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Change of the Ascitic Fluid Total Protein in Natural Progression of Liver Cirrhosis and Serum Ascites Albumin Gradient in Patients with Spontaneous Bacterial Peritonitis Versus Patients with Cirrhosis and Sterile Ascites

Djurkov V[1], Dimitrova E[2], Kiprin G[1*], Belev N[3], Djokleva M[4], Donchev B[4], Milchev H[5] and Krastev N[4]

[1]Ward of Gastroenterology, University Hospital "Eurohospital", Medical University, Plovdiv, Bulgaria

[2]Department of Informatics and Statistics, University of Food Technologies, Plovdiv, Bulgaria

[3]Ward of Surgery, University Hospital "Eurohospital", Medical University, Plovdiv, Bulgaria

[4]Clinic of Gastroenterology and Hepatology, University Hospital "St. George" - Plovdiv, Bulgaria

[5]Medical University - Plovdiv, Bulgaria

***Corresponding author:**

Georgi Kiprin,
Ward of Gastroenterology, University Hospital "Eurohospital", Medical University, Plovdiv, Bulgaria, E-mail: georgikiprin@gmail.com

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Crrhosis; Ascites; Spontaneous bacterial peritonitis; Ascitic fluid total protein; Serum ascites albumin gradient

1. Abstract

1.1. Background: Spontaneous Bacterial Peritonitis (SBP) is a big complication of liver cirrhosis with ascites. Ascitic Fluid Total Protein (AFTP) is still used to determine the risk of SBP in cirrhotic patients with ascites. There are single reports of the role of serum-ascites albumin gradient (SAAG) in the diagnosis of SBP

1.2. Aim: The aim of the study is to determine whether AFTP decline in natural progression of liver cirrhosis (predisposition of SBP) and to determine whether SAAG is significant higher in patients with SBP than in patients with liver cirrhosis and sterile ascites.

1.3. Patients and methods: 302 patients with liver cirrhosis and ascites grade II or III were investigated for ten year period (2007-2016). 68 patients were admited in hospital more than one time. SBP have been diagnosed in 54 patients (14,6% of patients with cirrhosis and ascites at the time of 370 hospitalizations).

1.4. Results: 11,5% of all patients with hepatic cirrhosis had AFTP <10g/L and 24,7% had >25g/L. AFTP was decreased in next (second and third) hospitalizations in 36,6% of patients. AFTP was significantly elevated in next hospitalizations in 44,6% of patients and in 17,9% was unchanged. Mean level of AFTP in patients with SBP (9,3g/L) was significant lower compared to AFTP in patients with sterile ascites, independent of consecutive of next hospitalization (20,2; 22,1; 27,9 g/L). /L). In patients with SBP AFTP was ≤12g/L in 92,3% but AFTP was 14g/L in 5,6%.

The SAAG was between 15 and 20g/L in half (49,5%) of patients with hepatic cirrhosis and sterile ascites and between 21 and 26g/L in almost half (48,1%) of patients with SBP.

1.5. Discussion: Diuretic therapy can elevate AFTP in patients with SBP (>10g/L and <15g/L). Not only diuretic treatment but progression of cirrhosis (Child-Pugh class C) and deterioration of portal hypertension is the most probably explanation of elevation of AFTP at the time of second and third hospitalization in almost half of the patients with cirrhosis and sterile ascites. The mean level of SAAG (22,2g/L) was significant higher in patients with SBP than in patients with cirrhosis and sterile ascites, independent of consecutive of next hospitalization (18,9; 18,2; 18,8g/L).

1.6. Conclusion: Combination of low AFTP (<15g/L) and high SAAG (>20g/L) is suspicion for SBP, especially in patients with PMNs in ascitic fluid ≤250/mm^3 and negative (false negative) bacterial cultures – at least 30% of patients, even if ascitic fluid was taken for examination in bottles for blood cultures at patient's bed.

2. Background

Spontaneous bacterial peritonitis (SBP) (H. Cohn, 1963) is a big complication of liver cirrhosis with ascites [1-3]. The incidence of SBP is ~10% of all hospitalized patients with cirrhosis and ascites (1,5-3,5% in outpatients) [4]. The incidence of SBP is even more frequent in patients with double elevated serum bilirubin and/or serum creatinin >88,4μmol/L [5]. SBP has been observed in 70-85% of patients with Child-Pugh class C liver cirrhosis (high level of serum bilirubin) [6]. MELD score is not related to SBP [7], but MELD ≥22 (high level of serum creatinine and bilirubin) define poor prognosis of SBP [8].

The ascitic bacterial cultures are rarely positive (≈40%) [9] due to the low concentration of microorganisms in ascitic fluid (1 bacteria/1 ml) [10], even if collected in blood culture bottle at patient's bed (≈70%) [9].

According to IAC (International Ascites Club) the SBP diagnosis is considered to be placed in polymorphonuclears (PMNs) >250/mm^3, independently of result of bacterial cultures [11]. PMNs in ascitic fluid increase >250/mm^3 in gram-negative flora, but it is not clear whether this is the same in gram-positive microorganisms [12]. At present, half of the episodes of SBP are caused by gram-positive bacteria [13].

Ascitic Fluid Total Protein (AFTP), apart from the transudate/exudate conception, is still used to determine the risk of SBP in cirrhotic patients with ascites (AFTP<10g/L), for differentiation of SBP from secondary bacterial peritonitis (higher level of AFTP in patients with Sec BP than in SBP) and in cardiac ascites [high AFTP (>25g/L) and high serum-ascites albumin gradient (SAAG) (>11g/L)] [14]. AFTP is greater than 30g/L („exudative ascites") in up to 30% of patients with cirrhosis and sterile ascites [15]. SAAG can be <11g/L in 5% (up to 15-16%) of patients with liver cirrhosis and sterile ascites [16], but in SBP SAAG significantly exceeds 11g/L, due to the low values of AFTP - the proportions of albumin in the total protein concentration is approximately 45% [15]. The SAAG is superior to the exudate–transudate concept in the differential diagnosis of ascites [14]. There are single reports of the role of SAAG in the diagnosis of SBP [17].

3. Aim

The aim of the study is to determine whether AFTP decline in natural progression of liver cirrhosis (predisposition of SBP) and to determine whether SAAG is significantly higher in patients with SBP than in patients with liver cirrhosis and sterile ascites.

4. Patients and Methods

302 patients with liver cirrhosis and ascites grade II and III were investigated for ten-year period (2007-2016) - 74 wemen and 228 men [mean age 59 (30-86) years.] 302 patients were admited in hospital 370 times. 68 patients were admited in hospital more than one time – 46 twice и 22 three times. Mean interval between first and second hospitalization was 3, 9 (1-26) months, and between second and third hospital admission - 8, 4 (1-38) months. SBP have been diagnosed in 14,6% [54/370 of in-patients with cirrhosis and ascites grade II or III], who was compared to 243 patients with cirrhosis and sterile ascites [Nine patients (9/307 - 2,9%) had secondary bacterial peritonitis (SecBP)]. Routine hematological, biochemical, immunological, virological and instrumental examinations (ultrasonography, upper gastrointestinal endoscopy) were performed in all patients. Ascitic fluid was investigated biochemically, with differential count (PMNs), bacterial cultures and cytologically. AFTP and SAAG in patients with SBP was estimated at the time of diagnosis, independently of serial hospital admission.

5. Statistical Methods

In accordance with the aims of the research it was necessary either to compare proportions of two independent groups or to compare several (more than two) means. In order to determine whether the difference in two proportions was statistically significant the Z-test was applied for samples with size more than 50 and T-test for the rest of cases. A Kruskal-Wallis H test was used for comparisons of the means since the samples were not normally distributed. Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons.

6. Results

One fourth (24,7%) of all patients with liver cirrhosis and ascites (grade II or III) have had AFTP>25g/L, but 11,5% had AFTP<10g/L (Figure 1).

Mean level of AFTP of all patients with cirrhosis was 19,2g/L and 9,3g/L in patients with SBP. There is significant difference between mean levels of AFTP in patients with cirrhosis and sterile ascites at the time of first (20,2g/L) and third hospitalization (27,9g/L) (Figure 2). Mean level of AFTP in patients with SBP (9,3g/L) was significantly lower versus AFTP in those patients with sterile ascites, independent of consecutive) of next hospitalization (20,2; 22,1; 27,9g/L) (Figure 2). Decreased of AFTP in the natural progression of liver cirrhosis and sterile ascites was established at the time of next hospitalizations (second and third hospitalization together) in more than third (37,5%) of the patients. However, in almost half (44,6%) of the patients AFTP was elevated at the time of next hospitalizations, and in 17,9% theree was unchanged.

More than 1/4 (27,8%) of patients with SBP have had AFTP>10g/L (Figure 3). Patients with SBP had AFTP ≤12g/L in 92,6% (Figure 3).

Difference between the level of SAAG in SBP and sterile ascites in patients with cirrhosis is significant ($p = 0{,}00002 < 0{,}05$ и $p = 0{,}00001 < 0{,}05$), independently of consecutive number of next hospitalization (Figure 4).

Levels of SAAG >20g/L have been established to be significant more frequent in patients with SBP compared to SAAG at the time of first hospitalization of patients with cirrhosis and sterile ascites (Figure 5).

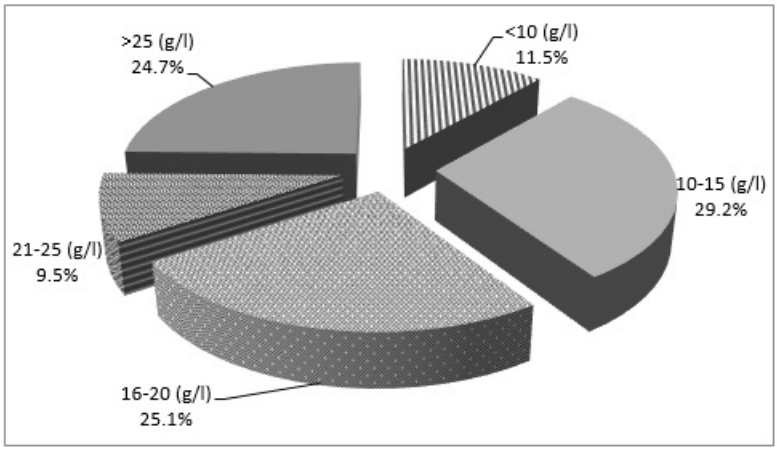

Figure 1: Total protein in ascitic fluid (ascites grade II or III) in all patients with liver cirrhosis at the time of first hospitalization

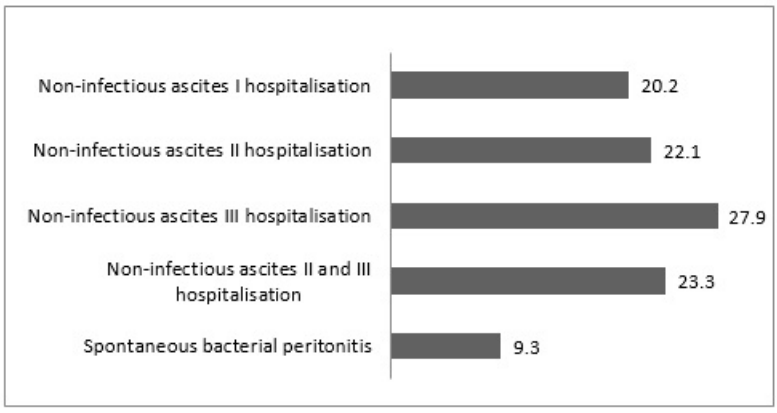

Figure 2: Mean levels of total protin (g/L) in ascitic fluid in patients with liver cirrhosis and sterile ascites grade II or III (at the time of first and next hospitalizations) and in patients with spontaneous bacterial peritonitis.

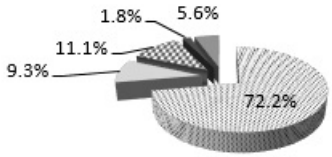

Figure 3: Total protin in ascitic fluid in patients with spontaneous bacterial peritonitis

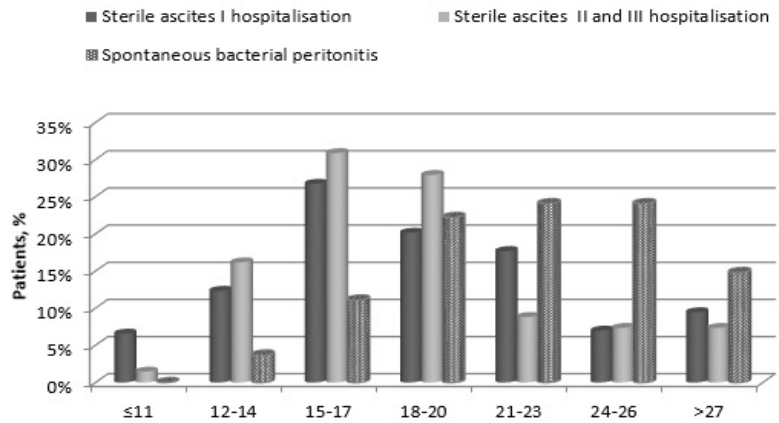

Figure 4: Serum ascites albumin gradient in patients with liver cirrhosis and sterile ascites grade II or III at time of the first and next hospitalizations (second and third hospitalizations together) versus serum ascites albumin gradient in patients with spontaneous bacterial peritonitis.

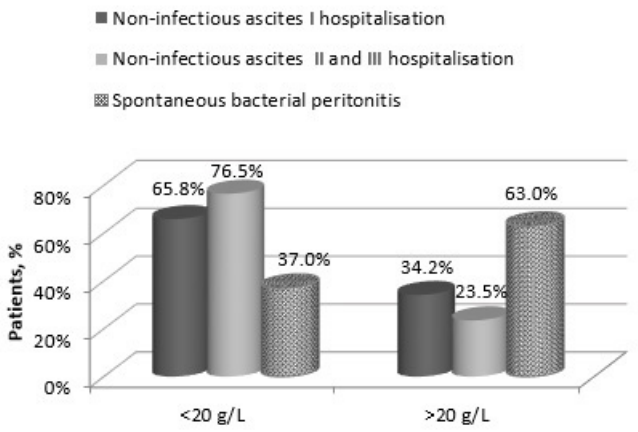

Figure 5: Serum ascites albumin gradient more than 20g/L and less than 20g/L in patients with liver cirrhosisis and sterile ascites grade II or III at the time of first and next hospitalizations (second and third hospitalizations together) versus spontaneous bacterial peritonitis.

The difference of SAAG between patients with SBP and next hospitalizations (second and third hospitalizations together) of patients with cirrhosis and sterile ascites was almost threefold higher in patients with SBP (p =0,00002 and p = 0,00001) (Figure 5)

7. Discussion

If AFTP is <10g/L in patients with cirrhosis and sterile ascites (11,5% in the study – (Figure 1), the risk of SBP increases tenfold [6]. After diuretic treatment AFTP increases (>25g/L) in 2/3 of patients [18] (24,7% at the time of first hospitalization in the study – (Figure 1) and SBP may occur at higher values of AFTP (usually <15g/L) [4, 9]. Patients with SBP had AFTP ≤12g/L in 92,3% but AFTP was 14g/L in 5,6% of them (Figure 3). In SBP permeability of peritoneal membranes is unchanged opposed to pleural and meningeal infections [14]. That is why AFTP in patients with SBP remains in low level. It is necessary the diagnosis of SBP to be revised if AFTP is ≥15g/L. AFTP in patients with SBP may be even ≥25g/L, but only in 0-6% [14]. Most likely secondary bacterial peritonitis is concerned in these cases [9, 19]. Higher AFTP levels established in most patients with Sec BP, is a consequence and not a prerequisite of secondary bacterial peritonitis [19].

Almost all patients in the study with cirrhosis and sterile ascites after first hospitalization and patients with SBP as well, were treated with diuretics, because sterile ascites was II or III degree and SBP occurs after the onset of ascites - up to third year in 1/4 of patients [10] (7-30% per year [20]).

Mean levels of AFTP in patients with SBP (9,3g/L) was significant lower versus sterile ascites in cirrhosis, independently of the time of next hospitalization (Figure 2).

Mean levels of AFTP in patients with cirrhosis and sterile ascites was significant lower at the time of first hospitalization versus third hospitalization (Figure 2).

On one hand decreased of AFTP (compared to baseline level) in the natural progression of liver cirrhosis with sterile ascites were established at the time of next hospitalizations in more than third (37,5%) of the patients - predisposition of SBP. Not all patients with cirrhosis and ascites develop SBP but in more than 1/3 of them (37,5% in the study) the risk is increased and in 1/10 (11,5% in the study) the risk of SBP increases tenfold [6]. On the other hand however almost in half of the patients AFTP were elevated (after diuretic treatment) and were unchanged in the rest. It is possible that diuretic therapy elevates not only AFTP (in 2/3 of the patients [18]), but higher elevetion during the long-time diuretic treatment.

AFTP concentration ranges between 5g/L and more than 60g/L [14] and is greater than 30g/L in up to 30% of patients with otherwise uncomplicated cirrhosis [15]. Not only AFTP, but leukocytes also increase in ascitic fluid after diuretic treatment, but not the PMNs [18].

The opsonic activity of ascitic fluid in cirrhosis is directly correlats with the total protein level in ascites and with the concentration of defensive substances, such as immunoglobulins, complement (C3) and fibronectin [21, 22]. Diuresis in cirrhotic ascites increases its opsonic activity and may help prevent SBP [23]. It is questionable whether diuretic therapy, which increases AFTP and the opsonic activity of ascitic fluid, prevents from the occurrence of SBP, but this is predisposition of occurrence of SBP in patients with higher level of AFTP (>10g/L and <15g/L).

AFTP depends on serum total protein and portal hypertension [24, 25]. In patients with cirrhosis portal vein pressure is elevated - 70% above upper limit of normal [16]. This explains the large difference in AFTP in patients in the same class and score of Child-Pugh classification, nevertheless that fenestration of splanchnic capillaries is 50-100 times lower than those of sinusoids [16]. This is the reason that AFTP may be elevated and reach up to 60g/L [16] (0,4% in the study). Not only diuretic treatment but progression both of cirrhosis and portal hypertension is the most probably explanations of elevation of AFTP in almost half of the patients at the time of second and third hospitalization of patients with cirrhosis and sterile ascites. In addition, etiology of every 20th ascites in patients with cirrhosis

is mixed [1] (e.g. peritoneal tuberculosis in patients with alcoholic cirrhosis etc.), which can explain elevation of AFTP in part of the patients with cirrhosis.

Difference between level of SAAG in SBP and SAAG in sterile ascites in patients with cirrhosis is significant independently of consecutive of next hospitalization (Figure 4). In patients with SBP there is gradual elevation of SAAG and almost half of the patients (48,1%) had SAAG between 21 and 26g/L (Figure 4). In patients with cirrhosis and sterile ascites this elevation is between 15 and 20g/L in half of the patients (49,5%) (Figure 4).

Mean level of SAAG (22,2 g/L) was significantly higher in patients with SBP compared to mean level of SAAG in patients with cirrhosis and sterile ascites, independent of consecutive or next hospitalization (18,9; 18,2; 18,8 g/L) (Figure 4).

Level of SAAG >20g/L had been established significant (almost twice) more frequent in patients with SBP compared to SAAG at the time of first hospitalization of patients with cirrhosis and sterile ascites (respectively - 63,4% and 34,2%) (Figure 5). Compared to next hospitalizations this difference is almost threefold (respectively - 63,4% and 23,5%) (Figure 5).

Albumin is the main barrier marker for selectivity. Low selectivity does not mean high permeability.

Possible explanation of lack of significant elevation of SAAG in natural progression of liver cirrhosis and sterile ascites is that albumin is part of AFTP (45%) [15] and AFTP is increases after diuretic treatment, high level of total protein in serum (because of hyperimmunoglobulinaemia) and deterioration of portal hypertension in advanced cirrhosis (Child-Pugh class C). In patients with SBP, AFTP is low and the level of albumin in ascitic fluid is also low (as percent of AFTP), regardless of low serum albumin with progression of cirrhosis - decreased synthesis of albumin in the liver.

8. Conclusion

Not only diuretic treatment but progression of cirrhosis and deterioration of portal hypertension is the most probably explanations of elevation of AFTP in almost half of the patients with cirrhosis and sterile ascites at the time of next hospitalizations. This is predisposition of occurrence of SBP in patients with higher level of AFTP (>10g/L and <15g/L). Not all patients with cirrhosis and ascites will develop SBP, but in more than 1/3 of patients the risk is increased (decrease of AFTP in next hospitalizations) and in more than 1/10 of them the risk of SBP increases tenfold (AFTP<10g/L).

Difference between SAAG in patients with SBP and in patients with cirrhosis and sterile ascites is significant.

Combination of low AFTP and high SAAG is suspicion for SBP, especially in patients with PMNs in ascitic fluid ≤250/mm^3 and negative (false negative) bacterial cultures – at least in 30% of patients, even if ascitic fluid was taken for examination in bottles for blood cultures at patient's bed.

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