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ABSTRACT

BACKGROUND AND PURPOSE: Swelling of the salivary glands, known as contrast-induced sialadenitis (CIS), is an adverse reaction to iodide contrast agents. However, the incidence and risk factors of CIS after therapeutic neuroendovascular procedures have not yet been established.

MATERIALS AND METHODS: Demographic and procedural factors that may influence the development of CIS were retrospectively analyzed to identify the incidence and risk factors of this condition. A total of 780 patients who underwent therapeutic neuroendovascular procedures between January 1, 2022 and December 31, 2022 were investigated. The risk factors affecting CIS were analyzed by using multivariate logistic regression, and the quantitative degree of association between the volume of contrast administered and occurrence of CIS was determined by using the receiver operating characteristic (ROC) curve.

RESULTS: The incidence of CIS after therapeutic neuroendovascular procedures was 4.2%. Multivariate logistic regression analysis showed that female sex (OR = 4.420, 95% CI: 1.377–14.190, $P = .013$), volume of contrast administered (OR = 1.007, 95% CI: 1.003–1.101, $P < .001$), and guiding catheter tip located within the external carotid artery (ECA) (OR = 8.701, 95% CI: 3.459–21.885, $P < .001$) were independently associated with CIS occurrence after therapeutic neuroendovascular procedures. The volume of contrast administered had an area under the ROC curve of 0.723 (95% CI: 0.635–0.810; $P < .001$), and the optimal cutoff value of the volume of contrast administered was 205 mL (sensitivity: 0.49, specificity: 0.87).

CONCLUSIONS: We observed CIS in 4.2% of our patients undergoing therapeutic neuroendovascular procedures. This represents a higher incidence than previously reported. Female sex, volume of contrast administered, and guiding catheter tip located within the ECA are associated with CIS incidence.

ABBREVIATIONS: AUROC = area under the receiver operating characteristic curve; BMI = body mass index; CIS = contrast-induced sialadenitis; ECA = external carotid artery; GFR = glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs; ROC = receiver operating characteristic; US = ultrasound

The swelling of the salivary gland after the administration of iodide contrast, known as contrast-induced sialadenitis (CIS) or iodide mumps, is a rare complication, and its pathophysiology remains unknown.[1,2] The first case of CIS after intravenous administration of iodide contrast was reported by Sussman and Miller in 1956.[3] Since then, many case reports about CIS, parotitis, or iodide mumps after CT or other angiographic examinations using contrast agents have been published.[4-13] Imaging modalities and treatments by using contrast agents are being used more frequently. Therefore, attention should be paid to the incidence of CIS, which was once considered as a rare complication. Although the incidence of CIS is not well known, a previous study that assessed reactions to iodide contrast agents found that the incidence of CIS was approximately 1%–2%.[2] To the best of our knowledge, no study has analyzed the incidence and risk factors of CIS after therapeutic neuroendovascular procedures.

Therefore, the present study aimed to identify the actual incidence and risk factors of CIS after therapeutic neuroendovascular procedures.

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SUMMARY

PREVIOUS LITERATURE: Swelling of the salivary glands, known as CIS, is rare complication. In most reported cases of CIS, the condition occurred after intravenous procedures, likely due to the indirect effect of contrast agents on the salivary glands after systematic distribution. Recently, therapeutic neuroendovascular procedures using contrast agents are more frequent. However, the incidence and risk factors of CIS after therapeutic neuroendovascular procedures have not yet been established.

KEY FINDINGS: The incidence of CIS after therapeutic neuroendovascular procedures (4.2%) was relatively higher than that of the previously reported cases.

KNOWLEDGE ADVANCEMENT: Female sex, volume of contrast administered, and guiding catheter tip located within the external carotid artery are the risk factors of CIS occurrence. Thus, the incidence of CIS should be considered in patients with these factors.

MATERIALS AND METHODS

Study Population

This study was approved by the institutional review board of our institution, and written informed consent was waived because of the low risk to patients. The electronic medical records of all consecutive patients who underwent neuroendovascular procedures between January 1, 2022 and December 31, 2022 at a large tertiary center were reviewed. The Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline was followed (Online Supplemental Data). A total of 833 patients underwent therapeutic neuroendovascular procedures under general anesthesia. Six patients who underwent simple transfemoral cerebral angiography due to procedural failure or identification of an infundibulum were excluded. Additionally, 47 patients were excluded because the volume of contrast agents administered was not accurately measured due to minor procedural treatments. As a result, 780 participants were ultimately included in the study.

Data Collection

Demographics and baseline clinical information, including age, sex, body mass index (BMI), glomerular filtration rate (GFR), volume of contrast administered, types of contrast agents, location of guiding catheter tip, laterality, time-to-onset of symptoms, time-to-resolution of symptoms, affected salivary glands, and treatment methods for sialadenitis, were retrospectively extracted from the medical records.

CIS was defined as warm and erythematous swelling of the salivary glands accompanied by tenderness and local pain occurring within minutes to days after the administration of contrast agents. Patients were excluded if they complained only of local pain without swelling of the salivary gland. The volume of contrast administered during therapeutic neuroendovascular procedures was calculated by subtracting the initial contrast volume from the residual contrast volume at the end of the procedures.

The location of the guiding catheter tip was divided into 2 subgroups on the basis of the location of the guiding catheter tip: external carotid artery (ECA) group (ECA or common carotid artery) and non-ECA group (internal carotid artery, vertebral artery, and internal jugular vein). The affected salivary glands were categorized into 3 groups on the basis of the location of swelling: parotid, submandibular, and combined (Fig 1). Ipsilateral side was defined as when sialadenitis occurred at the same side where the guiding catheter was located. With regard to renal function, the GFR was used. Three types of contrast agents were used, including 2 nonionic monomers (iohexol; 300 mg iodine/mL [Omnipaque; GE Healthcare] and iobitridol; 300 mg iodine/mL [Xenetix; Guerbet]) and 1 nonionic dimer (iodixanol; 320 mg iodine/mL [Visipaque; GE Healthcare]).

FIG 1. Three types of sialadenitis: (*A*) parotid, (*B*) submandibular, and (*C*) combined.

Table 1: Demographic and clinical characteristics of patients

Variables	All Patients (n = 780)	Non-CIS Group (n = 747)	CIS Group (n = 33)	P Value
Age, year (mean ± SD)	57.38 ± 11.94	57.48 ± 0.44	57.38 ± 0.43	.248
Female sex, *n* (%)	568 (72.8)	539 (72.7)	29 (85.3)	.047
BMI index (kg/m^2)	24.33 ± 3.49	24.33 ± 0.13	24.26 ± 0.53	.912
GFR (mL/min/1.73 m^2) (mean ± SD)	95.22 ± 27.45	95.40 ± 1.02	91.29 ± 3.23	.400
Diagnosis, *n* (%)				<.001
Aneurysm	730 (93.6)	709 (94.9)	21 (63.6)	
AVF or AVM (including dural lesion)	39 (5.0)	27 (3.6)	12 (36.4)	
Ischemia	8 (1.0)	8 (1.1)	0 (0.0)	
Others	3 (0.4)	3 (0.4)	0 (0.0)	
Volume of contrast administered (mL) (mean ± SD)	154.87 ± 65.98	152.19 ± 2.30	215.45 ± 17.50	<.001
Contrast type, *n* (%)				.119
Nonionic monomer	763 (97.8)	732 (98.0)	31 (93.9)	
Iobitridol	540 (69.2)	514 (68.8)	26 (78.8)	
Iohexol	223 (28.6)	218 (29.2)	5 (15.1)	
Nonionic dimer (iodixanol)	17 (2.2)	15 (2.0)	2 (6.1)	
Guiding catheter placement				.350
Unilateral placement	751 (96.3)	720 (96.4)	31 (93.9)	
Bilateral placement	29 (3.7)	27 (3.6)	2 (6.1)	
Guiding catheter tip location, *n* (%)				<.001
ECA group	37 (4.7)	27 (3.6)	10 (30.3)	
ECA	25 (3.2)	18 (2.4)	7 (21.2)	
CCA	12 (1.5)	9 (1.2)	3 (9.1)	
Non-ECA group	743 (95.3)	720 (96.4)	23 (69.7)	

Note:—CCA indicates common carotid artery; SD, standard deviation.

All procedures were performed under general anesthesia, and the contrast agents were used without dilution.

Statistical Analysis

The baseline characteristics between the CIS and non-CIS groups were compared. Categoric variables were presented as numbers and percentages and compared by using the $\chi 2$ test or Fisher exact test. Meanwhile, continuous variables were presented as the mean ± standard deviation and compared by using the independent *t* test and Mann-Whitney *U* test. Univariate and multivariate logistic regression analyses were used to assess the risk factors of CIS. Multivariate logistic regressions were performed by using the independent variables selected from all factors with a value of $P < .1$ in univariate analyses. The results were presented as OR with a 95% CI. The receiver operating characteristic (ROC) curve method was used to evaluate the volume of contrast administered for predicting CIS. The area under the receiver operating characteristic curve (AUROC) was obtained to determine the quantitative degree of the association. The optimal cutoff value was derived by using the Youden index. All statistical analyses were performed by using SPSS 27.0 software (IBM). Two-tailed *P* values less than .05 were considered statistically significant.

RESULTS

Study Participants and Characteristics

The baseline characteristics of all 780 patients are summarized in Table 1. The mean age of patients was 57.38 ± 11.94 years, and 568 (72.8%) patients were women. Coil embolization of intracranial aneurysms was the most common therapeutic neuroendovascular procedure (730, 93.6%), followed by arteriovenous fistula or arteriovenous malformation, including dural lesions (39, 5.0%), ischemia (8, 1.0%), and others (3, 0.4%). Iobitridol (540, 69.2%) was the most commonly used contrast agent during the procedures, followed by iohexol (223, 28.6%) and iodixanol (17, 2.2%). Based on the diagnostic criteria, 33 patients were diagnosed with CIS. All of these patients spontaneously complained of pain in the salivary gland area within minutes to days after therapeutic neuroendovascular procedures. The crude incidence rate of CIS after therapeutic neuroendovascular procedures was 4.2%. Compared with the non-CIS group, the CIS group had a significant difference in female sex ($P = .047$), diagnosis ($P < .001$), volume of contrast administered ($P < .001$), and guiding catheter tip location ($P < .001$). Age, BMI, GFR, contrast type, and guiding catheter placement did not differ significantly between the 2 groups ($P > .05$).

Among 33 patients with CIS, 23 cases (69.7%) occurred on the same side where the guiding catheter tip was located, 3 cases (9.1%) occurred on the opposite side, and 7 cases (21.2%) occurred bilaterally. The parotid gland was the most predominantly involved salivary gland (27, 81.8%), followed by the submandibular gland (3, 9.1%) and combined form (3, 9.1%). The mean time-to-onset of symptoms was 9.89 ± 7.81 hours (range, 1–26 hours), whereas the mean time-to-resolution of symptoms was 4.06 ± 1.56 days (range, 2–7 days). All patients with CIS received medical therapy, including hydration, nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and oral anti-inflammatory drugs such as streptokinase. All observed cases of CIS were temporary and improved with medical therapy.

Risk Factors of CIS

Logistic regression analysis was performed to identify the risk factors of CIS (Table 2). The variables obtained from the univariate analysis with $P < .1$ included female sex, volume of contrast administered, and guiding catheter tip located within the ECA. Multivariate analysis showed that the female sex (OR = 4.420, 95% CI: 1.377–14.190, $P = .013$), volume of contrast

Table 2: Logistic regression analysis showing the predictive factors of contrast-induced sialadenitis

Variables	Univariate		Multivariate	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age	0.983 (0.956–1.012)	.249		
Female sex	2.798 (0.972–8.056)	.057	4.420 (1.377–14.190)	.013
GFR	0.992 (0.975–1.009)	.356		
Volume of contrast administered	1.008 (1.005–1.012)	<.001	1.007 (1.003–1.011)	<.001
Guiding catheter tip located within ECA	11.594 (5.026–26.747)	<.001	8.701 (3.459–21.885)	<.001

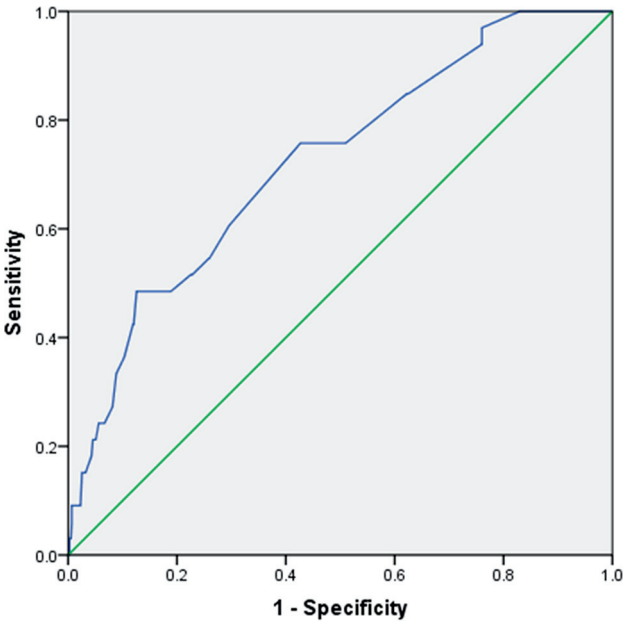

FIG 2. Receiver operating characteristic curve for volume of contrast administered in predicting the occurrence of CIS in patients after therapeutic neuroendovascular procedures.

administered (OR = 1.007, 95% CI: 1.003–1.011, $P < .001$), and guiding catheter tip located within the ECA (OR = 8.701, 95% CI: 3.459–21.885, $P < .001$) were independently associated with CIS occurrence after therapeutic neuroendovascular procedures.

Quantitative Assessment of Volume of Contrast Administered

The ROC curve between CIS and volume of contrast administered is shown in Fig 2. The volume of contrast administered had an AUROC of 0.723 (95% CI: 0.635–0.810; $P < .001$), indicating that it could be a good variable for predicting CIS. The optimal cutoff value of the volume of contrast administered was 205 mL, which was derived by using the maximum Youden index; however, the volume of contrast administered was poorly sensitive in determining CIS (sensitivity: 0.49, specificity: 0.87).

DISCUSSION

On the basis of a previous study, although CIS was not clearly defined, the documented frequency of adverse reactions to iodide contrast agents deemed appropriate for CIS was approximately 1%–2%.[2] However, given that not all CIS-associated symptoms were included and considering that a meta-analysis analyzing CIS-related studies from 1956–2018 found only 77 cases,[1] the reported incidence of CIS is likely lower than the actual occurrence rate. In addition, in a 2-month prospective observation study,[14] CIS was confirmed in 4 patients exposed to iodide contrast agents. In the present study, the incidence of CIS after therapeutic neuroendovascular procedures was 4.2%. In most reported cases of CIS, the condition occurred after intravenous procedures, likely due to the indirect effect of contrast agents on the salivary glands after systematic distribution. However, in cases of therapeutic neurovascular procedures, as in this study, the contrast agent is believed to directly affect the salivary glands through the arteries, leading to CIS. Therefore, we hypothesized that CIS occurrence is not rare, particularly after therapeutic neurovascular procedures.

The mechanism underlying CIS remains to be fully elucidated. One suspected mechanism involves the toxic accumulation of iodide within the salivary ductal mucosa, resulting in edema, duct obstruction, and enlargement of the salivary glands.[15] Approximately 98% of the iodide contrast is eliminated by the kidneys, and only 2% is excreted by other organs including the salivary glands, lacrimal glands, hepatobiliary system, and sweat glands.[16] Consequently, some researchers hypothesized that the risk of CIS increases in individuals with impaired renal function because of reduced elimination of iodide contrast agents,[17] leading to elevated serum iodide levels, occasionally measuring up to 100 times the plasma level (>10 mg/100 mL).[13] However, considering the similarity of plasma iodide levels in asymptomatic patients, there may be an inherent idiosyncratic component to CIS.[18] This is consistent with the findings of the present study, as renal function was not significantly associated with CIS.

Based on this toxic accumulation mechanism, CIS may occur more frequently in direct contrast administration via the ECA, which supplies blood to the salivary gland, or with the administration of high volume of contrast. In the present study, CIS occurrence was associated with the guiding catheter tip being located within the ECA. According to previous studies, the submandibular gland was the most affected solitary gland in patients receiving intravenous contrast administration (48%–100%).[1,14] The submandibular gland accounts for the highest proportion of saliva excretion (69%), which may elucidate its preferential involvement in the reported cases.[1] On the other hand, in the present study, which specifically focused on therapeutic neuroendovascular procedures, the most common site of occurrence was the parotid gland, which was vascularized via the superficial temporal, maxillary, and transverse facial arteries. Although the submandibular gland is also supplied by the ECA, such as the submental artery (branch of facial artery) and sublingual artery (branch of lingual artery), guiding catheter tips located within the ECA were often positioned more distally relative to the lingual

artery, resulting in more blood supply from ECA branches located even more distally than the distal tip end. Therefore, the parotid gland, which directly receives more contrast agents during procedures, may be more prone to developing CIS after therapeutic neuroendovascular procedures. Multivariate logistic regression analyses showed that the volume of contrast administered was also statistically significantly associated with CIS occurrence with a cutoff value of 205 mL However, a relatively low OR was observed (1.007 [1.003–1.011]). Similar to previous reports, we hypothesized that there is a greater association between CIS occurrence and the directly supplied toxicity of contrast agents on the salivary glands via the ECA rather than an increase in blood contrast concentration because of a higher volume of contrast agent being administered. In line with this, contrast type (nonionic monomer versus nonionic dimer) also showed no association with CIS occurrence in this study.

In this study, female sex was identified as a risk factor of CIS occurrence. On the other hand, a previous meta-analysis found that men had a slightly higher occurrence rate of CIS compared with women (61% versus 38%), but there was no significant predilection for sex.[1] Both our study and the previous meta-analysis had a limited number of patients (33 and 77 cases, respectively) with CIS; therefore, there may be statistical differences. However, because a previous study reported that adverse reactions to iodide contrast agents are more common in women (OR = 2.40),[19] female sex was identified as a risk factor of CIS occurrence in the present study.

The diagnosis of CIS is primarily clinical but can be supplemented with imaging modalities.[6] Ultrasound (US), CT, and MR imaging are the most commonly used diagnostic tools for suspected cases of CIS. US findings typically reveal a notable swelling of salivary glands with hypoechoic septa, heightened vascularity, and dilated ducts with no indications of sialolithiasis or infection.[1,6] CT and MRI examinations reveal gland enlargement without any evidence of fat stranding surrounding the glands or inflammatory changes in the surrounding fat and subcutaneous tissues.[1] Because the patients in the present study had no symptoms associated with CIS before the procedures, in the event of CIS-related symptoms emerging after the procedure, routine imaging tests were not conducted because of the low likelihood of causes other than CIS.

The natural history of CIS is typically benign and self-limited. In most cases, symptoms occurred in a median of 16 hours (ranging from immediate onset to 5 days) after the administration of contrast agent, and symptoms generally resolve over a median duration of 3 days (ranging from immediate resolution to 72 days).[1,5,14] Compared with these results, our study showed a slightly faster onset time of symptoms, with an average of 9.89 hours, and similar timing of symptom improvement, with a mean duration of 4.06 days. The relatively faster onset of symptoms in this study may be attributed to the direct impact of the contrast agent on the salivary glands through the ECA.

While there is currently no standardized treatment protocol for CIS, the management of CIS typically focuses on symptomatic relief, including hydration and administration of NSAIDs, antibiotics, and oral anti-inflammatory drugs. Although therapeutic interventions including medication can help alleviate symptoms, no statistically significant difference was observed in the time to symptom recovery between individuals who received therapeutic intervention and those who did not.[1,6,14] In line with this finding, this condition is not caused by allergic reactions, and pretreatment is ineffective in preventing recurrent CIS episodes.[1] All patients in the present study experienced resolution of symptoms with conservative treatment with medications prescribed according to the advice of an otolaryngologist.

Our study had several limitations. First, the study was conducted retrospectively at a single institution and included only 33 patients with CIS, potentially leading to limited statistical power. Second, in our quantitative assessment of contrast volume as a risk factor of CIS, the optimal cutoff value of contrast volume being administered was 205 mL. Although the specificity (0.87) appears acceptable, the sensitivity (0.47) was low. This is likely attributed to the limited frequency of CIS occurrences, resulting in insufficient data, and may have yielded a false-negative prediction. Third, CIS was defined solely on the basis of clinical symptoms without radiologic evaluation in this study. Consequently, some cases that were not suitable for CIS may have been included, and those with ambiguous clinical presentations of CIS may not have been included. Finally, in this study, undiluted contrast agents were used, and only therapeutic neuroendovascular procedures involving relatively high amounts of contrast agents were included. Consequently, the incidence of CIS may have been higher than typically reported. Larger-scale prospective multicenter studies are needed to verify the findings of the present study.

CONCLUSIONS

Although CIS is a rare adverse reaction of iodide contrast agents, it has been frequently observed in the field of therapeutic neuroendovascular procedures. Female sex, volume of contrast administered, and guiding catheter tip located within the ECA were identified as risk factors of CIS occurrence. Thus, the incidence of CIS should be considered in patients with these factors.

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