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Cerebral hemodynamics in patients with cirrhosis

LIVER

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Original Article

ABSTRACT

Background/Aims: Cirrhosis causes a decrease in cerebral blood flow because of a hyperdynamic circulatory state. We aimed to study the cerebral hemodynamic parameters in patients with decompensated cirrhosis and their relationship to the Child–Pugh and Model for End-Stage Liver Disease (MELD) scores.

Materials and Methods: We used transcranial Doppler to investigate the cerebral hemodynamic parameters, namely the mean flow velocity of the middle cerebral artery, pulsatility index (PI), and resistive index (RI), in 50 patients who had decompensated cirrhosis and in a control group of 50 healthy people. We also investigated their relationship to the Child–Pugh and MELD scores.

Results: Patients with cirrhosis had a lower mean flow velocity than those in the control group. Further, patients with cirrhosis had higher PI and RI values. There was a positive correlation between PI and the Child–Pugh score. In addition, there was a positive correlation among PI, RI, and the MELD score. The RI values of patients with ascites were higher than those of patients without ascites.

Conclusion: Cerebral autoregulation might be impaired in patients with cirrhosis. Cerebral resistance proportionally increases to disease severity. There was a positive correlation among PI, RI, and MELD scores, which means that transcranial Doppler might be useful not only in the follow-up of the severity of the disease but also in determining the survival of these patients.

Keywords: Cirrhotic patients, cerebral hemodynamics, Transcranial Doppler, Child–Pugh, MELD score

INTRODUCTION

Patients with cirrhosis show varied portal hypertension and splanchnic vasodilatation. These are often associated with a hyperdynamic circulatory state, which affects cerebral blood flow (CBF). CBF generally decreases in patients with cirrhosis (1-5).

Transcranial Doppler (TCD) is a relatively new non-invasive, bedside, and repeatable method that can measure blood flow velocity in intracranial arteries as well as other hemodynamic parameters such as pulsatility index (PI) and resistive index (RI). A TCD image can reveal vessel location, appearance, and flow direction to help further guide the spectral Doppler interrogation. These findings should be stored along with the velocity data and used for interpretation. With current technologies, the flow parameters should be documented for the following arteries: middle cerebral artery, anterior cerebral artery, posterior cerebral artery, terminal internal carotid artery, internal carotid artery siphon, ophthalmic artery, terminal vertebral artery, and basilar artery (6). Indications for a TCD ultrasound examination are the detection and follow-up of stenosis or occlusion in an intracranial artery, detection and monitoring of vasospasm in patients with spontaneous or traumatic subarachnoid hemorrhage, detection of cerebral vasculopathy, diagnosis of brain death, etc (6).

We measured the cerebral hemodynamic parameters in patients with cirrhosis, specifically the mean flow velocity (MFV) of the middle cerebral artery (MCA), cerebral PI, and RI in patients with cirrhosis and compared these results with those from a control group. PI is analogous to pulse pressure and is a measure of distal flow resis-

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tance and vascular wall rigidity. PI and RI are widely accepted as indices of vascular resistance; in contrast to the blood flow velocity, these are technically more reliable indices of CBF with better reproducibility for CBF than CBV (6,7). We investigated the correlation among these parameters and the severity and prognosis of patients with cirrhosis.

MATERIALS AND METHODS

The local ethics committee approved the research protocol, and informed consent was obtained from all evaluated patients. To avoid bias due to unbalanced distributions of comorbid diseases or drug therapy, we excluded patients with previous cerebrovascular, cardiac, peripheral vascular, or chronic pulmonary diseases and patients that had, at the time of the study, bacterial infections or hepatic encephalopathy. Patients were not taking any rifaximine or lactulose theraphy.

Fifty consecutive inpatients in our gastroenterology department were enrolled in the study. The patients with cirrhosis were graded according to the Child–Pugh (8) and Model for End-Stage Liver Disease (MELD) classification (9) (Child–Pugh score shows the severity of cirrhosis, while the MELD score shows the survival of the patients with cirrhosis). Fifty healthy control subjects were also enrolled. The ages and gender ratio of the control and patient groups were similar. We also recorded blood platelet levels, as these are related to the prognosis of these patients.

Cerebral hemodynamics were measured using a Multi-Dop T-TCD (DWL Elektronische Systeme GmbH, Singen, Germany) for analyzing the transcranial spectral signals derived from the systolic velocity, diastolic velocity, MFV in cm/s, pulsatility, and resistive indices (PI and RI) of the intracranial arteries. PI was calculated as follows: (peak systolic velocity–end-diastolic velocity)/MFV. RI was calculated as following: (peak systolic velocity–end-diastolic velocity)/end-diastolic velocity. (7,10).

All the control subjects abstained from beverages containing caffeine for at least 24 hours prior to the study. Pulsed-wave Doppler probes (2 MHz) were affixed over each transtemporal window with a probe holder. The signal for the M1 segment of the left MCA was obtained at 50–55 mm from the left temporal window (examination of the vessels of the circle of Willis was performed as previously described) (10). The PI and RI values of the patient and control groups were compared. The correlations among disease duration, Child–Pugh score, MELD score, platelet count, and the PI and RI values of the patients were investigated.

Statistical analysis

We calculated the descriptive statistics, including the mean±SD for the continuous variables. We compared the difference between the means of variables using the Mann-Whitney U test. To determine whether there is a correlation between the continuous variables, we used the Spearman and Pearson correlation coefficients. Significance was set at the 5% level ($p \leq 0.05$). The statistical analysis was performed with the statistical package program SPSS version 17.0 (SPSS Inc.; Chicago, USA).

RESULTS

Fifty cirrhosis patients (28 male, 22 female) with a mean age of 64.1±5.6 years and 50 healthy controls (28 male, 22 female) with a mean age of 62.6±3.3 were included in this study. We could not find any significant difference between the patients and healthy controls according to their age or gender status ($p>0.05$) (Table 1). The mean Child–Pugh score was 9.06±2.3. Using the Child–Pugh score, 9 patients were placed in class A, 20 were in class B, and 21 were in class C (all of them had decompensated cirrhosis) (Table 2). The mean MELD score of the patients was 15.2±7.3, and the mean blood platelet counts of patients and the control group were 95,220±54,500 and 218,000±43,000, respectively ($p=0.0001$).

The mean MFV values of patients with cirrhosis were lower compared to the control group ($p=0.0001$). PI and RI values of patients with cirrhosis were higher compared to the control group ($p=0.0001$, $p=0.0001$). Figure 1a shows normal TCD image. Figure 1b shows TCD image of a patient. There was a positive correlation between the PI values and the Child–Pugh scores of the patients with cirrhosis ($r=0.307$, $p=0.032$). Also, the PI values were increased with increasing severity of the cirrhosis. There was a positive correlation among PI, RI, and the MELD scores of patients ($r=0.28$, $p=0.05$), ($r=0.321$, $p=0.024$), respectively. Also, higher levels of PI and RI shows poor prog-

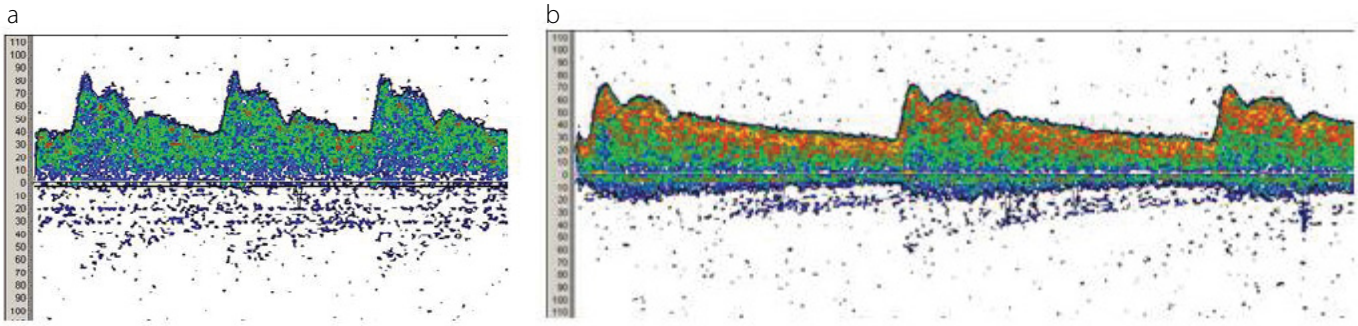

Figure 1. a, b. TCD image of a healthy control (a). Mean flow velocity (55 cm/sn) and pulsatility index (0.87) are normal. TCD image with a blunted signal of a patient with Child–Pugh C (b). Mean flow velocity is decreased (41 cm/sn), and pulsatility index (1.15) is increased.

Table 1. Characteristics of the subjects

Variables	Patients	Controls	p
Age	64.1±5.6	62.6±3.3	0.38
Gender	28 M, 22 F	28 M, 22 F	0.29
Duration of cirrhosis (years)	4.9±4.1	-	-
Child–Pugh score	9.06±2.3	-	-
MELD score	15.2±54.5	-	
Mean platelet count[1]	95.22±54.5	218±23	0.0001
Mean blood velocity[2] (cm/s)	45.4±14.6	56.8±12.2	0.0001
PI	1.12±0.24	0.93±0.12	0.0001
RI	0.71±0.23	0.59±0.05	0.0001

M: male; F: female; PI: pulsatility index; RI: resistive index
[1]x1000, [2]Middle cerebral artery

Table 2. PI and RI values of groups

Groups	PI	RI	p
A (n=9)	1.05±0.15	0.64±0.05	
B (n=20)	1.08±0.28	0.77±0.36	
C (n=21)	1.18±0.22	0.69±0.08	
Ascites (+), n=31	1.1±0.19	0.7±0.21	
Ascites (–), n=19	1.01±0.12	0.63±0.04	0.022
HE (+), n=23	1.16±0.25	0.72±0.23	0.21
HE (-), n=27	1.07±0.21	0.69±0.24	0.27

PI: pulsatility index; RI: resistive index; HE: hepatic encephalopathy

nosis. There was no correlation among PI, RI, and platelet count (p=0.09). Table 1 shows the Child–Pugh, MELD scores, platelet count, and the PI and RI values of the patients and the control group.

Thirty-one patients had ascites, while 19 did not. When we compared the PI values between these groups, we saw that the PI values of patients with ascites were higher, but without any statistical difference. RI values of the patients with ascites were higher, and with a statistical significance, compared to the patients who did not have ascites (p=0.022). Twenty-three patients had a history of encephalopathy at some point in the duration of the disease, while 27 did not. When we compared the PI and RI values of the two groups (patients with encephalopathy and without encephalopathy), the PI and RI values were higher in the encephalopathy group, but without any statistical difference (Table 2).

DISCUSSION

Patients with cirrhosis have hyperdynamic circulation, increased cardiac output, and reduced peripheral vascular resistance. These changes often cause arterial hypotension and insufficient CBF (11,12). Decreased CBF has also been shown in patients with alcoholic liver dysfunction, acute liver failure, and cirrhosis with subclinical encephalopathy (1-4). In this study, patients with cirrhosis predominantly showed hypo-perfusion in CBF with mean velocities less than normal values and increased PI and RI. PI and RI are widely accepted as indices of vascular resistance. Compared to the blood flow velocity, these indices are technically more reliable indices of CBF, with better reproducibility for CBF than for CBV. A study using 99 mTc HM-PAO single-photon emission computed tomography imaging has shown a significant regional CBF reduction ranging from 6 to 7% in the cortical region in a majority of patients with cirrhosis, as compared to controls. This regional CBF is normalized after liver transplantation (13).

In contrast to other methods, TCD sonography can record real-time variations in brain circulation without complications at the patient's bedside (6,7). The cutoff value of PI is 1.13 for increased intracranial pressure (7). We found a mean PI of 1.12 and detected a positive correlation among the Child–Pugh and MELD scores and PI values. The cerebral resistance increased with the severity of the disease, with higher levels of PI and RI showing poor prognosis. Kawakami et al. (14) showed that the derangement of CBF due to hepatic failure is reversible and can be improved by plasmapheresis or liver transplantation. A pulsatility index of >1.0 may indicate the need for liver transplantation. However, there were very few patients in this study (n=6).

Resistive index values were higher among patients with ascites than in patients without ascites, and cerebral autoregulation was more impaired in decompensated cirrhosis with ascites. Ascites is the most common complication of cirrhosis, and about 60% of patients with compensated liver disease develop ascites during the clinical course of the disease, where it usually occurs after portal hypertension develops (5).

Patients with cirrhosis have also been proposed to have an impaired autonomic regulation of cardiovascular homeostasis. Frokjaer et al. (15) found an association between severe autonomic dysfunction and cerebral autoregulation impairment in patients with severe liver fibrosis. Both parasympathetic and sympathetic innervations are involved in autonomic dysfunction. Guevara et al. (16) detected higher RI levels in patients with cirrhosis. They showed higher RI levels in the renal and cerebral arteries of 24 patients with cirrhosis who had ascites. These results indicate that in patients with cirrhosis and ascites, there is a cerebral vasoconstriction that is probably related to hypotension of the artery and overactivity of the vasoconstrictor systems.

Kawakami et al. (17) showed that increased cerebral vascular resistance, which may change with the severity of hepatic encephalopathy, is directly related to hepatic encephalopathy. They compared 27 patients with hepatic encephalopathy to 26 patients without hepatic encephalopathy and found that the PI and RI levels were higher in patients with hepatic encephalopathy. Another study compared 30 patients with hepatic enceph-

alopathy with 30 patients without hepatic encephalopathy and concluded that PI levels increase with the presence and severity of hepatic encephalopathy (18). We also found increased cerebral vascular resistance in patients who had a history of encephalopathy at some point in the duration of the disease compared to those who did not; however, this was not statistically significant. This finding shows that cerebral autoregulation is much more impaired in patients who have a history of encephalopathy. The reason that we could not find any significance might be that we did not apply TCD during hepatic encephalopathy, like Macías-Rodríguez et al. (18) did. None of our patients had acute encephalopathy during the application of TCD. The presence of infection, rising ammonia levels, and elevation of intracranial pressure cause patients to have encephalopathy. At this point, TCD might be effective for patients. Eventually, autoregulation is impaired in patients undergoing liver transplantation, even in the absence of acute fulminant liver failure. The identification and follow-up of these risky patients by TCD is suggested for preventing neurological complications and enabling prompt neuroprotective interventions (19).

To our knowledge, our study is the first to show the relationship among Child–Pugh and MELD scores and cerebral hemodynamic parameters. The limitation of our study is the small number of patients. However, previous studies have included much fewer patients than ours.

In conclusion, intracranial pressure increases with disease severity in patients with cirrhosis. There is a reverse correlation among PI, RI, and the survival of these patients. TCD might be a useful method for the follow-up of these patients and for estimating survival.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Pamukkale University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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