Original article

Acute pancreatitis is a very rare comorbidity of acute ischemic stroke

Kiyobumi Ota[1], Ayako Oniki[1], Zen Kobayashi[1], Shoichiro Ishihara[1],
Hiroyuki Tomimitsu[1], and Shuzo Shintani[1]

[1] *Department of Neurology, JA Toride Medical Center, Japan*

Abstract

Background: Although acute pancreatitis is listed among the exclusion criteria for the administration of recombinant tissue plasminogen activator according to the Japanese Guideline for the Management of Stroke, the co-occurrence of acute pancreatitis and acute ischemic stroke has not been investigated. The present study aimed to assess the incidence rate of acute pancreatitis in patients with acute ischemic stroke.
Methods: This study consecutively enrolled all patients with ischemic stroke admitted to the Department of Neurology, JA Toride Medical Center between April 2014 and March 2016. Diagnosis of acute pancreatitis was made according to the revised Atlanta Classification of Acute Pancreatitis. We retrospectively analyzed serum amylase activity and the frequency of acute pancreatitis as a comorbidity of ischemic stroke.
Results: A total of 411 ischemic stroke patients were included. Serum amylase activity was measured for 364 patients, 27 of whom presented with amylase activity exceeding the upper limit of normal. In two patients with serum amylase activity greater than three times-fold the upper limit of normal, computed tomography or transabdominal ultrasonography showed no characteristic findings of acute pancreatitis. No patient in the cohort met the diagnostic criteria for acute pancreatitis.
Conclusions: Acute pancreatitis is a very rare comorbidity of acute ischemic stroke.

Key words: acute pancreatitis, amylase, stroke, recombinant tissue plasminogen activator (rt-PA)

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Introduction

Intravenous administration of recombinant tissue plasminogen activator (rt-PA) is one of the most effective therapies for acute ischemic stroke[1, 2]. Owing to its potential to cause adverse drug reactions, especially hemorrhagic complications, rt-PA guidelines have strict exclusion criteria[3, 4], which vary somewhat by country and region. For example, cerebral arteriovenous malformation and brain tumor are listed as exclusion criteria according to the American Stroke Association (ASA) guidelines, whereas the Japanese stroke guidelines list these conditions as "careful administration" criteria rather than exclusion criteria. On the other hand, the Japanese stroke guidelines list acute pancreatitis as an exclusion criterion, in contrast to the ASA guidelines[3, 4]. Many Japanese neurologists are accustomed to screening for pancreatitis by measuring pancreatic enzyme (amylase or elastase) activity and waiting for laboratory confirmation before administering rt-PA therapy, in accordance with the Japanese stroke guidelines. However, as neurologists, we know empirically that acute pancreatitis rarely or never coincides with acute ischemic stroke. Therefore, is it necessary to measure pancreatic enzyme activity before starting rt-PA and thus delay treatment? It is unknown how often acute pancreatitis coincides with acute ischemic stroke. The present study aimed to assess the incidence rate of acute pancreatitis in patients with acute ischemic stroke.

Materials and Methods

This was a single-center, hospital-based, retrospective study that received approval from the hospital's institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki. The study included all patients who were admitted for the treatment of acute ischemic stroke, via the emergency room, to the Department of Neurology at JA Toride Medical Center between April

2014 and March 2016. The data included: (i) age and gender; (ii) stroke subtype; and (iii) screening test results for acute pancreatitis. Ischemic stroke was classified according to the criteria laid out by the Trial of ORG 10172 in Acute Stroke Treatment[5]. Diagnosis of acute pancreatitis was made according to the revised Atlanta criteria, which requires two of the following three features: (i) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (ii) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (iii) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CT) and, less commonly, magnetic resonance imaging or transabdominal ultrasonography[6].

Results

Patients and stroke subtypes

Of the 411 patients enrolled, 260 (63.3%) were male and 151 (36.7%) were female. The mean age of the patients was 75 ± 12.1 years. With regard to stroke subtypes, 110 patients (26.8%) presented with small-vessel occlusion, 117 (28.5%) with large-artery atherosclerosis, 100 (24.3%) with cardioembolism, and 84 (20.4%) with other/undifferentiated stroke. A total of 39 patients were treated with intravenous rt-PA (Table 1).

Screening tests for acute pancreatitis

Since the revised Atlanta pancreatitis criteria specify that the diagnosis of acute pancreatitis requires the presence of serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal[6], we used serum amylase activity (upper limit of normal in our institution: 126 IU/L), which can be measured at any time in our hospital, as a screen for pancreatitis. Serum amylase activity was measured in 364 of the 411 patients, 27 (7.4%) of whom exceeded the upper limit of normal and two (0.54%) of whom exceeded this limit by three-fold or more (> 378 IU/L), thereby meeting one of the diagnostic criteria for acute pancreatitis. The amylase activity levels in these two patients were 385 and 566 IU/L, respectively. None of the 27 patients with elevated amylase activity complained of abdominal or back pain in the acute stroke phase. Abdominal CT or transabdominal ultrasonography was performed for 15 patients with elevated amylase activity and revealed that five patients had gallstones, three had a fatty liver, and one had a pancreatic cyst, while nine patients showed normal findings and none showed the characteristic features of pancreatitis. Follow-up tests to re-assess amylase activity were performed for 25 patients within two weeks of admission. The amylase levels in 15 patients recovered to within the

Table 1 Baseline characteristics of stroke patients

Age (y)	75 ± 12.1
Male : Female, n (%)	260 (63.3) : 151 (36.7)
Subtype of ischemic stroke	
Small-vessel occlusion, n (%)	110 (26.8)
Large-artery atherosclerosis, n (%)	117 (28.5)
Cardioembolic stroke, n (%)	100 (24.3)
Others / undifferentiated stroke, n (%)	84 (20.4)
Treated with intravenous rt-PA, n (%)	39 (9.5)

rt-PA, recombinant tissue plasminogen activator.

normal range and remained elevated in 10 patients. We attempted to retrospectively discern the etiology of the high amylase levels in these 10 patients. Four patients had renal failure, one had a gallstone, and one had a pancreatic cyst; however, in the remaining four patients, the cause was unknown. Of the two patients who presented with amylase activity three-fold greater than the upper limit of normal, one patient regained a normal amylase level at follow-up and showed a normal appearance on abdominal CT, while the other retained elevated amylase activity of unknown cause, although the abdominal CT was normal. None of the total cohort of 411 patients met the diagnostic criteria for acute pancreatitis (Table 2).

Discussion

In the present study, we found no evidence of acute pancreatitis in 411 consecutively enrolled patients with acute ischemic stroke. In general, the incidence of acute pancreatitis ranges from about 30 to 50 per 100,000 person-years[7–10]. Major risk factors for pancreatitis include daily alcohol intake, hypertriglyceridemia, and gallstones[11]. Although heavy alcohol consumption and hypertriglyceridemia are also common risk factors for ischemic stroke[4, 11, 12], there are few case reports of acute pancreatitis accompanying this condition[13–16].

As neurologists, we know empirically that acute pancreatitis and acute ischemic stroke rarely or never coincide. However, to date, there has been no research on the prevalence of acute pancreatitis in the acute phase of ischemic stroke. This study is the first to provide evidence that acute pancreatitis rarely or never occurs alongside acute ischemic stroke.

Typically, about 90% of patients with acute pancreatitis complain of abdominal pain, 80% present with muscular defense, and 80% develop fever[17, 18]. Our department has laid down rules by which cases of acute pancreatitis can be clinically excluded without having to measure pancreatic enzyme activity before initiating rt-PA. We clinically excluded pancreatitis if one of the two following conditions was met:

Table 2 Characteristics of the screening tests for acute pancreatitis

Measurement of serum amylase activity on admission, n (%)	364/411 (88.6)
Serum amylase activity	
≤ 126 IU/L, n (%)	337/364 (92.6)
> 126 IU/L, n (%)	27/364 (7.4)
> 378 IU/L, n (%)	2/364 (0.55)
Abdominal or back pain in patients with elevated amylase activity	0/27 (0)
Follow-up serum amylase activity, n (%)	25/27 (93)
Decreased to normal range, n (%)	15/25 (60)
Remained abnormal, n (%)	10/25 (40)
Causes of remaining elevated amylase activity	
Renal failure, n	4
Gallstone, n	1
Pancreatic cyst, n	1
Unknown, n	4
Abdominal imaging results in patients with elevated amylase activity	15/27 (56)
Normal, n	9
Gallstone, n	5
Fatty liver, n	3
Pancreatic cyst, n	1
Met the criteria for acute pancreatitis, n (%)	0/411 (0)

(i) the stroke patient can speak and neither complains of abdominal pain nor presents with muscular defense; and (ii) the stroke patient cannot speak but presents with neither muscular defense nor fever. The policy of our department does not contradict the Japanese stroke guidelines. As these guidelines do not recommend methods that should be used to screen for acute pancreatitis and do not require the clinician to measure pancreatic enzyme activity, our department counsels that clinicians need not measure pancreatic enzymes when the patient does not present with the most common clinical signs and symptoms of acute pancreatitis.

Acute pancreatitis is one of the exclusion criteria for rt-PA in the Japanese stroke guidelines. However, the reasons why it is thus listed are not well described in the guidelines[3]. One reason may be related to the fact that acute pancreatitis can develop into tissue necrosis, infection, thrombocytopenia, and disseminated intravascular coagulation[11], all of which increase the risk of hemorrhagic complications upon rt-PA administration. However, the actual risks associated with rt-PA in patients with acute pancreatitis remain unknown because no ischemic stroke cases with comorbid acute pancreatitis that were treated with rt-PA have ever been reported. It is assumed that severe acute pancreatitis, which can develop into tissue necrosis, thrombocytopenia, and disseminated intravascular coagulation, carries a higher rt-PA-associated hemorrhage risk than that of non-severe acute pancreatitis. Given that severe acute pancreatitis is often accompanied by symptoms of peritoneal irritation, a simple physical examination is sufficient to distinguish between severe and non-severe acute pancreatitis[19]. Furthermore, pancreatic enzyme activity is not a clear predictor of the severity of acute pancreatitis[20–22].

For the following reasons, we suggest that it is unnecessary to check serum pancreatic enzyme activity in ischemic stroke patients before initiating rt-PA therapy: (i) our study demonstrated that acute pancreatitis rarely or never occurs in the acute phase of ischemic stroke; (ii) simple and rapid physical examinations to assess body temperature or abdominal pain can exclude most acute pancreatitis cases, especially severe cases with an associated increased risk of hemorrhage; (iii) even if acute pancreatitis were to co-occur with ischemic stroke, pancreatic enzyme activity is poorly predictive of the severity of acute pancreatitis; and (iv) when physical examinations suggest the possibility of pancreatitis, transabdominal ultrasonography in the emergency room can rapidly detect it.

There were several limitations to our study. First, this was a single-center study and therefore the possibility of selection bias cannot be excluded. However, the baseline characteristics of the study participants did not deviate significantly from those reported in the Japanese stroke registry database[23, 24]. Second, given the rarity of the combined diagnosis, our sample size may not have been sufficiently large to detect rare cases of acute pancreatitis alongside ischemic stroke. Third, we only investigated whether patients who were admitted with a diagnosis of ischemic stroke had acute pancreatitis. In the future, it will be necessary to discern whether patients admitted for acute pancreatitis are at risk

of acute ischemic stroke to further clarify the co-occurrence of these conditions.

Conclusion

None of the 411 acute ischemic stroke patients studied herein presented with acute pancreatitis.

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