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Constipation in Patients with Acute Ischemic Stroke: A Single-Center Retrospective Analysis

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Background: Constipation, a symptom of autonomic nervous system dysfunction affecting gastrointestinal motility, is common after acute ischemic stroke. The insular cortex is associated with autonomic symptoms, and damage to the left insula may result in constipation. We investigated the association between constipation and left-sided insular infarction in patients with acute stroke.

Methods: We retrospectively analyzed data from consecutive patients who received a diagnosis of acute infarction in the middle cerebral artery territory between January 2015 and December 2018. Constipation was defined as bowel movements less often than three times a week or a prescription for laxatives within 2 weeks of stroke onset. Clinical characteristics and factors associated with constipation were evaluated.

Results: Among 892 patients (mean age, 75 [66-82] years; male, 566 [63.5%]), 301 (32.8%) had constipation. Infarction involving the insula (57.7% vs. 25.1%) and left-sided infarction (62.5% vs. 46.4%) were more frequent in patients with constipation than in those without constipation. In multivariable analysis, infarction involving the insula (adjusted odds ratio [aOR], 2.30; 95% confidence interval [CI], 1.57-3.36; $P<0.001$), left-sided infarction (aOR, 1.93; 95% CI, 1.40-2.64; $P<0.001$), and baseline National Institutes of Health Stroke Score (aOR, 1.04; 95% CI, 1.01-1.06; $P<0.001$) were associated with constipation. The incidence of constipation was highest in cases of left-sided infarction with insular involvement (69.2%).

Conclusions: Left-sided infarction, infarction involving the insular cortex, and baseline National Institutes of Health Stroke Score were identified as independent factors associated with constipation in patients with acute stroke. (J Nippon Med Sch 2025; 92: 154–162)

Key words: constipation, insular cortex, ischemic stroke

Introduction

Constipation, a common complication of acute ischemic stroke (reported incidence, 16-52%)[1–4], may worsen acute stroke symptoms and outcomes[1,5–8]. Constipation is a symptom of autonomic nervous system dysfunction affecting gastrointestinal motility[9]. The innervation of the gastrointestinal tract is complex, and the vagus nerve has a central role[10].

The insular cortex was found to be associated with autonomic nervous symptoms[11]. In particular, stimulation of the right insula excites the sympathetic nervous system[12]. Consequently, bowel movements become impaired, increasing the likelihood of constipation. This suggests that damage to the left insula could lead to relative overactivity of the right insula, which might cause excitation of the sympathetic nervous system and result in constipation. However, it is unclear whether left- or right-sided insular lesions are more likely to cause constipation.

This study investigated whether constipation is associated with left-sided infarction, with or without involve-

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ment of the insular cortex, in patients with acute ischemic stroke.

Materials and Methods

The data collected for this study are available from the corresponding author upon reasonable request. This study follows the guidelines promulgated in Strengthening the Reporting of Observational Studies in Epidemiology.

1. Study Design and Population

We retrospectively reviewed our stroke registry for data from consecutive patients hospitalized with a diagnosis of acute ischemic stroke in the middle cerebral artery territory within 7 days after stroke onset between January 2015 and December 2018. The following exclusion criteria were applied: (1) bilateral infarction and (2) death or discharge within 7 days of hospitalization.

Patients were categorized into the constipation and non-constipation groups, and the characteristics these groups were compared. Patients were further divided into left- or right-sided infarction subgroups according to the laterality of the infarction in the middle cerebral artery territory and into insular and non-insular subgroups according to the presence of insular involvement.

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Nippon Medical School (approval number: O-2023-773). This retrospective observational study used an opt-out method on the hospital bulletin board.

2. Imaging Criteria

All patients underwent brain magnetic resonance imaging or computed tomography scanning on admission. Acute ischemic stroke was defined as a high-intensity lesion on diffusion-weighted images or a low-intensity lesion on an apparent diffusion coefficient map within 7 days after stroke onset. The insular cortex was defined as the area bounded by the frontoparietal and temporal lobes. Two expert neurologists (F.S. and Y.F.) confirmed whether the infarction involved the insular cortex.

3. Definition of Constipation

Constipation was defined on the basis of the following two criteria, as indicated in the Rome IV criteria[13]: (1) bowel movements less often than three times per week and (2) prescription for laxatives during acute hospitalization within 7 days after stroke onset.

4. Data Collection

Data were obtained on age; sex; history of hypertension, dyslipidemia, diabetes, and previous stroke; smoking status; presence of atrial fibrillation; vessel occlusion; intravenous thrombolysis; mechanical thrombectomy; National Institutes of Health Stroke Score (NIHSS); vital signs, blood glucose and brain natriuretic peptide levels, and electrocardiographic findings on admission; symptoms; modified Rankin Scale score after 3 months; and factors affecting gastrointestinal function during hospitalization, including (1) history of laparotomy, (2) history of oral laxative use before hospitalization, (3) laxative use during hospitalization (oral and or suppository), (4) tube feeding, and (5) pharmacotherapy use.

Tube feeding was defined as the need for tube feeding for at least 1 day during hospitalization and was used only in patients who were assessed as having dysphagia on a Repetitive Saliva Swallowing Test and Modified Water Swallowing Test. The pharmacotherapies surveyed included antiflatulent agents, antibiotics, antiallergic agents, antihistamines, benzodiazepines, antidepressants, and antidiabetic agents. Vital signs recorded on admission included systolic blood pressure, diastolic blood pressure, heart rate, and temperature. Evaluated electrocardiographic findings included negative T waves and ST-T segment changes on admission, follow-up, and Holter electrocardiography.

5. Definition of Other Complications

We also examined incidences of diarrhea, heart failure, and aspiration pneumonia, which could affect constipation. Diarrhea was defined according to the World Health Organization's definition as having three or more loose stools per day[14]. Heart failure was assessed using the Framingham criteria[15–17]. The definition of aspiration pneumonia was based on that used in a previous study[18].

6. Statistical Analysis

Continuous data are summarized as medians with quartiles, and categorical data are expressed as frequencies with percentages. Patients with missing data were excluded. For comparisons between groups, after tests of normality for continuous data, the t test and Mann-Whitney U test were used when data were and were not normally distributed, respectively. The t test was used for categorical data. Multivariable logistic regression analysis of variables with *P*-values of <0.1 in univariable analysis was used to identify factors independently associated with constipation, after adjusting for age and sex. Mechanical thrombectomy, intravenous thrombolysis, and internal carotid artery (ICA)-M1 occlusion were excluded because these parameters were related to a high NIHSS and infarction involving the insular cortex. Brain natriuretic peptide level on admission, a negative T wave, and ST-T change were excluded because they were related to

Table 1 Clinical, imaging, laboratory, and electrocardiographic findings according to the presence of constipation

Findings	All (n=892)	No Constipation (n=601, 67.4%)	Constipation (n=291, 32.6%)	*P*
Age, years, median (IQR)	75 (66-82)	73 (65-81)	77 (68-83)	<0.001
Male, n (%)	566 (63.5)	384 (63.9)	182 (62.5)	0.695
Vascular risk factor				
Hypertension, n (%)	606 (67.9)	408 (67.9)	198 (68.0)	0.963
Dyslipidemia, n (%)	356 (39.9)	250 (41.6)	106 (36.4)	0.137
Diabetes mellitus, n (%)	214 (24.0)	140 (23.3)	74 (25.4)	0.484
Smoker, n (%)	280 (31.4)	191 (31.8)	89 (30.6)	0.719
Atrial fibrillation, n (%)	203 (22.8)	115 (19.1)	88 (30.2)	<0.001
Previous history of stroke, n (%)	202 (22.6)	132 (22.0)	70 (24.1)	0.485
NIHSS score at baseline, median (IQR)	5 (2-15)	3 (1-9)	12 (4-21)	<0.001
ICA-M1 occlusion, n (%)	244 (27.4)	119 (19.8)	125 (43.0)	<0.001
Left-sided infarction group, n (%)	461 (51.7)	279 (46.4)	182 (62.5)	<0.001
Insular group, n (%)	319 (35.8)	151 (25.1)	168 (57.7)	<0.001
Mechanical thrombectomy, n (%)	248 (27.8)	113 (18.8)	135 (46.4)	<0.001
Intravenous thrombolysis, n (%)	180 (20.2)	110 (18.3)	70 (24.1)	0.053
Vital signs				
Systolic BP on admission, mmHg, median (IQR)	160 (140-180)	158 (140-179)	162 (140-182)	0.265
Diastolic BP on admission, mmHg, median (IQR)	88 (78-100)	89 (78-100)	87 (78-100)	0.058
Heart rate on admission, bpm/minutes, median (IQR)	80 (70-92)	80 (71-93)	78 (70-91)	0.422
Body temperature on admission, ℃ , median (IQR)	36.6 (36.3-36.9)	36.6 (36.3-36.9)	36.6 (36.3-36.9)	0.988
Laboratory findings				
Blood glucose level on admission, mg/dL, median (IQR)	118 (103-143)	117 (103-140)	124 (106-149)	0.009
BNP level on admission, pg/mL, median (IQR)	75.4 (26.5-192.6)	61.7 (22.2-183.0)	97.5 (38.8-210.6)	<0.001
Electrocardiographic findings				
Negative T wave, n (%)	154 (17.3)	93 (15.5)	61 (21.0)	0.051
ST-T changes, n (%)	169 (18.9)	91 (15.1)	78 (26.8)	<0.001
Complications				
Diarrhea, n (%)	159 (17.8)	87 (14.5)	72 (24.7)	<0.001
Heart failure, n (%)	91 (10.2)	38 (6.3)	53 (18.2)	<0.001
Aspiration pneumonia, n (%)	156 (17.5)	64 (10.6)	92 (31.6)	<0.001
Outcome				
mRS at 90 days	2 (1-4)	1 (0-4)	3 (2-5)	<0.001
Association with constipation				
History of laparotomy, n (%)	174 (19.5)	111 (18.5)	63 (21.6)	0.272
History of oral laxative use before hospitalization, n (%)	141 (15.8)	84 (14.0)	57 (19.6)	0.040
Laxative use during hospitalization, n (%)	477 (53.5)	186 (30.9)	291 (100.0)	<0.001
Oral , n (%)	434 (48.7)	170 (28.3)	264 (90.7)	<0.001
Suppository, n (%)	143 (16.0)	48 (8.0)	95 (32.6)	<0.001
Tube feeding, n (%)	330 (37.0)	143 (23.8)	187 (64.3)	<0.001
Pharmacotherapy use				
Antiflatulent agents, n (%)	140 (15.7)	75 (12.5)	65 (22.3)	<0.001
Antibiotics, n (%)	261 (29.3)	121 (20.1)	140 (48.1)	<0.001
Antihistamines, n (%)	12 (1.3)	7 (1.2)	5 (1.7)	0.502
Antiallergic agents, n (%)	34 (3.8)	20 (3.3)	14 (4.8)	0.308
Benzodiazepines, n (%)	94 (10.5)	66 (11.0)	28 (9.6)	0.536
Antidepressants, n (%)	20 (2.2)	11 (1.8)	9 (3.1)	0.275
Antidiabetic agents, n (%)	182 (20.4)	120 (20.0)	62 (21.3)	0.642

BNP, Brain Natriuretic Peptide; BP, Blood Pressure; ICA, Internal Carotid Artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

atrial fibrillation and heart failure. The modified Rankin Scale score at 90 days was excluded because it did not affect constipation in the acute phase of ischemic stroke. Laxative use during hospitalization was excluded because it was included in the criteria used for defining constipation in the present study, and diarrhea was ex-

Table 2 Multivariable logistic regression models for constipation

	Adjusted OR	95% CI
Age	1.01	0.99-1.02
Male	1.21	0.86-1.70
Atrial fibrillation	1.02	0.70-1.50
History of oral laxative use before hospitalization	1.33	0.87-2.03
Antiflatulent agents	0.95	0.62-1.47
Antibiotics	1.42	0.90-2.23
Blood glucose level on admission	1.00	0.99-1.00
Heart failure	1.19	0.71-2.00
Aspiration pneumonia	1.56	0.95-2.57
Baseline NIHSS score	1.04	1.01-1.06
Left-sided infarction	1.93	1.40-2.64
Infarction involving insular cortex	2.30	1.57-3.36

NIHSS, National Institutes of Health Stroke Scale.

cluded because of the side effects of laxatives. Finally, tube feeding was excluded because it was a treatment chosen by physicians. Therefore, age, sex, history of atrial fibrillation, baseline NIHSS, laxative use before admission, antiflatulent agent use, antibiotic use, blood glucose level on admission, heart failure, aspiration pneumonia, left-sided infarction, and infarction involving the insular cortex were chosen as the explanatory variables. We calculated 95% confidence intervals (CIs) and odds ratios (ORs). To obtain baseline NIHSS for use as the cutoff point for discriminating between patients with and without constipation, we constructed receiver operating characteristic (ROC) curves and calculated the area under the ROC curve (AUC) with 95% CIs. *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

Results

1. Patient Characteristics

A total of 1,602 patients were hospitalized during the study period. Magnetic resonance imaging was performed in 1,558 (97.3%) and computed tomography scanning in 44 (2.7%) patients. Of the 1,558 patients who underwent magnetic resonance imaging, 975 had infarctions in the middle cerebral artery territory. Among them, 27 patients had bilateral infarctions, 14 died within 7 days after stroke onset, 38 were discharged within 7 days after stroke onset, and four had missing data. Ultimately, 892 patients were included in this study. The mean age was 75 (range, 66-82) years, 566 (63.5%) patients were male, and the mean baseline NIHSS was 5 (2-15).

2. Constipation vs. Non-Constipation Groups

Constipation was observed in 291 (32.6%) patients. **Table 1** shows the patients' characteristics. Compared with those in the non-constipation group, patients in the constipation group were older (77 [68-83] vs. 73 [65-81] years; *P*<0.001) and had higher blood glucose levels on admission (124 [106-149] vs. 117 [103-140] mg/dL; *P*= 0.009) and higher baseline NIHSS (12 [4-21] vs. 3 [1-9] points; *P*<0.001). Patients in the constipation group also had a higher frequency of atrial fibrillation (30.2% vs. 19.1%; *P*<0.001), left-sided infarction (62.5% vs. 46.4%; *P*< 0.001), and infarction involving the insular cortex (57.7% vs. 25.1%; *P*<0.001). Heart failure (18.2% vs. 6.3%; *P*< 0.001), aspiration pneumonia (31.6% vs. 10.6%; *P*<0.001), history of oral laxative use before hospitalization (19.6% vs. 14.0%; *P*=0.031), antiflatulent agent use (22.3% vs. 12.5%; *P*<0001), and antibiotic use (48.1% vs. 20.1%; *P*< 0.001) were more common in the constipation group than in the non-constipation group.

In the multivariable logistic regression analysis, left-sided infarction (adjusted OR, 1.93; 95% CI, 1.40-2.64; *P*< 0.001), infarction involving the insular cortex (adjusted OR, 2.30; 95% CI, 1.57-3.36; *P*<0.001), and baseline NIHSS (adjusted OR, 1.04; 95% CI, 1.01-1.06; *P*=0.001) were identified as factors independently associated with constipation (**Table 2**).

3. Subgroup Analyses

On the basis of the results of multivariable analysis, patients were further categorized into four subgroups: left-sided infarction with insular involvement (L+I group; n=161, 18.0%), left-sided infarction without insular involvement (L-I group; n=301, 33.7%), right-sided infarction with insular involvement (R+I group; n=158, 17.7%), and right-sided infarction without insular involvement (R-I group; n=272, 30.5%). **Table 3** shows the characteristics of these four subgroups. The incidence of constipa-

Table 3 Clinical, imaging, laboratory, and electrocardiographic findings according to infraction laterality and insular involvement

Findings	L+I group (n=161, 18.0%)	R+I group (n=158, 17.7%)	L-I group (n=301, 33.7%)	R-I group (n=272, 30.5%)	*P*
Age, years, median (IQR)	77 (68-84)	77 (69-83)	73 (65-81)	72 (63-80)	<0.001
Male, n (%)	96 (59.6)	91 (57.6)	198 (65.8)	181 (66.5)	0.159
Vascular risk factor					
Hypertension, n (%)	101 (62.7)	107 (67.7)	221 (73.4)	177 (65.1)	0.066
Dyslipidemia, n (%)	60 (37.3)	51 (32.3)	124 (41.2)	121 (44.5)	0.076
Diabetes mellitus, n (%)	31 (19.3)	24 (15.2)	81 (26.9)	78 (28.7)	0.004
Smoker, n (%)	46 (28.6)	44 (27.8)	99 (32.9)	91 (33.5)	0.500
Atrial fibrillation, n (%)	53 (32.9)	64 (40.5)	54 (17.9)	32 (11.8)	<0.001
Previous history of stroke, n (%)	27 (16.8)	31 (19.6)	92 (30.6)	52 (19.1)	0.001
NIHSS score at baseline, median (IQR)	20 (11-24)	14 (6-19)	3 (1-5)	3 (1-5)	<0.001
ICA-M1 occlusion, n (%)	77 (47.8)	81 (51.3)	39 (13.0)	47 (17.3)	<0.001
Mechanical thrombectomy, n (%)	89 (55.3)	85 (53.8)	41 (13.6)	33 (12.1)	<0.001
Intravenous thrombolysis, n (%)	51 (31.7)	46 (29.1)	39 (13.0)	44 (16.2)	<0.001
Vital signs					
Systolic BP on admission, mmHg, median (IQR)	160 (138-185)	160 (140-176)	158 (142-182)	160 (141-179)	0.767
Diastolic BP on admission, mmHg, median (IQR)	87 (73-100)	88 (78-98)	89 (78-100)	90 (78-103)	0.098
Heart rate on admission, bpm/minutes, median (IQR)	81 (70-96)	81 (70-96)	79 (70-90)	80 (71-90)	0.355
Body temperature on admission, ℃, median (IQR)	36.6 (36.3-36.9)	36.6 (36.3-36.9)	36.5 (36.3-36.8)	36.6 (36.3-36.9)	0.227
Laboratory findings					
Blood glucose level on admission, mg/dL, median (IQR)	120 (107-148)	124 (108-142)	115 (100-141)	118 (101-142)	0.048
BNP level on admission, pg/mL, median (IQR)	151.9 (66.7-301.6)	136.3 (60.6-297.9)	53.6 (21.7-142.8)	41.1 (18.2-111.3)	<0.001
Electrocardiographic findings					
Negative T wave, n (%)	43 (26.7)	37 (23.4)	40 (13.3)	34 (12.5)	<0.001
ST-T change, n (%)	69 (42.9)	58 (36.7)	24 (8.0)	18 (6.6)	<0.001
Complications					
Constipation, n (%)	112 (69.6)	56 (35.4)	70 (23.3)	53 (19.5)	<0.001
Diarrhea, n (%)	48 (29.8)	40 (25.3)	40 (13.3)	31 (11.4)	<0.001
Heart failure, n (%)	42 (26.1)	28 (17.7)	14 (4.7)	7 (2.6)	<0.001
Aspiration pneumonia, n (%)	62 (38.5)	41 (25.9)	31 (10.3)	22 (8.1)	<0.001
Outcome					
mRS at 90 days	4 (2-5)	4 (1-5)	2 (0-3)	1 (0-3)	<0.001
Association with constipation					
History of laparotomy, n (%)	33 (20.5)	34 (21.5)	58 (19.3)	49 (18.0)	0.824
History of oral laxative use before hospitalization, n (%)	28 (17.4)	27 (17.1)	49 (16.3)	37 (13.6)	0.673
Laxative use during hospitalization, n (%)	127 (78.9)	102 (64.6)	135 (44.9)	113 (41.5)	<0.001
Oral, n (%)	105 (65.2)	96 (60.8)	124 (41.2)	109 (40.1)	<0.001
Suppository, n (%)	53 (32.9)	29 (18.4)	36 (12.0)	25 (9.2)	<0.001
Tube feeding, n (%)	134 (83.2)	123 (77.8)	42 (14.0)	31 (11.4)	<0.001
Pharmacotherapy use					
Antiflatulent agents, n (%)	43 (26.7)	41 (25.9)	34 (11.3)	22 (8.1)	<0.001
Antibiotics, n (%)	93 (57.8)	78 (49.4)	52 (17.3)	38 (14.0)	<0.001
Antihistamines, n (%)	2 (1.2)	5 (3.2)	3 (1.0)	2 (0.7)	0.172
Antiallergic agents, n (%)	6 (3.7)	10 (6.3)	10 (3.3)	8 (2.9)	0.322
Benzodiazepines, n (%)	11 (6.8)	21 (13.3)	33 (11.0)	29 (10.7)	0.298
Antidepressants, n (%)	3 (1.9)	5 (3.2)	6 (2.0)	6 (2.2)	0.848
Antidiabetic agents, n (%)	25 (15.5)	27 (17.1)	63 (20.9)	67 (24.6)	0.091

BNP, Brain Natriuretic Peptide; BP, Blood Pressure; ICA, Internal Carotid Artery; L+I, Left-sided infarction with insular involvement; L-I, Left-sided infarction without insular involvement; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; R+I, Right-sided infarction with insular involvement; R-I, Right-sided infarction without insular involvement.

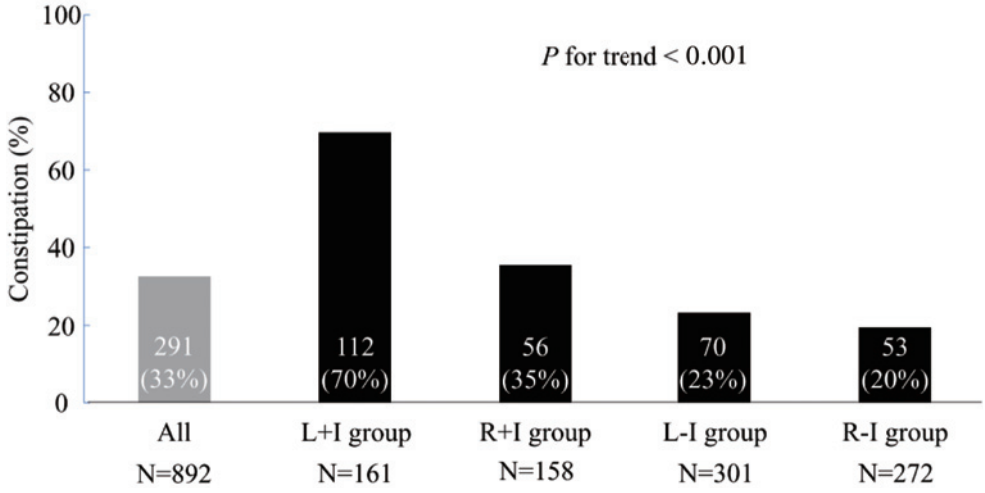

Fig. 1 Incidence of constipation in the acute stage after ischemic stroke, by laterality and insular involvement
The incidence of constipation was 69.6%, 35.4%, 23.3%, and 19.5% in the L+I, R+I, L-I, and R-I subgroups, respectively. The L+I subgroup had the highest incidence of constipation.
L+I, left-sided infarction with insular involvement; L-I, left-sided infarction without insular involvement; R+I, right-sided infarction with insular involvement; R-I, right-sided infarction without insular involvement.

tion was 69.6%, 35.4%, 23.3%, and 19.5% in the L+I, R+I, L-I, and R-I subgroups, respectively (**Fig. 1**). The L+I subgroup had the highest incidence of constipation (P< 0.001).

4. Infarction Involving the Left Insular Cortex and Baseline NIHSS

In the multivariable analysis, baseline NIHSS was also identified as a factor independently associated with constipation. The AUC of the ROC curve for predicting constipation was 0.709 (95% CI, 0.673-0.746; P<0.001). The optimal cutoff score of the NIHSS was ≥10, with a sensitivity of 58% and a specificity of 76%. The incidence of constipation among those with an NIHSS ≥10 and ≤9 was 54.2% (168/310) and 21.1% (123/582), respectively. Among patients with an NIHSS ≥10, the incidence of constipation was 77.8% (98/126), 39.8% (41/103), 35.8% (19/53), and 35.7% (10/28) in the L+I, R+I, L-I, and R-I subgroups, respectively (P for trend <0.001) (**Fig. 2A**). Among patients with an NIHSS ≤9, the incidence of constipation was 40.0% (14/35), 27.3% (15/55), 20.6% (51/248), and 17.6% (43/244) in the L+I, R+I, L-I, and R-I subgroups, respectively (P for trend =0.010) (**Fig. 2B**). The more severe the stroke ischemic symptoms, the more frequent the constipation. However, regardless of severity, the L+I subgroup had the highest incidence of constipation.

Discussion

This study identified left-sided infarction, infarction involving the insular cortex, and baseline NIHSS as independent factors associated with constipation in patients with acute ischemic stroke. Furthermore, in a comparison by infarction laterality and insular involvement, the left-sided insular infarction group had the highest incidence of constipation.

Constipation is strongly associated with intestinal motility and colonic sensorimotor dysfunction[19,20]. Intestinal motility is controlled by Auerbach's plexus, which is the peripheral enteric plexus involving the autonomic nerves. However, paralytic ileus can occur in patients with brainstem[3,21] and spinal cord lesions[22], suggesting that intestinal motility is controlled not only by the peripheral plexus but also by the central nervous system. In addition, the gastrointestinal tract has a complex innervation with afferent sensory neurons, including the vagus nerve[10], which innervates most of the gastrointestinal tract[23] and is a major component of the parasympathetic nervous system[24]. Approximately 80-85% of vagus nerve fibers are afferent and project from the visceral locus to the medial nucleus tractus solitarius. Secondary neurons then project from the nucleus tractus solitarius to the brainstem, hypothalamus, and amygdala; projections from the brainstem to the cerebral cortex include the orbitofrontal cortex, anterior cingulate gyrus, and insular cortex[25,26]. Direct

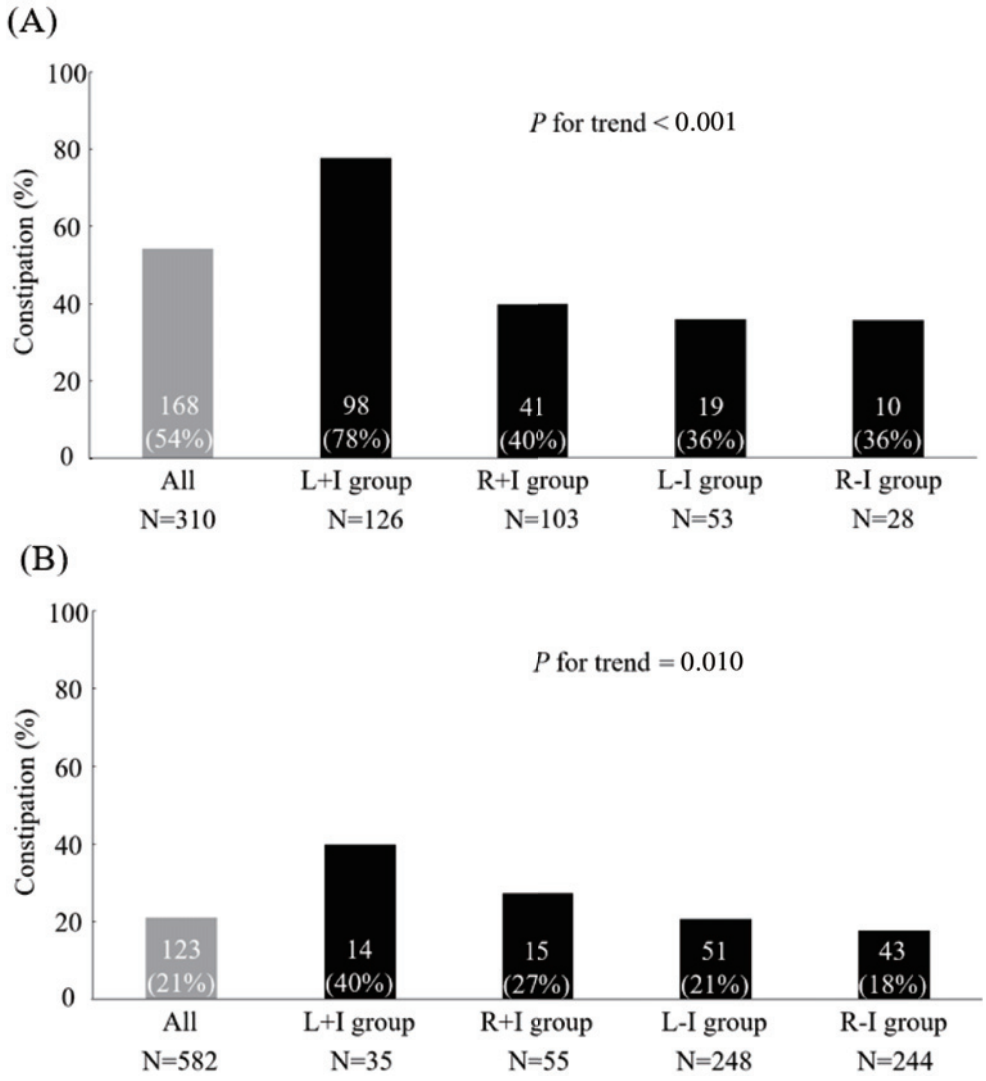

Fig. 2 Incidence of constipation in patients with NIHSS ≥10 (A) and ≤9 (B) in the acute stage after ischemic stroke, by laterality and insular involvement.
Among patients with an NIHSS ≥10, the incidence of constipation was 77.8% (98/126), 39.8% (41/103), 35.8% (19/53), and 35.7% (10/28) in the L+I, R+I, L-I, and R-I subgroups, respectively (*P* for trend<0.001). Among patients with an NIHSS ≤9, the incidence of constipation was 40.0% (14/35), 27.3% (15/55), 20.6% (51/248), and 17.6% (43/244) in the L+I, R+I, L-I, and R-I subgroups, respectively (*P* for trend =0.010). Regardless of severity, the L+I subgroup had the highest incidence of constipation.
L+I, left-sided infarction with insular involvement; L-I, left-sided infarction without insular involvement; R+I, right-sided infarction with insular involvement; R-I, right-sided infarction without insular involvement.

projections from the prefrontal and agranular insular regions to the nucleus tractus solitarius have also been described[27–29]. Therefore, the insular cortex might be associated with the role of the autonomic nervous system in intestinal motility.

The role of the insular cortex in controlling autonomic cardiovascular activity was suggested by a brain stimulation study in humans[12]. Bradycardia and depressor responses were more frequent than tachycardia and pressor effects after stimulation of the left insular cortex. Contrasting reactions were shown upon stimulation of the right insular cortex. Therefore, the left insular cortex is predominantly responsible for parasympathetic cardiovascular effects. Moreover, several studies on insular cortex stroke have reported electrocardiogram abnormalities[30,31], new-onset atrial fibrillation[30,32], and complex arrhythmias[33]. In one such study, acute left insular stroke increased the basal cardiac sympathetic tone[34].

The autonomic nervous system is involved in constipation[9]. Although a previous study reported that bilateral

lesions in the insular cortex, precentral gyrus, opercular part of the inferior frontal gyrus, the inferior parietal lobule, and right middle frontal gyrus were associated with acute constipation in patients with acute ischemic stroke[35], it was not reported whether left- or right-sided insular lesions were more likely to cause constipation. In the present study, the incidence of constipation was significantly higher in the left-sided infarction and insular subgroups than in the other subgroups. In particular, patients with left-sided middle cerebral artery infarction involving the insular cortex had the highest incidence of constipation (69.2%). These findings suggest that the left insular cortex is strongly associated with the autonomic nervous system and that damage to this brain region results in constipation.

This study demonstrated an association between constipation in acute ischemic stroke and baseline NIHSS. In previous studies, higher NIHSS values were associated with a higher incidence of constipation after stroke[36]. In patients with severe stroke, parasympathetic tone decreased and the sympathetic nervous system was dominant[37–39]. A shift toward sympathetic dominance might inhibit intestinal peristalsis and colonic motility, resulting in constipation[40,41].

This study had several limitations. First, it was a retrospective analysis of data obtained from a single stroke center, which may limit the generalizability of the findings. Second, the incidence of constipation may have been incorrectly estimated. Although we defined the criteria for constipation, because these criteria were applied to patients with impaired consciousness and aphasia, we had difficulties evaluating the subjective symptoms of constipation, which might have resulted in underestimation. In addition, laxatives were often used in patients with a low activities of daily living score, and the inclusion of laxative use in the definition of constipation might have led to overestimation. Third, we considered the impact of medications affecting constipation; however, information was limited on fentanyl, which is commonly used in emergency medicine and causes constipation. Fourth, we did not investigate the presence of pure insular infarction, as it is rare-only 13 of 892 cases (1.5%) were observed in the present study. Fifth, the presence of infratentorial lesions was not examined, and other lesions assessed in a previous study could not be investigated. Studies of patients with pure insular infarction are required in order to define the association between insular cortex infarction and constipation.

In conclusion, infarction involving the insular cortex, left-sided infarction, and baseline NIHSS were independent factors associated with constipation in patients with acute ischemic stroke. In particular, approximately 70% of patients with left-sided infarction involving the insular cortex had constipation. Therefore, patients with ischemic stroke, particularly when the left insular cortex is involved, should be carefully evaluated for constipation.

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References

1. Johnston KC, Li JY, Lyden PD, et al. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. RANTTAS Investigators. Stroke. 1998 Feb;29(2):447–53.
2. Su Y, Zhang X, Zeng J, et al. New-onset constipation at acute stage after first stroke: incidence, risk factors, and impact on the stroke outcome. Stroke. 2009 Apr;40(4): 1304–9.
3. Yi JH, Chun MH, Kim BR, Han EY, Park JY. Bowel function in acute stroke patients. Ann Rehabil Med. 2011 Jun; 35(3):337–43.
4. Cai W, Wang L, Guo L, et al. [Correlation analysis between post-stroke constipation and brain injury]. Nan Fang Yi Ke Da Xue Xue Bao. 2013 Jan;33(1):117–20. Chinese.
5. Robain G, Chennevelle JM, Petit F, Piera JB. [Incidence of constipation after recent vascular hemiplegia: a prospective cohort of 152 patients]. Rev Neurol (Paris). 2002 May; 158(5 Pt 1):589–92. French.
6. Weimar C, Roth MP, Zillessen G, et al. Complications following acute ischemic stroke. Eur Neurol. 2002;48(3):133–40.
7. Hong KS, Kang DW, Koo JS, et al. Impact of neurological and medical complications on 3-month outcomes in acute ischaemic stroke. Eur J Neurol. 2008 Dec;15(12):1324–31.
8. Sumida K, Molnar MZ, Potukuchi PK, et al. Constipation and risk of death and cardiovascular events. Atherosclerosis. 2019 Feb;281:114–20.
9. Mayer EA, Savidge T, Shulman RJ. Brain-gut microbiome interactions and functional bowel disorders. Gastroenterology. 2014 May;146(6):1500–12.
10. Sharma A, Lelic D, Brock C, Paine P, Aziz Q. New technologies to investigate the brain-gut axis. World J Gastroenterol. 2009 Jan 14;15(2):182–91.
11. Dutsch M, Burger M, Dorfler C, Schwab S, Hilz MJ. Cardiovascular autonomic function in poststroke patients. Neurology. 2007 Dec 11;69(24):2249–55.
12. Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992 Sep;42(9):1727–32.
13. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology. 2016 Feb 18;150(6):1393–407. e5.
14. World Health Organization. Diarrhoeal disease [Internet]. Geneva: World Health Organization; 2024 Mar 7. [cited 2023 Feb 6]. Available from: https://www.who.int/news-

room/fact-sheets/detail/diarrhoeal-disease
15. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996 May 22-29;275(20):1557–62.
16. Ahmed A. Clinical characteristics of nursing home residents hospitalized with heart failure. J Am Med Dir Assoc. 2002 Sep-Oct;3(5):310–3.
17. Ahmed A, Allman RM, Aronow WS, DeLong JF. Diagnosis of heart failure in older adults: predictive value of dyspnea at rest. Arch Gerontol Geriatr. 2004 May-Jun;38 (3):297–307.
18. Kim GE, Sung IY, Ko EJ, Choi KH, Kim JS. Comparison of videofluoroscopic swallowing study and radionuclide salivagram for aspiration pneumonia in children with swallowing difficulty. Ann Rehabil Med. 2018 Feb;42(1): 52–8.
19. Wang HL. Understanding the pathogenesis of slow-transit constipation: one step forward. Dig Dis Sci. 2015 Aug;60(8):2216–8.
20. Bharucha AE, Lacy BE. Mechanisms, evaluation, and management of chronic constipation. Gastroenterology. 2020 Apr;158(5):1232–49. e3.
21. Li J, Yuan M, Liu Y, Zhao Y, Wang J, Guo W. Incidence of constipation in stroke patients: a systematic review and meta-analysis. Medicine (Baltimore). 2017 Jun;96(25): e7225.
22. Chung EA, Emmanuel AV. Gastrointestinal symptoms related to autonomic dysfunction following spinal cord injury. Prog Brain Res. 2006;152:317–33.
23. Roman C, Gonella J. Extrinsic control of digestive tract motility. In: Johnson LR, Alpers DH, Christensen J, Jacobson ED, Walsh JH, editors. Physiology of the gastrointestinal tract. New York: Raven Pr; 1987. p. 507–53.
24. Breit S, Kupferberg A, Rogler G, Hasler G. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. Front Psychiatry. 2018 Mar 13;9:44.
25. Sawchenko PE. Central connections of the sensory and motor nuclei of the vagus nerve. J Auton Nerv Syst. 1983 Oct;9(1):13–26.
26. Leslie RA, Reynolds DJM, Lawes INC. Central connections of the nuclei of the vagus nerve. In: Ritter S, Ritter RC, Barnes CD, editors. Neuroanatomy and physiology of abdominal vagal afferents. Boca Raton: CRC Press; 1992. p. 81–98.
27. Saper CB. Convergence of autonomic and limbic connections in the insular cortex of the rat. J Comp Neurol. 1982 Sep 10;210(2):163–73.
28. Shipley MT. Insular cortex projection to the nucleus of the solitary tract and brainstem visceromotor regions in the mouse. Brain Res Bull. 1982 Feb;8(2):139–48.
29. van der Kooy D, McGinty JF, Koda LY, Gerfen CR, Bloom FE. Visceral cortex: a direct connection from prefrontal cortex to the solitary nucleus in rat. Neurosci Lett. 1982 Nov 30;33(2):123–7.
30. Abboud H, Berroir S, Labreuche J, Orjuela K, Amarenco P, GENIC Investigators. Insular involvement in brain infarction increases risk for cardiac arrhythmia and death. Ann Neurol. 2006 Apr;59(4):691–9.
31. Eckardt M, Gerlach L, Welter FL. Prolongation of the frequency-corrected QT dispersion following cerebral strokes with involvement of the insula of Reil. Eur Neurol. 1999;42(4):190–3.
32. Vingerhoets F, Bogousslavsky J, Regli F, Van Melle G. Atrial fibrillation after acute stroke. Stroke. 1993 Jan;24(1): 26–30.
33. Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. Stroke. 2004 Sep;35(9): 2094–8.
34. Oppenheimer SM, Kedem G, Martin WM. Left-insular cortex lesions perturb cardiac autonomic tone in humans. Clin Auton Res. 1996 Jun;6(3):131–40.
35. Han IJ, Lee JE, Song HN, et al. Imaging and clinical predictors of acute constipation in patients with acute eschemic stroke. Front Neurosci. 2023 Sep 13;17:1263693.
36. Sun Y, Lin Y, Wang J, et al. Risk factors for constipation in patients with acute and subacute ischemic stroke: a retrospective cohort study. J Clin Neurosci. 2022 Dec;106:91–5.
37. Liu Z, Ge Y, Xu F, et al. Preventive effects of transcutaneous electrical acustimulation on ischemic stroke-induced constipation mediated via the autonomic pathway. Am J Physiol Gastrointest Liver Physiol. 2018 Aug 1;315(2): G293–301.
38. Xiong L, Leung HW, Chen XY, Leung WH, Soo OY, Wong KS. Autonomic dysfunction in different subtypes of post-acute ischemic stroke. J Neurol Sci. 2014 Feb 15;337(1-2): 141–6.
39. De Raedt S, De Vos A, De Keyser J. Autonomic dysfunction in acute ischemic stroke: an underexplored therapeutic area? J Neurol Sci. 2015 Jan 15;348(1-2):24–34.
40. Camara-Lemarroy CR, Ibarra-Yruegas BE, Gongora-Rivera F. Gastrointestinal complications after ischemic stroke. J Neurol Sci. 2014 Nov 15;346(1-2):20–5.
41. Schaller BJ, Graf R, Jacobs AH. Pathophysiological changes of the gastrointestinal tract in ischemic stroke. Am J Gastroenterol. 2006 Jul;101(7):1655–65.

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