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Original Research Article

An Analytical Comparative Assessment of Prevalence of Hypothyroidism in Cirrhotic Patients and Normal Individuals

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Abstract

Aim: The aim and objective of this study was to compare the prevalence of hypothyroidism between cirrhotic patients and normal healthy individuals.

Methods: The prospective comparative study was conducted on 100 patients admitted at Department of General Medicine, Patna Medical College and Hospital, Patna, Bihar, India for one year and found to be clinically, biochemically and radiologically proved liver cirrhosis patients for the period of one year. All patients of age group 20-60 years male and female with confirmed case of liver cirrhosis were included in the study.

Results: Among the 50 cirrhotic patients, 40 (80%) were males and 10 (20%) were females, while in control 30 (60%) were males and 20 (40%) were females. Among total number of 50 cirrhosis patients, 38 (76%) had history of alcohol intake & in control group 4 (8%) had history of alcohol intake. All were male subjects. Not a single female in either of the group had history of alcohol consumption.

Conclusion: All cirrhotic patients should undergo for evaluation of endocrinological evaluation as these patients are associated with development of hypothyroidism. After diagnosis the treatment of endocrinological disorder especially hypothyroidism may increase survival.

Keywords: Liver disease, Alcoholism, Serum albumin, Hypothyroidism.

Introduction

In clinical terms, cirrhosis is described as are either "compensated" or "decompensated." Decompensation means cirrhosis complicated by one or more of the following features: jaundice, ascites, hepatic encephalopathy (HE), or bleeding varices. Ascites is the usual first sign. [1] Hepatorenal syndrome, hyponatremia, and spontaneous bacterial peritonitis are also features of decompensation, but in these patients, ascites invariably occurs first. Compensated cirrhotic patients have none of these features. [1] The thyroid gland produces two‑related hormones, thyroxine (T4) and triiodothyronine (T3). Acting through thyroid hormone receptors α and

β, these hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult. T4 is secreted from the thyroid gland in about twenty‑fold excess over T3. Both hormones are bound to plasma proteins, including thyroxine‑binding globulin, transthyretin (formerly known as thyroxine binding prealbumin), and albumin. [2]

The liver plays an important role in the metabolism of thyroid hormones, as it is the most important organ in the peripheral conversion of tetraiodothyronine (T4) to T3 by Type 1 deiodinase. [3,4] Type I deiodinase is the major enzyme in the liver and accounts for approximately 30%–40% of extra thyroidal production of T3, it can carry out both 5'‑and 5‑deiodination of T4 to T3. Moreover, the liver is involved in thyroid hormone conjugation and excretion, as well as the synthesis of thyroid binding globulin. [3,5] T4 and T3 regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function. The liver metabolizes the THS and regulates their systemic endocrine effects. Thyroid diseases may perturb liver function; liver disease modulates thyroid hormone metabolism; and a variety of systemic diseases affect both the organs. There are clinical and laboratory associations between thyroid and liver diseases. Patients with chronic liver disease may have thyroiditis, hyperthyroidism, or hypothyroidism. Patients with subacute thyroiditis or hyperthyroidism may have abnormalities in liver function tests, which return to normal as the thyroid condition improves. [6]

There is great variability in the amount of alcohol needed to cause cirrhosis (as little as 3-4 drinks a day in some men and 2-3 in some women). Infection with hepatitis C virus causes inflammation and low grade damage to the liver that over several decades can lead to cirrhosis. [7] Chronic hepatitis B is probably the most common cause of cirrhosis worldwide. [8] Many patients with cirrhosis have no symptoms in the early stage of the disease, however, as the disease progress, a person may experiences weakness; fatigue, loss of appetite, nausea, vomiting weigh lost, abdominal pain and bloating when fluid accumulates in abdomen, itching and spider like blood vessels on the skin. [9]

The aim and objective of this study was to compare the prevalence of hypothyroidism between cirrhotic patients and normal healthy individuals.

Materials and Methods

The prospective comparative study was conducted on 100 patients admitted at Department of General Medicine, Patna medical college and Hospital, Patna, Bihar, India for one year and found to be clinically, biochemically and radiologically proved liver cirrhosis patients for the period of one year. All patients of age group 20-60 years male and female with confirmed case of liver cirrhosis were included in the study. Patients >60 years of age, being treated with radioactive iodine, close relative having and autoimmune disease, radiation exposure, thyroidectomy, known cases of hyperthyroidism and patient with any other illness (except liver cirrhosis) e.g. cancer CKD were excluded from the study. The study was performed after taking ethical clearance from Institutional Ethical committee. The present study constitutes 50 patients with cirrhosis of liver who met inclusion criteria. Findings were compared between cirrhotic patients and equal number of normal healthy individual who were taken as controls.

Clinical examination

Presence of ascites, splenomegaly, dilated superficial abdominal veins, palmar erythema, gynaecomastia, spider nevi and edema feet.

Laboratory findings like

Low serum albumin, reverse A:G ratio; increased prothrombin time; transudative ascites, SAAG ratio >1.1; Normal or elevated total serum bilirubin and aminotransferases and serologic tests HBsAg, anti-HCV were done.

Shrunken liver with uneven borders, coarse nodular echo pattern, splenomegaly, dilated portal vein, and ascites were all found on ultrasonography. Splenomegaly, portosystemic collaterals, and reversal of the direction of flow in the portal vein were all indicators of portal hypertension on ultrasonography (hepatofugal flow). A portal vein width more than 13 mm and the absence of respiratory changes in the splenic and mesenteric veins have been shown in certain studies to be sensitive but non-specific markers of portal hypertension. In most centres, these criteria are not commonly employed in clinical practise.

Radioimmunoassay test for thyroid hormone

The current assay method is based on Berson and Yalow's concepts of radioimmunoassay. A determined amount of patient serum or thyroxine standard is mixed with radioactively labelled thyroxine (T-4 125 I) and 8-anilino-1-napthalene sulphonic acid (ANS) in the preferred embodiment's test process, followed by the addition of an immobilised T-4 antiserum (T-4 antiserum covalently bound to aqueous suspendable hydrolyzed polyacrylamide beads). At room temperature, the mixture is left to incubate. Thyroxine is displaced from serum proteins by the ANS. On the basis of their relative concentrations, the displaced thyroxine competes with the tagged thyroxine for the immobilised thyroxine antibodies throughout incubation (Berson, 1960). [10]

This invention additionally includes a novel reagent for use in the immunoassay, which consists of hydrolyzed cross-linked polyacrylamide particles with at least one dye selected from Alcian yellow and Alcian blue absorbed thereon. The laboratory technician doing the assay will benefit greatly from these coloured particles. The coloured polyacrylamide particles make it easier to monitor the initial filling processes of the various vessels used, as the polyacrylamide particles are water white and difficult to notice. Following the pellet formation step of centrifugation, the dye allows the pellet to be easily located for the remaining manipulative steps. The dye also prevents the technician from accidentally decanting beads with the supernatant after centrifugation. The dyes used in this reagent have been found to be one-of-a-kind in that they can be surface absorbed on polyacrylamide particles and stay there in the ionic buffer environment that exists during the various steps of the assay procedure. The overall assay procedure has a number of distinguishing features.

The ability to form stable hydrophyllic suspensions distinguishes the hydrolyzed cross-linked polyacrylamide particles used as solid phase substrates for the antibodies. As a result, no agitation is required to maintain the desired homogeneous condition in the reaction mixture during which thyroid hormone is separated from serum proteins and competitive binding with the antibody occurs in the presence of radioactive tracer. The method calls for accelerating the incubation step by using heat, such as incubation at temperatures between 37 and 50 °C °C. Because agitation is not required, this heating can be accomplished quickly with the current method.

Prior art procedures such as those of Axen et al (dextran particles), sorin (cellulose particles), and corning (glass particles) differ in that such particles settle out relatively quickly, and the assays require continuous stirring of the immobilised reagents during addition and constant agitation of the solution throughout the incubation period. Constant agitation is a

very inconvenient operation when heating is used. For completeness, it should be noted that in short assays, the Corning procedure, which uses glass particles to immobilise the antibody, may have less of a settling problem than the others. However, the settling issue still exists in general. The fact that commercially available materials come in factory pre-filled tubes for each assay sample demonstrates the difficulty in obtaining uniform suspensions for precise aliquot sampling. Other distinguishing features of the present invention are the polyacrylamide particles' low non-specific binding properties. Non-specific binding is so low that the radioactivity levels of the initially separated solid phase particles after incubation can be measured directly without any initial washings. Prior art solid phase supports, such as the one described in the Axen et al patent, require pre-washing steps before the radioactive tracer can be measured.

The removal of the washing steps, as well as the addition of other elements such as surfactants, as used by Axen et al to reduce non-specific absorption, improves the speed and convenience of the current assay procedure significantly. The above benefits are obtained by using hydrolyzed cross-linked polyacrylamide particles with a particle size of 0.1-10 μ in the unhydrolyzed form, usually about 1-5 μ, and preferably a particle size distribution centred around 5 microns.

Statistical analysis

Results were expressed as proportions for qualitative data and as mean±SD for quantitative data. For non-parametric data chi-square test and for parametric comparison between two groups independent sample `t` test was applied. The p value was calculated based on the above tests and values <0.05 was considered significant.

Results

Table 1: Age and sex distribution

Age (years)	Cirrhosis patients (N=50)			Control (N=50)		
	Male	Female	Total	Male	Female	Total
<30	3	0	3	5	6	11
31-40	12	3	15	10	5	15
>40	25	7	32	15	9	24
Total	40	10	50	30	20	50

Among the 50 cirrhotic patients, 40 (80%) were males and 10 (20%) were females, while in control 30 (60%) were males and 20 (40%) were females.

Table 2: Prevalence of alcohol consumption in cirrhosis and control subjects

Alcohol consumption	Cirrhosis			Control		
	Male	Female	Total	Male	Female	Total
Yes	38	0	39	4	0	
No	2	10	11	26	20	
Total	40	10	50	30	20	50

Among total number of 50 cirrhosis patients, 38 (76%) had history of alcohol intake & in control group 4 (8%) had history of alcohol intake. All were male subjects. Not a single female in either of the group had history of alcohol consumption.

Table 3: Etiology of cirrhosis of liver in study group

Variables	ALD	HBV	HCV	ALD+HBV	Other	Total
Male	37	1	0	1	1	40
Female	0	4	0	0	6	10
Total	37	5	0	1	7	50

Among the various etiologies, alcoholic liver disease was the most common causative factor (76%) for cirrhosis, followed by cirrhosis due to other causes. Etiology could not be found out in 14% of cirrhotic patient.

Table 4: Association between severity of liver disease and hypothyroidism

Child Pugh Turcotte grade	Increased TSH (hypothyroidism)	Decreased T3	Decreased T4
A	0	4	4
B	2	0	2
C	13	13	12
Total	15	17	18

From the above table it is seen that 86.66% increased TSH, 76.47% decreased T3 and 66.66% decreased T4 level of cirrhotic patients with hypothyroidism were in CPT grade C with indicating that as severity of liver disease increases, the prevalence of hypothyroidism increases. CPT grade B was second most common among cirrhotic patients with hypothyroidism.

Table 5: Association between serum albumin level and decreased T3 level in cirrhotic patient, Association decreased T3 level and S. bilirubin level in cirrhotic patients and Association between decreased T3 level and INR.

Variables		**Serum albumin level (µg/ml) g/dl**			**Total**
		>3.5 (I)	2.8-3.5 (II)	<2.8 (III)	
T3 Level	Decreased (<0.7ng/ml)	4	3	10	17
T4 Level	Decreased (<5.5µg/dl)	2	4	12	18
TSH Level	Increased (4.20µU/ml)	0	5	10	15
Association decreased T3 level and S. bilirubin level in cirrhotic patients					
Variables		**Serum bilirubin level**			**Total**
		>3.5 (I)	2.8-3.5 (II)	<2.8 (III)	
T3 Level	Decreased (<0.7 ng/ml)	4	1	12	17
T4 Level	Decreased (<5.5 µg/dl)	2	4	12	18
TSH Level	Increased (4.20 µU/ml)	0	5	10	15
Association between decreased T3 level and INR					
Variables		**INR**			**Total**
		>3.5 (I)	2.8-3.5 (II)	<2.8 (III)	
T3 Level	Decreased (<0.7 ng/ml)	4	1	12	17
T4 Level	Decreased (<5.5 µg/dl)	4	2	12	18
TSH Level	Increased (4.20 µU/ml)	2	2	11	15

Decreased T3 level in cirrhotic patients as compare to serum albumin in cirrhotic patient, T3 level as compare to level of serum albumin cirrhotic patient in majority were from serum albumin class 3 about. Decreased T4 level, as compare to level of serum albumin in cirrhotic patient the serum albumin level was decreased then percentage of decreased T4 level (low) was increased. Majority were from serum albumin level class III. When serum albumin level was decreases then percent of TSH level increase was increased.

Discussion

The study included 50 patients with liver cirrhosis and 50 normal healthy individuals as control and compared the prevalence of Hypothyroidism in patient of cirrhosis. Out of 50 patient with cirrhosis 40 (80%) were male and 10 (20%) were female. In control group 30 (60%) were

males and 20% were female. Most (64%) of the patient with cirrhosis were in >41 age group. Alcoholic liver disease was the cause of cirrhosis in 37 (76%) patients. All patients with alcoholic cirrhosis were males. HBV was next most common cause of cirrhosis. Etiology could not be elucidated in 7 (14%) patients. These finding are in accordance with the study by Borzoi et al where alcoholic cirrhosis formed the major etiology group. Study by Calvet et al had shown HCV infection as major etiological factor in cirrhosis followed by alcohol. [11,12]

The comparison of sex distribution in patients with cirrhosis between hypothyroidism and non- hypothyroidism group was not statistically significant ($p>0.05$) which is in accordance in study by Jacques et al. [13] But in contrast to study by Sapin et al which showed that male sex was risk factor for hypothyroidism in cirrhosis. [14] Regarding the etiology of cirrhosis in those with hypothyroidism our study found alcoholic cirrhosis to be the most common etiology (80%) which in accordance with study by Jacques et al. [13] Review of data in literature on this aspect gives varying in formation. In study by Schlienger et al, Sapin et al, hypothyroidism was more frequent in HBV cirrhosis. [13,14] In study by Tasi et al hypothyroidism was most common in HCC related cirrhosis. [10]

Clinical signs of hypothyroidism develop after a prolonged period of thyroid hormone depletion. Our patients probably did not have T3 depletion long enough to become myxedematous although many of them had biochemical hypothyroidism. Symptomatic hypothyroidism disease was present in none of cirrhotic patients with hypothyroidism (0%) and compared to control. 5 out of 50 hypothyroidism without cirrhotic. The difference was not statistically significant ($p>0.05$). In our study all the patients are in compensated group. Statistical comparison of hypothyroidism and non-hypothyroidism group in cirrhosis without regard to CPT grade revealed that in 50% of cells the expected count <5, hence, Chi-square test was not possible. However, the value of Chi-square in this existing situation was 9.946 with probability of test which was significant. The findings are in comparison with study by Schlienger et al, Jacques et al, Sapin et al, which showed that hypothyroidism was common in patients with advanced liver disease. [10,13,14] This was in contrast to study by Kumamoto, which showed that hypothyroidism prevalence is independent of severity of liver disease. [13] In present study serum decreased T3, serum decreased T4 and increased TSH significantly correlated with increased serum bilirubin, decreased serum albumin & increased prothrombin time in both group of patients. The findings were in comparison with study by Borzoi et al. [11] The present study showed that severity of liver disease increases as indicated by serum bilirubin grade. The present study showed that as severity of liver disease increased as indicated by serum INR (prothrombin time) level grade. [15]

Conclusion

According to this study all cirrhotic patients should undergo for evaluation of endocrinological evaluation as these patients are definitely associated with development of hypothyroidism. After diagnosis the treatment of endocrinological disorder especially hypothyroidism may increase survival.

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