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Original Article

Clinical Characteristics of Contrast Leakage and Contrast-Induced Encephalopathy Following Endovascular Treatment for Unruptured Intracranial Aneurysm

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Objective: Contrast-induced encephalopathy (CIE) is a rare but severe complication that can occur following intravascular treatment of intracranial vascular disease. Although CIE is considered a transient neurological disorder, its natural history, pathophysiology, and risk factors are poorly understood. Contrast leakage (CL) is a more frequently observed adverse event than CIE and can lead to CIE. This retrospective study aimed to elucidate the clinical characteristics of CL and CIE and identify the risk factors for each.

Methods: We retrospectively reviewed the medical records of 61 patients with unruptured intracranial aneurysms who were treated at our institution between January 2019 and May 2023. Risk factors for CIE and CL were identified by Fisher's exact test for univariate analysis of categorical variables and by unpaired *t*-test for continuous variables. One-way analysis of variance (ANOVA) was conducted, followed by the Tukey-Kramer test for multiple comparisons.

Results: Of the 61 patients, 22 (36%) had CL and 4 (6%) had CIE. Among the clinical characteristics analyzed, older age ($p = 0.031$), larger aneurysm ($p = 0.003$), lower serum creatinine ($p = 0.026$), and use of a distal access catheter ($p = 0.030$) were significant risk factors for CL. CIE occurred only in CL-positive patients ($p = 0.014$). Of the 4 patients with CIE, neurological symptoms improved within 3 days in 3 patients, and neurological deficit persisted in 1 patient.

Conclusion: Older age, larger aneurysm, lower serum creatinine, and use of a distal access catheter are risk factors for developing CL, and female sex and greater volume of contrast medium are potential risk factors. No risk factors for developing CIE from CL were identified.

Keywords endovascular treatment, intracranial aneurysms, contrast-induced encephalopathy

Introduction

Contrast-induced encephalopathy (CIE) is a rare but severe complication that can occur after intravascular treatment of intracranial vascular disease. Neurological deficits due to CIE include headache, hemiparesis, blindness, language disorders, seizures, and mental deterioration.[1–3] CIE can also cause prolonged severe neurological deficits requiring intensive care. Although CIE is reported to be a transient neurological disorder, its natural history, pathophysiology, and risk factors are poorly understood, which has made it challenging to establish a unified treatment protocol.[4,5] In fact, there is little evidence linking the development of CIE with temporary disruption of the blood–brain barrier caused by the toxicity of the contrast medium.[6]

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Furthermore, whether there is an increased risk of developing CIE due to the use of hyperosmotic contrast requires validation.[7] The adverse event of contrast leakage (CL) is observed more frequently than CIE following neuroendovascular therapy, and more frequent occurrences have been reported in the elderly population.[8] CL is considered a precondition that can lead to CIE, and although a small proportion of patients with CL have appeared to develop CIE,[9] the correlation is unknown.

This retrospective study aimed to elucidate the clinical characteristics of CL and CIE associated with endovascular treatment of intracranial unruptured aneurysms and identify the risk factors contributing to developing CL and CIE.

Materials and Methods

Subjects and materials

Asahikawa Medical University review board approved the study protocol (approval No. 23045), complying with the Declaration of Helsinki. The requirement for written informed consent was waived due to the study's retrospective nature. The clinical and radiological data of patients who underwent endovascular treatment for unruptured cerebral aneurysm at Asahikawa Medical University between January 2019 and May 2023 were collected. Patients with insufficient data, who received iso-osmolar contrast medium for endovascular treatment, and who had severe treatment-related permanent complications were excluded from the analysis.

Endovascular treatment and identification and quantification of CL

All procedures were performed under general anesthesia. A nonionic contrast medium (Iopamidol; Fuji Pharma, Tokyo, Japan) was administered intraarterially in all patients during endovascular treatment. An amount of 4 ml of contrast medium was diluted with 4 ml of saline, 4 ml of which was manually injected when needed during the procedure. The contrast medium was occasionally injected from the distal access catheter (DAC) when available. Computed tomography (CT) of the head was performed immediately after endovascular treatment. Three neurosurgeons reviewed the CT images and classified them as positive or negative according to the presence or absence of CL. CL was considered positive if any of the 3 reviewers labeled the case positive. CL was defined as a persistent edematous change in the brain that extended beyond the infarct core, accompanied by contrast staining apparent as a hyperdense lesion in the brain parenchyma or subarachnoid space on post-treatment CT.[9] In quantitative analysis of the images, the ratio of the CT value of each cortical hyperdense lesion to that in the contralateral location was calculated. In patients whose images showed no cortical hyperdense lesions, the ratio of CT values of the centrum semiovale on the approach and non-approach sides was calculated.

Definition of CIE

The diagnostic criteria for CIE were any of the following, occurring within 24 hours after endovascular treatment: (1) unequivocal clinical deterioration in Glasgow Coma Scale (>2 points) or muscle strength and (2) onset of new neurological symptoms such as disorientation or cortical blindness that could not be explained as ischemic or hemorrhagic complications or metabolic abnormalities.[10,11]

Clinical data collection and statistical analysis

Clinical data were collected regarding age, sex, previous history of any neurological disorder, approach side, renal function, presence of hypertension, diabetes mellitus, dyslipidemia, location and size of the aneurysm, dose of contrast medium, the use of a DAC with its delivered location, and types of devices used in the treatment procedure. Fisher's exact test was used for univariate analysis of categorical variables, and an unpaired *t*-test was used for continuous variables. A multi-logistic regression analysis was performed for multivariate analysis. One-way analysis of variance (ANOVA) was conducted, followed by the Tukey-Kramer test for multiple comparisons. All statistical analyses were performed using GraphPad Prism 10 (GraphPad Software, Boston, MA, USA), and a p value of less than 0.05 was considered statistically significant.

Results

Clinical characteristics associated with the development of CL

Of 72 patients with unruptured intracranial aneurysms treated at our institution between January 2019 and May 2023, 10 were excluded from analysis due to insufficient data or the use of an iso-osmolar contrast medium. Another patient was excluded due to severe treatment-related ischemic complications. Thus, a final total of 61 patients were analyzed. CL was identified in 22 (36%) patients. **Table 1** summarizes the clinical characteristics according to the presence or absence of CL. Older age ($p = 0.031$), larger

Table 1 Patient characteristics and comparison between those with CL and without CL

	Total (n = 61)	No CL (n = 39)	CL (n = 22)	Univariate analysis *p* Value	Multivariate analysis *p* Value
Age (years)	66 (36–86)	64 (39–86)	70.5 (36–83)	0.031	0.234
Sex (female)	39 (63.9)	21 (53.8)	18 (81.8)	0.051	
Previous stroke	13 (21.3)	7 (17.9)	6 (27.3)	0.517	
Treatment side (left)	32 (52.5)	21 (53.8)	11 (50)	0.796	
Renal functions					
BUN (mg/dL)	13.8 (5.9–23.4)	14.8 (5.9–23.4)	12.4 (8.2–20.5)	0.115	
Cr (mg/dL)	0.7 (0.4–1.4)	0.71 (0.4–1.4)	0.62 (0.5–0.9)	0.026	0.023
eGFR (mL/min/1.73 m^2)	70.0 (35.8–234.4)	69.2 (35.8–234.4)	74.85 (54.70–132.6)	0.884	
Chronic kidney disease	5 (8.2)	5 (8.2)	0 (0)	0.149	
Hypertension	41 (67.2)	27 (69.2)	14 (63.6)	0.778	
Diabetes mellitus	10 (16.4)	7 (17.9)	3 (13.6)	0.735	
Dyslipidemia	31 (50.8)	20 (51.3)	11 (50)	1.000	
Aneurysm location				0.769	
Internal carotid artery	43 (70.5)	26 (66.7)	17 (77.3)		
Anterior cerebral artery	10 (16.4)	7 (17.9)	3 (13.6)		
Posterior circulation	8 (13.1)	6 (15.4)	2 (9.1)		
Size (mm)	6.4 (3–26)	6.1 (3–22)	10.2 (4–26)	0.003	0.043
Contrast dose (mL)	121 (40–180)	120 (40–180)	140.5 (54–180)	0.055	
Use of distal access catheter	35 (57.4)	18 (46.2)	17 (77.3)	0.030	0.588
Small-diameter DAC	12 (19.7)	8 (20.5)	4 (18.2)		
Large-diameter DAC	23 (37.7)	10 (25.6)	13 (59.1)		
Location of DAC (Fisher classification)				0.568	
Below C4	2 (5.7)	1 (5.6)	1 (5.9)		
C3-4	19 (54.3)	8 (44.4)	11 (64.7)		
Above C3	14 (40)	9 (50)	5 (29.4)		
Type of procedure				0.087	
No adjunct technique	19 (31.1)	15 (38.5)	4 (18.2)		
Balloon assisted	13 (21.3)	10 (25.6)	3 (13.6)		
Conventional stent	10 (16.4)	6 (15.4)	4 (18.2)		
Flow diverter stent	19 (31.1)	8 (20.5)	11 (50)		
CIE	4 (6.6)	0 (0)	4 (18.2)	0.014	

Continuous variables are presented as the median (range), and categorical variables are presented as number (%).
BUN, blood urea nitrogen; CIE, Contrast-induced encephalopathy; CL, contrast leakage; DAC, distal access catheter; eGFR, estimated glomerular filtration rate

aneurysm ($p = 0.003$), lower serum creatinine ($p = 0.026$), and use of DAC ($p = 0.030$) were significant risk factors for CL. DAC was positioned at the intracranial internal carotid artery in nearly all cases (33 out of 35). The locations of DAC were not significant risk factors for CL ($p = 0.568$). In addition, the female sex ($p = 0.051$) and a larger dose of contrast medium ($p = 0.055$) were marginally significant risk factors for CL. CIE was identified in 4 patients (6%), all of whom had CL ($p = 0.014$).

Clinical characteristics in patients with CL according to the presence or absence of CIE

Table 2 lists the clinical characteristics of patients with CL according to the presence or absence of CIE. Four clinical characteristics that are statistically significant for presenting CL were selected for this analysis. There was no significant difference in clinical characteristics between the 2 CIE groups. Quantitative analysis of CT values showed a similar trend (**Fig. 1**). The ratio of CT values was significantly higher in patients with CIE or CL compared to those with no adverse event ($p = 0.0003$ and <0.0001, respectively). Among patients with CL, there was no significant difference in the ratio of CT values in terms of the presence or absence of CIE ($p = 0.359$). **Table 3** summarizes the characteristics and clinical course in patients who developed CIE. Of these 4 patients, neurological symptoms due to CIE improved within 3 days in 3 patients, and 1 patient had a persistent neurological deficit. Detailed radiological findings of the fourth case in **Table 3** are provided in **Fig. 2**.

Table 2 Patient characteristics and comparison between those with CIE and without CIE among the CL present patients

	Total (n = 22)	No CIE (n = 18)	CIE (n = 4)	*p* value
Age (years)	70.5 (36–83)	70.5 (53–83)	70.5 (36–81)	0.363
Size (mm)	10.2 (4–26)	9.5 (4–26)	15 (4.6–22)	0.354
Cr (mg/dL)	0.6 (0.5–0.9)	0.6 (0.5–0.9)	0.6 (0.5–0.8)	0.784
Use of distal access catheter	17 (77.3)	14 (77.8)	3 (75)	1.000

Continuous variables are presented as the median (range), and categorical variables are presented as number (%).
CIE, contrast-induced encephalopathy; CL, contrast leakage

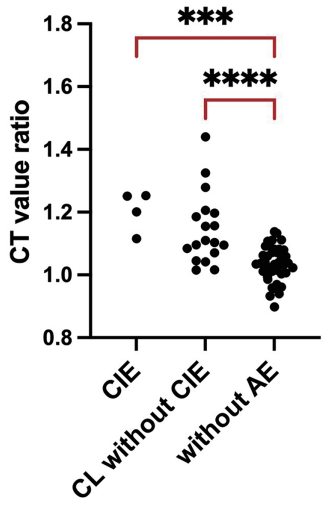

Fig. 1 Plot of ratio of CT values according to the presence of CIE, presence of CL without CIE, and without any AEs. ***p = 0.0003, ****p< 0.0001. The presence of CL was considered an AE for this analysis. AE, adverse event; CIE, contrast-induced encephalopathy; CL, contrast leakage

Discussion

The present retrospective study evaluated the clinical characteristics of CL and CIE associated with endovascular treatment of intracranial unruptured aneurysms and assessed the risk factors that contributed to these events. CL was observed in 36% of patients, which is higher than in a previous report.[9] The inflated rate of CL observation could be due to overestimation of diagnosing CL, such as labeling it as CL positive if any of the 3 observers considered the case CL positive. On the other hand, CIE was observed in 6% of the cases, which is comparable to previous reports.[9,12]

The present study identified older age (p = 0.031), larger aneurysm (p = 0.003), lower serum creatinine (p = 0.026), and use of DAC (p = 0.030) as risk factors, and female sex (p = 0.051) and larger contrast medium doses (p = 0.055) as potential risk factors for developing CL. Except for sex and lower serum creatinine, these findings align with those reported previously as possible risk factors.[9,13–15] However, no additional factors were identified regarding further development into CIE from CL. While the authors could not explain the rationale for lower serum creatinine being a risk factor for CL, renal function evaluated by estimated glomerular filtration rate (eGFR) did not differ between the patients developing or not developing CL (**Table 1**). As the renal functions were, in general, within the normal range for this particular cohort, it is possible that smaller body size could have some influence on CL development.

Furthermore, it is noteworthy that there was no difference in the ratio of CT values in terms of the presence or absence of CIE in patients who had CL (**Fig. 1**). A previous study has suggested that contrast injection from an intradurally placed intermediate catheter is a risk factor for CIE development.[12] Large-bore, flexible DACs are increasingly used in endovascular treatment due to the high maneuverability of the microcatheter and are routinely used at our institution for flow diverter aneurysm treatment. The multiple angiograms obtained with an intradurally placed DAC during flow diverter treatment have been suggested as a potential risk factor for CIE,[3] and the present study could not confirm this finding. The findings from the current research indicate that caution should be taken when using DAC if multiple risk factors, such as older age and larger aneurysm, coexist within the patient.

Little is known concerning the pathophysiology of CL and CIE. Subarachnoid hemorrhage or cerebral infarction might disrupt the blood–brain barrier, thus allowing contrast medium to exhibit neurotoxicity and cause CIE.[12] This model is supported by the elevated concentrations of iodine in CSF observed in patients who developed CIE.[16] Renal dysfunction is another proposed mechanism,[9,10] as it impairs the clearance of the contrast medium, exacerbating the accumulated osmolality and neurotoxicity.[17] However, it should be noted that CIE can occur in patients with normal renal function.[2] Despite the possibility that the incidence of CIE could be affected by the type of contrast medium, little is known due to its low incident rate and increased use of nonionic and low-osmolar contrast medium.[13]

Table 3 Patient characteristics and the clinical course of patients developing CIE

Age	Sex	History of stroke	Aneurysm location	Size (mm)	Contrast dose (ml)	Use of DAC	Type of procedure	Clinical course
36	F	SAH (1 month prior)	Basilar tip	4.6	150	None	Simple technique	Cortical blindness recovered in 3 days. Treated with glycerin, edaravone, antiepileptic drug and steroid.
67	F	SAH (3 months prior)	Left internal carotid	22	180	Yes	Flow diverter	Consciousness disorder recovered in 2 days. Treated with edaravone.
81	F	None	Right internal carotid	20	150	Yes	Flow diverter	Consciousness disorder and hemiparesis recovered in 3 days. Treated with edaravone, steroid and deep sedation.
74	F	None	Left internal carotid	10	150	Yes	Flow diverter	Consciousness disorder, hemiparesis, aphasia, higher brain dysfunction. Treated with glycerin, edaravone, antiepileptic drug, steroid and deep sedation. Mild hemiparalysis remainded as a permanent deficit.

CIE, contrast-induced encephalopathy; DAC, distal access catheter; SAH, subarachnoid hemorrhages

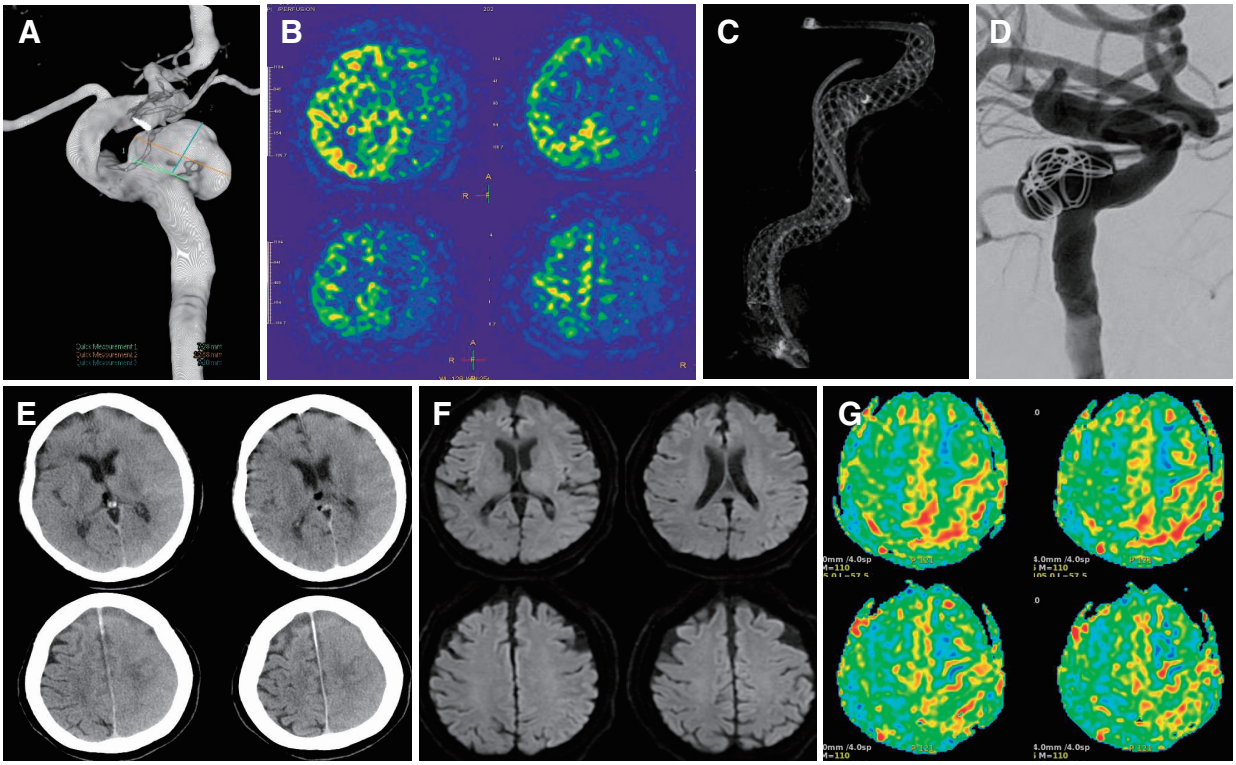

Fig. 2 Representative case of a 74-year-old female who underwent a flow diverter stent with coil embolization treatment for a left internal carotid artery aneurysm. The 3D cerebral angiography shows maximum aneurysm diameter of 10 mm (**A**). Pretreatment ASL MR perfusion study shows either reduced CBF or underestimated CBF due to delayed blood arrival in the left hemisphere (**B**). The aneurysm was treated with a flow diverter stent (Pipeline Shield 5 ×30; Medtronic, Minneapolis, MN, USA) with rough packing via coil embolization (**C, D**). A distal access catheter (6Fr Navien; Medtronic) was used during treatment. The procedure time was 195 min, and a total volume of 150 mL of contrast medium was used. Postoperatively, the patient had delayed awakening from anesthesia, consciousness disturbance, severe right hemiplegia, and total aphasia without epilepsy. Uncontrasted CT shows CL in the left cerebral hemisphere (**E**). Although there is no apparent ischemic complication on diffusion-weighted imaging (**F**), ASL reveals hyper-perfusion of the affected hemisphere (**G**). ASL, arterial spin labeling; CBF, cerebral perfusion; CT, computed tomography; CL, contrast leakage

The authors additionally propose decreased cerebral perfusion as a potential risk factor for CIE development, as illustrated in our representative case (**Fig. 2**). Although there are several interpretations for the decreased cerebral blood flow shown on pretreatment arterial spin labeling MR perfusion for this case, it is reasonable to assume that rapid recovery of cerebral perfusion after endovascular treatment might overload the blood–brain barrier, causing leakage of contrast medium into the brain parenchyma that subsequently develops into CIE. Due to a lack of knowledge of its pathophysiology, there is no unified treatment protocol for CIE. However, as it is evident that CIE occurs only when CL is present, patients with risk factors for developing CL should be treated with caution, such as intensive CT follow-up and careful neurological examinations.

Conclusion

The present findings suggest that older age, larger aneurysm, and use of DAC are risk factors for developing CL and that female sex and larger contrast medium doses are potential risk factors for CL. No risk factors were identified for developing CIE from CL.

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Disclosure Statement

All authors declare that they have no conflicts of interest.

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