Kuffer cells, neutrophils, Ito cells, endothelial cells, or the hepatocytes themselves. These cells act in concert to protect the liver and host against toxin, noxious stimuli and other pathogens. Kuffer cells may orchestra the immunologic function, directing production

of tumor necrosis factor (TNF) and interleukin-1 (IL-1) or other cytokines as well as by engulfing endotoxin or other microbials[1]. This protection is because of its central location with a large number of immunologic cells[2] as well as being the first organ to receive substances absorbed or microorganisms translocated from gastrointestinal tract (GIT). Bacterial translocation occurs from GIT after infection /inflammation [3,4] or even in healthy persons[5]. Most of the time it is cleared by immunological action of the liver and it remains sterile[6]. But when the bacterial flow overwhelms the liver causes change in hepatocellular function either directly by septic damage or indirectly by altering blood flow to the liver. The hepatic microcirculation is very sensitive to disease and consists of portal venules, hepatic arterioles, sinusoids, hepatic venules and lymphatics[7]. Various disease processes including sepsis can alter blood flow via effects on the hepatic sinusoids. Impairment of sinusoidal blood flow may result from Kuffer cell activation. Sepsis significantly affects the arrangements of the Kuffer cells in the sinusoids as well as causes progressive microcirculatory impairment.[8]

Dysfunction or damage of the liver leads to abnormality in the metabolism of substances. This can be assessed by routine liver function test that reflects the damage or dysfunction of hepatocytes, in which there is decreased excretion of substances either produced by liver (e.g. bilirubin and ALT) or by some other organs (e.g. ALP and AST). Routine biochemical test of liver function can detect disease and its severity, prognosis and helps to evaluate therapy. It is routinely used to diagnose disease and its severity but it does not differentiate one from another. Routine LFT includes estimation of serum bilirubin, ALT, AST, and ALP.

Normal serum bilirubin concentration ranges from 0.3-1.1 mg/dL. More than 90% of serum bilirubin in normal individuals is in unconjugated form. The process of production of conjugated bilirubin involves: hepatic uptake, conjugation and excretion of bile. Of these three steps, excretion appears to be the rate limiting step and the most susceptible to impairment, when liver cell is damaged.[9] When chemical analysis (Vanden Bergh reaction) is done, it reveals following type of hyperbilirubinemia. Predominantly unconjugated hyperbilirubinemia, when a patient with 80-85% of total serum bilirubin is unconjugated. Similarly a patient with more than 50%direct reacting fraction (conjugated serum bilirubin) is considered to have conjugated hyperbilirubinemia. Predominantly conjugated hyperbilirubinemia usually results from one of the three groups of disorders, hepatocellular disease, intrahepatic billiary obstruction and extra hepatic billiary obstruction. Conjugated hyperbilirubinemia without liver enzyme abnormalities is relatively uncommon but can be seen in pregnancy, sepsis or after recent surgery. Predominantly unconjugated (indirect) hyperbilirubinemia occurs due to hemolytic disorders such as autoimmune or microangiopathic hemolytic anemia. [6,10,11]

Increased liver transaminase level in liver disease reflects leakage from injured cells. The degree of elevation of transaminase generally reflects the severity of hepatic necrosis except in important setting e.g. alcoholic hepatitis, when level seldom exceeds 200-300 U/L. Marked elevation of amino-transferase suggests hepatocellular damage, most commonly seen in toxic, Viral or ischemic hepatitis (200-350U/L or more elevation). While prominent elevation (≥3times) of ALP is most suggestive of intrahepatic cholestasis or extra hepatic obstruction. Slight (one time of normal) to moderate (2 times of normal) elevation occurs in many patients with parenchymal liver disorders such as hepatitis and cirrhosis. Transient increase occurs in all type of liver disease. Striking increase in ALP (10 times of normal or more) occur more consistently with extra hepatic billiary obstruction (mechanical) or with intrahepatic (functional) cholestasis e.g. drug induced or primary billiary cirrhosis.[6,10,11]

Materials and Methods

This is a prospective study conducted at NGMC Teaching hospital Nepalgunj, Nepal during January 2004 – December 2005. 50 Consecutive cases of acute appendicitis admitted in surgical unit III were recruited for the study. Clinically suspected cases were subjected to investigations to confirm the diagnosis. Investigations included total leucocytes count, differential leucocytes count, urine analysis and ultrasound. These cases were also subjected to liver function test. Subsequently these cases were operated and clinical diagnosis was confirmed per–operatively and post operatively by histopathological examination. Their clinical and investigative data were compiled and analyzed, and following observations were obtained. Routine liver function test results were compared with laboratory reference values given in table I. **Criteria of selection for the cases**: Patient with history of alcohol intake with AST/ALT <2 or no history of alcohol and hepatotoxic drug intake, HBsAg negative and no past history of jaundice with acute appendicitis were included in the study whereas the patient with history of alcohol intake and AST/ALT >2, history of hepatotoxic drug intake, HBsAg positive and /or past history of jaundice with acute appendicitis/normal appendix were excluded from the study. **AIM:** To evaluate the effect of acute inflammation of appendix on routine liver function test.

Table: 1 Reference Range of Serum Bilirubin and Liver Enzymes

Test	Normal Range
Serum Bilirubin+	
Total	1.1mg/dL
Direct	0.2mg/dL
Liver Enzymes+	
SGPT (ALT)	≤ 35U/L
SGOT (AST)	≤ 40U/L

Alkaline Phosphatase (ALP)

Age Group	Normal Range	
	Female (U/L)	Male (U/L)
1-30 days*	48-406	75-319
1 month – 1 year*	124-341	82-383
1-3 years*	108-317	104-345
4-6 years*	96-297	93-309
7-9 years*	69-325	86-315
10-12 years*	51-332	42-362
13-15 years*	50-162	74-390
16-18 years*	47-119	52-171
20-50 years**	53-128	42-98
>50 years**	56-119	53-141

+Semi-automatic analyzer measured serum bilirubin and Enzymatic assay measured liver enzymes. *Soldin JS, Hicks JM. Pediatric reference ranges. Washington: AACC Press, 1996. P5. **Burtis CA, Ashwood ER. Eds. Teitz textbook of clinical, Chemistry. 3rd ed.Philadelphia: W.B. Saunders Company, 199,p.1829

Observation

Total number cases recruited for study were50. Among 50 cases diagnosed as acute appendicitis clinically (preoperatively), per operatively, 49 cases had inflammation of appendix and its complication included finally as they fulfill the criteria of selection. Of 49, 23 were adult males and 16 were adult females whereas 5 cases were of each male and female child. Their age ranged from 11years to 70 years. The average was 28.3 years. Duration of symptoms ranged from 5 hours to maximum 9 days. Of 49 cases of acute inflammation of appendix, 40 had inflammed appendix, 3 had gangrene, 6, had perforation with peritonitis (2 localized and 4 generalized peritonitis).

Liver function test revealed the following results. Among 49 cases, Serum bilirubin was raised (hyperbilirubinemia) in 43 (87.75%) cases where as 6 (12.25%) cases had normal serum bilirubin level (Table III). It ranged from 1.2 mg/dL to 8.4 mg/dL. The average level of serum bilirubin was 2.34 mg/dL. All the cases had direct fraction of serum bilirubin above 15%.

Liver enzymes e.g. ALT was within normal ranges in 36 (73.46%) and elevated in 13 (26.5%) cases. Among the cases that had elevated levels, in 11 (84.6%) of the cases there were marginal elevation (rise <1 time of normal, <60 U/L), rest; in 2(15.38%)cases it was minimal (<2 times, <115U/L) elevation. So, over all in 95.91% of the cases either there was normal or marginal elevation in ALT. The elevated ALT ranged from 37-102unit/liter with mean and SD57.96±19.3(Table IV)

AST was normal in 30(61.22%) cases where as it was elevated in 19(38.77%) cases Among the cases that had elevated AST, in 17 (89.47%) cases there was minimal elevation (<one time of normal) whereas in 2(10.52%)cases there was moderate elevation (>one time of normal). The elevation in all cases was less than <3 times (<100U/L) of the normal range. The elevated AST ranged from 41-100.5 unit/ L with mean and SD 61.78±24.6 (Table V). Age and sex adjusted ALP was elevated in 24 (48.98 %) cases where as 25 (51.02%) cases had normal enzyme level. Among the cases that had elevated level, one time elevation (slight elevation) was observed in21 (87.50%) of the cases, <2 times elevation was observed in 2(8.33%) of cases (moderate elevation) while only a single case1 (4.16%) had >2 times elevation (severe elevation). Over all 97.95% cases had either normal or slight to moderate (1-<2times) elevation in ALP (Table VI).

Table: 2 Age Group Wise Distribution of the Cases of AA **(n=49)**

Age Group	No. Of cases (%)
0-10	Nil
10-20	10 (20.40)
20-30	15 (30.61)
30-40	16 (32.65)
40-50	03 (06.12)
50-60	04 (08.16)
>60	01(02.04)
Total	**49 (100%)**

Table: 3 Distribution of Serum Bilirubin in cases of AA **(n=49)**

Serum Bilirubin Level	No. Of cases (%)
Elevated Serum Bilirubin	43 (87.75)
Normal Serum Bilirubin	06 (12.25)
Total	**49(100%)**

Table: 4 Distribution of ALT in cases of AA (n=49)

Observed Values	No. (%)	Value Of ALT at 95% Confidence Interval (CI)
Normal	36 (73.46%)	58.9, 85.1
Elevated*	13 (26.54%)	14.9, 41.1
Total	**49 (100%)**	

*Mean ± SD = 57.96 ± 19.3
*Range = 37-102/UL

Table: 5 Distribution of AST in cases of AA (n=49)

Observed Values	No. (%)	Value Of AST at 95% Confidence Interval (CI)
Normal	30 (61.22%)	46.2, 74.8
Elevated*	19 (38.78%)	25.2, 53.8
Total	**49 (100%)**	

*Mean ± SD = 61.78 ± 24.6
*Range = 41-1005/UL

Table: 6 Age & Sex Adjusted ALP incases of AA (n=49)

Observed Values	No. (%)	Value Of ALP at 95% Confidence Interval (CI)
Normal	25 (51.02%)	36.3, 65.6
Elevated	24 (48.98%)	34.4, 63.7
Total	**49 (100%)**	

Discussions

LFT results of the present study showed that serum bilirubin was raised in most of the cases (87.75%). Among the cases that had elevated levels, in majority of the cases (84.6%) hyperbilirubinemia was of mixed type (i.e. conjugated and unconjugated) where as in small no of the cases (8%) it was predominantly conjugated type.

The liver enzymes e.g. ALT was normal in majority of the cases (73.46%) where as elevated in (26.54%) of the cases. AST was normal in 30(61.22%) cases where as it was elevated in 19(38.77%) cases. Age and sex adjusted ALP was normal in 51.2% of the cases where as it was elevated in 48.97% of the cases. Statistical analysis (95% CI) results revealed that elevation of AST and ALP is of no diagnostic value where as elevation of ALT can be helpful to rule out acute inflammation of appendix at 95% level of confidence in clinically suspected cases of acute appendicitis. An extensive Medline search was done but no human study on this subject was found in the literature till date to the best of my knowledge.

The possible mechanism of isolated mixed hyperbilirubinemia (rise in serum bilirubin without significant elevation in ALT, AST and ALP) in majority of the cases suggests that there is neither hepatocellular damage nor intra hepatic cholestasis. It appears that at least two steps of bilirubin metabolism are affected. 1. Hepatic uptake, there is depression in hepatic uptake that led to elevation in level of unconjugated bilirubin. 2. Excretion, there is depressed excretion of conjugated bilirubin due to depression in functioning of ductule membrane enzyme (Na-K ATPase), a rate-limiting step (lead to regurgitation of conjugated bilirubin) by bacteria, their toxins or cytokines. So, combined effects of the above both defective steps in the process of bilirubin metabolism lead to elevation in unconjugated and conjugated fraction of serum bilirubin giving rise to a biochemical picture of mixed type of hyperbilirubinemia.

Similar results were also observed in various experimental studies in rats. In which it was concluded that hepatocellular function is deranged/depressed in sepsis. The depression of hepatocellular function in early, hyperdynamic stage of sepsis does not appear to be due to reduction in hepatic perfusion but it is associated with elevated circulating pro-inflammatory cytokines such as TNF and IL-6. This observation was duplicated, by administering recombinant murine TNF-alpha, in a dose that does not reduce cardiac output and hepatic perfusion showed the depression in hepatocellular function. This produces hepatocellular dysfunction and increases IL-6 level in rats. The hepatic extraction of indo-cyanine green was also depressed (in early sepsis). The site of lesion was proposed to be at the site of membrane enzyme (Na-K ATPase) that is responsible for active transport of bilirubin from cell to intrahepatic biliary canaliculi. Because of this abnormality in the functioning of the enzyme, proper excretion of liver excretory products does not occur. So there is leakage of product in sinusoids and rise in blood levels[12-15]

Conclusion

Following conclusion can be drawn from the present study. **Firstly:** There was mixed type of hyperbilirubinemia in most of the patients that was because of dysfunction rather than

damage of the liver **Secondly:** The hyperbilirubinemia might be a combined effect of depressed hepatocellular uptake of unconjugated bilirubin (depressed function of hepatocytes) and decrease excretion of the conjugated bilirubin (inhibition of membrane enzyme Na-KATPase) by bacteria, their toxins or cytokines. **Thirdly:** The elevation of AST and ALP is of no diagnostic value where as moderate or severe elevation of ALT can be helpful to rule out acute inflammation of appendix at 95% level of confidence in clinically suspected cases of acute appendicitis.

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References

1. Mayers WC, Ricciard R. Liver Function. In: Sabiston Text Book of Surgery. The biological basis of modern surgical practice, Book-I, 11th ed., T M Townsend et al. (eds.), Heart Court Publisher international Company. A Heart Court Asia PTE LTD. 2001:1010.
2. Pastor CM, Billiar TR, Losser MR, et al. Liver injuries during sepsis. J Crit Care 1995; **10:**183.
3. Beg R B and Garlungton AW. Translocation of certain endogenous bacteria from the GI tract to mesenteric lymph node and other organ in Gonobiotic mouse model. Infect Immunol 1979; **23**: 403-411.
4. Juric I, Primorac D, Zagar Z, Biocic M, et al. Frequency of portal and systemic bacteremia in acute appendicitis. Pediatr Int 2001 Apr; **43(2)**: 152-6.
5. Koito Scathen WE, Desprez JD and Holden WD. A bacteriologic study in portal blood in man. Arch Surg 1995; **71**: 404-409.
6. Ranson JHC, Madayag MA, Localio SA and Spencer FC: New diagnostic and therapeutic technique in management of Liver Abscess. Ann Surg1975; **181:**508.
7. Compara JL, Ryjnotab TB: The hepatic microcirculation. In Arias IM, Popper H, Schacter D, ShafritzDA (eds): Pathology of the liver. New York, Raven 1982: 627-45
8. Clavin PA, Noseug Straberg BM. Preservation and reperfusion injuries in liver allografts. An over view and synopsis of current studies. Transplantation 1992; **53:**457.
9. Podolsky DK., Isselbacher KJ. Evaluation Of Liver Function. In: Harrison's Text Book of Internal Medicine Vol. II, 15th ed., Eugene Braunwald S, Faucci, Kasper D L, et al. (eds), Mac Graw Hill, Medical Publishing Division. 2001: 919.
10. Kaplan L M, Isselbacher K J. Jaundice. In: Harrison's Text Book of Internal Medicine Vol. II, 15th ed. Eugene Braunwald, et a l. (eds), Mac Graw Hill, Medical Publishing Division. 2001:249-55.
11. Sherlock S and Dooley J. Assessment of Liver Function. In: Liver and hepatobiliary Diseases. 11th ed., Sheila Sherlock et al. (eds), Black Well Publishing Company 2002: 20.
12. Wang P, Ayala A, Ba ZF, et al. Tumor Necrosis Factor –Alpha produces hepatocellular dysfunction despite of normal cardiac out put and hepatic microcirculation. Am J Physiol Gastrointest Liver Physiol 1993: **265(1)**: 126-32.
13. Wang P, Ba ZF, Chaudhary IH. Hepatic extraction of indo-cyanine green is depressed in early sepsis despite increase hepatic blood flow and cardiac out put. Arch Surg Feb 1991; **2**:126.
14. Wang P and Chudhary IH. Mechanism of hepatocellular dysfunction during hyper dynamic sepsis. Am J Physiol Regul Integr Comp Physiol 1996; **270**: 927-38 & 363-61.
15. Whiting JF, Green RM, Rosen AB, et al. TNF-alpha decreases hepatocyte bile salt uptake and mediated endotoxin-induced cholestasis. Hepatol 1995; **22**: 1273.