

Clinical And Laboratory Evaluation Of Ascites For Tuberculosis In Patients With Cirrhosis Of Liver. Comparison Of Conventional Lab Parameters With Cbnaat

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Abstract

Background And Objectives: Tuberculosis remains major health problem, with an estimated 9.6 million deaths every year worldwide. Diagnosis of Extrapulmonary tuberculosis (EPTB) particularly tubercular ascites with lymphocytic predominance remains a challenge over decades due to paucibacillary nature of ascitic fluid. Detection of tuberculosis by CBNAAT in ascitic fluid has improved the sensitivity and specificity. The objectives are to diagnose secondary abdominal tuberculosis in patients with cirrhosis of liver and to compare conventional lab parameters with CBNAAT.

Methodology: After institutional ethics committee approval and written informed consent from participants, an observational study was conducted among 31 patients with ascites due to cirrhosis of liver above 18 years age attending Rajarajeswari Medical College and Hospital.

Results: Among the 31 cases with liver cirrhosis, four were diagnosed with abdominal tuberculosis. All four were CBNAAT positive, one among the same population was AFB positive and 3 were ADA positive. Based on the study conducted, CBNAAT showed higher sensitivity and its comparison with AFB gave a 'p' value of 0.04, showing statistical significance. Whereas comparison of CBNAAT with ADA gave a 'p' value of 0.32, showing no statistical significance.

Conclusion: The outcome of the study concluded that CBNAAT has a definite role in the diagnosis of abdominal tuberculosis. CBNAAT should be routinely utilized for rapid diagnosis of EPTB along with other conventional methods like AFB smear examination, ADA and culture for better overall results in the diagnosis of EPTB.

Keywords: Extra pulmonary tuberculosis, CBNAAT, Liver cirrhosis, ADA, Abdominal tuberculosis

Introduction

Tuberculosis is one of the most threatening infections and is affecting nearly one third of the population worldwide. Though effective and affordable therapies are available for the disease still it remains as a dangerous infection. Tuberculosis remains as a major health problem, with an estimated 9.6 million deaths every year worldwide. In India approximately 1.5 million cases are put on treatment¹.

Although in approximately 80% cases of the disease manifest as pulmonary tuberculosis, in last few decades, especially after HIV epidemic, incidence of extrapulmonary tuberculosis has increased in India and globally. The other most affected sites in the body are lymph nodes, bones, abdomen, spinal cord, brain and pleura¹.

Abdominal tuberculosis occurs most commonly in immunocompromised patients². Diagnosis of EPTB particularly tubercular ascites with lymphocytic

predominance remained challenging over decades due to paucibacillary nature of ascitic fluid. Ascites can be a manifestation of various pathological conditions including, non-infectious and infectious etiologies. Abdominal tuberculosis, where ascites is the result of tubercular infection per se, other conditions like cirrhosis of liver, CHF, nephrotic syndrome, hypoproteinemia might be secondarily infected with tuberculous bacilli, predominantly in high tuberculosis burden countries like India³.

The lack of explicit clinical features ascertaining the tubercular infection in cases of cirrhosis of liver, delays diagnosis and treatment of the secondary tuberculosis leading to high mortality rate.

The conventional diagnostic methods such as cytology, ADA, ZN staining and LJ culture done from ascitic fluid are not very sensitive for diagnosis of abdominal tuberculosis.⁴

Liquid culture methods adopted by most countries in the last ten years have improved the sensitivity to some extent but are time consuming, expensive and need sophisticated laboratory infrastructure, which is a deterrent to their widespread application in countries where disease is endemic and resources are scarce, such as India. Detection of tuberculosis by CBNAAT in ascitic fluid has improved the sensitivity and specificity. Nucleic acid amplification assays are used to amplify the quantity of mycobacterium tuberculosis DNA in diagnostic specimens where organisms may be present in amounts too small to be seen by routine staining techniques.

Two NAA tests were approved by the United States food and drug administration (FDA) as of 2012, but only for use with sputum or respiratory secretions obtained by bronchoscopy. However, in 2014 guidelines issued by the WHO the CBNAAT has been validated for extra pulmonary tuberculosis too.⁵ So routine inclusion of CBNAAT of ascitic fluid in all patients with liver cirrhosis would help us in detecting secondary tuberculosis and precise diagnosis would cut down the use of empirical use of Antitubercular drugs which is hepatotoxic and detrimental for patients with liver cirrhosis.

Methodology

The present study was a Cross sectional, Observational Study conducted on patients with ascites due to cirrhosis of liver above 18 years age

attending Rajarajeswari Medical College and Hospital. Prior to the initiation of the study Ethical and Research Committee clearance was obtained from Rajarajeswari medical college and Hospital, Bengaluru. The present study included a total 49 liver cirrhosis with ascites patients reviewed in OPD and IPD, among that 31 (63.26%) patients were enrolled into the study according to the study inclusion criteria and 18 (36.73%) patients were excluded according to exclusion criteria.

Patients were included in the study based on the inclusion and the exclusion criteria as mentioned below.

Inclusion Criteria

1. Age group: > 18 years
2. Patients willing to give informed consent
3. Ascites due to cirrhosis of liver

Exclusion criteria

1. Ascites due to other causes like Nephrotic syndrome, CCF, Hypoproteinemia, Pancreatitis.
2. Primary abdominal tuberculosis
3. Patients unwilling for the study.

Study Protocol: Subjects fulfilling inclusion criteria will be selected for the study. Each subject will be admitted as an inpatient to the study hospital during which medical history, physical examination, systemic examinations, and relevant investigations will be carried out. General examination including vitals i.e., pulse, blood pressure, abdominal girth, weight will be recorded. Systemic examination of cardiovascular, abdomen, nervous system, respiratory system will be done. Patients will be examined, investigated, and evaluated for abdominal tuberculosis.

Investigations will include:

1. Ascitic fluid analysis for cell count, cell type, gram's stain, ZN stain for AFB, sugars, proteins, LDH, ADA, CBNAAT
2. USG abdomen
3. CBC
4. LFT
5. PT, APTT, INR

Informed Consent: All the patients fulfilled selection criteria were explained about the details of

the disease process, options of treatment, ultimate outcome, possible side effects, complications, and chances of recurrence of the procedure and a written informed consent was obtained before the enrolment. They were informed of their right to withdraw from the study at any stage.

Data Collection: All the data was collected from the patients that were diagnosed with ascetic due to liver cirrhosis and tuberculosis in the wards of general medicine department and those patients who attended out-patient and in-patient department with detailed history & thorough physical examinations. It included age, sex, nationality, complaints, duration of symptoms, predisposing factors.

Statistical Analysis: The collected data was entered into Microsoft Excel Worksheet-2010 and data was taken into IBM SPSS Statistic for windows, version 24 (IBM Corp., Armonk, N.Y., USA) software for calculation of frequency, percentage, mean, standard deviation and Probability value.

Results

During the study period total 49 patients were reviewed among them, 31 (60.78%) patients were enrolled into the study according study inclusion criteria and 18 (36.73%) patients were excluded according to study exclusive criteria.

Among the study group of 31 patients with liver cirrhosis, 4 patients were diagnosed to have abdominal TB. (Table 1).

Among 31 patients distributed according to symptoms, 26 (83.87%) patients found to have abdominal distension and discomfort followed by 20 (64.51%) patients having myalgia, 17 (54.83%) patients having weight loss, 14 (45.16%) patients having nausea and vomiting, 11 (35.48%) patients having pruritus, 7 (22.58%) patients having anorexia, fever and 6 (19.35%) patients having dark colored urine.

Among 31 patients, 12 (38.70%) patients were observed to have anemia, 08 (25.80%) patients were observed to have thrombocytopenia and 4 (12.90%) patients had leukocytopenia. In 9 (29.03%) patients abnormal serum creatinine was observed. Total bilirubin was elevated in 23 (74.19%) patients, liver enzymes- S.G.O.T was elevated in 29 patients (93.54%) and S.G.P.T was elevated in 28 (90.32%), low total Protein level was observed in 21 (67.74%) patients, low serum albumin levels were observed in 26 (83.87%) patients, low serum globulin levels were observed in 18 (58.06%) patients and USG of all the patient's showed ascites and increased echo-texture of liver suggestive of cirrhosis.(Table 2)

Among the study group of 31 patients with liver cirrhosis, 4 patients were diagnosed to have abdominal TB., Ascitic fluid examination compared in Table 3.

AFB examinations was done among 31 patients, 1(3.33%) patient was AFB positive, and 30 (96.77%) patients were AFB negative. (Table 4)

Among 31 patients, ADA examination was done, 3 (9.67%) patients were ADA positive, and 28(90.32%) patients were ADA negative. 4 (12.9%) patients showed **CBNAAT positive**, and 27 (87.09%) patients showed CBNAAT negative.(Table 5)

Among four patients, all the patients were CBNAAT positive and in the same set of patients, AFB was positive in 01 (25%). Statistically it has shown that CBNAAT is more sensitive when compared to AFB, with a P-Value of 0.04. Among 4 patients, all the patients showed positive CBNAAT reports meaning 100% were positive and the same patients ADA was positive in 03 (75%). Statistically showing that, P-Value is 0.32, which is statistically insignificant.(Table 6).

Table 1: Patients distribution according to Final Diagnosis

Diagnosis	No. of Patients	Percentage	Ratio
Liver Cirrhosis	27	87	

Liver Cirrhosis with TB	4	13	5.2:1
Total	31	100	

Table 2: Summary of Lab Values of Patients

Lap tests	No. of Patients	Percentage
Anemia	12	38.7
Leukocytopenia	4	12.9
Thrombocytopenia	8	25.8
S. Creatinine (> 1.3mg/dl)	9	29.03
Total bilirubin (>1.3mg/dl)	23	74.19
S.G.O.T (> 150 IU/L)	29	93.54
S.G.P.T (> 150 IU/L)	28	90.32
Total Protein (<6.2gm/dl)	21	67.74
S.Albumin (<3.5gm/dl)	26	83.87

S.Globulin (<1.3gm/dl)	18	58.06
USG of Abdominal (Ascites)	31	100

Table 3: Ascitic fluid examination in liver cirrhosis without TB and liver cirrhosis with TB.

Ascitic fluid examination	Number of patients	Cirrhosis Patients	Cirrhosis with TB patients
Total Protein (>2.5g/dl)	6	2 (30%)	4 (70%)
Glucose (low)	8	4 (50%)	4 (50%)
Cell Count (>250/μl)	25	22 (88%)	3 (12%)
LDH (High)	3	1 (33.3%)	2 (66.6%)

Table 4: Patients distribution according to AFB examination

AFB examination	Frequency	Percentage
AFB Positive	1	3.33
AFB Negative	30	96.77
Total	31	100

Table 5: TB patient distribution according to ADA examination

Test	Frequency	Percentage
ADA Positive	3	9.67
ADA Negative	28	90.32
CBNAAT Positive	4	12.9
CBNAAT Negative	27	87.09

Table 6: Comparison of AFB and ADA reports Vs CBNAAT reports in Abdominal TB patients

Test	Abdominal TB Positive	P- Value
AFB	01 (25%)	0.04
CBNAAT	04 (100%)	
ADA	03(75%)	0.32
CBNAAT	04(100%)	

Discussion

The observations and results of present study were compared with the available previous similar studies. In the present study, there was a male preponderance for cirrhosis with a male to female ratio of 3.42: 1. In the studies done by Ervilla Dass³⁸(2018), Apurva S³⁹ (2018) and Sudeshna Mallik⁴⁰ (2018) there was a similar male preponderance with a male to female ratio of 8:1, 5.4: 1 and 2.2: 1 respectively. This difference in incidence in sex ratios might be because of social habits of males at various stages of life.

In the present study, 41.93% of patients are in the age group of 41-50, and 29.03% of patients are of age group 51-60. Among 31 patients, 83.87% patients were diagnosed as liver cirrhosis and 16.12% patients were diagnosed as liver cirrhosis with TB.

In the present study, 83.87% of patients have abdominal distension and discomfort; similar percentage was observed in other studies Sudeshna Mallik⁴⁰et,al(2018) and David Ce⁴¹et, al (2019), 80% and 75% respectively. And, 64% patients have myalgia in this study, 50% patients had same symptoms in David C et, al⁴¹ (2019) study. In the present study, weight loss was seen in 54.83% patients, similar percentage was observed in other studies like Hemang Suthar et,al⁴² (2013), Sudeshna Mallik et,al⁴⁰(2018) and David C et,al⁴¹ (2019) 48.57%, 30% and 53% respectively. 45.16% patients have nausea and vomiting in this study, 48.57 % patients have same symptoms Sudeshna Mallik⁴⁰et,al(2018) study. In present study, 22.58% patients have anorexia nearly same percentage were observed in other studies Sudeshna Mallik⁴⁰et,al(2018) and Hemang Suthar⁴²et,al (2013),

62.86 % and 40% respectively and 22.58% patients have fever; nearly same percentage were observed in other studies Sudeshna Mallik⁴⁰et,al(2018), Hemang Suthar⁴²et,al (2013) and David C⁴¹et,al (2019) 40%, 30% and 69% respectively. Also in this study, 19.35% patients have dark colored urine. 24% patients have same symptoms Hemang Suthar ⁴³et,al (2013) study.

In present study, 06.45% patients have hepatomegaly, Sudeshna Mallik⁴⁰ (2018) ; Behera and Dash⁴⁴ (2020), 72.61%, 71.43% and 55% respectively. 45.16% patients have Splenomegaly, in another study by Joshi, et al.⁴³(2018), Sudeshna Mallik⁴⁰(2018) and Behera and Dash⁴⁴(2020), 76.19%, 74% and 50.72% respectively observed. In present study, pallor was observed in 45.16% patients, similar percentages were observed in other studies like Joshi, et al.⁴³(2018) and Behera and Dash⁴⁴(2020) 71.48% and 60.87% respectively. 38.70% patients have icterus in this study, in other studies Joshi, et al.⁴³(2018), Sudeshna Mallik⁴⁰(2018) and Behera and Dash⁴⁴ (2020), 26.19%, 42.86% and 20.29% respectively. In present study, 19.35 % patients have leukonychia, 98.09% patients have same symptoms n the Joshi⁴³, et al. (2018) study. In this study, 25.80% patients have spider naevi; 34.52% patients have same signs in Joshi⁴³, et al. (2018) study.

In our study, we found that 38.7% of the patients have anemia. A study by Gonzalez-Casas⁴⁵et al. showed that anemia in CLD patients was 75%. Hegde⁴⁶et al. study also found severe anemia in 43% of cases.

According to an interesting article by Kujovich MD⁴⁷ – “Hemostatic defects in end stage liver disease,”

critical care clinics 21 (2005), mild-to-moderate thrombocytopenia occurred in 49–64% of patients with decompensated CLD. In our study, 25.80 % patients have thrombocytopenia (<1.5 lakhs/mm²).

In this study, the creatinine is increased in 29.03% patients, which is comparable with 39.4% in a study by Pathak⁴⁸ *et al.* and 30% in a study by Hegde⁴⁶ *et al.* It was observed that 23 patients had glomerular filtration rate (GFR) <60 ml/min. The absolute value of SGOT and SGPT is usually <300 U/L in patients with liver cirrhosis disease 90.32% of patients showed increase in SGPT level in the present study, which is comparable with Mendel hall⁴⁹ *et al* 91%.93.54% patients increase SGOT level, which is comparable with pathak⁴⁸ *et al* 89% .Serum Albumin was low in 83.87% patients, while in Chacko and Chacko⁴⁹ *et al* study 73% and Mendelhall⁴⁹ *et al* it was 81.47% which is comparable with our study. Serum bilirubin was increased in 67.74% patients in present study, which is comparable with Chacko and Chacko⁵⁰ *et al.* Thus, the result of our study establishes most of the known facts about liver cirrhosis disease in Indian population.

Among all the patients with cirrhosis, ascitic fluid AFB examination was done, one patient showed AFB positive. In previous study conducted by Bhargava DK⁵¹, *et.al* staining for AFB was positive in less than 3% of cases and a positive culture is seen in only 20% of cases.

ADA is positive in 3 patients, Serum ADA level above 54 U/L. Ascitic fluid ADA level above 36 U/L and an ascitic fluid to serum ADA ratio more than 0.98 is suggestive of tuberculosis.

CBNAAT is positive in 4 patients . Same percentage was observed in other studies like Ashi Singh⁵²*et.al* 92% and specificity was 100%. Positive predictive value was 100%. And, another study conducted by Komanapalli SK⁵³ *et al* (2018) observed 84.34% patient CBNAAT reports were positive.

Among four patients, CBNAAT reports was positive in all the four patients and in the same patients ADA was positive in 03 (75%) patients, and 01 (25%) patient showed ADA negative., at P-Value of 0.32. Which is insignificant.

Among four patients, AFB was positive in 01 (25%) patient and 03 (75%) patients shown AFB negative .Statistically has shown CBNAAT more specific

compared to AFB, at P-Value 0.04. Likely due to the pauci bacillary nature of extra pulmonary tuberculosis.

CBNAAT is a semi-quantitative nucleic acid amplification test based on molecular detection of mutated gene. It is simple, rapid and cost effective and doesn't require technical expertise. It can be carried out in automated manner including bacterial lysis, nucleic acid extraction, and amplification and detection. It can diagnose TB within 2 hours and gives accurate results with added advantage of disposable closed cartridges preventing cross contamination.¹⁰ In settings where resources are limited for facilities like culture DST, CBNAAT is extremely useful, simple and reliable test. It also has a significant role to play in the diagnosis of extra pulmonary tuberculosis. Its potential in EPTB detection has been underutilized due to lack of awareness regarding the same. Hence, we conducted the study to determine effectiveness of this rapid and logistically simplified test in the diagnosis of EPTB.

These findings suggest that CBNAAT plays a major and important role in the diagnosis of EPTB, particularly in places with high burden and limited availability of resources. CBNAAT could be the best aid for physicians in diagnosing EPTB if more awareness is brought among them regarding its utility. Our study highlighted that CBNAAT can be a faster alternative to time taking methods like culture and at the same time a more efficient alternative to other rapid methods like AFB smear examination in the diagnosis of EPTB. With our study, we conclude that CBNAAT is more effective as compared to AFB smear in the diagnosis of abdominal tuberculosis.

Conclusion

The present study conducted over 02 years with a study population of 31 cases of liver cirrhosis and 4 patients are diagnosed to have liver cirrhosis with TB. The outcomes of present study concluded that liver cirrhosis is commonly seen in males compared to females, the ratio of female to male was 3.42:1 suggestive of male predominance and contributing almost 77% of total study population. Most patients with liver cirrhosis present with abdominal distension and discomforts and the most common method of detection is USG abdomen.

CBNAAT has a definite role in the diagnosis of abdominal tuberculosis, considering only AFB and ADA positivity, abdominal TB in liver cirrhosis is under diagnosed, and patients are denied of getting anti tubercular treatment.

CBNAAT should be routinely utilized for rapid diagnosis of EPTB along with other conventional methods like AFB smear examination and culture for better overall results in the diagnosis of EPTB.

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