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Acute cholecystitis as a rare and overlooked complication in stroke patients

A retrospective monocentric study

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Abstract

Acute cholecystitis (AC) is a rare but possible medical complication found in stroke patients. As many stroke patients present with neurologic symptoms, such as altered mental status, motor weakness, global aphasia, or dysarthria, clinical symptoms and signs of AC are often unexpressed or overlooked. As a result, the diagnosis of AC is often delayed with subsequent secondary complications in these stroke patients. This study aims to evaluate the clinical incidence, manifestations, and predictive factors of AC in stroke patients.

A retrospective cohort study was conducted between January 2013 and December of 2017 of all stroke patients (n = 2699) who have been admitted to our stroke center of the university hospital. We evaluated patient demographics, presenting symptoms, vital signs, laboratory results, mean initial consecutive fasting time, mean total fasting time, modified Rankin Scale (mRS), as well as radiological findings of abdominal computed tomography (CT) or ultrasonography.

AC was diagnosed in 28 of the 2699 patients (1.04%). Of these patients with AC, gallbladder stones (calculous cholecystitis) were found in 4 patients (14.3%), and 24 patients (85.7%) were diagnosed with a calculous cholecystitis. Subgroup analysis revealed that of the 28 stroke patients with AC, those who underwent neurosurgical intervention (n = 15) had increased incidence of AC compared with those who did not (2.3% vs 0.6%, respectively, $P < .001$). Furthermore, the initial consecutive fasting time, total fasting time, and mRS were all predictive factors ($P < .05$) for developing AC in stroke patients.

The incidence of AC was higher in acute stroke patients who required neurosurgical intervention, with longer initial consecutive fasting time, total fasting time, and higher mRS. We recommend early enteral nutrition and to maintain a high degree of clinical suspicion to make an early diagnosis of AC in stroke patients for improved outcome.

Abbreviations: AC = acute cholecystitis, CT = computed tomography, mRS = modified Rankin Scale.

Keywords: acute cholecystitis, early enteral nutrition, stroke, total fasting time

1. Introduction

Stroke patients are susceptible to various medical complications. Aspiration pneumonia, urinary tract infection, fever, pain, pressure sores, medical falls, and thromboembolisms (pulmonary embolism, deep vein thrombosis) can occur after a stroke.[1] Among these medical complications, acute cholecystitis (AC) can develop in stroke patients, but AC after stroke is not common, and it is often difficult to diagnose easily and promptly.

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In the general population, 90% to 95% of people with AC have gallstones (calculous cholecystitis) at the time of diagnosis.[2,3] However, in critically ill patients, such as those with trauma, sepsis, or burns, AC without gallstones (acalculous cholecystitis) occur more commonly and result in higher mortality.[4] Similarly, acute acalculous cholecystitis is a more common presentation in patients with stroke.[5] Early diagnosis and treatment of AC are critical to avoid rapid progression to perforation and mortality. Unfortunately, stroke patients with significant neurologic deficits, such as altered mental status, global aphasia, and severe dysarthria have difficulty expressing the classic symptoms of AC. Furthermore, radiological evaluations such as abdominal computed tomography (CT) or ultrasonography are not typically performed for fever work-up in patients with acute stroke.

To the best of our knowledge, there are only 2 studies from Japan that have investigated the frequency of AC as a medical complication after an acute stroke. The purpose of this study is to evaluate the clinical incidence, manifestations, and predictive factors of AC in Korean stroke patients.

2. Methods

2.1. Subjects

In this retrospective cohort study, medical records obtained from 2699 patients admitted to our university hospital for acute stroke management from January of 2013 to December of 2017 were reviewed. In our cohort of stroke patients with significant neurologic deficits who could not express abdominal pain, AC was diagnosed with clinical findings of fever, right upper quadrant (RUQ) tenderness on percussion, Murphy sign, and elevated liver function tests. Stroke patients with AC were evaluated for their characteristics, vital signs, laboratory findings, radiological images, initial symptoms and signs, mean initial consecutive fasting time, mean total fasting time, modified Rankin Scale (mRS), and abdominal CT or ultrasonographic findings during hospitalization. Patients were excluded based on the radiological confirmation if it was not appropriate findings for AC. This retrospective study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong (IRB No. KHNMC-IRB-2018–05–013). The requirement for written informed consent for each patient was waived due to its retrospective nature.

2.2. Design

Of the 2699 stroke patients admitted to the stroke center of our university hospital for acute stroke management, 407 patients underwent an abdominal ultrasound or abdominal CT for the diagnosis of AC. Thirty-two patients with AC with suspected cholecystitis on ultrasonography or CT were included in this study. We excluded 4 patients based on the radiological confirmation of distal common bile duct (CBD) obstruction and CBD cancer. The Department of Internal Medicine (infectious and hepatobiliary diseases) is usually consulted when patients have elevated liver function tests (LFT), abdominal pain, or fever lasting more than 1 day. After a thorough clinical evaluation by the general surgeon or the internist, each patient underwent one of the 3 therapeutic plans: laparoscopic cholecystectomy (LC) performed by general surgeons, percutaneous transhepatic gallbladder drainage (PTGBD) performed by interventional radiologists, and conservative management with antibiotic therapy. The degree of disability in our cohort patients was measured using the modified Rankin Scale (mRS), often used in stroke clinical trials.[6] The scale ranges from 0 (perfect health without symptoms) to 6 (death). The stroke patients with AC were further divided into 2 groups of those who underwent neurosurgical intervention (n=15) or conservative medical management (n=13). The mean initial consecutive fasting time, mean total fasting time, and mRS of these 2 AC groups were compared. In general, all stroke survivors were restricted to receive nil per mouth (NPO) initially due to high aspiration risk. We defined the mean initial consecutive fasting time as the first continuous fasting periods without enteral feeding. In addition, the mean total fasting time was defined as the total fasting periods without enteral feeding between admission and the diagnosis of AC.

2.3. Statistical analysis

Clinical data are presented as mean ± standard deviation, number, and percentage. As noted above, the mean initial consecutive fasting time, mean total fasting time, and mRS of the 2 groups were compared using the nonparametric Mann–Whitney *U* test. We defined statistical significance as $P<.05$ and all statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 software package (SPSS Inc., Chicago, IL).

3. Results

Of the 2699 stroke patients admitted to the stroke center, clinical features of the 28 patients (1.04%) eventually diagnosed with AC are summarized in Table 1. The types of stroke in the patients who were diagnosed AC were as follows: cerebral hemorrhage (13), subarachnoid hemorrhage (7), lacunar stroke (2), atherothrombosis (4), and cardiac embolism (2). Gallbladder distention or enlargement, gallbladder wall thickening, or gallbladder stones or sludge were detected on abdominal CT or ultrasonography in 20/28 (71.4%) and 8/28 (28.6%) cases, respectively. There was a higher incidence of acalculous cholecystitis (85.7%) in our stroke cohort than calculous cholecystitis (14.3%). The initial symptom of AC was RUQ tenderness in 6/28 (21.4%), fever in 9/28 (32.1%), and elevation of LFT in 13/28 (46.5%). The mean time from admission to the diagnosis of AC was 31.8 ± 26.7 days (range, 7–122 days). The mean initial consecutive fasting time was 6.6 ± 6.7 days (range, 1–16 days) and the mean total fasting time was 8.5 ± 7.7 days (range, 1–36 days). At the time of AC diagnosis, the nutritional status of our patients was as follows: 18 patients received enteral feeding (18/28, 64.3%), and 10 received total parenteral nutrition (TPN) (10/28, 35.7%). Among those diagnosed with AC, 6 (21.5%; mean age 59.6 ± 11.2 years, range, 43–75 years) were treated with LC, 13 (46.4%; mean age 63.4 ± 14.5 years, range, 26–77 years) were treated with PTGBD, and 9 (32.1%; mean age 63.4 ± 11.6 years, range, 57–79 years) were conservatively managed with antibiotic therapy (Table 2).

Table 1

Dermographics and baseline clinical characteristics of 28 patients with hemiplegic stroke.

Parameters	Storke patients with AC (n=28)
Sex, n (%)	
Male	14 (50)
Female	14 (50)
Age, y	57.8 ± 13.5
Past medical history, n (%)	
HTN	26 (92.8)
DM	9 (32.1)
Dyslipidemia	7 (25)
Atrial fibrillation	5 (17.8)
Type of strorke, n (%)	
Hemorrhage with surgery	14 (50.1)
Hemorrhage without surgery	6 (21.4)
Ischemia with surgery	1 (3.6)
Ischemia without surgery	7 (24.9)
Mean initial consecutive fasting time, d	6.6 ± 6.7
Mean total fasting time, d	8.5 ± 7.7
Mean onset time of AC from admission, d	31.8 ± 26.7
Initial symptom of AC, n (%)	
RUQ pain or tenderness	|6 (21.4)
Fever	9 (32.1)
Elevation of LFT	13 (46.5)
mRS score	4.0 ± 0.9
Diagnostic method, n (%)	
Abdominal CT	20 (71.4)
Abdominal US	8 (28.6)
Type of AC, n (%)	
GB stone	4 (14.3)
AAC	24 (85.7)
Nutritional status at the time of AC diagnosis, n (%)	
Enteral feeding	18 (64.3)
TPN	10 (35.7)

Data are presented as mean ± standard deviation or number (%).
AC=acute cholecystitis, AAC=acute acalculous cholecystitis, DM=diabetes mellitus, GB=gallbladder, HTN=hypertension, LFT=liver function test, mRS=modified Rankin Scale, RUQ=right upper quadrant, , TPN=total parenteral nutrition.

Table 2

Comparision of treatment for acute cholecystitis between ischemic and hemorrhagic stroke.

Treatment	Ischemic stroke (n=8)		Hemorrhagic stroke (n=20)		
	C (n=7) n (%)	S (n=1) n (%)	C (n=6) n (%)	S (n=14) n (%)	Total (n=28) n (%)
Antibiotics	5 (71.4)	0 (0)	0 (0)	4 (28.6)	9 (32.1)
PTGBD	1 (14.3)	1 (100)	3 (50)	8 (57.1)	13 (46.4)
LC	1 (14.3)	0 (0)	3 (50)	2 (14.3)	6 (21.5)

Values are presented as number (%).

C=stroke patients with conservative treatment, LC=laparoscopic cholecystectomy, PTGBD=percutaneous transhepatic gallbladder drainage, S=stroke patients with surgical treatment.

Further subgroup analysis revealed that the AC patients with ischemic stroke were treated more conservatively (antibiotic therapy) compared with those with hemorrhagic stroke, who were treated with invasive or surgical interventions (PTGBD or LC). In addition, LC was performed more frequently in patients with hemorrhagic stroke, who received conservative management for the hemorrhage (3/6, 50%). In the hemorrhagic stroke patients who underwent neurosurgical intervention, the proportion of patients treated with PTGBD (8/14, 57.1%) was higher than that of those treated with LC (2/14, 14.3%) (Table 2).

Among the 970 hemorrhagic stroke patients (970 of total stroke cohort of 2699), 501 patients underwent surgery, including craniotomy or decompressive craniectomy, and 469 were treated conservatively. Of the remaining 1729 patients with ischemic stroke, 133 patients underwent decompressive craniectomy, and 1596 patients underwent conservative management.

Twenty-eight stroke patients with AC were divided into 2 groups: those with ischemic and hemorrhagic stroke treated surgically, and those who underwent conservative treatment. The frequency of AC was 2.3% (15/634) in the surgical treatment group and 0.6% (13/2065) in the conservative management group ($P<.001$). In addition, the mean initial consecutive fasting time, mean total fasting time, and mRS of the 28 stroke patients with AC were investigated. The initial consecutive fasting time and total fasting time were about twice longer, and mRS was higher in stroke patients who underwent surgical treatment, and the difference was statistically significant for all 3 values (initial consecutive fasting time, $P=.021$; total fasting time, $P=.035$; mRS, $P=.035$) (Table 3).

4. Discussion

In our study, the incidence of AC after an acute stroke was 1.04%. Specifically, the incidence of AC was 0.5% in ischemic stroke and 2.1% in hemorrhagic stroke. Furthermore, we have found that those who underwent neurosurgical intervention had an increased incidence of AC compared with those managed conservatively for their stroke (2.3% vs 0.6%).

There are no available data on the incidence of AC in the Korean population. Generally, >90% of patients with AC are associated with gallstones in the general population.[7] The prevalence of gallstones is approximately 4% in the general population (about 20% in the elderly people >70 years old).[8]

Huang et al[9] showed that the average rates of hospital admissions for symptomatic AC related to severe gallstone diseases that require a surgical or endoscopic procedure was 0.046% for men and 0.045% for women in Taiwan. In particular, the average incident hospital admission rate for AC in the elderly population (aged ≥60) was higher.

It was difficult to compare the findings in our study with those in previous reports, because to the best of our knowledge this is the first study to determine the frequency of AC after acute stroke in Korea. To our knowledge, there have been few studies regarding AC as a medical complication and the occurrence of AC after acute stroke. Only 2 studies have reportedly been conducted on Japanese patients with acute stroke and 1 study conducted on Japanese patients with acute cerebral infarction. Ushiyama et al[10] reported an incidence of AC in 1.2% (12 of 1003 patients) of their stroke cohorts. In a subsequent Japanese study, Koizumi et al[11] have reported a higher incidence of AC in stroke patients (2.7%, 7 of 252 patients). More recently published study by Fukuoka et al[12] have reported a similar AC incidence rate of 1.4% (24 of 1682 patients) as the earlier study in 1997. In this study, the frequency of patients with ischemic stroke was 0.5%, which was lower than that reported in the Japanese studies.

It has been suggested that cerebrovascular disease is a risk factor in the pathogenesis of AC. Cho et al[13] have proposed in their study that acute stroke was the most significant independent risk factor for developing AC. Their results showed that in the patients with a history of cerebrovascular disease, the adjusted odds ratio for developing AC was 8.107. Approximately 85% of the patients with a history of cerebrovascular disease presented with AC and 46% of these patients experienced complicated AC such as empyema, hydrops, gangrenous AC, perforation, and abscess. Ushiyama et al[10] reported that elderly patients with stroke presenting with disturbance of gallbladder contractility associated with fasting period may be predisposed to the development of AC. The consumption of food containing proteins and long-chain triglycerides stimulates cholecystokinin (CCK) secretion, and loss of enteric stimulation during fasting impedes the gallbladder function.[14] AC tends to occur during fasting, likely in a setting of hyposecretion of CCK, resulting in contractile dysfunction of the gallbladder.[15]

Yang et al[16] have demonstrated that the mean initial consecutive fasting period for aneurysmal subarachnoid hemorrhage patients is a risk factor for AC. The mean initial consecutive

Table 3

Comparison of the mean fasting time and mRS between stroke patients with surgical and conservative treatment.

Parameters	Surgical treatment (n=15)	Conservative treatment (n=13)	P
The initial consecutive fasting time, d	7 (5–35)	4 (0–15)	.021*
The total fasting time, d	7 (5–36)	5 (0–20)	.035*
mRS	4 (2–5)	3 (2–5)	.035*

Data are presented as median (range).

mRS=modified Rankin Scale.

* Statistical significance.

fasting period was 5.38 ± 2.78 days. The 2 Japanese studies by Ushiyama et al[10] and Koizumi et al[11] have also described the correlation between fasting period and the incidence of AC, and the mean fasting period was 13 and 18.7 days, respectively. Fukuoka et al[12] also have reported mean fasting period of 10.7 days. The mechanism underlying the development of AC after acute stroke included bile stasis, as a result of the fasting period. Due to bile stasis, acalculous cholecystitis is usually caused by gallbladder mucosal inflammation. In our study, the mean initial consecutive fasting time and mean total fasting time was 6.6 and 8.5 days, respectively. In the 3 Japanese studies, the longer fasting time may be attributed to the higher frequency of AC.

Other underlying mechanism included a correlation between the clinical signs of autonomic dysfunction and cholestasis in stroke patients. Sevastos et al[17] have demonstrated that sympathetic stimulation with increased catecholamine secretion and vagal paresis caused by strong damage to the brain center, in conjunction with the temporary stopping of oral feeding, resulted in hypertonicity of the sphincter of Oddi. The sphincter of Oddi is a muscular valve that controls the flow of bile and pancreatic juice into the duodenum. In patients with acute stroke and clinical evidence of autonomic dysfunction, a temporary biochemical cholestasis may develop AC.

In the present study, the period from the admission to the diagnosis of AC was 31.8 days, but 4 patients took >1 month until diagnosis of AC. It is believed that the use of antibiotics for 2 weeks for the treatment of aspiration pneumonia or urinary tract infection, which often occurs in stroke patients, had resulted in delay in the diagnosis of AC.

As mentioned above, >90% of AC in the general population was due to gallstones. It is noteworthy that in the present study, the incidence of acute acalculous cholecystitis was higher than that of AC with gallstones. Unlike in the general population, AC with gallstones was only observed in 14.3% of our patients. Koizumi et al[11] have reported that 1 of 7 patients had AC with gallstones (14.3%), and 6 patients had acute acalculous cholecystitis (85.7%). Ushiyama et al[10] have also reported that 10 of 12 patients had acute acalculous cholecystitis (83.3%), and 2 patients had AC with gallstones (16.7%). Yang et al[16] have demonstrated that 4 of the 6 patients (66.6%) with pathologically proven AC had acalculous cholecystitis. Acute acalculous cholecystitis occurs especially in critically ill patients of trauma, sepsis or burns with a mortality rate between 10% and 90%, with an average of 30% as opposed to 1% in calculous cholecystitis.[4] Patients of acalculous cholecystitis have a higher morbidity and mortality than those of acute calculous cholecystitis.[18] The atypical nature of clinical symptoms in elderly patients and the presence of acalculous cholecystitis can make the diagnosis of AC difficult. Among patients older than 70 years with AC, RUQ tenderness or pain was absent in 27% and fever was absent in 45%.[19] Stroke patients are often elderly, asymptomatic, and physical examination may be irrelevant. Moreover, laboratory data may not helpful or may be mildly positive. The patient might be unable to express the exact symptoms due to global aphasia and dysarthria. Therefore, the risk of death is closely related to delayed diagnosis, and an early diagnosis and treatment can lead to an improvement and better prognosis. An early diagnosis and treatment should be applied to stroke patients.

When stroke patients were divided into 2 groups of those who underwent neurosurgical intervention or conservative medical management, as shown in Table 3, stroke patients who had a neurosurgical intervention demonstrated longer initial and total fasting time and higher mRS scores. Moreover, the frequency of AC was 2.3% (15/634) and 0.6% (13/2065) in the groups with neurosurgical intervention and conservative management, respectively.

In the present study, the degree of disability was severe in the group with neurosurgical intervention (mean mRS score 4.3). Prevention of aspiration pneumonia during hospitalization, intracranial pressure-induced vomiting, ileus, and diarrhea may have resulted in a longer fasting period and higher frequency of AC in the group with neurosurgical intervention. Hence, we need to maintain a high degree of suspicion for patients who have undergone surgical treatment after stroke. In this study, as shown in Table 2, in patients with ischemic stroke due to antiplatelet therapy, antibiotics might be preferred because of a low risk of bleeding rather than an invasive method such as LC or PTGBD. A relatively more invasive method was used in the hemorrhagic stroke patients.

There were some limitations to the current study. First, we could not statistically show the risk factors of AC after stroke. Although the cases were collected over a 5-year period, the samples were from a single hospital center. Second, we could not determine the pathophysiology of AC after stroke, even though we were aware that the factors contributing to bile congestion were fasting period and immobilization. Therefore, our cases might have been affected by multiple factors causing AC. However, in order to overcome these limitations, further research is needed.

5. Conclusion

AC as a medical complication after stroke has been underestimated in previous studies because of a lower incidence than aspiration pneumonia or urinary tract infection. Patients with acute stroke who had undergone neurosurgical intervention with a severe degree of disability have a relatively longer fasting time and a higher incidence of AC than expected. Therefore, we suggest that a short fasting period with early enteral nutrition and a high level of suspicion may help prevent AC in the clinical setting of stroke patients.

Author contributions

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