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Effect of Hyperbilirubinemia on Renal Function in Cases of Acute Hepatitis A

KEYWORDS: Acute hepatitis A (AHA), Acute Renal failure (ARF), Fulminant Hepatitis

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ABSTRACT *Acute hepatitis A is a self limiting infectious disease. Inspite of rare Extrahepatic manifestations, cases of acute renal failure are reported. Awareness of the potential renal involvement in hepatitis virus infection has become a need. | AIM : To co-relate serum levels of Total Bilirubin with Renal parameters in Acute hepatitis A patients. | METHODLOGY: Blood samples of 40 diagnosed Acute Hepatitis A patients, within age group of 30-60 yrs were collected on day1, day6 and day12 of hospitalization and analysed for liver and renal profile. Results were compared and co-related statistically. | RESULT: Serum total bilirubin (14.7+1.11 mg/dl) was increased on day 1 which decreased on day6 (13.8+1.99 mg/dl); with significant decrease on day12 (12.8+0.34 mg/dl, p<0.0001). On day6 Serum Creatinine (5.6+0.51) and BUN (119 ±12.4mg/dl, p < 0.0001) showed statistically significant increase. Total Bilirubin showed strong positive correlation with Creatinine (r=0.675) and BUN (r=0.955) on day6. | CONCLUSION: Hyperbilirubinemia may be considered as one of the cause of functional renal impairment in Acute Hepatitis A infection.*

Table No. 1: Descriptive statistics of LFT and RFT on Day 1,6 and 12

Tests parameters	DAY 1	DAY 6	DAY 12
Total Bilirubin (mg/dl)	14.7± 1.06	13.8± 1.99	12.8± 0.34
Direct Bilirubin (mg/dl)	10.9± 2.16	9.7± 1.9	6.15± 1.06
SGOT (U/L)	1028 ± 387.1	617.6± 77.5	263± 35.7
SGPT (U/L)	1087± 351.3	667.2± 82.6	279.8± 39.7
ALP (U/L)	113.3± 12.2	113.2± 10.23	108.5± 10
Total Protein (gm/dl)	5.79± 0.42	5± 0.25	4.9± 0.25
Albumin (gm/dl)	3.13± 0.29	2.76± 0.25	2.74± 0.21
Creatinine(mg/dl)	2.53± 0.93	5.63± 0.51	3.8± 1.16
BUN(mg/dl)	42.4± 13.1	119± 12.4	69.1± 9.08

Table No. 2: Comparision of LFT and RFT levels on Day 1 and day6 in AHA patients

Tests parameters	DAY 1	DAY 6	P value
Total Bilirubin (mg/dl)	14.7± 1.06	13.8± 1.99	0.0146
Direct Bilirubin (mg/dl)	10.9± 2.16	9.7± 1.9	0.01
SGOT (U/L)	1028 ±387.1	617.6± 77.5	<0.0001*
SGPT (U/L)	1087± 351.3	667.2± 82.6	<0.0001*
ALP (U/L)	113.3± 12.2	113.2± 10.23	0.968
Total Protein (gm/dl)	5.79± 0.42	5± 0.25	<0.0001*
Albumin (gm/dl)	3.13± 0.29	2.76± 0.25	<0.0001*
Creatinine (mg/dl)	2.53± 0.93	5.63± 0.51	<0.0001*
BUN(mg/dl)	42.4± 13.1	119± 12.4	<0.0001*

*Significant at 1% Level of Significance

Table No. 3: Comparison of LFT and RFT levels on Day 6and day 12 in AHA patients

Tests parameters	DAY 6	DAY 12	P value
Total Bilirubin (mg/dl)	13.8± 1.99	12.8± 0.34	0.0024
Direct Bilirubin (mg/dl)	9.7± 1.9	6.15± 1.06	<0.0001*
SGOT (U/L)	617.6± 77.5	263± 35.7	<0.0001*
SGPT (U/L)	667.2± 82.6	279.8± 39.7	<0.0001*
ALP (U/L)	113.2± 10.23	108.5± 10	0.04
Total Protein(gm/dl)	5± 0.25	4.9± 0.25	0.0775
Albumin(gm/dl)	2.76± 0.25	2.74± 0.21	0.6995
Creatinine (mg/dl)	5.63± 0.51	3.8± 1.16	<0.0001*
BUN(mg/dl)	119± 12.4	69.1± 9.08	<0.0001*

* Significant at 1% Level of Significance

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Table No. 4: Comparison of LFT and RFT levels on Day 1 and day 12 in AHA patients

Tests parameters	DAY 1	DAY 12	P Value
Total Bilirubin (mg/dl)	14.7± 1.06	12.8± 0.34	<0.0001*
Direct Bilirubin (mg/dl)	10.9± 2.16	6.15± 1.06	<0.0001*
SGOT (U/L)	1028 ± 387.1	263± 35.7	<0.0001*
SGPT (U/L)	1087± 351.3	279.8± 39.7	<0.0001*
ALP (U/L)	113.3± 12.2	108.5± 10	0.0368
Total Protein (gm/dl)	5.79± 0.42	4.9± 0.25	<0.0001*
Albumin (gm/dl)	3.13± 0.29	2.74± 0.21	<0.0001*
Creatinine (mg/dl)	2.53± 0.93	3.8± 1.16	<0.0001*
BUN(mg/dl)	42.4± 13.1	69.1± 9.08	<0.0001*

*Significant at 1% Level of Significance

Figure 1: Graphical presentation of Total bilirubin, Creatinine and BUN levels on day 1, 6 &12

Table 5: Co-relation between Total Bilirubin, creatinine and BUN on day 6

Parameter	Co-relation co-efficient	P value
T.BILI & CREAT	0.675**	<0.01
T.BILI & BUN	0.955**	<0.01

** Significant at 1% Level of Significance

Figure 5: Co-relation between

Figure 6: Co-relation between Serum Creatinine and Total bilirubin levels serumTotal Bilirubin and BUN levels on day 6 levels on day 6

INTRODUCTION:

Acute Hepatitis A (AHA) is one of the most common infectious diseases affecting the liver [1] The first description of hepatitis (epidemic jaundice) is generally attributed to Hippocrates and outbreaks of hepatitis A have been recognized for centuries. Approximately 1.5 million clinical cases of hepatitis A occur worldwide annually.[2] According to The Integrated Disease Surveillance Programme of the NCDC (National Centre Of Disease Control) 2,90,000 cases of acute viral hepatitis were notified in India in 2013. [3] However in actual scenario, the rate of infection is probably as high as ten times the current.[2] Increased incidence of AHA in adults has being observed, mostly because of the rapid sero-epidemiological shifts associated with accelerated economic development.[1] The incidence rate is strongly related to socioeconomic indicators and access to safe drinking water.[2] With the increased incidence and associated complications, Hepatitis A has now become a serious public health problem.[1]

Hepatitis A virus (HAV) is a small, non-enveloped, single-stranded RNA virus that belongs to the genus *Hepatovirus* within the family Picornaviridae.[1] It is thermostable and acid-resistant.[2] During incubation period of about 4 weeks, HAV replicates in hepatocytes and interferes with liver function, sparking an immune response that causes liver inflammation.[2] HAV is transmitted via feco-oral route. [4] Person-to-person transmission is common and generally limited to close contacts.[5] A typical symptomatic presentation includes non specific prodromal symptoms with variable combinations of fever, malaise, weakness, anorexia, nausea, vomiting, arthralgia and myalgia. Prodromal symptoms tend to decrease with the onset of jaundice, although anorexia, malaise and weakness may persist or increase transiently. Jaundice lasts for several weeks and is followed by a convalescent period. The peak infectivity occurs during two weeks before the onset of jaundice or elevation of liver enzyme levels when the concentration of virus in the stool is highest. When jaundice appears, the viral concentration in the stool declines and most patients are non-infectious after one week.[5,6]

The main complication of HAV infection is Fulminant Hepatitis (FH), i.e Acute Liver Failure with encephalopathy, which occurs in <1% of cases.[7]. Although extrahepatic manifestations are relatively rare, some have been reported in patients with AHA such as arthritis, vasculitis and cryoglobulinemia.[8] Acute renal failure (ARF) is commonly found in patients with Fulminant AHA but it is a rare complication of non-fulminant AHA.[9] Yet due to sharp increase in the frequency of AHA infections, this rare complication, ARF has become common even in non-fulminant Hepatitis A cases. [1]

The differentiation between the Hepatorenal syndrome (HRS) and ARF in non fulminant AHA is difficult, but is important in clinical practice.[1] In Hepatorenal syndrome, kidneys are functionally normal but failure is due to splanchnic vasodilatation and arteriovenous shunting which lead to profound renal vasoconstriction.[4] Hepatocellular failure induces functional renal failure. Very little is known about the pathophysiology of functional renal failure in cases of hepatitis A.[1] Hecker and Sherlock described a patient with fulminant hepatic failure who, in retrospect, had the features of functional renal failure.[10] Ritt et al found impairment of renal function in 13 out of 31 patients diagnosed with Acute hepatic necrosis. [11]

Awareness of the potential renal involvement of hepatitis virus infection has become the need. The association of Hepatitis A, B and C viruses with renal dysfunction has been reported in literature, but very little information is available about association of renal dysfunction and Hepatitis A.[1] Hence the study was undertaken to study changes in renal functions in diagnosed cases of acute hepatitis A.

Material and Methods:

The study was conducted at MGM Medical College and Hospital, Navi Mumbai. Forty indoor patients diagnosed with Acute Hepatitis A admitted in medicine ward, within the age group of 30-60 years were selected for the study. The diagnosis of acute hepatitis A was based on routine screening tests followed by detection of IgM antibodies by ELISA method for confirmation. Patients having total Bilirubin levels between 10-20 mg/dl were included in study group. Cases with pre-existing renal failure, alcoholic liver disease, portal hypertension and AHA combined with other acute viral infections were excluded from study. Purpose of the study was explained and informed written consent was taken from patients before inclusion in study. Ethical clearance was obtained from Institutional Ethical Committee.

Blood samples were collected on 3 different days i.e. on day1, day6 and day12 of hospitalization period. Samples

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were collected in plain vaccutainer and centrifuged at 2800 RPM for 15 minutes. Serum samples were analysed for liver function tests (LFT) and renal function tests (RFT) on Biochemistry AU480 Autoanalyser.

Statistical analysis
All biochemical parameters on day1, day6 and day 12 were compared and co-related statistically using SPSS 13.0 version. Results were expressed in Mean and SD. Pearson co-relation coefficient was calculated for studying co-relation.

RESULT:
Serum levels of Total Bilirubin were found to be raised on day 1 (14.7 $\pm$ 1.11 mg/dl) of hospitalization which started declining with treatment. Significant decrease was observed on day12 (12.8 ± 0.34 mg/dl, $p < 0.0001$) (table 1). Aminotransferases were also found to be increased on day 1 which significantly decreased on day 12 with treatment (table 1). In renal profile, significant rise was observed in values of serum Creatinine (5.6 $\pm$ 0.51mg/dl) and BUN (119± 12.4 mg/dl) on 6th day of hospitalization compared to values of day 1 and day 12. ($p < 0.0001$).

When we co-related Total bilirubin levels with serum Creatinine and BUN values on day 6, a strong positive correlation was observed. Total Bilirubin levels on day6 showed strong positive co-relation with serum Creatinine(r=0.675) and also with BUN (r=0.955).

Discussion :
The clinical manifestations of Acute hepatitis A may vary from mild liver dysfunction to fulminant hepatic failure, inspite of being self limiting in nature.[1] Acute renal failure is common in fulminant hepatitis, however little is known about the risk factors and outcome predictors for ARF in acute hepatitis A cases.Functional renal failure and acute tubular necrosis may also occur in Fulminanat hepatic failure, but are rare in non-fulminant hepatitis A cases.[1] Studies have shown association of acute renal failure in patients of hepatitis B and C which is due to immune complex deposition. [12,13]

We have made an attempt to study renal dysfunction in known cases of Hepatits A by analyzing various biochemical parameters. We estimated Liver and Renal profiles of hepatitis A patients on Day 1, day 6 and day 12 .

Total Bilirubin levels were highest on day 1, 14.7± 1.11 mg/dl which subsequently decreased on day 6 and day 12.We observed a peak in serum Creatinine (5.6 ±0.51 mg/dl) and BUN (119 ±12.4 mg/dl) levels on day6 of hospitalization. Co-relation study between Total Bilirubin levels on day6 showed strong positive co-relation with serum Creatinine(r=0.675) and also with BUN (r=0.955). Thus a derangement in renal parameters secondary to Hyperbilirubinemia was observed on day 6. We followed these patients further and found that eight patients of our study group were advised haemodialysis based on their creatinine levels so as to prevent irreversible damage to kidney.

Variety of mechanisms have been postulated, the exact process behind hepatitis A-induced acute renal failure remains to be elucidated. First, Most patients with AHA have nausea, vomiting, fever and poor oral intake, which can cause volume depletion, activation of the renin–angiotensin system and reduced renal blood flow. Secondly, Hyperbilirubinemia decreases peripheral vascular resistance which may cause renal vasoconstriction and reduce renal blood flow leading to renal failure. Furthermore, bile salts may have toxic effect on the renal tubules by nonspecific detergent effects.[1] Thirdly, HAV-induced endotoxemia, probably due to failure of kuffer cells to filter endotoxins absorbed from gut, either as a result of portosystemic collateral circulation or because of impaired reticuloendothelial function may lead to alterations in the renal flow that contribute to the development of renal injury.[1] Fourth is immune complex-mediated mechanisms which is more common in Hepatitis B and C infections.[1,12,13] .

According to study of Jung YJ et al, biopsy-proven cases suggested that acute tubular necrosis is the principal mechanism in AHA-associated functional renal impairment[1].This finding of acute tubular necrosis is also supported by Faust and Pimstone.[14,15] Vaboe et al described combination of Interstitial Nephritis and ATN (Acute Tubular Necrosis) associated nonfulminant hepatitis A requiring dialysis support [15,16]

Our findings are in accordance with Shroff et al who reported two cases of ARF associated with hepatitis A out of which one patient required dialysis. They suggested beneficial role of high dose acetylcysteine in recovery of renal function.[17] Vesely et al co-related the peak bilirubin levels to the requirement of hemodialysis in patients who developed ARF in the setting of viral nephritis.[18] They observed temporal relationship between improvement of the bilirubin concentration and improvement in renal functions. [15]

Demircin et al also reported two cases of hepatitis A complicated with acute glomerulonephritis (AGN). It is possible that in rare cases of HAV infection, immunologically derived reactions similar to AGN will occur.[19] These reactions, which can also occur with other viral infections, may explain some of the systemic involvement known to be associated with HAV infection.[19] The most common pattern of glomerulopathy observed is mesangial deposition of immunoreactants. [19,20,21] In 1995, Zikos et al reported a 33-year-old man who had nephrotic syndrome and acute renal failure that developed 8 days after the onset of HAV infection. Light microscopic examination of a renal biopsy specimen showed mesangial proliferative glomerulonephritis with intense focal granular deposition of IgM and C3 and immunofluorescent examination revealed weak staining of IgG, IgA, and albumin.[21]

The prognosis of renal failure as a result of HAV infection is generally benign, although recovery can be substantially delayed. [1] Patients with AHA associated ARF in this study had a benign clinical course. The result of our study is consistent with previous reports that have shown association of ARF with HAV infection. Drawback of our study was, we were unable to perform histological evaluation to understand underlined pathophysiology.

Conclusion
Hyperbilirubinemia may be considered as one of the cause of functional renal impairment in Acute Hepatitis A infection. This renal dysfunction more often goes unnoticed, and can lead to irreversible damage and poor prognosis. Physicians must be aware of spectrum of systemic involvement associated with Hepatitis A, including the possibility of Acute Renal Failure and there should be close monitoring of renal function in patients of acute hepatitis A.

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