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Cholesterol crystal embolism-related cerebral infarction: Magnetic resonance imaging and clinical characteristics

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ABSTRACT

Background and aims: Cholesterol crystal embolism-related cerebral infarction (CCE-CI) is frequently misdiagnosed due to the lack of specific symptoms. To aid in differential diagnosis, this study comprehensively characterized the magnetic resonance imaging (MRI) and clinical manifestations of CCE-CI and compared these features to those of atherothrombotic cerebral infarction (ACI).
Methods: This single-center, retrospective, observational study was conducted at Kitasato University Hospital, Kanagawa, Japan. We identified 37 clinically or histopathologically confirmed CCE-CI cases and 110 ACI cases treated from January 2006 to May 2020. Groups were compared for mean age, sex ratio, clinical presentations, imaging manifestations, precipitating factors, comorbid conditions, medications, and smoking history.
Results: Of 37 eligible patients with CCE-CI, 10 (27.0%) received brain MRI, of which 8 (21.6%) exhibited high-intensity signals indicative of brain lesions on diffusion-weighted imaging (DWI). However, two patients with DWI lesions exhibited no detectable neurological abnormalities. Patients with CCE-CI frequently demonstrated bilateral DWI lesions involving the bilateral anterior and posterior circulation, a pattern absent in ACI (50% vs. 0%, $p < 0.001$). Compared to patients with ACI, CCE-CI patients also demonstrated significantly lower estimated glomerular filtration rate ($p < 0.001$) as well as more frequent eosinophilia ($p = 0.006$), atherosclerotic plaques ≥4-mm thick in the ascending aorta or proximal arch ($p = 0.001$), and aortic aneurysm ($p < 0.001$).
Conclusions: Patients with CCE-CI develop multiple DWI lesions across several vascular territories, even in the absence of neurological symptoms. Comorbid aortic aneurysm may increase CCE-CI risk. These findings could help in the differential diagnosis of CCE-CI.

1. Introduction

Cholesterol crystal embolism (CCE) is caused by the release of cholesterol crystals from ruptured atherosclerotic plaques in large proximal arteries, leading to arterial flow blockade and ischemia of downstream tissues [1,2]. These CCE events usually occur following intraarterial procedures or anticoagulant therapy, but may also occur spontaneously [3,4]. As atherosclerotic plaques are usually detected in the descending aorta, the kidneys and skin of the lower extremities are frequently affected by CCE [5]. Plaques derived from the ascending

Abbreviations: ACI, Atherothrombotic cerebral infarction; CAS, Carotid artery stenting; CCE, Cholesterol crystal embolism; CI, Confidence intervals; CRP, C-reactive protein; CTA, Computed tomography angiography; DWI, Diffusion-weighted imaging; IRB, Institutional review board; LDL, Low-density lipoprotein; MRA, Magnetic resonance angiography; MRI, Magnetic resonance imaging; OR, Odds ratios; PCI, Percutaneous coronary intervention; TIA, Transient ischemic attack.

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aorta and/or proximal arch can also cause CCE-related cerebral infarction (CCE-CI), leading to a variety of neurological symptoms and signs including mental confusion, focal neurological deficits, headache, and amaurosis fugax [6–8]. However, these symptoms and signs are nonspecific, complicating CCE-CI diagnosis and potentially exacerbating ischemic damage. Moreover, definitive diagnosis requires histopathological evidence of embolization to other organs such as kidney and skin [7].

Previous histopathological studies have revealed multiple, small ischemic lesions and border zone infarcts in patients with CCE-CI [9,10] that paralleled neuroradiological findings [10]. Nonetheless, acute cerebral infarction with multiple ischemic lesions also has many differential diagnoses. For instance, in patients with malignancy-related Trousseau syndrome, a cancer-related disorder characterized by hypercoagulation and vessel inflammation, brain diffusion-weighted imaging (DWI) revealed multiple lesions involving three different vascular territories of the bilateral anterior and posterior circulation (termed the "Three-Territory Sign") [11,12].

Here we describe the clinical, laboratory, and neuroimaging characteristics of patients with CCE-CI treated at a single institution to aid in early diagnosis and potentially prevent further atheroembolism and poor outcome. Further, signs and symptoms were compared to patients with atherothrombotic cerebral infarction (ACI) to identify those with potential value for differential diagnosis.

2. Material and methods

2.1. Study design and population

This is a single-center, retrospective, observational study. We collected the medical records of consecutive adult patients diagnosed with CCE by clinical or histological criteria [13] at Kitasato University Hospital, Sagamihara, Kanagawa, Japan, between January 2006 and May 2020. In most cases, systemic CCE was suspected based on clinical findings, including deteriorated renal function with or without simultaneous embolic symptoms in the lower abdomen and/or extremities, and the presence of known precipitating factors such as arterial angiography, vascular surgery, and anticoagulant treatment [13]. In some cases, diagnosis was confirmed by identifying typical histological features, such as cholesterol crystal clefts in the small arterial lumens and arterioles of affected organs or hyperplastic intimal tissue with giant cells surrounding spaces of the clefts [7,13].

Patients with CCE-CI were identified among the CCE group by review of clinical, laboratory, neuroradiological, and histopathologic data. Atherosclerotic risk factors, comorbid conditions, and precipitating factors were also evaluated.

Brain MRI scans were acquired at the time of neurological deficit presentation in cases of spontaneous CCE or during neurological evaluation following vascular procedures in cases of iatrogenic CCE. Clinicodemographic information, including age, sex, clinical presentation profile, precipitating factors, comorbid conditions (hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease, and malignancy), and concomitant medications (anticoagulants, antiplatelet drugs, and hydroxymethylglutaryl-CoA [HMG-CoA] reductase inhibitors), were obtained from medical records.

Precipitating procedures for CCE in this patient group were as follows: coronary angiography (CAG), carotid artery stenting (CAS), and percutaneous coronary intervention (PCI).

The control group consisted of 110 patients with ACI diagnosed using brain MRI at the same institution from the same patient registry. Patients with transient ischemic attack (TIA) or missing computed tomography angiography (CTA) data were excluded. The subtype of stroke was determined according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification criteria [14]. For each ACI patient, we extracted age, sex, and comorbid conditions (hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, and smoking history).

This study was approved by the institutional review board (IRB) of Kitasato University School of Medicine (the approval No. B20–205) and conducted according to the principles of the Declaration of Helsinki and later amendments. The IRB requirement for informed consent was waived due to the retrospective study design. Information from medical records was anonymized and deidentified before analysis.

2.2. Statistical analysis

Continuous variables are expressed as median (interquartile range [IQR]) unless otherwise indicated and categorical variables as counts and percentages. Continuous variables were compared between groups by Mann–Whitney *U* test, while bimodal or categorical variables were compared using Fisher's exact test. Odds ratios (ORs) were calculated together with 95% confidence intervals (CIs) for all univariate comparisons. Multivariate analysis was not performed due to an insufficient number of CCE patients developing CCE-CI.

Laboratory data including urinalysis, estimated glomerular filtration rate (eGFR), blood eosinophil count, low-density lipoprotein cholesterol (LDL), glycosylated hemoglobin A1c (HbA1c), and C-reactive protein (CRP) were obtained on the day of MRI scan or at least within 7 days before MRI scan. Smoking history was obtained from a standard questionnaire. Hypertension was defined as blood pressure $\geq$ 140/90 mmHg or by use of antihypertensive drugs, hyperlipidemia as LDL level $\geq$ 140 mg/dL or use of antihyperlipidemic agents, and diabetes mellitus as HbA1c) $\geq$6.5% or use of hypoglycemic agents. The eGFR (mL/min/1.73 m^2) was calculated using the formula validated for Japanese patients [15].

Comparison of the distribution of DWI lesions indicative of CI was performed according to the aforementioned "Three-Territory Sign" [11,12], as well abnormalities on fluid-attenuated inversion-recovery and T2*-weighted images. The hyperintense sign on DWI associated with acute ischemic stroke was classified according to the cerebral vascular territories affected as follows [11]: region 1 lesions unilateral lesions involving the anterior or the posterior circulation; region 2 lesions unilateral lesions involving the anterior and posterior circulation, or bilateral anterior circulation; region 3 lesions bilateral lesions involving the anterior and posterior circulation.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [16], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A $p < 0.05$ (two-tailed) was considered statistically significant for all tests.

2.3. Theory

The French Study of Aortic Plaques in Stroke Group reported that atherosclerotic lesions of the aortic arch >4 mm in thickness are associated with cerebral embolism of an unknown embolic source [17]; hence, atherosclerosis of the aorta was defined as an aortic wall thickness $\geq$ 4 mm.

3. Results

Six departments of Kitasato University Hospital, Neurology, Neurosurgery, Dermatology, Nephrology, Cardiology, and Cardiovascular Surgery, provide inpatient care for CCE patients. During the study period, 48 CCE patients were registered in the hospital medical record system, of which 27 cases were confirmed by histopathology (2 at autopsy, 22 from skin biopsy, and 3 from renal biopsy) and 10 by clinical criteria. The remaining 11 cases were excluded for not meeting histopathological or clinical diagnostic criteria. Of the 37 patients with confirmed CCE, 10 received brain MRI. Two of these patients (both with histological confirmation) had no high-signal lesions on DWI and two received no CTA evaluation. The remaining six patients showing high-signal lesions on DWI and receiving vasculature imaging (5 by CTA

Table 1
Clinical and laboratory features of CCE-related cerebral infarction.

Patient No.	1	2	3	4	5	6	7	8	9	10
Age, y	71	68	75	70	71	79	77	84	66	81
Sex	M	M	M	M	M	M	F	M	M	F
Clinical presentation										
Skin lesions										
Toe petechiae and ischemia	+	NA	+	+	+	+	+	+	+	+
Livedo reticularis on the lower legs and feet	+	NA	+	+	+	−	+	−	−	+
Extracutaneous findings										
Renal dysfunction	+	+	+	+	+	+	+	+	+	+
Retinal lesions	NA	−	−	−	+	NA	NA	NA	NA	NA
Conjunctival petechiae	NA	−	−	−	+	NA	NA	NA	NA	NA
Consciousness disturbance	−	+	−	−	−	−	+	−	−	−
Cognitive impairment	−	−	−	−	−	−	−	−	−	−
Hemiparesis	−	−	−	+	−	−	+	+	−	−
Hemodialysis	+	+	+	+	−	−	−	−	+	−
Laboratory findings										
Urinalysis	normal	protein 2+, RBC 4/HPF, WBC <5/HPF, waxy casts 1+	NA	NA	NA	protein 2+, RBC 2/HPF, WBC <5/HPF, hyaline casts 1+	protein -, RBC >100/HPF, WBC <5/HPF	NA	protein 2+, RBC 4/HPF, WBC >100/HPF	NA
eGFR, mL/min/1.73m^2	9.9	5.2	17.0	4.6	42.0	39.5	28.7	39.0	12.9	27.0
Blood eosinophil count, cells/μL	1800	1460	991	2151	482	441	25	35	110	638
CRP, mg/dL	0.31	10.95	2.36	0.47	0.24	0.17	1.90	0.87	1.47	0.49
Precipitating factors	vascular surgery	−	CAG	−	CAS	anti-coagulation	CAG	PCI	−	PCI
Days to MRI after precipitating factors	47	−	9	−	0	239	0	0	−	42
Diagnostic procedures	autopsy	autopsy	skin biopsy	skin biopsy	skin biopsy	clinical	clinical	clinical	skin biopsy	skin biopsy
Comorbid conditions										
Hypertension	+	+	+	+	+	+	+	+	+	+
Dyslipidemia	+	+	+	+	+	+	+	+	+	+
Diabetes mellitus	−	−	+	+	−	+	+	+	−	+
Coronary artery disease	−	−	+	−	+	−	+	+	−	+
Atrial fibrillation	−	−	−	−	−	−	−	−	−	+
Anticoagulant use	−	−	−	−	−	+	−	−	−	+
Antiplatelet drug use	−	+	+	−	+	−	+	+	−	−
Positive history of smoking	+	+	+	+	+	+	NA	NA	+	+
Malignancy	−	−	−	−	−	−	−	−	−	−
Neuroradiological findings										
High-signal lesions on DWI	+	+	+	+	+	+	+	+	−	−
Supratentorial lesion on MRI	+	+	+	+	+	+	+	+	−	−
Infratentorial lesion on MRI	+	+	+	+	−	+	+	+	−	−
CTA performed	+	+	(MRA)	−	+	+	+	−	−	+
Plaque of ascending aorta and/or proximal arch	+	+	+	NA	+	+	+	NA	NA	+
Aortic aneurysm (TAA, AAA)	+	+	+	NA	−	+	+	NA	NA	−
CCA, ICA stenosis, or vulnerable plaque	−	−	−	NA	+	−	−	NA	NA	+

Abbreviations: CCE, cholesterol crystal embolism; NA, not applicable; RBC, red blood cell; HPF, high-power field; WBC, white blood cell; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; CAG, coronary angiogram; CAS, carotid artery stenting; PCI, percutaneous coronary intervention; DWI, diffusion-weighted image; CTA, computed tomography; MRA, magnetic resonance angiography; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; CCA, common carotid artery; ICA, internal carotid artery.

Table 2
Comparison of CCE-related CI and ACI clinicodemographic features.

Variables	CCE-related CI (n = 6)	ACI (*n* = 110)	*p*-value
Age, y (IQR)	73 (71–76.5)	73 (68.25–79.0)	0.940
>75 y, n (%)	3 (50)	50 (45.5)	1.000
Male sex, n (%)	5 (83.3)	91 (82.7)	1.000
Comorbid conditions, n (%)			
Hypertension	6 (100)	94 (85.5)	0.594
Dyslipidemia	6 (100)	64 (58.2)	0.080
Diabetes mellitus	3 (50)	41 (37.3)	0.672
Coronary artery disease	3 (50)	21 (19.1)	0.102
Positive history of smoking	5/5 (100)	75/108 (69.4)	
Atrial fibrillation	0 (0)	6 (5.5)	1.000
Anticoagulant use	1 (16.7)	5 (4.5)	0.278
Antiplatelet drug use	4 (66.7)	37 (33.6)	0.183
Hemodialysis	3 (50)	0 (0)	<0.001***
Laboratory and clinical data			
eGFR, mL/min/1.73m^2	22.9 (11.7–36.8)	64.4 (51.8–76.9)	<0.001***
Blood eosinophil count, cells/μL	736.4 (451.0–1342.4)	121.6 (57.9–196.1)	0.006**
CRP > 1.0 mg/dL, n (%)	3 (50)	18 (16.4)	0.072
Consciousness disturbance	2 (33.3)	33 (30)	1.000
Hemiparesis	1 (16.7)	87 (79.1)	0.003**
Malignancy	0 (0)	16 (14.5)	0.594
Neuroradiological findings			
Plaque of ascending aorta and/or proximal arch	6 (100)	34 (30.9)	0.001**
Aortic aneurysm (TAA, AAA)	5 (83.3)	13 (11.8)	<0.001***
CCA, ICA stenosis, or vulnerable plaque	1 (16.7)	92 (83.6)	0.001**
Supratentorial lesion on MRI	6 (100)	98 (89.1)	1.000
Infratentorial lesion on MRI	5 (83.3)	13 (11.8)	<0.001***
1 vascular territory DWI lesions	0 (0)	101 (91.8)	<0.001***
2 vascular territories DWI lesions	3 (50)	9 (8.2)	0.014*
3 vascular territories DWI lesions	3 (50)	0 (0)	<0.001***

Abbreviations: CCE, cholesterol crystal embolism; CI, cerebral infarction; ACI, atherosclerotic cerebral infarction; IQR, interquartile range; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; CCA, common carotid artery; ICA, internal carotid artery; DWI, diffusion-weighted imaging.

and one by Magnetic resonance angiography (MRA)) were included in the comparative analysis with ACI.

Clinical and laboratory characteristics of the 10 patients who received brain MRI are summarized in Table 1, and those receiving CTA or MRA ($n = 6$) are compared to patients with ACI in Table 2. Among these 10 patients, 8 exhibited DWI lesions (5 with histologically confirmed CCE and 3 with clinically confirmed CCE). Nine patients who were evaluated by dermatologists had skin lesions including toe petechiae and livedo reticularis. Four of these 10 patients received fundoscopic examinations. Gastrointestinal findings were not available. Five of these 10 patients received dipstick and microscopic examinations of urine (Table 1). Mean eGFR (SD) was 22.6 (14.5) mL/min/1.73m^2 which was markedly below the normal range, while eosinophil count was significantly above normal and serum CRP level slightly above normal.

The precipitating procedure or treatment was determined in 7 of these 10 patients with CCE-CI (during or after CAG in 2 patients, during or after PCI in 2 patients, after abdominal aortic aneurysm resection and graft in 1, after CAS in 1 patient, and during anticoagulant treatment in 1), while the other 3 cases developed spontaneously.

Representative brain DWI scans from 8 patients with CCE-CI are shown in Fig. 1. Axial DWI revealed multiple high-intensity lesions involving the bilateral anterior and posterior circulation. Supratentorial infarcts were found predominantly in the cortical border zone and deep perforating regions, including basal ganglia and thalamus, while infratentorial lesions were found in the cerebellum and pons. Five patients (Nos. 2, 4, 6, 7, and 8 from Table 1) developed multiple infarcts across three vascular territories of the bilateral anterior and posterior circulation, while three others (Nos. 1, 3, and 5 from Table 1) exhibited DWI lesions across two territories. Fig. 2 summarizes the distribution of DWI lesions in each patient. The vertical axis shows the number of DWI lesions stratified by size. In 6 of these patients, T2* weighted images were also obtained, but no hemorrhagic lesions were found corresponding to infarcts on DWI. Atherosclerotic plaques more than 4 mm in thickness were found among all six patients receiving CTA or MRA evaluation.

The clinical and laboratory features of the aforementioned six patients with CCE-CI receiving brain MRI or CTA were then compared to those of patients with ACI (Table 2). These patients with CCE-CI demonstrated significantly lower eGFR ($p < 0.001$) and higher blood eosinophil count ($p = 0.006$). Patients with CCE-CI also showed markedly greater prevalence of aortic aneurysm (unadjusted OR = 35.2, 95% [CI] 3.6–1760.6), infratentorial lesions (unadjusted OR = 35.2, 95% [CI] 3.6–1760.6), and hemodialysis requirement, but lower prevalence of hemiparesis (unadjusted OR = 0.055, 95% CI, 0.001–0.521) and stenosis and/or vulnerable plaque of the common carotid artery or internal carotid artery (unadjusted OR = 0.041, 95%CI, 0.001–0.394).

Of the six patients with CCE-CI who underwent CTA or MRA, 50% ($n = 3$) showed multiple infarcts across three vascular territories of the bilateral anterior and posterior circulation, and the remaining 3 patients developed infarcts across two vascular territories. Among patients with ACI, there were no infarcts across three vascular territories and only 8.2% ($n = 9$) developed infarcts across two vascular territories, while the majority (91.8%, $n = 101$) exhibited lesions in only one vascular territory. Patients with CCE-CI demonstrated a significantly higher incidence of DWI lesions across two and three vascular territories of the bilateral anterior and posterior circulation compared to patients with ACI ($p = 0.014$ and $p < 0.001$, respectively).

4. Discussion

Patients with histologically or clinically confirmed CCE-CI developed multiple brain infarcts involving several vascular territories of the bilateral anterior and posterior circulation. In contrast, most patients with ACI demonstrated infarct in only a single vascular territory. Additionally, patients with CCE-CI demonstrated greater frequencies of dyslipidemia, aortic aneurysm, severe atherosclerosis in the ascending aorta, eosinophilia, poor renal function, and hemodialysis requirement than patients with ACI. Further, these neuroimaging manifestations of CCE-CI could be detected in patients with no detectable neurological symptoms, underscoring the importance of identifying such signs for early diagnosis. Collectively, these findings may facilitate the differential diagnosis of CCE-CI.

Comorbid conditions associated with CCE are well described, including aortic atherosclerosis [7,18]. Indeed, CCE and aortic atherosclerosis share a large number of common risk factors, including age over 60 years, male sex, diabetes mellitus, hypertension, and smoking history [7]. In addition to atherosclerosis, a large review of cases by Fine and colleagues found that 61% of CCE cases had comorbid hypertension, 44% ischemic heart disease, 34% renal failure, and 25% aortic aneurysm [18]. Severe atherosclerosis of the ascending aorta also has been reported as a risk factor for CCE during or following cardiac surgery [19]. In addition, approximately one-third of CCE patients have predisposing iatrogenic factors, including vascular procedures and anticoagulant therapy [18]. Scolari and colleagues reported that 78.7% of CCE patients developed acute or subacute renal impairment and one-third required hemodialysis [13]. Thus, the small patient cohort examined in this study appears typical in terms of risk factors and initiating events.

Eosinophilia is a common abnormal laboratory finding during the

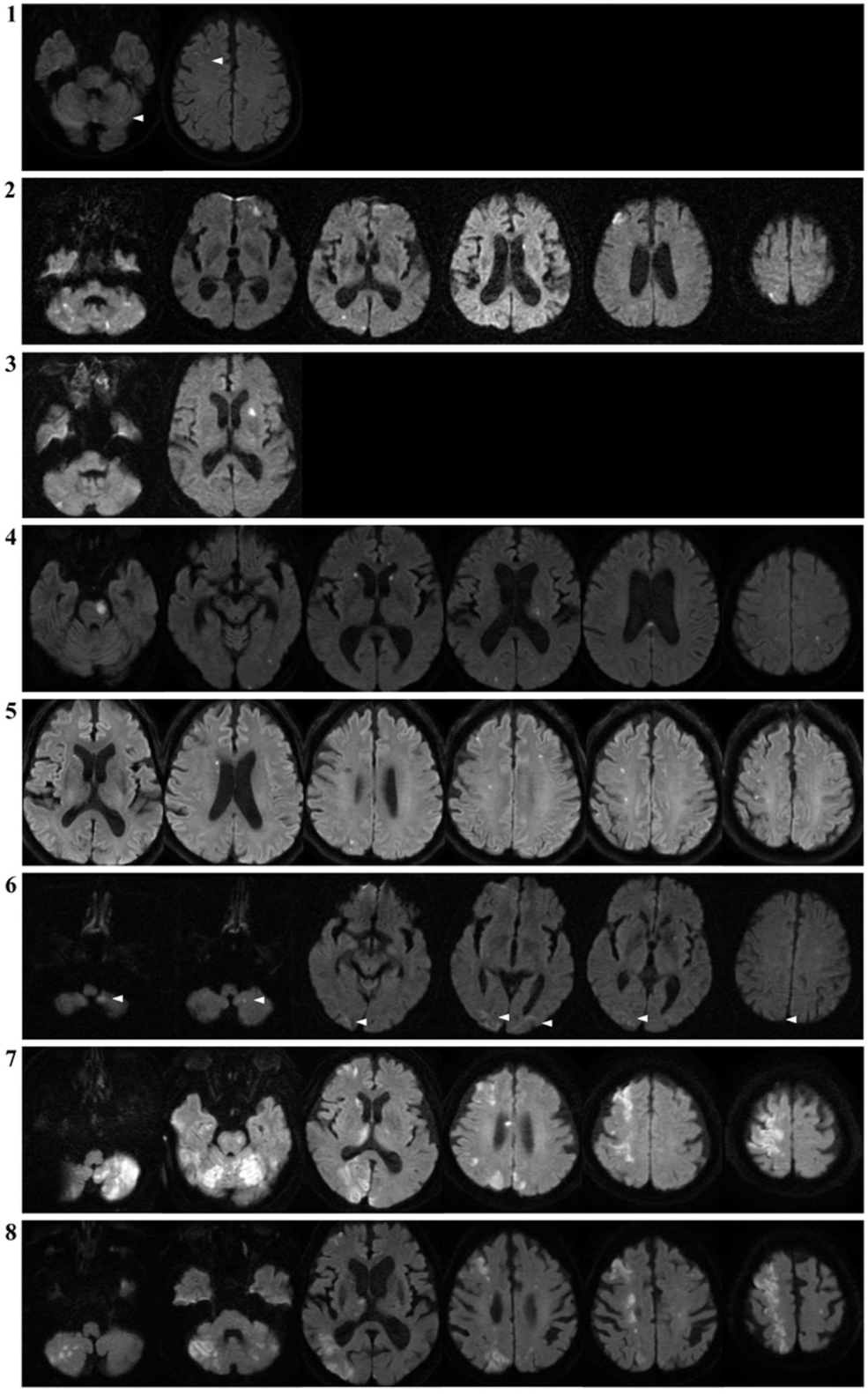

Fig. 1. Representative axial diffusion-weighted magnetic resonance images from patients with CCE-CI showing infarcts in multiple vascular territories: Five patients (Nos. 2, 4, 6, 7, and 8 from Table 1) developed multiple infarcts in three territories (arrowhead), while three others (Nos. 1, 3, and 5 from Table 1) developed infarcts in two territories.

acute phase of CCE, as is leukocytosis and increased levels of the inflammatory marker CRP [4,20]. While these findings can help establish CCE diagnosis among patients with precipitating factors and stroke symptoms, they are generally nonspecific [6]. Urinalysis findings in patients with CCE are also nonspecific, with low levels of proteinuria and no elevation in cell count, as is consistent with ischemic renal impairment [3,4,18].

Deteriorated renal function and the presence of precipitating factors,

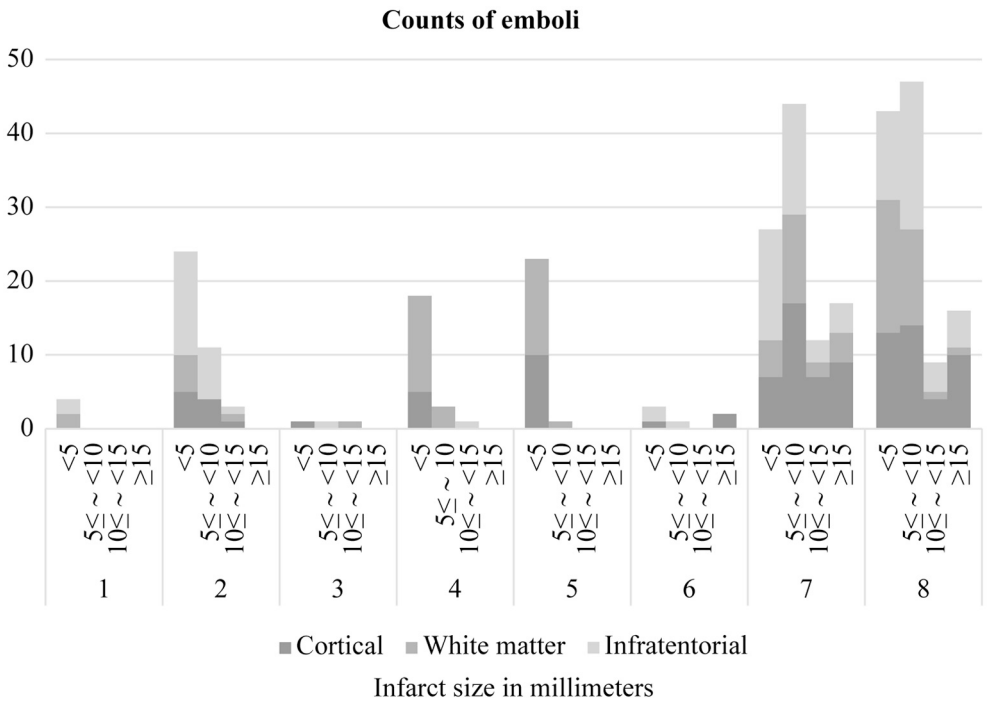

Fig. 2. Distribution of DWI lesions: The vertical axis indicates the number of DWI lesions stratified by size for each patient.

with or without systemic embolic symptoms, highly suggest CCE [13]. In spite of the high incidence of cutaneous ischemic lesions in patients with CCE-CI, in a range from 35% to 96% [4,18], the skin lesions are frequently overlooked during routine stroke care.

A fundoscopic examination should not be omitted, as retinal emboli of cholesterol crystals affect 10–25% of patients with systemic CCE [3,4,21]. Gastrointestinal symptoms are reported to affect 33% of patients with CCE [3] although it is not investigated in this study, and an accurate physical examination including the symptoms may lead to the diagnosis of CCE-CI.

A previous histological and neuroradiological study found that among 17 CCE patients receiving neuroradiological examination after neurologic symptom onset (4 by brain MRI and 13 brain by CT), 6 exhibited no acute brain lesions while 11 patients had multiple small infarcts or border zone infarcts [10]. The mean diameter of involved arteries was 107 μm (range, 25 to 500 μm), and multiple emboli were detected as bihemispheric and diffuse lesions [10]. According to Hiramoto and colleagues, the number of fragments released from arterial plaque and reaching the renal artery increases with decreasing particle size [22]. Hundreds of fragments in the 100–500 μm size range could occlude a substantial fraction of distal arteries, and greater than 10,000 fragments in the 20–40 μm size could markedly disrupt flow through small arteries [22]. Cholesterol crystal fragments released into the cerebral circulation may also breach the blood brain barrier and initiate a local inflammatory response, even in the absence of ischemia (and ensuing infarct development). It has been speculated local neuroinflammation from microemboli may lead to deterioration of memory and other higher-order cerebral functions [23].

Central nervous system manifestations of CCE can range from TIA and acute stroke to gradual deterioration of neurological function, resulting in mental confusion, focal neurological deficits, and amaurosis fugax among other symptoms [7]. However, the incidence of CCE-CI is still difficult to estimate accurately as a definite diagnosis requires histopathological evidence of embolization to other organs. Previous large studies have reported prevalence rates of 9.8% (35/354) [13] and 15.4% (4/26) [6], in the range of that found here (21.6%, 8/37), again suggesting that this sample is representative despite its small size.

Cholesterol embolism has poor prognosis because it is associated with advanced atherosclerosis, a major risk factor for fatal cerebrovascular events including stroke [18,24]. Although there have been no large-scale studies on specialized treatments for CCE-CI, smaller-scale investigations have documented the efficacy of corticosteroids [25,26] and low-density lipoprotein (LDL) apheresis [27]. Since the treatment of CCE differs greatly from other types of stroke, including ACI, early diagnosis is crucial.

This study has several limitations. First, this was a small-scale study from a single-center, although multiple findings were roughly consistent with previous original investigations and reviews, including overall CCE-CI incidence among CCE patients and the prevalence rates of several previously documented risk factors. Second, we did not compare findings among stroke types, such as cardiogenic embolism and malignancy-related cerebral infarction, or assess the influences of all possible confounders and factors previously implicated in CCE-CI. Finally, the indications for neuroradiological examination were not standardized because some cases were neurologically asymptomatic or nonspecific, and thus selection bias was not eliminated.

5. Conclusions

Nonetheless, this is the first comprehensive description of clinical, pathological, laboratory, and neuroimaging abnormalities in CCE-CI. These findings, particularly the comorbidity profile and lesion distribution, may help distinguish CCE-CI from other forms of stroke, thereby facilitating timely treatment and improving clinical outcome.

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Credit author statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content. Furthermore, each author certifies that this material or similar material has not been and will not

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