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Intra- and extracranial atherosclerotic disease in acute spontaneous intracerebral hemorrhage

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ABSTRACT

Background: There is little information about intracranial atherosclerotic disease (ICAD) and extracranial atherosclerotic disease (ECAD) in patients with acute spontaneous intracerebral hemorrhage (ICH). The purpose of the present study was to elucidate the prevalence of and the factors that correlate with ICAD and ECAD in patients with ICH.
Methods: A total of 274 patients with acute spontaneous ICH were enrolled. ICAD and ECAD (moderate to severe stenosis or occlusion) were mainly assessed by intracranial magnetic resonance angiography and carotid duplex sonography, respectively.
Results: Fifty-one patients (19%) had ICAD or ECAD; 32 had ICAD, and 21 had ECAD. On multivariable analyses, age (OR, 1.52; 95% CI, 1.06–2.28 for every 10 years), monocyte count (OR, 1.37; 95% CI, 1.02–1.87 for every 100/mm^3), hemoglobin A1c (OR, 2.25; 95% CI, 1.08–5.15 for every 1%), and low-density lipoprotein cholesterol levels (OR, 1.23; 95% CI, 1.08–1.42 for every 10 mg/dL) were independently associated with ICAD. Age (OR, 2.20; 95% CI, 1.20–4.38 for 10 years) and dyslipidemia (OR, 3.95; 95% CI, 1.01–15.97) were independently associated with ECAD.
Conclusions: ICAD and ECAD were detected in approximately one-fifth of patients with spontaneous ICH. Age and dyslipidemia (or lipid profile) were associated with both ICAD and ECAD. Monocyte count and hemoglobin A1c were associated with ICAD.

1. Introduction

Intracerebral hemorrhage (ICH) and ischemic stroke account for about 10–30% and 60–80% of all strokes, respectively [1]. A German study found that a quarter of recurrent stroke was classified as ischemic in a cohort of ICH survivors [2]. Thus, it is important to consider the risk for recurrence of ischemic stroke among ICH survivors.

Atherosclerotic disease of intra- or extracranial arteries is an important cause of ischemic stroke. ICH and ischemic stroke share several common atherosclerotic risk factors such as advancing age, hypertension, and ethnicity [3,4]. There are few reports regarding the relationship between ICH and atherosclerotic occlusive lesions of the intra- or extracranial arteries, so-called intracranial atherosclerotic disease (ICAD) and extracranial atherosclerotic disease (ECAD), which have a potential risk for future ischemic stroke [5–7].

The purpose of the present study was to elucidate the prevalence and correlates of ICAD and ECAD in patients with acute spontaneous ICH using data from our prospective database.

2. Subject and methods

2.1. Patients

The National Cerebral and Cardiovascular Center (NCVC) Stroke Registry is a prospective database of all patients with acute stroke treated in our stroke care unit. Data of 315 patients with ICH who were admitted within 7 days after onset between January 2011 and June 2012 were extracted from this database. Of these patients, 41 were ineligible and excluded: those with secondary ICHs due to arteriovenous malformation (4 patients) and moyamoya disease (1 patient), and those whose information regarding intra- or extracranial arteries verified by magnetic resonance angiography (MRA), CT angiography (CTA), conventional digital subtraction angiography (DSA), or carotid duplex sonography (CDS) were unavailable due to early death (29 patients) or unstable condition (7 patients). A total of 274 patients were included in the present analysis. The Regional Ethics

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and Hospital Management Committees approved the studies from the NCVC Stroke Registry. The Ethics Committee approved waiver of consent as a registry study.

2.2. Clinical characteristics

Baseline data were collected for all eligible patients, including sex, age, comorbidities, risk factors, and laboratory data on admission. Risk factors were defined as: 1) hypertension, history of using antihypertensive medication, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg before or ≥2 weeks after stroke onset; 2) diabetes mellitus, use of antidiabetic medication, random glucose level ≥ 200 mg/dL, or glycosylated hemoglobin (HbA1c) ≥ 6.9% on admission; 3) dyslipidemia, use of antidyslipidemic medication, total cholesterol level ≥ 220 mg/dL, low-density lipoprotein (LDL) cholesterol level ≥ 140 mg/dL, or high-density lipoprotein (HDL) cholesterol level < 40 mg/dL; and 4) ever smoking. The estimated glomerular filtration rate (eGFR) was calculated using the equation proposed by the Japanese Society of Nephrology as follows: eGFR (mL/min/1.73 m^2) = 194 × [serum creatinine (mg/dL)]$^{-1.094}$ × [age (year)]$^{-0.287}$ × 0.739 (if female) [8].

2.3. Neuroimaging

ICH was diagnosed by CT on admission. ICH volume was determined with the ABC/2 [(length × width × height) / 2] method [9] at the bedside by the stroke specialist on admission. Time-of-flight MRA of the intracranial arteries using a commercially available echo planar instrument operating at 1.5 T was evaluated in 237 patients, and CTA of intracranial arteries was evaluated in another patient. DSA of the intra- and extracranial arteries was performed in 11 patients. CDS of the extracranial arteries was performed in 247 patients. ICAD was defined as intracranial arterial stenosis (≥50%) or occlusion that was identified according to a previously published scoring scheme in patients with MRA [10,11] and the Warfarin–Aspirin Symptomatic Intracranial Disease Trial method in patients with DSA or CTA [12]. Severe ICAD was defined as ≥75% narrowing in diameter or occlusion. ECAD was defined as extracranial arterial stenosis or occlusion that was diagnosed when the peak systolic velocity was ≥125 cm/s with plaque, moderate luminal narrowing (≥50%) with plaque, or occlusion with plaque on CDS [13,14]. In patients who underwent DSA, ECAD was defined as stenosis of ≥50% according to the North American Symptomatic Carotid Endarterectomy Trial method [15]. Severe ECAD was defined as peak systolic velocity ≥ 230 cm/s with plaque, severe luminal narrowing (≥70%) with plaque, or occlusion. In patients with information available about both MRA and DSA or both DSA and CDS, the DSA data were used. Three board-certified stroke neurologists rated degree of stenosis. Two readers (S.S. and T.U.) independently reviewed the images. If the judgment was not concordant between them, a decision was made by a third reader (M.H.).

2.4. Statistical analysis

Statistical analysis was performed using JMP 9.0.3 (SAS Institute Inc., Cary, NC). Clinical characteristics were compared between patients with and without ICAD/ECAD using χ^2 tests and unpaired *t*-tests. The ORs for associated variables with ICAD and ECAD were determined using multivariable logistic regression analyses by the forced entry method adjusted for sex, age, established risk factors for atherosclerosis including hypertension, diabetes mellitus, dyslipidemia, and ever smoking [5,14,16–18], and variables with $p < 0.10$ on univariable analyses. A value of $p < 0.05$ was considered significant for all results.

3. Results

A total of 274 patients (154 men; aged 71 ± 13 years) were enrolled. Of these, 238 patients had sufficient-quality information regarding the intracranial arteries using MRA, CTA, or DSA, and 247 had sufficient-quality information regarding the extracranial arteries using CDS or DSA. The median time from admission to first intracranial vascular examination (MRA, CTA, or DSA) was 8 (interquartile range, 2–11) days. All CDS examinations were performed on admission.

Table 1
Patients' clinical characteristics.

	n = 274
Demographics	
Male sex (%)	154 (56)
Age, mean year ± SD	71 ± 13
BMI, kg/m^2 mean ± SD	22.3 ± 4.5
NIHSS score on admission, median (IQR)	13 (6–20)
mRS score at discharge, median (IQR)	4 (2–5)
Volume of ICH, median (IQR) mL	11.6 (4.6–28.8)
Location of ICH (%)	
Deep	192 (70)
Lobar	45 (16)
Brain stem	21 (8)
Cerebellum	13 (5)
Intraventricular	2 (1)
Multiple	1 (0.4)
ICAD (%)[a]	32/238 (13)
Internal carotid artery	2
Anterior cerebral artery	2
Middle cerebral artery	7
Vertebral artery or basilar artery	3
Posterior cerebral artery	7
Other lesion	2
Multiple lesions	9
ECAD (%)[b]	21/247 (9)
Internal carotid artery	13
Vertebral artery	4
Multiple lesions	4
Comorbidities and risk factors (%)	
Hypertension	244 (89)
Diabetes	36 (13)
Dyslipidemia	77 (28)
Coronary heart disease	17 (6)
Peripheral artery disease	6 (2)
Hemodialysis	11 (4)
Drinking habit	108 (39)
Ever smoking	142 (48)
Prior all strokes	71 (26)
Prior ischemic stroke	38 (14)
Prior medication (%)	
Antihypertensive drugs	125 (46)
Antidiabetic drugs	17 (6)
Statin	33 (12)
Laboratory data	
Leukocyte count, mean/mm^3 ± SD	8142 ± 3354
Monocyte count, mean/mm^3 ± SD	479 ± 196
hs-CRP, mean mg/dL ± SD	0.51 ± 1.31
Serum creatinine, mean mg/dL ± SD	1.08 ± 1.47
eGFR, mean mL/min/1.73 m^2 ± SD	71 ± 28
Fibrinogen, mean mg/dL ± SD	331 ± 85
Blood glucose, mean mg/dL ± SD	140 ± 42
HbA1c, mean % ± SD	5.8 ± 0.8
HDL cholesterol, mean mg/dL ± SD	58 ± 16
LDL cholesterol, mean mg/dL ± SD	114 ± 35
Total cholesterol, mean mg/dL ± SD	197 ± 41
Triglyceride, mean mg/dL ± SD	122 ± 89

BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; ICAD, intracranial arterial disease; ECAD, extracranial arterial disease; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] Data were analyzed for 238 patients whose intracranial magnetic resonance, CT, or digital subtraction angiography results were available.

[b] Data were analyzed for 247 patients whose duplex sonography or digital subtraction angiography results were available.