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GASTROESOPHAGEAL REFLUX IN CIRRHOTIC PATIENTS WITH ESOPHAGEAL VARICES WITHOUT ENDOSCOPIC TREATMENT

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ABSTRACT – ***Background*** - Portal hypertension in patients with liver cirrhosis causes manifestations such as esophageal varices, ascites and edema. Some studies have been conducted about the role of esophageal varices in the development of esophageal motor disorders and abnormal gastroesophageal reflux in these patients. Ascites could be a factor promoting gastroesophageal reflux and it has been questioned whether reflux would favor the rupture of varices. However there are a few studies using ambulatory esophageal pH recording in the evaluation of these patients. ***Aims*** - Evaluate gastroesophageal reflux by pH recording in cirrhotic patients with esophageal varices and possible predictors. ***Methods*** - Fifty one patients (28 men, 23 women, mean age of 54 years) with liver cirrhosis, diagnosed by clinical, laboratorial, image and histological findings were prospectively evaluated. All patients had esophageal varices confirmed by endoscopy and were submitted to a questionnaire about typical gastroesophageal reflux disease symptoms (heartburn and or acid regurgitation). pH recording was performed with the probe placed 5 cm above the superior lower esophageal sphincter limit, as determined by manometry. Abnormal reflux (% total time with pH <4 >4.5%) was related to the size of varices, congestive gastropathy, ascites, severity of cirrhosis and typical gastroesophageal reflux disease symptoms. ***Results*** - The caliber of the varices was considered to be small in 30 patients (59%), medium in 17 (33%) and large in 4 (8%), 21 (41%) congestive gastropathy. Ascites was observed in 17 (33%), 32 patients (63%) were classified as Child-Pugh A, 17 (33%) Child-Pugh B and 2 (4%) Child-Pugh C. Twenty seven patients (53%) presented with typical gastroesophageal reflux disease symptoms. Abnormal reflux at pH recording was found in 19 patients (37%). One of them presented with erosive esophagitis at endoscopy. There was no relation between ascites, variceal size, congestive gastropathy and Child-Pugh score and abnormal reflux. There was a correlation between typical gastroesophageal reflux disease symptoms and abnormal reflux. ***Conclusions*** - Abnormal gastroesophageal reflux was found in 37% of the patients with hepatic cirrhosis and esophageal varices. Only typical gastroesophageal reflux disease symptoms predicted these findings.

HEADINGS – Gastroesophageal reflux. Liver cirrhosis. Esophageal and gastric varices.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a highly prevalent disorder, with 7% of a healthy population presenting heartburn daily[23, 29]. GERD clinical symptoms can be typical or atypical[20, 38]. Only half of GERD patients present with esophageal erosions[7, 8, 16, 18].

The prevalence of liver cirrhosis is also large, with high morbidity and mortality[11]. Portal hypertension is responsible for the development of esophageal and gastric varices[36]. Varices are potential sources of bleeding, increasing the mortality risk of these patients. The mechanisms that underlie the rupture of esophageal and gastric varices must be studied.

In the last years, the role of esophageal varices (EV) as a factor for the development of esophageal motors disorders and abnormal gastroesophageal reflux (GER) in liver cirrhotic patients has been discussed[1, 3, 15, 32]. It is doubtful whether these abnormalities can contribute to the bleeding of varices. Some studies demonstrate motors disorders in the esophageal body, a delay in esophageal clearance time[12] and abnormal gastroesophageal reflux[1] in cirrhotic patients with EV[3, 15, 32], as compared to cirrhotic patients without varices and a control group. These studies suggest that motor disorders would be caused by EV and not by cirrhosis.

Other studies suggest that ascites would be able to increase intra-gastric and intra-abdominal pressure[3, 26, 37]. However, there are few studies using ambulatory esophageal pH recording (pHR) in cirrhotic patients with EV, with or without ascites[1, 15, 28].

The aim of this study was to evaluate the prevalence of abnormal GER in cirrhotic patients with EV, without previous endoscopic treatment and its possible predicting factors.

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METHODS

Patients

From June 2000 to June 2002, patients with liver cirrhosis and EV non submitted to endoscopic treatment were prospectively evaluated. The patients came from the Liver Outpatient Clinic of "Clementino Fraga Filho" University Hospital, Federal University of Rio de Janeiro, RJ, Brazil. We excluded patients with systemic disease related to esophageal motors disorders and/or gastroesophageal reflux disease (progressive systemic sclerosis, diabetes mellitus, neuromusculars disorders), alcohol abusers until 6 months before this study and chronic users of drugs that influence esophageal motility (calcium channel blockers, teophyline, nitrates).

All patients were evaluated by the same physician (RBS), according a protocol for classifying cirrhosis etiology, Child-Pugh score[34] ascites and GERD typical symptoms, such as heartburn and/or acid regurgitation.

The diagnosis of liver cirrhosis and its etiology was made by clinical, laboratory, image and histopathological methods. The latter included the presence of parenchymal nodules separated by fibrous septa, differences in liver cell size and appearance between one area and another, fragmentation of the biopsy specimen, altered architecture and vascular relationships without septa formation[2] . Ascites was classified as small, moderate or large according to clinical criteria[36].

METHODS

Upper gastrointestinal endoscopy

All patients performed upper gastrointestinal endoscopy, in the standard fashion, in order to evaluate EV, classified as small (variceal diameter less than 3 mm), medium (diameter from 3 to 6 mm) or large (diameter greater than 6 mm)[31]. Gastric varices and/or congestive gastropathy associated[24] were also described. Esophagitis if present was classified according to SAVARY and MILLER[35] grade I – isolated erosions; grade II – confluent but not circumferencial erosions; grade III – confluent and circumferencial erosions; grade IV – ulcers, stenosis. Hiatal hernia was considered as present if the gastroesophageal junction was at least 2 cm above the diaphragmatic impression[27] .

Esophageal manometry

Esophageal manometry (EMN) was performed to situate the superior limit of the lower esophageal sphincter (LES). Manometric studies used an eight lumen, 4,5 mm diameter polyvinyl catheter, continuously perfused with distilled water at 0,6 mL/min by a low-compliance pneumohydraulic capillary infusion system (Biomedics – California, EUA) or solid-state intraluminal transducers (Kronisberg). The technique had already been described elsewhere[22]. Briefly, the probe was passed by one of the nostrils until the stomach. LES studies used slow pulltrough technique, with catheter tractions with 1.0 cm increments. The superior limit of the lower esophageal sphincter was the place (in centimeters) immediately before the register of the esophageal body pattern, when the tracing drops below the gastric baseline pressure.

24-hour pH ambulatory recording

The technique had been described elsewhere[21]. Briefly, it was carried out with a portable digital system (MK III Synectis) composed of a catheter with an antimony electrode and external reference electrode, placed 5 cm above superior limit of LES as defined by manometry. The recording of an esophageal pH of less than 4 for at least 15 sec was considered to be a reflux episode. The patient had a normal activity and was under a normal diet, avoiding citric fruits and soft drinks. Proton pump inhibitor if in use, were discontinued at least 7-10 days prior to the exam, H2 blockers 48-72 h and prokinetics agents 24 h. Abnormal reflux was defined[17] when the percentage of the total time of pH below 4 was greater than 4.5%, or the percentage of the upright time in which pH below 4 was grater than 7.0% or the percentage of supine time when pH was lower than 4 was greater than 2.5. In upright reflux, only upright time percentage was abnormal, supine reflux if just supine time percentage was abnormal and in both positions if both time percentages were abnormal[6].

Data analysis

Abnormal reflux was related to the following variables: presence of ascites and severe ascites, typical GERD symptoms, Child-Pugh score (grouping Child-Pugh in two groups, A and B + C), congestive gastropathy, esophageal variceal size (also considering only two groups, small size varices and medium + large size varices).

To evaluate the meaning of these differences we used Chi-square test.

In abnormal pHR tests, for comparisons of % total time (TT), % upright time (UT), % supine time (ST) between the groups with ascites/severe ascites and without ascites, we employed Mann-Whitney test, as well to compare the group with and without GERD symptoms. A P value <0.05 was used for significance.

RESULTS

Fifty one patients met the inclusion criteria, 28 male (55%) and 23 female (45%), mean age 54 $\pm$ 10.5 years (17-77).

The diagnosis of hepatic cirrhosis was done by histopathological criteria in 47 (92%) of the patients. Its etiology included C virus in 31 patients (60,%), alcohol in 8 (16%), B virus in 3 (6%), primary biliar cirrhosis in 2 (4%), hemochromatosis in 1 (2%), auto-imune em 1 (2%), non-alcoholic steatohepatitis in 1 (2%) and cryptogenic in 4 patients (8%).

The patients were classified as Child A – 32 patients (63%), Child B – 17 patients (33%) and Child C – 2 patients (4%).

Ascites was present in 17 (33%) and absent in 34 (67%). In the patients with ascites, eight (47%) presented small ascites, three (18%) with moderate ascites and six (35%) with severe ascites.

Typical symptoms of gastroesophageal reflux disease were present in 27 patients (53%).

The EV presented small size in 30 patients (59%), medium size in 17 patients (33%) and large size varices in 4 (8%).

Gastric varices were present in 4 patients (8%) and congestive gastropathy in 21 patients (41%).

Erosive esophagitis (Savary-Miller grade I) was present in one patient (2%) and there was no hiatal hernia.

The pH recording demonstrated abnormal reflux in 19 patients (37%), 04 (21%) just in upright position, 07 (37%) in supine position and 08 (42%) in both positions.

Relation between variables

Ascites and abnormal reflux

Ascites was present in 17 patients. Seven of them (41%) presented with an abnormal pHR. In the 34 patients without ascites, 12 (35%) had abnormal pHR. There was no relation between ascites presence and abnormal reflux ($P = 0.682$) (Table 1).

TABLE 1. pHR versus ascites (n=51)

	Abnormal pHR	Normal pHR	Total
With ascites n = 17	07 (41%)	10 (59%)	17 (100%)
Without ascites n = 34	12 (35%)	22 (65%)	34 (100%)
Total n = 51	19 (37%)	32 (63%)	51 (100%)

P value = 0.682
pHR = ambulatory esophageal pH recording

Severe ascites and abnormal reflux

From 17 patients with ascites, 6 (35%) presented with severe ascites and 4 of these (67%) presented an abnormal pHR. There was no relation between severe ascites and abnormal reflux, when compared to patients without ascites ($P = 0.148$).

Typical symptoms and abnormal reflux

In 27 patients with typical reflux symptoms, 14 (52%) presented with abnormal pHR and 13 (48%) with normal pHR. In 24 patients without typical reflux symptoms, 5 (21%) had abnormal pHR. There was a significant relation between typical reflux symptoms and abnormal reflux ($P = 0.022$)* (Table 2).

TABLE 2. Abnormal pHR versus typical gastroesophageal reflux symptoms (n = 51)

	Abnormal pHR	Normal pHR	Total
With symptoms(n = 27)	14 (52%)	13 (48%)	27 (100%)
Without symptoms(n = 24)	05 (21%)	19 (79%)	24 (100%)
Total n = 51	19 (37%)	32 (63%)	51 (100%)

P value = 0.022*
pHR = ambulatory esophageal pH recording

Child-Pugh score and abnormal reflux

In 32 patients Child A, 11(34%) presented with abnormal pHR and 21(66%) had normal pHR.

From 19 patients with Child B + C score, 8 (42%) had an abnormal pHR and 11 (58%) had it normal. There was no relation between Child-Pugh score and abnormal reflux ($P = 0.581$).

Congestive gastropathy and abnormal reflux

In 21 patients with congestive gastropathy, 6 (29%) presented abnormal pHR and 15 (71%) normal pHR and in 30 patients without congestive gastropathy, 13 (43%) had abnormal pHR and 17 (57%) had not. There was no relation between congestive gastropathy and abnormal reflux ($P = 0.283$).

EV size and abnormal reflux

In 30 patients with small size varices, 13 (43%) had abnormal pHR and 17 (57%), pHR was normal.

In 21 patients with medium + large size varices, 6 (29%) had an abnormal pHR and 15 (71%) had it normal. There was no relation between varices size and abnormal reflux ($P = 0.283$).

DISCUSSION

Gastroesophageal reflux in cirrhotic patients with EV has been studied for many years. Older studies based on necropsy paid great importance to esophageal acid reflux as a factor for the rupture and bleeding of EV[5, 39]. They believed that extensive mucosal erosion of the varices would suffice to cause perforation. Other studies reinforced these initial findings, as they showed a higher prevalence of esophagitis[33] and acid reflux[37] in cirrhotic patients with non-bleeding varices and a lower LES pressure in cirrhotic patients with massive ascites[30, 37].

However, later studies weakened this hypothesis, because they could not demonstrate either lower LES pressure[9, 25] nor a higher incidence of abnormal GER in this group of patients[10, 25]. Since then, the importance of GER in EV bleeding diminished.

In the last decades, as variceal bleeding continued to be a severe complication[10], new risk factors for rupture have been evaluated. Esophageal acid reflux was again studied and its prevalence among cirrhotic patients with EV has been studied. This renewed interest possibly came from the greater diffusion of pHmetry recording, as well as from the existence of patients with reflux without esophagitis[1, 15, 27].

In our study, abnormal reflux was demonstrated in 37% of patients, these 80% had abnormal reflux during the night, when esophageal defenses are lower, with reduction of saliva production, swallowing and esophageal clearance[7]. Increase in contact time between acid and varices could lead to the eventual erosion of the mucosa and the consequent bleeding.

It is possible to question, if this prevalence of abnormal reflux is related to the presence of cirrhosis with EV or if it is just a coincident finding in this population sub-group. AHMED et al.[1] studied by pHmetry, 25 cirrhotic and 30 GERD patients. Abnormal reflux was observed in 64% of the cirrhotic patients and in 70% of the GERD patients without liver disease. Among the cirrhotic patients with GERD, 81% presented EV and no relation was found concerning variceal size. These authors suggest that GERD is common in cirrhotics with EV, independent of caliber or GERD symptoms. In our study we did not find any correlation between abnormal GER, variceal caliber.

Ascites in cirrhotic patients is another factor potencially important for the development of GERD and some studies have considered this hypothesis[3, 28, 37]. Although the LES pressure

protective function against reflux remains intact during the resting state, a functional loss could occur during abrupt raises of intra-abdominal pressure and/or during transitory relaxations of LES[3, 30, 39]. In our study, we could not find any relation between ascites itself and abnormal GER.

Typical symptoms of GERD, heartburn and/or acid regurgitation, were observed in 53% of patients, its presence being correlated to abnormal GER. As described in the literature, typical reflux symptoms, despite their low sensitivity, have high specificity[19]. Therefore, in face of typical symptoms, GERD should be suspected**.** However, we could not find a correlation between the presence or absence of symptoms and the intensity of reflux.

It was also not possible to make a correlation of symptoms with gastrointestinal endoscopy findings because only one patient had erosive esophagitis and he presented only with occasional heartburn. This confirms the literature in that it is not possible to preview endoscopic findings by the intensity or frequency of symptoms[16].

In our study, with exception of typical GERD symptoms, there was no correlation between any other studied factor and the presence of abnormal GER.

We question what would be the cause of the high prevalence of GERD found in this study and in the few others that employed pHR as their research tool[1, 28]. Studies have demonstrated that no changes in LES pressure occur in patients with EV, with or without ascites[3, 28, 37]. Some authors, have found esophageal motor disorders in cirrhotic patients with EV, as well as a decrease in amplitude of the peristaltic waves, in opposition to that observed in cirrhotic without varices and an asymptomatic control group[32]. These changes associated to EV, independent of the cirrhosis itself, could delay esophageal clearance and increase contact time between acid and mucosa, promoting injury[32].

Other comments can be advanced. It has currently been established the importance of nitrous oxide (NO), a potent vasodilator, in the exacerbation of portal hypertension in liver cirrhosis. This substance can be found in large amounts in the systemic circulation of cirrhotic patients[4]. NO excessive systemic action has risen investigative interest.

There are studies about the effect of NO in the esophageal peristalsis and LES. NO has been shown to decrease amplitude of distal esophageal peristaltic waves, as well as the velocity of the peristaltic contractions in the proximal esophagus[13]. It is true to question if the excess of NO in cirrhotic patients could exacerbate these manifestations, prolonging esophageal clearance, increasing contact time between acid and the esophageal mucosa. Besides, NO has an important role in the development of transitory relaxations in LES secondary to gastric fundus distension, which are followed by reflux episodes[13]. LES transitory relaxations is the commonest mechanism of GER, either in healthy volunteers (70%-100%) as in GERD patients (63%-74%)[19, 26].

More recently, a study with healthy volunteers[14] showed that the use of substances that inhibit NO synthesis (l-arginine N monomethyl) significantly diminish the frequency of transitory relaxations in LES, after solid food intake, as well as decrease the number of total reflux episodes. However, gastric emptying time interval, LES pressure and/or the relaxation of LES secondary to deglutition are not affected.

These findings support the importance of NO, albeit not alone, in the activation of transitory relaxations in LES and the subsequent GER episodes. If NO synthesis inhibition can decrease the occurrence of transitory relaxations in the LES, then its excessive production could lead to an increase in the frequency of transitory relaxations and consequently in the total number of reflux episodes. In liver cirrhosis, as there is NO excess, could this be the causal factor for the development of an elevated prevalence of abnormal reflux? In this case, abnormal GER would occur independently of any associated factor such as EV and/or ascites.

Studies on the role of NO in VE cirrhotic patients with reflux are necessary to clarify this aspect.

CONCLUSIONS

Abnormal gastroesophageal reflux was found in 37% of cirrhotic patients with EV. There was correlation only between typical symptoms of gastroesophageal reflux disease and abnormal reflux. The questioning about typical reflux symptoms must be a part of the cirrhotic patients interrogatory. If present, a work-up for abnormal reflux must be done or the patient should be empirically treated.

Long-term ambulatory follow-up of this group of patients is important, since, if the ”erosive” theory holds true, patients with abnormal reflux could present a higher incidence of variceal bleeding. This, however, needs to be demonstrated.

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RESUMO - ***Racional*** - A hipertensão porta que acomete os pacientes com cirrose hepática é causa de varizes de esôfago, ascite e edema. Alguns estudos têm sido realizados para avaliar a importância das varizes de esôfago no desenvolvimento dos distúrbios motores esofagianos e do refluxo gastroesofágico anormal neste grupo de pacientes. A ascite pode ser um fator promotor de refluxo gastroesofágico e tem sido questionado se o refluxo anormal poderia favorecer a rotura das varizes de esôfago. Entretanto, são poucos os estudos que utilizam a pHmetria esofagiana prolongada ambulatorial na avaliação destes pacientes. ***Objetivos*** - Avaliar a presença de refluxo anormal a pHmetria esofagiana prolongada ambulatorial em pacientes cirróticos com varizes de esôfago e seus possíveis fatores preditivos. ***Métodos*** - Cinqüenta e um pacientes (28 homens, 23 mulheres, média de idade de 54 anos) com cirrose hepática diagnosticada por métodos clínicos, laboratoriais, de imagem e histopatológicos foram avaliados de forma prospectiva. Todos os pacientes apresentavam varizes de esôfago à endoscopia digestiva alta e foram submetidos a um questionário para avaliação da presença de sintomas típicos da doença do refluxo gastroesofágico (pirose e/ou regurgitação ácida). pHmetria esofagiana prolongada ambulatorial foi realizada posicionando-se o cateter 5 cm acima do limite superior do esfíncter esofagiano inferior, determinado previamente pela esofagomanometria. Refluxo anormal (% tempo total com pH <4 >4,5%) foi relacionado com o tamanho das varizes, gastropatia congestiva, ascite, gravidade da cirrose e presença de sintomas típicos da doença do refluxo gastroesofágico. ***Resultados*** - O calibre das varizes foi considerado pequeno em 30 pacientes (59%), médio em 17 (33%) e grosso em 4 (8%), 21 (41%) gastropatia congestiva. Ascite foi observada em 17 (33%); 32 pacientes (63%) foram classificados com Child-Pugh A, 17 (33%) Child-Pugh B e 2 (4%) Child-Pugh C. Vinte e sete pacientes (53%) apresentavam sintomas típicos da doença do refluxo gastroesofágico. Refluxo anormal a pHmetria esofagiana prolongada ambulatorial foi demonstrado em 19 pacientes (37%). Apenas um deles apresentava esofagite erosiva à endoscopia digestiva alta. Não houve relação entre ascite, calibre das varizes, gastropatia congestiva e classificação de Child-Pugh com refluxo anormal. Houve correlação entre a presença dos sintomas típicos da doença do refluxo gastroesofágico e refluxo anormal. ***Conclusões*** - Refluxo anormal foi demonstrado em 37% dos pacientes com cirrose hepática e varizes de esôfago. Apenas os sintomas típicos foram preditores de refluxo anormal.

DESCRITORES – Refluxo gastroesofágico. Cirrose hepática. Varizes esofágicas e gástricas.

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