

Two findings of portal hypertension: Evaluation of correlation between serum-ascites albumin gradient and esophageal varices in non-alcoholic cirrhosis

Portal hipertansiyonun iki bulgusu: Serum-asit albumin gradienti ve özofagus varisleri arasındaki ilişkinin alkol dışı sirozlarda değerlendirmesi

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Background/aims: Esophageal varices and serum-ascites albumin gradient (SAAG) are two major findings of portal hypertension. Recently, correlation between these two findings in patients with cirrhosis due to alcohol has been attracted attention. We aimed at evaluating whether a correlation exists between these parameters in the patients with non-alcoholic cirrhosis. **Methods:** Albumin levels in the serum and ascites and esophageal varices were studied and the correlation between these parameters was assessed in 45 patients with non-alcoholic cirrhosis detected between January 2002 and June 2003. **Results:** Thirty-two of the patients were male and 13 female. The average age of the patients was 56.3±12.5 years (range 22-85 years). The causative agents were found to be hepatitis B virus in 35 patients and hepatitis C virus in six patients; no etiology could be determined in the remaining four patients. Serum level of albumin was determined as 2.53±0.53 g/dl, ascites level of albumin as 0.42±0.31 g/dl and SAAG as 2.1±0.51. Endoscopic esophageal examination revealed first-degree esophageal varices in 15 patients, second-degree esophageal varices in 18 patients and third-degree esophageal varices in eight patients; no esophageal varices could be found in four patients. There was no correlation between the degree of the esophageal varices and serum levels of albumin (p=0.7) and SAAG (p=0.2); but a weak correlation was found between the degree of the esophageal varices and ascites levels of albumin (p=0.03, r=0.30). Furthermore, the patients were classified by their SAAG values, and their varices were then assessed. Two of four patients with SAAG values between 1.1 and 1.49 had esophageal varices, as did 13 of 15 patients with SAAG values between 1.5 and 1.99, and all of the patients with SAAG values greater than 2.0. **Conclusion:** All SAAG values were greater than 1.1 in our non-alcoholic cirrhosis cases. The correlation that has been found to exist between SAAG and esophageal varices could not be found in our patients with non-alcoholic cirrhosis. It is remarkable that most of the patients with non-alcoholic cirrhosis presenting with ascites and all of the patients with an SAAG value greater than 2.0 had esophageal varices.

Key words: Ascites, albumin gradient, portal hypertension, cirrhosis, esophageal varices

Amaç: Özofagus varisleri ve serum asit albumin gradiyenti (SAAG) portal hipertansiyonun önemli iki bulgusudur. Son yıllarda alkole bağlı siroz hastalarında bu iki bulgu arasında korelasyon gösterilse de nonalkolik siroz vakalarına ait veri azdır. **Yöntem:** Ocak 2002-Haziran 2003 tarihleri arasında asit tespit edilen 45 nonalkolik sirozlu hastada serum ve asit albumin ölçümleri yanında özofagus varisleri değerlendirildi. **Bulgular:** 45 hastadan 32'si erkek, 13'i kadındı. Ortalama yaş 56.3 ±12.5, yaş aralığı 22-85 arasında bulundu. 35 hastada etken hepatitis B, 6 hastada Hepatitis C tespit edilirken 4 hastada etyoloji saptanamadı. Olgularda serum albumin düzeyi 2.53±0.53 gr/dl, asit albumin düzeyi 0.42±0.31 gr/dl, SAAG 2.1±0.51 bulundu. Endoskopik özofagus incelemesinde 4 olguda varis görülmezken 15 olguda birinci derece, 18 olguda ikinci derece, 8 olguda üçüncü derece varis görüldü. Özofagus varis derecesi ile serum albumini (p=0.7) ve SAAG (p=0.2) arasında korelasyon yoktu, asit albumini ile çok zayıf da olsa korelasyon bulundu (p=0.03, r=0.30). Ayrıca SAAG değerlerine göre olgular sınıflandırılarak varisleri değerlendirildi. SAAG 1.1-1.49 arasındaki 4 olgunun 2'sinde varis vardı, SAAG 1.5-1.99 arasındaki 15 olgudan 13'ünde varis vardı, SAAG 2'nin üzerinde olan olguların ise tümünde varis vardı. **Sonuç:** Tüm non alkolik siroz olgularımızda literatürü destekler şekilde SAAG 1.1 değerinin üzerindedir. Alkole bağlı siroz hastalarında özofagus varisleri ile arasındaki korelasyon, nonalkolik sirozlu hastalarımızda gösterilememiştir. Asit tespit ettiğimiz 45 nonalkolik sirozlu hastanın 41'inde varis olması, SAAG 2.0' nin üzerinde olan tüm olgularda özofagus varislerinin bulunması da dikkat çekicidir.

Anahtar kelimeler: Asit, albumin gradienti, portal hipertansiyon, siroz, özofagus varisleri

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INTRODUCTION

Ascites, defined as fluid accumulation in the peritoneal cavity, may accompany several diseases. Biochemical, microbiological and cytological analyses of ascites fluid are very important for differential diagnosis among the diseases causing ascites. In several studies recently carried out, it was emphasized that serum-ascites albumin gradient (SAAG) based on the difference between the albumin levels of serum and ascites fluid should be used to determine the etiology of the ascites cases instead of discrimination between transudate and exudate. It was shown that such a classification has a validity rate of 90% or more in detecting the ascites of portal hypertension (1-4). In several studies on cirrhosis due to alcohol, the correlation between SAAG and esophageal varices was emphasized and additionally, SAAG was proposed to be a factor determining the degree of portal hypertension and the prognosis of the patients in cirrhosis due to alcohol (3). We aimed at evaluating whether such a correlation exists between SAAG values and esophageal varices in the patients with non-alcoholic cirrhosis.

MATERIALS AND METHODS

The study included the patients with ascites due to cirrhosis examined between January 2002 and June 2003. Cirrhosis diagnosis of the cases were based on laparoscopy, liver biopsy or ultrasound. It was attempted to take the blood samples simultaneously within 30 minutes following paracentesis. The patients with peritonitis were evaluated after treatment whereas diuretic use was not considered in analysis of serum and ascites fluid. The patients with hepatic or extra-hepatic metastasis, thrombosis of splenic vein or portal vein or different etiologies of ascites were excluded from the study. In addition to alcohol use, history of viral hepatitis, and serum antigen and/or antibodies related to autoimmune hepatitis were evaluated to determine the etiology of the cirrhosis in all patients. Ultrasound examination of the patients was performed by ATL 3500 ultrasound device. Endoscopic examinations of all of the patients were performed by GIF XQ 230-240 video endoscopes following topical anesthesia. Varix size was evaluated on a scale of 3. First-degree was considered as those varices that became smaller when the esophagus was inflated with air during endoscopies, whereas third-degree was considered as infiltrating lesions that narrowed the lumen completely. Vari-

ces falling between these two spectra were classified as second-degree.

Statistical Analysis

SPSS software (version 10.0) was used for statistical analysis. P values below 0.05 were considered as significant. Spearman and Pearson tests were used for correlation analysis.

RESULTS

Thirty-two males and 13 females (45 patients) meeting the study criteria were recruited into the study. The mean age of the patients was 56.3 ± 12.5 years (range: 22-85). The causative agents were found to be hepatitis B virus in 35 patients and hepatitis C virus in six patients, whereas no etiology could be determined in the remaining four patients.

Serum level of albumin was 2.53 ± 0.53 (1.8-3.6 g/dl), ascites level of albumin was 0.47 ± 0.34 (0.1-1.8 g/dl), and SAAG was 2.1 ± 0.53 (1.1-3.2). Regarding other parameters used to classify the patients, bilirubin level was 3.6 ± 6.5 mg/dl (6-37 mg/dl), and prothrombin time was 17.7 ± 3.8 sec. (11-26 sec.). History of spontaneous bacterial peritonitis or evidence showing presence of spontaneous bacterial peritonitis following the analysis was found in seven patients, whereas only six patients had a history of variceal bleeding. The main evaluation of patients with portal hypertension was based on two major findings of portal hypertension, i.e. SAAG and esophageal varices. The patients were classified according to Child-Pugh classification as well as to varix size. Twenty patients were found to be class B and the other 25 as class C according to the Child-Pugh classification system. No patients were rated as class A. The lack of patients in class A was due to the higher scores of the patients because only the patients with ascites were included in this study. Endoscopic esophageal examination revealed first-degree esophageal varices in 15 patients, second-degree esophageal varices in 18 patients and third-degree esophageal varices in eight patients, while no esophageal varices were found in four patients (Figures 1, 2). In the correlation analysis (Spearman test), no correlation was found between the degree of esophageal varices and either serum level of albumin ($p=0.7$) or SAAG ($p=0.2$). Only a weak correlation was found between ascites level of albumin and the degree of esophageal varices ($p=0.03$, $r=0.31$). The patients were classified by

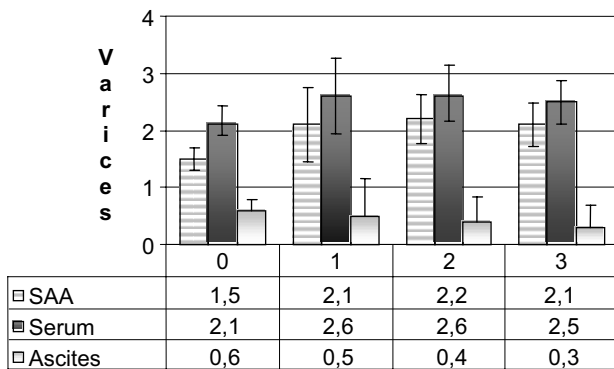


Figure 1. Serum-ascites albumin gradient (SAAG), and serum and ascites albumin levels (g/dl) according to varix size

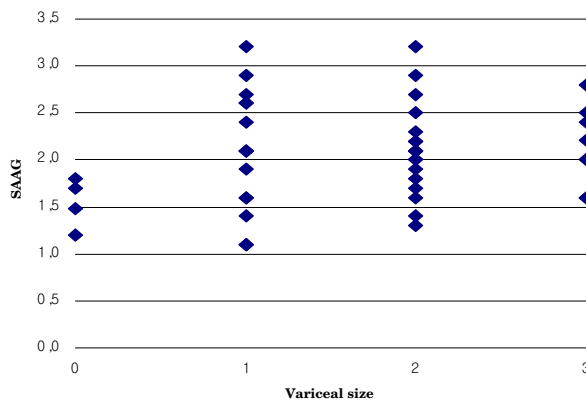


Figure 2. Distribution of the cases according to the varix size and serum-ascites albumin gradient (SAAG) values

their SAAG values and then their varices were evaluated. Two of four patients with SAAG values between 1.1 and 1.49 had esophageal varices, as did 13 of 15 patients with SAAG values between 1.5 and 1.99, and all of the patients with SAAG values greater than 2.0.

DISCUSSION

Basic evaluation of the cause of ascites is based on the examination of ascitic fluid. In addition to several investigations in the ascites fluid, it seems that albumin level is of particular importance as a basic distinguishing factor in ascites. Distinguishing transudate from exudate, which is based on the criteria requiring total protein level in ascites fluid above 2.5 g/dl, has a validity rate of 55.6% in the presence of portal hypertension (2). In the last years, the concept that exudative ascites arises from peritoneal inflammation has been abandoned

because total protein levels above 4.0 g/dl were found in peritoneal fluid samples of healthy women (5). To propose that portal hypertension exists by the serum-ascites albumin gradient (SAAG) possesses a validity rate of 96.7% in the adult population (2).

In a study performed by Hoefs et al. in 1983, it was shown that an excellent correlation exists between portal hypertension and SAAG (6). In this study, a numeric formula was established for the first time between portal hypertension and SAAG in 56 patients, 52 cases of which were due to alcohol. While it was established in this formula that $p < 0.05$ and $r = 0.73$, the numeric formula was as follows: Portal gradient = $7.08 \times [SAAG + 3.62]$. A similar correlation was found by Rector et al. in a study on 18 patients (7). In this study on patients with alcoholic cirrhosis, the correlation between portal hypertension and SAAG was $p = 0.001$ and $r = 0.8$. In 1990, Kajani et al. investigated the correlation in patients with alcoholic cirrhosis and with cirrhosis due to other causes separately (3). In this study, a correlation was found between SAAG and either portal pressure ($r = 0.62$) or esophageal varices ($r = 0.53$) in alcoholic patients. But in the patients with non-alcoholic cirrhosis, no correlation was found between SAAG and portal pressure ($r = 0.39$), while the correlation between SAAG and the varix degree was found to be weaker ($r = 0.02$). Although the studies performed on children yielded some common properties, there are remarkable differences between the results of the studies performed on adults versus children. In a study performed by Das et al. (8) on 26 pediatric patients with cirrhosis with primarily unknown etiologies, SAAG was found to be greater than 1.1 in 22 (84%) of the patients, and less than 1.1 in the remaining four (16%) patients. While 20 (91%) of the patients with SAAG values greater than 1.1 had esophageal varices, 50% of the patients with SAAG values less than 1.1 had varices. Although SAAG in this study was found to have a low specificity and sensitivity, it appeared to be a highly reliable guide for esophageal varices. In a recent study by Torres et al., the correlation between SAAG and esophageal varices was studied. In this study, 14 patients with alcoholic cirrhosis were compared by their endoscopic findings and esophageal varices were determined in all of the patients with alcoholic cirrhosis. A correlation was shown between SAAG and esophageal varices in this study ($p = 0.001$, $r = 0.54$) (9). In a study by Al-Knawy, esophageal

varices were found in all 87 patients with non-alcoholic cirrhosis (10). SAAG was found to be ≥ 1.1 in 82 of these patients and < 1.1 in the remaining five, and it was emphasized that a linear correlation does not exist between SAAG and portal hypertension.

There are scant studies in the literature to evaluate SAAG and esophageal varices in the patients with non-alcoholic cirrhosis. Although the present study was designed to make such an evaluation, invasive portal measurements were not done. Our study group consisted of only the non-alcoholic cirrhosis patients with ascites. Thus, no patient was in Child class A in our study. SAAG values were above 1.1 in all the patients with non-alcoholic cirrhosis. Our study supports the observation that SAAG values increase in ascites due to portal hypertension. But it supports neither the presence nor the severity of the esophageal varices,

which is another important finding of portal hypertension with a close correlation. It was remarkable that esophageal varices were present in all of the patients with an SAAG value greater than 2.0. Tores et al. (9) observed this in their own data. There was a correlation in our study only between the degree of the esophageal varices and ascites level of albumin ($p=0.03$), but the correlation coefficient was found to be low ($r=0.30$). The fact that most of the patients reported in the literature are those patients with cirrhosis due to alcohol makes it difficult to interpret the results on this matter. Although the present data shows no linear correlation between SAAG and esophageal varices, it is noteworthy that 90% of the patients with non-alcoholic cirrhosis presenting with ascites and all of the patients with an SAAG value greater than 2.0 had esophageal varices.

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