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Prevalence and prognosis of intracranial stenosis in acute ischemic stroke; a single center registry from Turkey

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Background/aim: Intracranial stenosis (ICS) is identified in 2.2%–70.4% of patients with ischemic stroke and transient ischemic attack. This study aimed to determine the prevalence of ICS in a single center registry from Turkey.

Materials and methods: We reviewed the charts of 619 patients with acute ischemic stroke. ICS was defined as any ICS > 50% on cerebrovascular imaging. The demographic data, risk factors, NIHSS scores and C reactive protein level at admission, mortality in hospital, recurrent stroke, and mRS in the follow-up period were recorded.

Results: A total of 72 (11.6%) patients with ICS (45 males (62.5%); mean age 68.3 ± 12.6 years) were included. Sixty-seven patients (10.8%) had symptomatic ICS and 44 patients (7.1%) had ICS without extracranial stenosis. Diabetes mellitus (DM) was significantly higher in the ICS group compared to the others ($P = 0.017$). Disability was significantly better in patients with ICS compared to the others ($P < 0.001$). On logistic regression analysis, DM and follow up mRS were significantly associated with ICS ($P < 0.05$).

Conclusion: ICS was seen in 11.6% of acute ischemic stroke cases in our registry. DM appears to be the major risk factor for ICS. Disability was better in patients with ICS. Ethnicity could be a factor causing better disability.

Key words: Intracranial stenosis, ischemic stroke, prevalence, stroke severity, prognosis

1. Introduction

Intracranial stenosis (ICS) is a leading cause of ischemic stroke or transient ischemic attack (TIA). ICS is identified in 2.2%–70.4% of patients with ischemic stroke and/or TIA (1–15). Ethnicity appears to be a major risk factor for ICS. It is common among stroke patients of Asian, Black, and Hispanic ancestry (1–9,11). Recent European studies have found a much higher prevalence of ICS than commonly presumed (10,12–15). However, the prevalence of ICS in patients with acute ischemic stroke has not been reported yet in Turkey. Only, Alkan et al. evaluated the prevalence of ICS in patients with extracranial artery stenosis and coronary artery bypass grafting surgery in Turkish patients (16).

It is known that stroke patients with ICS have higher recurrence rates of ischemic stroke and death than those without ICS (12,13). Diabetes mellitus (DM), hypertension, and hypercholesterolemia have been found independently associated with ICS in previous studies (3,11,13–21). The present study aimed to determine the prevalence, risk factors, and prognosis of ICS in our stroke registry.

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2. Materials and methods

The medical records of 619 consecutive patients who were admitted with acute ischemic stroke from January 2012 to November 2014 were retrospectively evaluated. Approval was obtained from the research ethics committee in advance of the study. ICS was defined as any intracranial stenosis >50% on cerebrovascular imaging such as computerized tomography angiography, magnetic resonance angiography, or digital subtraction angiography performed within 1 week of ischemic stroke. The degree of stenosis was calculated according to the WASID method (22). Clot was defined if there was an angiographic evidence of abrupt cut-off or there was vascular imaging evidence that the occluded intracranial artery has been completely recanalized. The patients were divided into two groups: group 1 included patients with ICS and group 2 included patients without ICS.

Patient demographics and medical risk factors, including history of hypertension, diabetes, hyperlipidemia, atrial fibrillation, congestive heart failure, coronary artery disease, previous transient ischemic attack, previous stroke, the National Institutes of Health Stroke Scale (NIHSS) scores at admission, and C reactive protein (CRP) level were collected using a standard data collection form and entered into an institutional database. Hypertension was defined as blood pressure ≥140/90 mmHg on repeated measurements or prior use of antihypertensive medication, diabetes mellitus as fasting blood glucose level ≥126 mg/dL on repeated measurements or the use of medications to lower blood glucose, and atrial fibrillation by previous history or if detected on ECG or Holter. Coronary artery disease included any history of angina, myocardial infarction, or coronary revascularization.

A single rater (MHS) determined etiologic stroke subtypes using the automated Causative Classification System (CCS, available at https://ccs.mgh.harvard.edu) (23). The CCS subtypes included supraaortic large artery atherosclerosis, cardioaortic embolism, small artery occlusion, other causes, and undetermined causes. Etiologic work-up included vascular imaging studies, such as carotid Doppler ultrasonography, computerized tomography angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA), transthoracic or transesophageal echocardiography, 24-h cardiac rhythm monitoring, and laboratory tests for hypercoagulability and vasculitis. CTA, MRA, and DSA were performed in a total of 418, 130, and 71 patients, respectively. The modified Rankin Scale (mRS) scores were recorded according to follow-up visits of the patients.

2.1. Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc. Chicago, IL, USA). Descriptive statistics were expressed as means/standard deviations for normally distributed continuous variables and median/interquartile range for nonnormally distributed variables. Statistical analysis was performed to determine the prevalence and prognosis of the patients with ICS and without ICS. The group rates were compared using a chi-squared test and the means were compared using Student's t test. Univariate and multivariate analyses were performed with the use of logistic regression to identify predictor variables of ICS. $P < 0.05$ was considered to be statistically significant.

3. Results

A total of 72 (11.6%) patients (45 males (62.5%) and 27 females (37.5%); mean age 68.3 ± 12.6 (37–98) years) who were included in the study had ICS (Table 1). Symptomatic ICS was found in 67 (10.8%) and 44 (7.1%) patients had ICS without extracranial stenosis (Table 2). Twenty-eight of them had extracranial stenosis. The extracranial stenoses of these patients were in different localizations with ICS.

ICA was localized in the distal internal carotid artery in 32 patients, the middle cerebral artery in 26 patients, the anterior cerebral artery in 2 patients, the intracranial vertebral artery in 2 patients, the basilar artery in 4 patients, and the posterior cerebral artery in 6 patients (Table 2).

No between-group differences in history of hypertension, hyperlipidemia, atrial fibrillation, congestive heart failure, coronary artery disease, previous transient ischemic attack, or previous stroke were observed ($P > 0.05$). DM was significantly higher in the ICS group compared to the others ($P = 0.017$). Otherwise, atrial fibrillation was significantly higher in group 2 compared to group 1 ($P = 0.019$) (Table 1). There was no significant difference between the groups in terms of NIHSS score or CRP levels at admission (Table 1).

There were 58 (80.6%; symptomatic ICS; n = 57, asymptomatic ICS; n = 1) patients with large artery atherosclerosis and 2 (2.8%; asymptomatic ICS; n = 2) patients with cardioaortic embolism, according to the CCS. Twelve (16.7%; symptomatic ICS; n = 10, asymptomatic ICS; n = 2) patients remained undetermined/unclassified (Table 3).

Mortality in hospital was not significantly different between the groups ($P = 0.126$). The follow-up information was accessible for 43 patients in group 1 and 265 patients in group 2. The mean follow-up time of the patients was 9 (1–32) months and the mean mRS was 1.7 ± 1.7 (0–6) in group 1 and 2.6 ± 2.4 (0–6) in group 2 during the follow-up period. The outcome was significantly better in the patients with ICS ($P < 0.001$). Recurrent stroke occurred in 3 (4.2%) patients with ICS and in 10 (1.8%) patients without ICS. It was higher in the ICS group, but not significantly ($P = 0.19$) (Table 1).

On logistic regression analysis, DM, follow-up mRS ≤ 3, and non-AF were significantly associated with ICS (Table 4).

4. Discussion

4.1. Prevalence of ICS

The occurrence of ICS has been found more frequent than that of extracranial artery stenosis in the Chinese population. Previous studies reported that ICS with a frequency of 25.9%–70.4% was the leading cause of ischemic stroke or TIA in this population (1,2,4–9). De Silva et al. evaluated 200 patients with acute ischemic stroke from South Asia. Adequate intracranial vessel assessment was performed in 188 patients. ICS was found in 54% of all stroke subtypes. A total of 80% (16 of 20) of patients with extracranial carotid artery stenosis/occlusion had ICS (11).

In the USA, Sacco et al. prospectively evaluated 438 patients with acute ischemic stroke (Black 35%, Hispanic 46%, White 19%). ICS was documented in 32 patients (8%, 10 Black, 21 Hispanic, 1 White). ICS was more common in patients of Black and Hispanic ancestry than in Caucasians

Table 1. Epidemiologic and clinical characteristics of patients with ICS and without ICS.

	ICS n = 72	Non-ICS n = 547	P
Age, year, Mean ± SD	68.3 ± 12.6	69.6 ± 13.4	0.27
Sex, n (%)			
Female	27 (37.5)	263 (48.1)	0.091
Male	45 (62.5)	284 (51.9)	
Medical history			
- Hypertension, n (%)	48 (66.7)	384 (70.2)	0.539
- Diabetes mellitus, n (%)	30 (41.7)	153 (28.0)	0.017
- Atrial fibrillation, n (%)	7 (9.7)	118 (21.6)	0.019
- Hyperlipidemia, n (%)	20 (27.8)	138 (25.2)	0.641
- CAD, n (%)	21 (29.2)	123 (22.5)	0.207
- CHF, n (%)	4 (5.6)	66 (12.1)	0.101
- Previous TIA history, n (%)	8 (11.1)	40 (7.3)	0.257
- Previous stroke history, n (%)	12 (16.7)	94 (17.2)	0.913
CRP, mg/L	17.7 ± 22.4	24.2 ± 41.6	0.384
Admission NIHSS, Mean ± SD (Min–Max)	5.61 ± 3.53 (0–14)	6.13 ± 4.64 (0–26)	0.684
Mortality in hospital, n (%)	4 (5.6)	63 (11.5)	0.126
Follow-up mRS, Mean ± SD (Min–Max)	1.7 ± 1.7 (0–6)	2.6 ± 2.4 (0–6)	<0.001
Follow-up months, Mean ± SD	8.1 ± 6.9	9.9 ± 8.4	0.099
Recurrent stroke, n (%)	3 (4.2)	10 (1.8)	0.193

SD: standard deviation, CAD: coronary artery disease, CHF: congestive heart failure, TIA: transient ischemic attack, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale scores, CRP: C reactive protein

Table 2. Location of intracranial atherosclerosis.

	ICS n = 72
ICA, n (%)	32 (44)
MCA, n (%)	26 (36)
ACA, n (%)	2 (3)
PCA, n (%)	6 (8)
BA, n (%)	4 (6)
VA, n (%)	2 (3)
With ECS, n (%)	67 (93)

ICA: internal carotid artery, MCA: middle cerebral artery, ACA: anterior cerebral artery,
VA: vertebral artery, BA: basilar artery, PCA: posterior cerebral artery, ECS: external carotid artery stenosis

(3). Prevalence of ICS was also evaluated in patients with stroke or TIA in European populations, and found in approximately 2.2% to 12% of these cases (10,12–15). Weimar et al. studied 4157 patients with acute ischemic stroke from Germany who had complete cerebrovascular imaging results. Symptomatic ICS was detected in 6.5% (n = 272) of all stroke subtypes (10). In another study from Germany, Weber et al. evaluated 13,584 patients with acute ischemic stroke and ICA was found in 304 (2.24%) patients (12).

Meseguer et al. evaluated 1881 patients with a suspected TIA in France and ICS was documented in 148 (8.1%) patients by using TCD (13). Tsivgoulis et al. evaluated 467 patients with ischemic stroke prospectively. ICS was found in 51 (10.9%) Greek patients and 43 of them were symptomatic (14).

Logallo et al. included 607 patients with ischemic stroke or TIA and ICS was documented in 69 (11.4%) patients in their Norwegian stroke population. A possible

Table 3. Etiologic stroke subtypes using the automated Causative Classification System of patients' intracranial stenosis (ICS).

	Symptomatic ICS n = 67	Asymptomatic ICS n = 5
CCS classification, n (%)		
- Large-artery atherosclerosis	57 (85.1)	1 (20)
- Cardioaortic embolism	0 (0)	2 (40)
- Small artery occlusion	0 (0)	0 (0)
- Other causes	0 (0)	0 (0)
- Undetermined causes	10 (14.9)	2 (40)

ICS: intracranial stenosis, CCS: Causative Classification System

Table 4. Logistic regression analysis of ICS.

	OR	95%, CI	P
Diabetes mellitus, n (%)	2.145	1.113–4.133	0.023
Atrial fibrillation, n (%)	3.504	1.041–11.787	0.043
Follow-up mRS ≤ 3	3.719	1.590–8.696	<0.001

mRS: modified Rankin Scale

atherosclerotic etiology was found in 62 (10.2%) patients with ICS, while 45 (7.4%) patients were symptomatic (15).

Conflicting rates of ICS in previous studies may be explained by different imaging methods such as transcranial color coded sonography, computerized tomography angiography, magnetic resonance angiography, and digital subtraction angiography for evaluating ICS.

In our registry, ICS was found in 72 (11.6%) patients with acute ischemic stroke and/or TIA. Symptomatic ICS was found in 67 (10.8%) patients and 44 (7.1%) patients had ICS without extracranial artery stenosis. Prevalence of ICS in our stroke registry was similar to that in the Norwegian and Greek stroke populations.

4.2. Location of ICS

The middle cerebral artery appeared to be most commonly involved in most studies, followed by the internal carotid artery, basilar artery, vertebral artery, posterior cerebral artery, and anterior cerebral artery (1,2,4–9,12,14,19,24).

Meseguer et al. found that the most common ICS location was the carotid siphon arteries (n = 78, 4.3%) followed by the middle cerebral artery (n = 61, 3.5%), basilar artery (n = 26, 1.4%), and vertebral artery (n = 23, 1.3%) (13).

Alkan et al. reported that the internal carotid artery was the most common location of ICS in Turkish patients with extracranial artery stenosis and coronary artery bypass grafting surgery (16).

In our registry, ICS was most commonly localized in the distal internal carotid artery (n = 32) followed by the middle cerebral artery (n = 26), the basilar artery (n = 4), the posterior cerebral artery (n = 6), the anterior cerebral artery (n = 2), and the vertebral artery (n = 2), similar to these two studies.

4.3. Risk factors of ICS

In previous studies, it has been determined that DM was associated with ICS (3,13–17,19,21). Tsivgoulis et al. found that DM was the strongest predictive factor of ICS (14). Arenillas et al. reported that high lipoprotein (a) level and DM were independent markers of a greater extent for ICS (19).

There are also several studies showing a significant association between ICS and other vascular risk factors, including hypertension, hyperlipidemia, and metabolic syndrome (3,9,11,13,14,17,18,20,21,25). Advancing age was detected as a significant risk factor for MCA stenosis (13,26). Meseguer et al. documented that male sex and ABCD2 score > 4 were related to ICS (13).

In our registry, only DM was significantly associated with ICS (P = 0.007). We conclude that DM could be the major risk factor for ICS.

4.4. Stroke severity

Admission NIHSS was used for evaluation of stroke severity in previous studies. In some studies, stroke severity in patients with ICS was higher than in patients without ICS (10,11). Logallo et al. did not find any significant difference between the groups, similar to our result (15).

4.5. Recurrent stroke rate, mortality in hospital, and disability of ICS

Recurrent ischemic stroke or TIA due to ICS has been reported as ranging from 7% to 38.2% (10,12,13,24). We found recurrent ischemic stroke to be 4.2% in patients and it was the lowest in the literature.

Meseguer et al. found that the incidence of recurrent vascular events, including TIA recurrence, stroke, myocardial infarction, and vascular death, was 7.0% in patients with ICS and 2.4% in patients without ICS after 1 year follow up on best preventive therapy ($P < 0.007$) (13). In our registry, recurrent stroke was higher in the ICS group, but was not significantly so ($P = 0.193$). In addition, there was no significant difference between the groups in terms of mortality in hospital ($P = 0.126$).

Logallo et al. reported that the rate of follow-up mRS > 2 was significantly higher in patients without ICS (15). The mRS score on follow-up was lower in patients with ICS compared to patients without ICS ($P < 0.001$). Ethnicity could be a factor causing better disability. Further studies with larger patient numbers are needed to clarify this issue.

There are several limitations of our study, including its retrospective design, different methods used for detecting ICS, and relatively short follow-up duration. In addition, this is a restriction of the cohort to a single medical center. However, all of our patients underwent a detailed work-up for determining ICS.

In conclusion, ICS was seen in 11.6% of acute ischemic stroke patients in our registry. It was similar to that in the Norwegian and Greek stroke populations, but it was lower than that in an Asian population. DM appears to be the major risk factor for ICS. Disability was better in patients with ICS. It could be related to ethnicity.

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