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Original Research Article

STUDY OF BIOCHEMICAL PARAMETERS OF ASCITIC FLUID IN EXUDATIVE ASCITES WITH SPECIAL REFERENCE TO TUBERCULOUS PERITONITIS

Dr. Monika Jayaswal^{1*}, Dr. Vijay Kumar², Dr.(Prof.) Sude Kumar Singh³

¹*Tutor, Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar

² Additional Professor, Department of General Medicine, All India Institute of Medical Sciences(AIIMS), Patna

³Professor & Head, Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga, Bihar

***Corresponding author:** Dr. Monika Jayaswal

*Tutor, Department of Biochemistry, Darbhanga medical College, Laheriasarai, Darbhanga, Bihar

ABSTRACT :

In an attempt to differentiate between three important but clinically similar conditions of exudative ascites like tuberculous peritonitis, spontaneous bacterial peritonitis (SBP) and malignant ascites, we evaluated the biochemical parameters of ascitic fluid as a diagnostic aid. The serum ascitic albumin gradient (SAAG), lactate dehydrogenase (LDH), pH, adenosine deaminase (ADA), carcino-embryonic antigen (CEA), carbohydrate antigen (CA-125) and gamma Interferon levels were measured in 34 patients with tuberculous peritonitis, 24 patients with SBP and 22 patients with ascites due to malignant disorders. The LDH level was significantly lower in tuberculous peritonitis patients than in malignant and SBP groups. A value of < 110 U/l gave the assay a sensitivity of 94% and a specificity of 93 %, positive predictive value of 89 % and negative predictive value of 96% for tuberculous peritonitis. The ADA activity was significantly higher in tuberculous peritonitis group than in the other two groups. A cut off value > 33 U/l gave the ADA test a sensitivity of 88 %, specificity of 100 %, positive predictive value of, 100 % and a negative predictive value of 94 % for tuberculosis. A pH value of <7.26 with high SAAG (> 1.1 g/dl) predicted SBP with reasonable accuracy. Elevated ascitic fluid CEA (> 2 ng/ml) and CA -125 (> 35 U/l) was found exclusively in cases of malignant ascites. Gamma Interferon level was higher in tuberculous peritonitis than in other cause of exudative ascites and cut off =>3.2u/ml gave the assay a sensitivity of 93% and specificity of 98%, positive predictive value and negative predictive value of 96%. All these tests are rapid, non-invasive, and easily reproducible and offer good predictive accuracy which is comparable to that of more invasive procedures like peritoneoscopy and biopsy

INTRODUCTION:

The first documented case of ancient 'tuberculosis (TB)peritonitis' was described in humans in 1843. The peritoneum is one of the most common extrapulmonary sites of tuberculous infection. Peritoneal tuberculosis remains a significant problem in parts of the world where tuberculosis is prevalent. The risk is increased in patients with cirrhosis, HIV infection, diabetes mellitus, underlying malignancy, following treatment with anti-tumor necrosis factor (TNF) agents, and in patients undergoing continuous ambulatory peritoneal dialysis.

Peritoneal tuberculosis is currently the sixth most common site of extrapulmonary tuberculosis in India and accounts for 0.5% to 1% of all tuberculosis related hospital admissions and has an overall mortality rate of 7%. With *Mycobacterium tuberculosis* now emerging as a major pathogen in human immunodeficiency virus(HIV) positive patients, the impact of HIV infection and acquired immunodeficiency syndrome(AIDS) on tuberculosis is of great concern. The diagnosis of peritoneal tuberculosis is made difficult because of the paucity of *Mycobacterium tuberculosis* in peritoneal fluid. It is often necessary to differentiate this condition from clinically similar situations like

spontaneous bacterial peritonitis(SBP) and malignant ascites. Even one of the most recent diagnostic methods like polymerase chain reaction has a variable sensitivity and low specificity. Therefore new technique which are rapid and less invasive but which maintain high sensitivities, specificities, and positive/negative predictive value need to be evaluated to aid in the diagnosis of tubercular peritonitis. Seven biochemical parameters were evaluated e.g, serum ascitic albumin gradient(SAAG), lactate dehydrogenase (LDH), pH, adenosine deaminase(ADA), carcinoembryonic antigen (CEA), carbohydrate antigen(CA-125) and gamma interferon in ascitic fluid from patient with exudative ascites to differentiate tubercular peritonitis from SBP and malignant ascites.

MATERIALS & METHODS:

The study was conducted in Department of Biochemistry, Darbhanga Medical College, Laheriasarai, Darbhanga during October 2017 to September 2018. Out of total 80 cases of recent onset (<3 months) exudative ascites (defined as ascitic fluid total protein >2.5 g/dl and ascitic fluid:serum LDH ratio >0.6), 34 cases were diagnosed as tuberculous peritonitis [based on peritoneal biopsy, nodules, positive culture for mycobacterium tuberculosis, polymerase chain reaction (PCR) for myco tuberculosis and therapeutic response to antituberculous drug]. Of the remaining 46 cases 24 were diagnosed as SBP (based on ascitic fluid neutrophil count >250/ul, demonstration of single micro organism on culture of ascitic fluid, with ultrasonic evidence of cirrhosis with or without endoscopic evidence of varices) and remaining 22 cases as malignant ascites (malignant cells on pap smear or peritoneal biopsy with or without unequivocal evidence of primary malignancy). Two cases of tuberculous peritonitis had underlying chronic liver disease which was discovered during investigations.

In all 80 cases, we then went on determining the aforesaid seven biochemical parameters in the ascitic fluid. (1) Ascitic fluid and serum albumin were measured by biuret method, (2) ADA activity was measured spectrophotometrically. (3) LDH was measured by photometric method while (4) pH was detected by pH metre. (5) CEA, (6) CA-125 and (7) gamma interferon in the ascitic fluid estimated by enzyme immunoassay.

OBSERVATIONS:

Tuberculous peritonitis was diagnosed in 34 patients based on following criteria: positive ascitic fluid culture for mycobacterium tuberculosis in 14 cases (41.17%), granuloma on peritoneal biopsy in 80%, peritoneal nodule in 84%. Ascitic fluid PCR for myco tuberculosis was positive in 92%. After diagnosing cases of tubercular peritonitis by above procedure biochemical parameters in these cases were measured. ADA was elevated in all cases of tuberculous peritonitis and cut off value >33 U/L occurred in 88.23% cases (30 out of 34). Elevated level was also encountered in 3 cases of infective cirrhotic and malignant ascites. An absolute LDH value of <108 U/l was encountered in 32 (94%) out of 34 cases of tuberculous peritonitis. LDH elevated in 2 out of 24 cases of SBP. 3 cases of peritoneal tuberculosis occurred in background of chronic liver disease, these cases have SAAG value >1.1g/dl. None of the remaining 31 cases of tuberculous peritonitis had SAAG elevated above 1.1g/dl. 22 out of 24 cases of SBP (diagnosed on the basis of ascitic fluid culture and elevated neutrophil count or positive ascitic fluid culture) had SAAG value greater than 1.1g/dl. Barring a single case of malignant ascites, ascitic fluid pH <7.26 was found exclusively in SBP and none of the tubercular peritonitis showed decrease in pH. Elevated ascitic fluid CA 125 (>35u/l) and CEA (>2 ng/ml) occurred in 19 (86%) out of 22 cases of malignant ascites. Elevated CA 125 level was found in only two cases of tuberculous peritonitis. Gamma Interferon level was higher in tuberculous peritonitis (31 out of 34 cases) than in other cause of exudative ascites ($p < 0.0001$) and cut off value ≥ 3.2 u/ml gave the assay sensitivity of 93% and specificity of 98%.

Table 1 shows percentage of cases in each group with biochemical marker exceeding or below a predetermined value for each marker. The sensitivities, specificities, positive negative predictive value of various parameters at their respective cut off values are shown in table 2.

TABLE 1:

Percent distribution of cases in three major groups with cut off value for biochemical marker			
Biochemical Marker	Tuberculous peritonitis(n=34)	Spontaneous bacterial peritonitis(n=24)	Malignant ascitis(n=22)
SAAG>1.1 g/dl (with TP>2.5 g/dl)	3(8.8%;all had chr liver disease)	22(91.6%)	1(4.5%)
ADA>33U/l	30(88.23%)	0	0
LDH<108U/l (with ascitic:serum LDH fradient>0.6)	32(94.23%)	2(8.3%)	2(9.0%)
pH <7.26	0	24(100%)	1(4.5%)
CA-125 >30U/l	2(5.8%)	0	9(40.9%)
CEA>2 ng/ml	0	0	10(45.45%)
Gamma IFN=>3.2u/ml	31(92%)	0	1(4.5%)

TABLE2:

Statistical Presentation of Diagnostic Accuracy of biochemical markers for three major groups			
Biochemical Marker	Tuberculous peritonitis	Spontaneous bacterial peritonitis	Malignant ascites
Absolute LDH<108u/l	sensitivity 94%		
	specificity 93%		
ADA>33u/l	sensitivity 88%		
	Specificity 100%		
LDH<108 u/l + ADA >33 u/l	sensitivity 97%		
	specificity 100%		
CA-125 >35u/l + CEA>2 ng/ml			sensitivity 86%
			specificity 98%
High SAAG>1.1g/dl + low pH <7.26		sensitivity 93%	
		specificity 96%	
Gamma Interferon=>3.2u/ml	sensitivity 93%		
	specificity 98%		

DISCUSSION:

Gastro intestinal and peritoneal tuberculosis remain common problem in the developing world like India. Most cases of tuberculous peritonitis are thought to result from reactivation of latent foci in the peritoneum established previously via haematogenous spread from a primary focus in the lungs(commonly to mesenteric lymph node).Up to one third cases may be associated with pulmonary tuberculosis. The differential diagnosis of tubercular peritonitis include spontaneous bacterial peritonitis and malignant ascites. All the three condition present as exudative ascites with elevated total protein (>25 g/l) and LDH(with an ascitic fluid :serum ratio of >0.6).Counting total cell and its typing can be confusing at times because some cases of tuberculous peritonitis can have polymorphs(like SBP) or red blood cells(like malignancy)as the predominant cell type. Yield for malignant cells in the ascitic fluid is often poor in malignant ascites. The gold standard for diagnosis of tuberculous peritonitis remains laproscopy directed biopsy.

Recently several non invasive diagnostic tests have become available. In this study the target was to develop simple, reliable and non-invasive reproducible parameters to aid in differentiation of tuberculous peritonitis from SBP and malignant ascites without the need of peritoneoscopy and biopsy.For this purpose .seven biochemical markers of ascitic fluid namely SAAG,LDH,pH,ADA,CEA,CA-125 and gamma interferon were evaluated in 80 patients of exudative ascites who were divided into 3 groups based on other investigating findings.High SAAG value >1.1g/dl established a diagnosis of cirrhosis with good accuracy(sensitivity 94% and specificity

97%). High SAAG value combined with low pH (<7.26) was virtually diagnostic of SBP. Ascitic fluid ADA level >33u/l gave a sensitivity of 88%, specificity of 100%, p(+) 100% and p(-) 94%. One study report that using a value >40u/l reached a sensitivity of 100% and specificity of 97%. Ascitic fluid absolute LDH value <108u/l had a sensitivity of 94%, specificity of 93%, p(+) of 89%, p(-) of 96% in establishing a diagnosis of tuberculous peritonitis. Taken together they have sensitivity of 97% and specificity of 100%. Gamma interferon ascitic fluid level using a cut off value of 3.2u/ml gave the assay a sensitivity of 93%, specificity 98%, P(+) and p(-) 96%. With greater experience both tests of LDH and ADA could potentially supersede invasive procedures for the diagnosis of tuberculous peritonitis in countries like ours.

CONCLUSION:

1. Tuberculous peritonitis is an endemic disease among socio economically disadvantaged communities.
2. Peritoneal tuberculosis is one of the most common extrapulmonary site of tuberculosis.
3. Peritoneal tuberculosis needs to be differentiated from clinically similar condition like spontaneous bacterial peritonitis (SBP) and malignant ascites.
4. Tubercular peritonitis is confirmed by laparoscopy directed peritoneal biopsy which is an invasive and difficult procedure.
5. Seven biochemical parameters namely serum ascitic albumin gradient (SAAG), lactate dehydrogenase (LDH), adenosine deaminase (ADA), carcinoembryonic antigen (CEA), carbohydrate antigen (CA-125), pH and gamma interferon can differentiate tuberculous peritonitis from SBP and malignant ascites with high sensitivity and specificity.
6. It is found that ADA activity was significantly higher in tuberculous peritonitis group than in other two groups. A cut off value >33 u/l gave the ADA test sensitivity of 88% and specificity 100%.
7. Ascitic fluid absolute LDH value <108u/l had a sensitivity 94% specificity 93% in establishing a diagnosis of tuberculous peritonitis.
8. High gamma interferon level more than 3.2u/ml gave the assay sensitivity of 93% and specificity 98% in tuberculous peritonitis.
9. High SAAG value (>1.1g/dl) combined with low pH (<7.26) was virtually diagnostic of SBP.
10. Elevated ascitic fluid CA-125 (>35 u/l) and CEA (>2 ng/ml) had sensitivity of 86% and specificity of 98% in malignant ascitis.

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