A STUDY ON ALTERED LIVER FUNCTION IN CONGESTIVE HEART FAILURE

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ABSTRACT

BACKGROUND

Coronary Vascular Disease is currently the leading cause of death in India and its prevalence is projected to rise. In 2000, there were an estimated 30 million people with coronary heart disease (CHD) alone in India, or a nearly 3% prevalence. The prevalence of other risk factors of HF is also rising in India. One of the most common manifestations of congestive heart failure is enlargement of the liver. This fact has led several investigators such as Jollife and Robertson to study liver function tests in an attempt to evaluate hepatic dysfunction in congestive heart failure. Historically, the first association of liver pathology and congestive heart failure was noted by Keirnan who described the nutmeg liver. Seventy-eight years later Mallory described the typical microscopic appearance of central congestion with focal necrosis. The three main theories of the pathogenesis of the altered liver anatomy were: infection, mechanical compression, and hypoxia with secondary nutritional deficiency. The deficiency in oxygen supply to liver cells in heart failure seems to be due not only to the slowing of blood flow through the liver but even more so to arterial unsaturation resulting from pulmonary lesions.

METHODS

All cases of congestive cardiac failure admitted at King George Hospital (N= 75), of varied aetiologies from May 2017 to May 2018 (12 months) were taken up for study. Liver function tests were performed in all CCF cases, namely, serum bilirubin, AST, ALT, SAP, serum proteins and prothrombin time both on day 1 and day 7 of admission. This study was a cross sectional descriptive study, comparing the liver function tests between cases of various causes of heart failure. Results were entered in Microsoft Excel Spread sheet and analysed. Significance values were analysed using Minitab software, Epi Info software. Chi-square test. Students 't' test values were applied for significance. A p value below 0.05 was considered significant.

RESULTS

The profile of LFTs on day 1 and day 7 showed a strong correlation of serum bilirubin and serum alkaline phosphatase levels with disease activity with a p value of <0.00001 and a p value of <0.001 respectively. Aminotransferase levels paralleled the severity and indicated poor prognosis associated with low serum albumin levels.

CONCLUSIONS

Liver function abnormalities were mostly present in patients with coronary artery disease developing heart failure. Liver function abnormalities were least in patients with cardiomyopathy developing heart failure. The serum bilirubin, serum alkaline phosphatase and serum transaminases returned to normal with remission. The serum bilirubin, serum enzymes and prothrombin time were elevated with exacerbation. Severe congestive cardiac failure with hypotension leads to a gross elevation of serum aspartate transaminase and alanine transaminase. Serum alkaline phosphatase elevation correlated with the presence of hepatomegaly. Serum bilirubin levels at presentation of more than 5 mg and presence of hypoalbuminemia were associated with a poor prognosis.

KEYWORDS

Transaminases D08.811.913.477.700 Heart Failure C14.280.434 Jaundice C23.550.429.500

HOW TO CITE THIS ARTICLE: Narasingarao S, Kanaka Mahalakshmi A, Beesetty M. A study on altered liver function in congestive heart failure. J. Evid. Based Med. Healthc. 2019; 6(24), 1663-1667. DOI: 10.18410/jebmh/2019/336

Financial or Other, Competing Interest: None.
Submission 25-05-2019, Peer Review 31-05-2019,
Acceptance 08-06-2019, Published 12-06-2019.
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DOI: 10.18410/jebmh/2019/336

BACKGROUND

Congestive cardiac failure (CCF) represents a clinical syndrome of abnormal left ventricular function. Clinically manifests as effort intolerance, fluid retention and reduced longevity. The liver is vulnerable akin to a direct communication and pressure transmission from right side of heart. Hepatic damage also occurs secondary to some of the most common diseases in humans, such as heart failure, disseminated cancer, and extra hepatic infections. Both acute and chronic heart failure may result in abnormalities of liver. Liver receives 25% of cardiac output. A fall in cardiac output will result in hepatic hypo perfusion. Liver has the

capacity to withstand changes in blood flow by vasoactive mechanisms and oxygen extraction from blood. However, when critical levels are reached, hepatic injury ensues. Both right and left sided heart failure can result in liver injury. In right sided heart failure, elevation of right heart pressure resulting in raised pressure in hepatic sinusoids, hepatic congestion and liver cell hypoxia. In left sided heart failure, decreased cardiac output results in hepatic hypoperfusion and hypoxia. The common pathway is centrilobular hepatocellular necrosis. Zone 3 of the liver lobule is most vulnerable to hypoxic injury due to organization of hepatic blood flow. Heart failure affects nearly twenty-three million people worldwide. The crude incidence rate of heart failure in the general population ranges from 1 to 5 cases per 1000 population per year, with a steep increase with advancing age. The prevalence or risk of developing HF in emerging nations is less defined due to a lack of population-based studies. Rheumatic heart disease (RHD) remains a major cause of HF in Africa and Asia. Heart failure has a profound effect on quality of life.

Aim and Objectives

1. To study the relationship between liver function tests and remission and exacerbation of congestive cardiac failure.
2. To study whether liver function tests can be used as a prognostic indicator in cases of congestive cardiac failure.

METHODS

The study groups identified were informed about the nature of the study. Willing participants were taken up after getting a written informed consent from them. In this study the following liver function tests were performed:

1) Serum bilirubin
2) Serum transaminases
3) Serum alkaline phosphatise
4) Serum proteins
5) Prothrombin time

In our study, patients were included as having congestive cardiac failure, if they had at least one Major and Minor criteria of Framingham criteria.

Framingham Criteria

- **Major**
  1. Paroxysmal nocturnal Dyspnoea.
  2. Neck vein distension.
  3. Crackles.
  4. Cardiomegaly.
  5. Acute pulmonary oedema.
  6. S3 gallop.
  7. Increased venous pressure (16 cm H_20).
  8. Positive hepatojugular reflux.

- **Minor Criteria**
  1. Extremity oedema
  2. Night cough
  3. Dyspnoea on exertion
  4. Hepatomegaly
  5. Pleural effusion
  6. Vital capacity reduced by one third to normal
  7. Tachycardia > 120/ min
  8. Weight loss over 4.5 Kg over 5 days treatment.

Inclusion Criteria

Cases of congestive cardiac failure, as per Framingham's criteria; of various age groups and aetiologies such as:

1) Rheumatic valvular heart disease.
2) Ischemic heart disease.
3) Hypertensive heart disease.
4) Congenital heart disease.
5) Cardiomyopathies.
6) Cor-pulmonale.
7) Congestive cardiac failure of varied presentation either acute or chronic.

Exclusion Criteria

1) Known alcoholic.
2) Past history of jaundice.
3) Recent intake of hepatotoxic drugs or drugs causing raised liver parameters, such as Rifampicin, INH, Steroids, Chlorpromazine, amiodarone, statins, hydralazine, phenytoin and sodium valproate.
4) Positive viral markers.

RESULTS

A total number of 75 patients were included in the present study (n=75). Gender percentage was 52% males vs. 48% females. The mean Age ± SD was 53.79 ± 14.01 years, median Age was 55 years. Aetiology included coronary heart disease, cardiomyopathy, cor pulmonale hypertensive heart disease and, rheumatic heart disease, of which CAD predominated this study (table-1).

Disease	Duration 1 Year	1-5 Years	5 Years Above	Total
CAD	00	16(21.33)	15(20.00)	31(41.33)
CM	05(6.67)	01(1.33)	01(1.33)	07(9.33)
CP	04(5.33)	04(5.33)	03(4.00)	11(14.67)
HHD	03(4.00)	03(4.00)	01(1.33)	07(9.33)
RHD	02(2.67)	07(9.33)	10(13.33)	19(25.33)
Total	14(18.67)	31(41.33)	30(40.00)	75(100.0)
Table 1. Aetiology of Heart Failure				
X^2 value	27.1509; d.f.= 8; P <0.001			

Out of 75 patients 49(65.3%) showed abnormal liver function and the remaining 26 (34.7%) showed normal LFT. Aetiology wise RHD patients showed 63.1 % abnormal LFT (table-2).

RHD	19	12	63.1%
CAD	31	23	59.8%
CP	10	6	60%
CM	7	3	42.8%
HHD	8	5	62.5%
Table 2. Abnormal Liver Function Tests as Per Aetiology			

Clinical jaundice was observed in 10 patients 13.3 %. Ascites was noted in 11 patients 14.6 %. Hepatomegaly was noted in 46 patients 61.3%. Serum alkaline phosphatase levels paralleled the presence of hepatomegaly. (Table-3)

No. cases with hepatomegaly	46 (out of 75)
No. of cases with raised SAP	11 (out of 75)
No. of cases with raised SAP in Hepatomegaly and CCF	11 (out of 46)
No. of cases with raised SAP without hepatomegaly	0 (out of 29)

Table 3. No. of Cases with Hepatomegaly Showing Increased Serum Alkaline Phosphatase (SAP)

The liver function tests on day of admission depicted as follows (table-4).

Sl. No.	Test	Normal Range	Results		
			Range	No. of Patients	Percentage (%)
1.	Serum Bilirubin	0.3-1.2 mg/dl	<1.2	31	41.3%
			1.2-3 mg/dl	34	45.3%
			3-5 mg/dl	8	10.6%
			>5 mg/dl	2	2.6%
2.	AST	Up to 40 IU	Normal range	36	48%
			Increased	39	52%
3.	ALT	Up to 35 IU	Normal range	44	58.6%
			Increased	31	41.3%
4.	SAP	Up to 130 IU	Normal range	64	85.3%
			Increased	11	14.6%
5.	Serum Albumin	>3 g%	Normal	55	73.3%
			Reduced	20	26.6%
6.	Prothrombin time	Control (12-14 sec), test abnormal if 11/2 times greater than control	Normal	51	68%
			Prolonged	24	32%

Table 4. Liver Function Tests on Admission

The profile of LFTs on day 1 and day 7 showed a strong correlation of serum bilirubin and serum alkaline phosphatase levels with disease activity with a p value of <0.00001 and a p value of <0.001 respectively (table-5).

I) Profile of Liver Function Tests in the Study Population						
Mean Difference	Standard Deviation	Standard Error (SE)	t Value	d.f n-1	p Value	
1. Serum bilirubin D1 and after 7 days (n=75)						
-0.6	0.95	0.11	5.45	74	0.000070	P<0.00001
2. AST -D1 and after 7 days (n=75)						
7.12	24.86	2.87	2.48	74	0.0154158	P<0.02
3. ALT – D1 and after 7 days(n=75)						
6.65	17.52	2.02	3.29	74	0.0016393	P<0.01
4. S ALP- D1 and after 7 days (n=75)						
12.96	28.12	3.25	3.99	74	0.0001535	P<0.001
5. Serum proteins Total: D1 and after 7 days (n=75)						
-0.032	0.3058	0.035	0.906032	74	0.367869	P>0.05
6. Serum albumin d1 and after 7 days (n=75)						
-0.060	0.2295	0.0265	-2.264	74	0.0265423	P<0.05
7. Serum globulin: D1 and after 7 days (n=75)						
-0.011	0.2952	0.0340	-0.2941	74	0.755269	P>0.05
8. Prothrombin Control: D1 and after 7 days (n=75)						
-0.2133	1.64	0.1893	-1.12678	74	0.263051	P>0.05
9. Prothrombin Test: D1 and after 7 days (n=75)						
-0.32	2.87	0.3314	-0.9656	74	0.337699	P>0.05

Table 5. Profile of Liver Function Tests in The Study Population- Day 1 and 7

DISCUSSION

According to poeizl et al. Liver dysfunction is frequently observed in CCF. Cholestatic enzyme profile correlates with disease severity and prognosis.[1] The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial provides a unique opportunity to perform an in-depth characterization of LFTs during hospitalization and in the early post discharge period in a large contemporary cohort of patients hospitalized for worsening HF with reduced ejection fraction (EF) and well treated with evidence-based therapies.[2,3,4] The EVEREST study population had a mixed LFT pattern with features consistent with both cholestasis and hepatocellular injury (i.e. elevated AST and ALT). The present study correlate with EVEREST trial in view of mixed cholestatic and hepatocellular injury based LFT abnormalities.[5]

In Vasconcelos et al study roughly 40% patients age was above 70 yrs.[6] In Narasingarao S et al study 70% patients were between 41-70yrs (10). In VN Van Deursen et al study mean age was 39-68 years.[7] In Md Toufiqur Rahman et al most of the patients between 51-70 yrs. My results correlate with Narasingarao S et al and VN Van Deursen et al study[7,8] (table 6).

Sl. No.	Author	Common Age Group of CCF Observed in Other Studies
1.	VN Van Deursen et al	40-68 yrs.
2.	Md Toufiqur Rahman et al	51-70 yrs.
3.	Narasingarao S et al	41-70 yrs.
4.	This study	41-70 yrs.

Table 6. Age Group Comparison

Among 75 patients selected for the study there were 39 males and 36 females with M:F ratio 1.1:1 but this should not be considered as a true proportion of heart failure cases between the two genders because exclusion factors predominated in male gender. In Vasconcelos et al study 64% female and 36% male.[6] In Narasingarao S et al study 64% Were female and 36% were male patients.[8] White et al found hepatomegaly in 95% of their cases of congestive cardiac failure.[9] Dunn et al have also described hepatomegaly in 95% of cases.[10] Richman et al have described hepatomegaly more than 5 cm in as many as 50% of patients.[11] White et al have reported clinically apparent jaundice in 20% of cases.[9] Gravin et al and Kubo et al have also described clinical jaundice in less than 20% of cases.[12,13]

In this study abnormal liver function tests observed in 49 patients among 75(65.3%) in the form of raised bilirubin elevated transaminases, elevated alkaline phosphatase, hypoalbuminemia, and prolonged prothrombin time, correlate with Jan Biegusetal study where 71% showed abnormal LFT.[14] In M. Nikolaou et al only 20% showed

abnormal LFTs.[15] L. A. Allen et al study they observed mild abnormalities of LFTs predominately cholestatic pattern of greater elevation in bilirubin and transaminases, additionally total bilirubin is a strong predictor of adverse prognosis.[16]

Kubo et al have reported that serum bilirubin is increased in 20 to 80% of patients with congestive cardiac failure; it rarely exceeds 5 mg/dl and is usually less than 3 mg/dl. This correlates with present study where patients with bilirubin >5 mg/dl are only 2.3%. Zieve has reported that unconjugated bilirubin is usually higher than conjugated bilirubin.[14] Sherlock and Richman et al have also reported that levels usually range between 1 mg/dl and 5 mg/dl with the unconjugated form constituting the major fraction.[17,18] Sherlock has reported that only rarely have levels exceeded 20 mg/dl in patients with severe right sided heart failure. Richman et al has observed that with improvement of the right sided heart failure elevated serum bilirubin levels return to normal quite rapidly over a period of 3-7 days.[19] (Table 7)

Sl. No.	Authors	% of Cases with Hyperbilirubinemia
1.	Felder et al	52%
2.	Sherlock	68%
3.	L.A. Allen et al	26%
4.	Jan Biegus et al	33%
5.	White et al	45%
6.	Naresh bhu	58%
7.	Poelzl G et al	25%
8.	This study	58%

Table 7. Hyperbilirubinemia Compared with Other Studies

Richman has reported that aspartate transaminase levels are typically more marked than alanine transaminase levels, the former values ranging from 40-80 IU. This degree of marked elevation is seen in acute heart failure secondary to cor-pulmonale or rheumatic heart disease with tricuspid insufficiency or due to heart failure complicated by shock and hypertension. In L.A. Allen et al study the analysis of liver function tests in 2679 patients they observed elevated aspartate transaminases in 4.1%, elevated alanine transaminases in 3.1% only.[16]

In Jan Biegus et al study on admission median levels of AST, ALT, Albumen were 29(21-45) IU/L, 25(17, 47) IU/L, 1.2(0.8, 1.9) mg/dl, 3.8(3.5, 4.1) mg/dl respectively and 29% had all LFTs within normal limits.[14] Abnormal liver function tests common in their study group with the prevalence of 46% for AST, 31% for ALT, 33% for bilirubin and 44% for albumin. M. Nikolaou et al study showed abnormal alanine transaminase levels in 25% cases and abnormal aspartate transaminase levels in 33% cases.[15] In the present study 11 cases (15%) showed elevation in alkaline phosphatase levels. Elevation of serum alkaline phosphatise levels did not correlate with increases in serum bilirubin or aminotransferases. The highest elevations are usually seen in patients with marked liver enlargement. With improvement in the cardiac status serum alkaline phosphatase returned to normal. In 49% of cases that had hepatomegaly, 23% showed elevation in alkaline phosphatase which correlate with Richman et al study. With remission of hepatic congestion these levels returned to normal within 1 week.

Richman et al and Sherlock have reported elevation of serum alkaline phosphatise levels in 10-20% of patients with right sided heart failure.[17,18] In M.Nikolaou et al study they observed elevation of alkaline phosphatase levels in 21% cases.[15] Dunn et al however reports that in most patients the levels are within normal limits rarely do they exceed twice normal.[11] Felder's et al have also reported increased serum alkaline phosphatise in 10-20% of patients with congestive cardiac failure. L. A. Allen et al reported increase in serum Alkaline Phosphatase in 14% congestive cardiac failure patients.[16]

The serum albumin was decreased in 30-50% of patients with congestive cardiac failure as per Richman et al. In Horwich et al study 25% of heart failure patients showed hypoalbuminemia.[10,20] In their study the degree of hypoalbuminemia was usually mild, and the majority of patients exhibit levels between 2.5 and 2.9 g/dl. Dunn et al reported that serum albumin concentrations below 1.5 g/dl are rarely observed and are often associated with marked ascites and oedema. With resolution of the underlying cardiac disease, improvement in serum albumin usually occurs over a period of a few months.[21] In Jan Biegus et al study on admission 44% of congestive cardiac failure patients showed hypoalbuminaemia.[14] L. A. Allen et al observed low albumin levels in 18.7% cases in their study group.[16] According to Richman et al hyperglobulinemia occurred in 37-50% of patients with right sided heart failure and is more common in patients with acute than with chronic heart failure. The elevation tends to be mild, with levels between 3.5 and 4.1 g/dl in the majority of patients. In contrast to other liver tests, the hyperglobulinemia usually does not return to normal after successful treatment of congestive cardiac failure.[18] The increase in serum globulin levels and the decrease in serum albumin levels lead to reversal of Albumin/Globulin ratio. In the present study 20 cases (26%) showed decreased albumin (considering a cut off 3 mg%) which correlates with study of Horwich et al.[21]

CONCLUSIONS

Liver function abnormalities were mostly present in patients with coronary artery disease developing heart failure. Liver function abnormalities were least in patients with cardiomyopathy developing heart failure. Serum bilirubin, serum alkaline phosphatase and serum transaminases returned to normal with remission. Serum bilirubin, serum enzymes and prothrombin time were elevated with exacerbation. Severe congestive cardiac failure with hypotension leads to a gross elevation of serum aspartate transaminase and alanine transaminase. Serum alkaline phosphatase elevation correlated with the presence of hepatomegaly. Serum bilirubin levels at presentation of more than 5 mg, presence of hypo albuminemia were associated with a poor prognosis.

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