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Clinical features in liver cirrhosis patients who have experienced ischemic stroke

LIVER

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Original Article

ABSTRACT

Background/Aims: The actual incidence of ischemic stroke in patients with liver cirrhosis remains controversial. The aim of this study was to analyze the clinical features of patients with liver cirrhosis who have experienced ischemic stroke.

Materials and Methods: A retrospective analysis was performed on the medical records of 23 ischemic stroke cases who were also diagnosed with liver cirrhosis, over a 10 year period from January 2001 to December 2010.

Results: Using the Child-Pugh classification system, Class B (39%) was the most common among the liver cirrhosis patients with ischemic stroke. There were six patients who presented with Class C (26%). Alcohol was analyzed as the main cause for liver cirrhosis in 14 patients (60.8%). Among the risk factors of ischemic stroke, nine of the 23 patients (39.1%) were diagnosed with obesity, and seven patients each (30.4%) were diagnosed with arrhythmia or smoking history. In total, only two patients (8.7%) had no association with any of the risk factors for ischemic stroke.

Conclusion: Our results show that a comparatively high frequency of ischemic stroke occurs in patients with alcohol-induced liver cirrhosis and in patients with a less compromised liver function. In addition, it was found that most patients possessed at least one risk factor of ischemic stroke.

Keywords: Liver cirrhosis, stroke, risk factors, coagulopathy

INTRODUCTION

Stroke has been recognized as the leading cause of adult physical disability in the United States and Europe, and as the third most common cause of death in other developed countries, including Korea (1). According to the data surveyed by the National Statistical Office of Korea, stroke was rated as the primary cause of death among Koreans in 2006 (2). A stroke can be defined as a lack of blood flow to the brain resulting in a loss of brain function; it is largely classified into hemorrhagic stroke and ischemic stroke, depending on the cause of the interrupted blood flow to the brain. In general, approximately 20% of strokes are hemorrhagic strokes, while the remaining 80% are classified as ischemic strokes. The Korean Stroke Registry also documented that ischemic stroke patients accounted for 89.6% of all strokes, which surpasses the ratio of hemorrhagic strokes (3).

However, in patients with liver cirrhosis, it has been reported that ischemic stroke does not frequently occur due to coagulation disturbance and platelet abnormalities, as well as the tendency for low blood pressure (4,5). Although ischemic stroke is rare, it is still occasionally reported among liver cirrhosis patients. Despite controversy concerning the actual incidence of ischemic stroke in patients with liver cirrhosis, studies have not, to our knowledge, been performed to assess the clinical characteristics of ischemic stroke in liver cirrhosis patients. The purpose of this study was to analyze the clinical features of liver cirrhosis patients who have experienced ischemic stroke, including clinical manifestations, laboratory findings, and clinical progress.

MATERIALS AND METHODS

Patients

This study retrospectively reviewed the medical records of 23 ischemic stroke cases who were also diagnosed

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with liver cirrhosis among patients that received treatment for ischemic stroke at the Samsung Changwon Hospital in Changwon, Korea, over a 10 year period from January 2001 to December 2010. Liver cirrhosis was diagnosed by comprehensively reviewing laboratory findings (e.g., thrombocytopenia or prolonged prothrombin time), endoscopic findings (e.g., esophageal varix or gastric varix), and abdominal ultrasound or abdominal computerized tomography, in patients with underlying liver disease. Ischemic stroke was diagnosed in patients experiencing symptoms for general or local disorders in the central nervous system for at least 24 hours without any other vasculogenic lesions and the lesions were verified through brain magnetic resonance imaging (MRI). Medical records, including the interpretation of the neurologist or radiologist at the time, were reviewed for reference. Patients that were diagnosed with liver cirrhosis along with ischemic stroke were included in this research study, even if the relevant patient was not diagnosed with liver cirrhosis before hospitalization. This study reviewed the medical records of 23 patients that met the above diagnostic criteria to investigate the gender, age, cause of liver cirrhosis, Child-Pugh classification score, administration of antiplatelet agent or anticoagulant drug, treatment progress, and presence of risk factors for ischemic stroke including diabetes, hypertension, hyperlipidemia, arrhythmia, and high body mass index (BMI). Blood collected within 24 hours of ischemic stroke occurrence was used for the blood test. A total Child-Pugh classification score of 5-6 is considered as grade A, 7-9 as grade B, and 10-15 as grade C.

On the basis of the investigation of patients' alcohol consumption patterns, the cause of liver cirrhosis was established as alcohol if the patient had a daily alcohol intake of more than 40 g. In addition, the cause of liver cirrhosis was classified in consideration of a hepatitis virus marker, an autoantibody test, and the presence of fatty liver. Among the risk factors for ischemic stroke, hypertension was defined as a mean systolic blood pressure ≥140 mmHg and/or mean diastolic blood pressure ≥90 mmHg, or if the subject was on any antihypertensive medication. Patients that presented only a temporary increase in blood pressure in the early phase of the ischemic stroke were excluded. Patients diagnosed as diabetic included patients with a previous record of diabetes before hospitalization or patients that were classified with diabetes based on the American Diabetes Association guidelines during hospitalization. A cardiologist examined the electrocardiograph during hospitalization. BMI was calculated based on the formula weight (kg)/[height (m)]^2. Patients above 30 kg/m^2 were classified as obese. Hyperlipidemia was defined as a total cholesterol level ≥240 mg/dL, or low-density lipoprotein cholesterol ≥160 mg/dL, or triglyceride level ≥200, or the use of lipid lowering medication. The Ethics Committee of Samsung Changwon hospital approved this study protocol and we conducted the study in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from patients who participated in this study.

RESULTS

There were 23 liver cirrhosis patients that experienced ischemic stroke, during the study period. Basic characteristics of the 23 patients are shown in Table 1. The mean age of the patients was 65.1 ± 9.6 years and the males outnumbered the females by 20 (87.0%) to 3 (13.0%).

The majority of patients (39%) in the series had Child-Pugh class B score and 6 patients presented with class C score (26%); of these, 5 had a Child-Pugh classification score of 10 and 1 of 11. Alcohol was analyzed as the main cause for liver cirrhosis in 14 patients (60.8%) and 8 patients (34.8%) had hepatitis B-related liver cirrhosis.

Regional distribution of ischemic stroke indicated 8 patients showing multiple cerebral areas (34.7%), followed by the cerebral cortex only in 7 patients (30.4%), although the cerebral cortex was involved in all patients that had experienced ischemic stroke in multiple areas. The middle cerebral artery was the most common site for the occurrence of ischemic stroke, presenting in 12 patients (52.1%, Table 2).

Among the risk factors for ischemic stroke, 9 of the 23 patients (39.1%) were diagnosed with obesity, whereas 7 patients (30.4%) each were diagnosed with arrhythmia or smoking history. Among the 7 patients with arrhythmia, 6 were diagnosed with atrial fibrillation. Diabetes was present in 6 patients (26%), whereas 5 were diagnosed with hypertension (21.7%). Hyperlipidemia was detected in 2 patients. The number of patients who did not have any risk factors for developing ischemic stroke was 2 (8.7%, Table 3).

Blood tests revealed that 14 patients (60.8%) had thrombocytopenia during hospitalization. Seven patients (30.4%) presented with a prolonged prothrombin time (PT) but the international normalized ratio (INR) was below 1.7 in all but one patient. Administration of antiplatelet agents, such as aspirin or clopidogrel, was performed for 16 patients during hospitalization for ischemic stroke, and anticoagulant drugs, such as heparin or warfarin, were simultaneously administered to 6 patients (26%). A total of 7 patients (30.4%) received conservative treatment without the administration of any relevant drugs. Twenty of the 23 patients recovered or improved and were discharged from the hospital. However, ischemic stroke worsened in 3 patients and generated complications including pneumonia, cerebral hemorrhage, and septicemia, leading to death in 2 patients.

DISCUSSION

As the final stage of various chronic liver diseases, liver cirrhosis reduces hepatic function and generates changes in the blood stream flow, resulting into various symptoms and signs (6-8). In particular, thrombocytopenia and coagulopathy are well-known clinical manifestations of liver cirrhosis. It has been

Table 1. Clinical characteristics of liver cirrhosis patients with ischemic stroke

Patient No.	Age, years	Sex	Cause of liver cirrhosis	Child-pugh score	Risk factors for ischemic stroke
1	60	M	Chronic hepatitis B	9	DM, HTN
2	74	M	Alcohol	9	Obesity
3	67	M	Alcohol	6	AF, smoking
4	75	M	Alcohol	7	AF
5	67	M	Alcohol	10	Smoking
6	56	M	Alcohol	10	AF, smoking, obesity
7	67	M	Alcohol	5	Smoking
8	74	M	Alcohol	6	AF
9	54	M	Alcohol	6	DM, HTN, AF, smoking
10	47	M	Chronic hepatitis B	5	Dyslipidemia, smoking, obesity
11	76	M	Alcohol	11	Obesity
12	68	M	Alcohol	10	AF
13	74	M	Alcohol	7	DM
14	46	M	Chronic hepatitis B	10	Obesity
15	74	M	Alcohol	7	DM
16	63	M	Chronic hepatitis B	8	DM
17	74	F	Chronic hepatitis B	9	HTN, AF, obesity
18	49	M	Chronic hepatitis B	8	Obesity
19	74	M	Alcohol	6	-
20	73	M	Alcohol	7	Smoking
21	64	F	Chronic hepatitis C	10	-
22	50	M	Chronic hepatitis B	5	DM, HTN, dyslipidemia, obesity
23	71	F	Chronic hepatitis B	5	HTN, obesity

DM: diabetes mellitus; HTN: hypertension; AF: atrial fibrillation

reported that autonomic dysfunction and disturbance of cerebral auto-regulation are commonly presented in many liver cirrhosis cases (9-11). This, in turn, led to the assumption that the prevalence rate of stroke in liver cirrhosis patients would be different from that of the general population along with changes in blood stream flow, thrombocytopenia, and coagulopathy. Several studies have reported an increased risk of cerebral hemorrhage in liver cirrhosis (12-14). However, there have also been reports that argue that the correlation between liver cirrhosis and cerebral hemorrhage cannot be verified (5,15,16). Moreover, Berzigotti et al. (4) reported that the occurrence of ischemic stroke decreases in liver cirrhosis patients. Thus, although there are no established results regarding the correlation between liver cirrhosis and stroke, a large-scale retrospective study recently conducted in Taiwan reported that hemorrhagic stroke among patients with non-alcohol-induced liver cirrhosis did not present significant differences from the general group, although ischemic stroke displayed a noticeably lower risk than the general group (17). Further, Northup et al. (18) reported that even if hospitalized liver cirrhosis patients possess coagulopathy, it cannot sufficiently prevent thrombophilic events such as peripheral venous thromboembolism or pulmonary embolism, and other studies reported that portal vein thrombosis existed in 54% of liver cirrhosis patients according to extensive sets of autopsy data (19,20). It has been suggested that such a relatively high incidence of portal vein thrombosis might be associated with local factors, including changes in periportal lymphangitis and fibrosis, leading to flow reduction and endothelial activation in addition to systemically altered coagulation function (21-23). However, there has not been enough research in Korea on ischemic stroke in liver cirrhosis patients to verify this suggestion. In 2007, a large-scale cohort study by Sung et al. (24) reported that the group with positive hepatitis B surface antigen (HBsAg) presented lower risk of ischemic stroke and myocardial infarction and higher risk of hemorrhagic stroke when compared with the contrast group. The authors suggested that decreased risks for ischemic stroke and increased risks for hemorrhagic stroke among

Table 2. Brain lesions and involved arterial territory

Variables	No. of patients (n=23)
Brain lesion	
Cerebral cortex only	7 (30.4%)
Cerebellum only	2 (8.7%)
Basal ganglia only	4 (17.4%)
Thalamus only	1 (4.3%)
Pons only	1 (4.3%)
Multiple involvement	8 (34.8%)
Cerebral cortex + basal ganglia	1 (4.3%)
Cerebral cortex + caudate nucleus	1 (4.3%)
Cerebral cortex + cerebellum	1 (4.3%)
Cerebral cortex + insular	3 (13.0%)
Cerebral cortex + cerebellum + basal ganglia	1 (4.3%)
Cerebral cortex + pons + caudate nucleus	1 (4.3%)
Arterial territory	
Middle cerebral artery	12 (52.2%)
Anterior cerebral artery	3 (13.0%)
Posterior cerebral artery	2 (8.7%)
Vertebral artery	1 (4.3%)
Posterior inferior cerebellar artery	2 (8.7%)
Multiple involvement	3 (13.0%)
Middle cerebral artery + Anterior cerebral artery	1 (4.3%)
Middle cerebral artery + Vertebral artery	1 (4.3%)
Middle cerebral artery + Posterior cerebral artery	1 (4.3%)

Values are number of cases and (percent of sample).

Table 3. Incidence of risk factors associated with ischemic stroke

Variables	Presence of risk factors (no. of patients =23)
Hypertension	5 (21.7%)
DM	6 (26%)
AF	7 (30.4%)
Dyslipidemia	2 (8.6%)
Obesity	9 (39.1%)
Smoking	7 (30.4%)

Values are presented as n (%).

DM: diabetes mellitus; HTN: hypertension; AF: atrial fibrillation

HBsAg-positive patients appeared to be secondary to hepatitis B virus-associated liver dysfunction as represented by lower levels of clotting factors II and VII and fibrinogen. Similarly, the results of the present study demonstrated that ischemic stroke was more frequent in patients with alcohol-induced liver cirrhosis than in patients with liver cirrhosis caused by hepatitis B. Furthermore, liver cirrhosis patients that presented a low Child-Pugh classification score, indicating a relatively well-maintained favorable liver function, showed frequent occurrence of ischemic stroke when compared with that of other patients.

In particular, as there was only 1 case with PT (INR) above 1.7, it was verified that liver function was relatively well maintained in most liver cirrhosis patients with ischemic stroke occurrence. On the other hand, 21 out of 23 patients in this study possessed at least one of the risk factors for ischemic stroke (91.3%). Thus, it can be stipulated that ischemic stroke risk factors may have intervened more in the occurrence of ischemic stroke in liver cirrhosis patients than the effect of liver cirrhosis itself.

According to the medical records of patients with previous diseases regarded as risk factors for ischemic stroke, such as arrhythmia, diabetes, or high blood pressure, none of the patients were administered antiplatelet agents, such as aspirin or clopidogrel, before the occurrence of ischemic stroke. It is assumed that this was due to the patients' reluctance to using antiplatelet agents in relation to the risk of bleeding caused by thrombocytopenia or coagulopathy of liver cirrhosis or due to the lack of verified research results in relation to this matter. Similarly, this study began when a liver cirrhosis patient that had a prolonged PT with thrombocytopenia had visited the hospital for ischemic stroke and questions were raised regarding the continuous administration of antiplatelet agents following the patient's discharge. Therefore, this study suggests that the administration of antiplatelet agents should be considered for Child-Pugh class A or B patients with relatively well-maintained liver function who simultaneously possess specific risk factors for ischemic stroke, such as obesity, arrhythmia, smoking, diabetes, or high blood pressure, especially in situations where patients have both alcohol-induced liver cirrhosis and atrial fibrillation.

Chronic liver diseases, such as liver cirrhosis, commonly accompany thrombocytopenia or coagulopathy. Many patients with liver cirrhosis die of massive hemorrhage such as bleeding in the esophageal varix. However, as esophageal varix bleeding is caused by physical blood vessel damage rather than thrombocytopenia or coagulopathy, these two symptoms cannot act as the direct cause of bleeding, although they may trigger adverse effects in the progress of bleeding symptoms (25). Thus, actual bleeding symptoms may not be observed in liver cirrhosis patients that present severe thrombocytopenia or coagulopathy. Recent studies reported that venous thromboembolism is frequently generated in liver cirrhosis or liver cancer patients when compared with the normal population (26). It is suggested that this is related to rebalanced hemostasis, in which thrombocytopenia and platelet dysfunction, shown in liver diseases, balance through the decrease of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) and increase of Von Willebrand factor (vWF), whereas the deficiency of blood coagulation factors balance

through the increase of factor VIII and vWF and the decrease of protein C, protein S, and antithrombin (27). Thus, ischemic stroke can occur in liver cirrhosis patients that display thrombocytopenia or coagulopathy. In addition, risk factors, such as obesity, arrhythmia, smoking, diabetes, or hypertension, can increase the occurrence rate of stroke in relevant patients.

Among the 23 patients analyzed in this study, 2 patients died due to cerebral hemorrhage, pneumonia, and septicemia experienced as complications of ischemic stroke and cirrhosis. One patient was eventually transferred to a nursing hospital following the persistence of severe symptoms without improvement. Overall, 20 patients were discharged from the hospital as symptoms showed improvement following treatment. However, as long-term follow-up observation was not conducted on these patients, there are limitations in the analysis of the prognosis of ischemic stroke in relation to liver cirrhosis. Furthermore, as this study is based on retrospective research conducted on a small number of patients, it is stipulated that a large-scale prospective study must be additionally conducted to clearly investigate the prevalence of ischemic stroke in liver cirrhosis patients and its causal relationship.

In conclusion, although ischemic stroke is not common among liver cirrhosis patients, this study presented a comparatively high frequency of ischemic stroke in patients with alcohol-induced liver cirrhosis and in patients with a less compromised liver function. In addition, it was found that most patients possessed at least one risk factor of ischemic stroke.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Samsung Changwon Hospital.

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

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