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Evaluation of intracranial atherosclerotic disease risk factors in patients with acute ischemic stroke

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Abstract

Background & Objective: Intracranial atherosclerotic disease (ICAD) is a prevalent cause of ischemic stroke and is related to recurrent strokes. In this study, we aim to identify the ICAD rate and establish the risk factors in patients with acute ischemic stroke (AIS) in our population in Turkey. *Methods*: Eight hundred sixty-two patients diagnosed with AIS in our tertiary centre between 01-01.2019 and 01.01.2021 were retrospectively included in this study. *Results*: We detected ICAD in 172 (20%) patients. While the independent risk factors of anterior ICAD were hypertension and diabetes mellitus, the risk factors of posterior ICAD were advanced age, diabetes mellitus, hyperlipidaemia and vertebral artery hypoplasia. There were more frequent posterior ICAD.
Conclusion: There was difference in the risk factors for anterior ICAD and posterior ICAD in this Turkish study.

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is a prevalent cause of ischemic stroke and is related to recurrent stroke risk.[1,2] Recent studies have found that the prevalence of ICAD is higher than predicted.[1,3] The global rate of acute ischemic stroke (AIS) from ICAD is thought to increase as the population grows in regions where ICAD is common.[1] ICAD causes approximately 5–10% of AIS in white people, 15–29% of AIS in black people and 30–50% of AIS in Asian people. The prevalence of asymptomatic ICAD was between 3–13.5%.[4-8] Age and ethnic origin are independent risk factors. Risk factors and the affected segment differ from society to society. The most common race is Asian, followed by Latin America, Africa and White. Geographical and environmental features may also affect its prevalence. Risk factors have been reported to be age, gender, race and diabetes mellitus (DM).[9] Recent clinical studies have provided a better understanding of the prognosis, imaging features and risk factors related to the risk of recurrent stroke in AIS patients with ICAD. However, more studies are needed to identify patients at risk of AIS due to ICAD and to develop new treatments to reduce the risk of stroke in these patients.[3,10] Recognising risk factors may help to take precautions. In this study, we aim to identify the ICAD rate and establish the risk factors in AIS patients in our population in Turkey.

METHODS

Eight hundred sixty-two patients diagnosed with AIS in the neurology department of the tertiary centre in Uludağ University Medicine Faculty between 01.01.2019 and 01.01.2021 were retrospectively included in this study. Approval for this study was received from the local ethics committee with a letter dated 11.04.2023, numbered 2023-7/37. Since this is a retrospective study, a consent form is not necessary. Inclusion criteria for the study were determined as a patient's admission to the emergency service for the first 24 hours following the focal neurological deficit, diagnosis of AIS following neuroimaging, cranial magnetic resonance imaging (MRI), brain–neck computed tomography (CT) angiography, echocardiography, rhythm Holter and regular follow-ups in neurology stroke outpatient clinic for three months to determine the clinical outcome. Exclusion criteria for this study were as follows: a patient's aetiology of the stroke could not be clarified and when a patient had

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significant vessel occlusion and high creatinine. Between 01.01.2019 and 01.01.2021, 1,160 patients were diagnosed with AIS. Following the study's inclusion and exclusion criteria, 862 patients were included (Figure 1). A neurologist examined all patients. The patients were admitted to the neurology service for further examination and treatment. Brain–neck CT angiography, transthoracic echocardiography and 24-hour rhythm Holter were performed in all patients to elucidate the aetiology of stroke in the neurology service. Medical history, smoking history, presence of DM, hypertension (HT), heart failure and history of coronary disease were recorded during the patients' hospitalisation. The stroke aetiology of the patients was determined using the Trial of Org 10172 in Acute Stroke Treatment (*TOAST*) stroke classification. In our study, anterior circulation was defined as the branch of the internal carotid arteries (ICA).[11] Posterior circulation was described as vertebral artery (VA), basilar artery (BA) and the components of BA.[12] The VA was evaluated in four segments[13], and the BA was considered in three parts.[14] ICAD was assessed by CT angiography and calculated by referring to the Warfarin–Aspirin Symptomatic Intracranial Disease study.[15] CTA examinations were performed using a 128-slice Somatom Definition AS+ (Siemens, Erlangen, Germany) multidetector CT device. The images of the patients were evaluated unthinkingly by a radiologist. The diameters of both VA of all patients were measured, and the diameter difference of the VA was recorded in the data. The patient's clinical outcome was determined in the third month (mRs 0–2 good clinical outcome, mRs 3–6 poor clinical outcome).

Statistical analysis

Patients diagnosed with AIS were categorised as those with and without ICAD. The demographic, clinical and radiological data were analysed. Statistical analysis was implemented with the IBM SPSS Statistics 25.0 package (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test and Q-Q plot were applied to verify the normality of the data distribution. Frequencies and percentages are given for categorical variables. The Mann–Whitney U test or independent sample t-test was used to determine characteristics in continuous

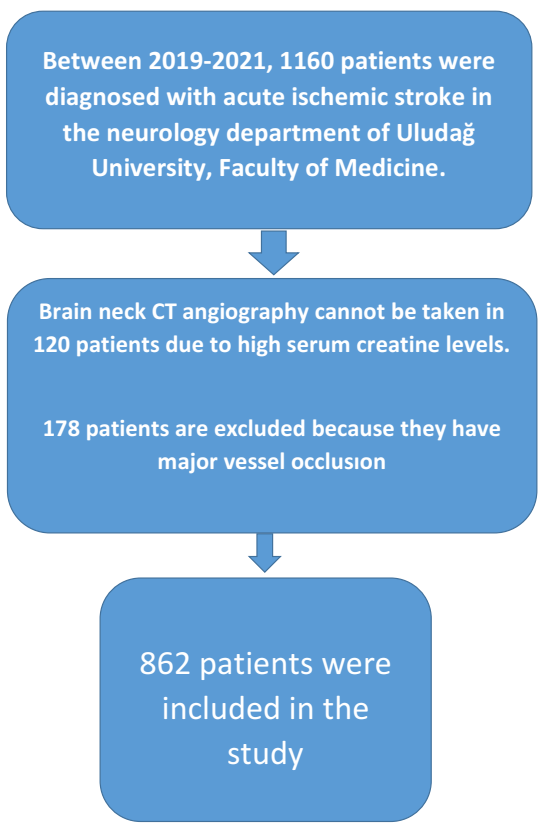

Figure 1: Flowchart of inclusion of the patients with acut ischemic stroke

variables between AIS patients with and without ICAD. Pearson's chi-square test and Fisher's exact test were applied to determine the characteristics of categorical variables between AIS patients with and without ICAD. We used binary logistic regression analysis to determine the independent risk factors for ICAD in our AIS population. P < 0.05 was considered statistically significant. Receiver operating characteristics (ROC) analysis was applied to analyse the cut-off value of the VA diameter difference.

RESULTS

A total of 862 patients, 333 (38.6%) female and 529 (41.4%) male, were included in the study. The mean age of the men was 64.84 ± 10.688 year. The mean age of the women was 65.84 ± 13.688 year. There was a statistically significant difference in the mean age of men and women (p = 0.033). HT was present in 661 (76.68%) of the patients. A total of 361 (41.87%) patients had a diagnosis of DM, 368 (42.69%) patients were smokers, 129 (14.96%) patients had a diagnosis of heart failure and 143 (16.58%) patients had a history of stroke recurrence. A stroke neurologist classified stroke aetiologies of the AIS patients; it was determined that 341 (39.6%) patients had an AIS due to large vessel atherosclerosis, 231 (26.8%) patients had an AIS due to cardioembolism in 231 (26.8%) patients, 146 (16.9%) patients had an AIS due to small vessel disease, 31 (3.6%) patients had an AIS due to other causes and 111 (13.1%) patients were found to have an AIS of unknown cause. In our study, 179 patients were treated with thrombolytic treatment. A total of 211 (24.47%) patients had poor clinical outcomes, and 651 (75.53%) had good clinical outcomes.

ICAD was present in 172 (20%) of the patients. While 82 (9.5%) patients had ICAD in the anterior circulation, 131 (15.20%) had ICAD in the posterior circulation. Involvement of the ICA was detected in 41 (4.7%) patients, middle cerebral artery (MCA) in 41 (4.7%) patients, anterior cerebral artery (ACA) in 9 (1.04%) patients, posterior cerebral artery (PCA) in 8 (0.92%) patients, VA V4 segment in 70 (8.1%) patients and BA in 68 (7.8%) patients. When anterior circulation was evaluated, ICAD was found in the cavernous segment of the ICA in 30 (3.5%) patients and in the supraclinoid segment of the ICA in 11 (1.3%) patients. In the MCA M1 segment in 36 (4.17%) patients, ICAD was detected in the M2 segment in 7 (0.81%) patients. When the posterior circulation was evaluated, ICAD was found in the B1 (proximal) segment of the BA in 40 (4.64%) patients, in the B2 (middle) segment in 21 (2.43%) patients and in the B3 (distal) segment in 7 (0.81%) patients.

When demographic, clinical and radiological features related to ICAD were evaluated, there was a significant relationship between HT (p = 0.042), presence of DM (p < 0.001), recurrence of stroke (p = 0.002), serum low-density lipoprotein (LDL) value (p = 0.001), serum glucose value (p = 0.002), serum hbA1c value (p = 0.014), diameter difference of VA (p < 0.001) and *TOAST* stroke aetiology (p < 0.001). No statistically significant correlation was found between age, gender, heart failure, smoking, coronary artery disease, serum creatinine level, serum haemoglobin level and clinical outcome (p < 0.05) (Table 1).

When the demographic, clinical and radiological features correlated with ICAD in the anterior circulation were evaluated, we found a significant relationship between HT (p < 0.001), DM (p < 0.001), stroke recurrence (p < 0.001), serum glucose level (p = 0.027), serum hbA1c value (p = 0.05) and *TOAST* stroke aetiology (p < 0.001). No significant relationship was identified between age, gender, smoking, heart failure, coronary artery disease, serum haemoglobin value, serum LDL value, serum creatinine value and clinical outcome (p > 0.05) (Table 2).

When the significant variables related to ICAD in the anterior circulation were analysed by binary logistic regression, HT (p = 0.034, OR = 2.315) and DM (p = 0.010, OR = 1.878) were found to be independent risk factors (Table 3).

When demographic, clinical and radiological features related to ICAD in the posterior circulation were evaluated, there was a significant relationship between DM (p < 0.001), stroke recurrence (p = 0.003), serum glucose level (p < 0.001), serum LDL level (p = 0.009), serum hbA1c level, VA diameter difference (p < 0.001) and *TOAST* stroke aetiology (p < 0.001). No statistically significant correlation was identified between gender, age, presence of HT, heart failure, coronary artery disease, serum haemoglobin value, serum creatinine level and clinical outcome (Table 2).

When the significant variables associated with ICAD in the posterior circulation were assessed by binary logistic regression, advanced age (p = 0.021, OR = 1.023), VA diameter difference (p < 0.01, OR = 1.058), serum LDL value (p < 0.01, OR = 1.010) and the presence of DM (p = 0.006, OR = 1.741) were found to be independent risk factors (Table 4).

Table 1: Evaluation of clinical demographic and radiological features associated with intracranial atherosclerotic stenosis

Variables	Patients with ICAD n=172	Patients without ICAD n=690	P value
Age*	66.45±10.719	64.93±12.213	ns
Sex (male gender)**	107(62.20%)	422(61.15%)	ns
Hypertension**	142(82.55%)	519(75.21%)	**0.042**
Diabetus mellitus**	94(54.65%)	267(38.69%)	**<0.001**
Being smoker**	82(47.67%)	286(41.44%)	ns
Heart failure**	22(12,79%)	107(15.50%)	ns
Coronary artery disease**	46(26.74%)	172(24.92%)	ns
Stroke recurrence**	45(26.16%)	98(14.20%)	**<0.001**
Serum LDL value*	134.81±47.235	121.26±37.275	**0.001**
Serum Glucose value*	160.58±93.629	136.12±63.055	**0.002**
Serum Hba1c value*	7.24±2.105	6.55±1.593	**0.014**
Serum creatinine value*	0.94±0.355	0.95±0.540	ns
Haemoglobin value*	13.13±1.764	13.11±1.916	ns
Vertebral artery diameter difference*	14.02±13.055	8.08±9.86	**<0.001**
Toast Stroke aetiology **			**<0.001**
Large artery disease	112(70.93%)	229(33.18%)	
Cardioembolic stroke	22(12.79%)	208(30.14%)	
Small vessel disease	22(12.79%)	124(17.97%)	
Other causes	5(2.90%)	26(3.76%)	
Cryptogenic stroke	10(5.80%)	103(14.92%)	
Clinical outcome** (poor clinical outcome)	43(25%)	167(24.20%)	ns

Significant variables are shown in bold. *Mann-Witney U test, **Pearson chi-square test/continuity correction test/ Fisher Exact test, ICAD; Intracranial atherosclerotic disease, LDL; low-density lipoprotein, ns; nonsignificant

ROC analyses were performed because the VA diameter difference is one of the posterior circulation's most significant risk factors. The cut-off value for the VA diameter difference was determined as 1.4 mm ($p < 0.001$; the area under the curve = 0.688; sensitivity = 53.44%; specificity = 80.44%] (Figure 2).

DISCUSSION

In this study, ICAD risk factors were HT, DM, high serum LDL level and vertebral artery hypoplasia (VAH) in our AIS population, and stroke recurrence was statistically significantly higher in AIS patients with ICAD. European and American studies have shown that the most common ICAD arteries were the ICA, MCA, BA, VA, PCA and ACA.[16,17] In Asian studies, the most common ICAD was the MCA, followed by the ICA, BA, VA, PCA and ACA.[18]

In our study, the most common ICAD was the BA and the V4 segment of the VA, which is a surprising result. As age progresses, intracranial arteries reply with a gradual loss of elastin fibres, medial muscle elements and an expansion in collagen tissue, replacing muscle fibres in the tunica media. There are some histopathological differences in age-related anterior and posterior circulation changes. With age, more elastin loss and concentric intimal thickening have been found in the posterior circulation.[19] As a result of the increase in average age all over the world, the average age of our population is above that in the literature. This may explain why ICAD is seen more frequently in the posterior circulation than in the anterior circulation. The most common ICAD segment of the BA was the B1 (proximal) segment, and the most common ICAD segment

Table 2: Evaluation of clinical demographic and radiological features associated with intracranial atherosclerotic stenosis in anterior and posterior circulation

Variables	Patients with anterior ICAS n=82	Patients without anterior ICAS n=780	P value	Patients with posterior ICAS n=131	Patients without posterior ICAS n=731	P value
Age*	66.99±11.47	66.05±11.97	ns	67.09±9.79	64.90±12.26	ns
Sex(male gender)**	50(60.97%)	479(61.41%)	ns	47(35.87%)	286(39.12%)	ns
Hypertension**	74(90.24%)	587(75.25%)	**<0.001**	106(80.91%)	555(75.92%)	ns
Diabetus mellitus**	49(59.75%)	312(40%)	**<0.001**	72(54.96%)	289(39.53%)	**<0.001**
Being smoker**	35(42.68%)	333(42.69%)	ns	65(49.61%)	303(41.45%)	ns
Heart failure**	12(14.63%)	117(15%)	ns	18(13.74%)	111(15.18%)	ns
Coronary artery disease**	23(28.04%)	195(25%)	ns	37(28.24%)	181(24.76%)	ns
Stroke recurrence**	26(31.70%)	117(15%)	**<0.001**	34(25.95%)	109(14.91%)	**0.003**
Serum Ldl value*	132.31±44.21	123.12±39.27	ns	137.39±48.16	121.55±37.63	**<0.001**
Serum Glucose value*	161.43±89.64	138.86±68.30	**0.027**	165.78±97.39	136.56±64.03	**<0.001**
Serum Hba1c value*	7.20±2.16	6.63±1.66	**0.057**	7.48±2.28	6.56±1.59	**0.009**
Serum creatinine value*	12.97±1.86	13.13±1.88	ns	13.18±1.74	13.10±1.91	ns
Haemoglobin value*	0.96±0.42	0.95±0.52	ns	0.95±0.37	0.95±0.53	ns
Vertebral artery diameter difference*	11.38±12.03	9.04±10.68	ns	16.55±13.42	13.10±1.91	**<0.001**
Toast Stroke aetiology **			**<0.001**			**<0.001**
Large artery disease	56(68.29%)	286(36.66%)		88(67.17%)	254(34.74%)	
Cardioembolic stroke	7(8.53%)	223(28.58%)		20(15.26%)	210(28.72%)	
Small vessel disease	12(14.63%)	134(17.17%)		13(9.92%)	133(18.19%)	
Other causes	3(3.65%)	28(3.58%)		3(2.29%)	28(3.83%)	
Cryptogenic stroke	4(4.87%)	109(13.97%)		7(5.34%)	106(14.50%)	
Clinical outcome** (poor clinical outcome)	18(21.95%)	192(24.61%)	ns	30(22.90%)	181(24.76%)	ns

Significant variables are shown in bold. *Mann-Witney U test, **Pearson chi-square test/continuity correction test/Fisher Exact test, ICAD; Intracranial atherosclerotic disease, LDL; low-density lipoprotein, ns; nonsignificant

in the ICA was the cavernous segment, which is consistent with the literature. However, in our study, the most common ICAD segment of the MCA was the M1 segment, which was not compatible with the literature.

Previous literature has reported that ICAD risk factors differ in anterior and posterior circulation. While DM and Black race were risk factors in the anterior circulation, age, male gender,

Table 3: Evaluation of significant variables by binary logistic regression for patients with anterior circulation atherosclerotic stenosis

Variables	P value	Odds ratio	%95 C.I for EXP(B)	
			lower	upper
Age	0.447	1.009	0.986	1.031
Hypertension Ref: present vs absent	**0.034**	2.315	1.064	5.036
Diabetes mellitus Ref: present vs absent	**0.010**	1.878	1.165	3.029

Significance of the model: p<0.001. Significant variables are shown in bold letters. vs: versus, Ref: Reference

Table 4: Evaluation of significant variables by binary logistic regression for patients with posterior circulation atherosclerotic stenosis

	p value	Odds ratio	%95 C.I for EXP(B)	
			lower	upper
Age	**0.021**	0.21	1.012	2.592
Sex Ref: female gender vs male gender	0.415	1.191	0.782	1.813
Vertebral artery diameter difference	**<0.01**	1.058	1.041	1.075
Serum LDL value	**<0.01**	1.010	1.005	1.015
Diabetes mellitus Ref: present vs absent	**0.06**	1.741	1.005	2.592

Significance of the model: p<0.001. Significant variables are shown in bold letters. Vs: versus, Ref: Reference

hyperlipidaemia and coronary artery disease were determined as risk factors in the posterior circulation.[3,20,21]

According to our study's binary logistic regression results, the independent risk factors were HT and DM in the anterior circulation. At the same time, age, DM, VAH and hyperlipidaemia were determined in the posterior circulation.

Age, a nonmodifiable risk factor, is an independent risk factor for intracranial and extracranial atherosclerosis. According to our study, advanced age is an independent risk factor for posterior ICAD.[3,22,23] The incidence of extracranial atherosclerosis is high in men, but this relationship is less pronounced for ICAD, and the course of the disease is highly variable in men and women.[22,23]

In males, common ICAD is seen in the 4th and 5th decades and progresses moderately with age. In women, ICAD begins in the 6th decade and

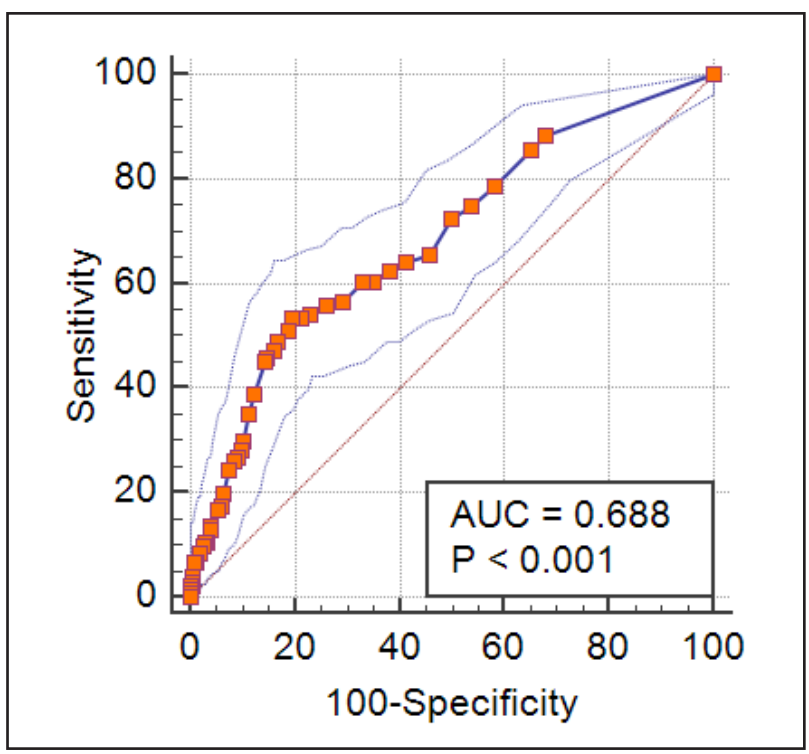

Figure 2: Evaluation of ROC analyses vertebral artery diameter difference in the posterior circulation.

progresses rapidly. It is more common in women in the 8th and 9th decades.[24] Although Asian studies have shown differences in ICAD and gender, no relationship was found between gender and ICAD in our research.[24,25] DM has been defined as an independent risk factor for ICAD.[3,26,22] Diabetic patients may predispose themselves to ICAD due to impaired cerebral vasomotor reactivity secondary to autonomic neuropathy.[27] The high prevalence of ICAD in Asian patients may be due to the high prevalence of DM.[28] Studies in Korea state that DM is a risk factor for posterior ICAD only for those over 50.[29] In our study, DM was found to be a risk factor for both anterior and posterior ICAD. Atherosclerosis is a chronic inflammatory and progressive disease. Although all risk factors are systemic, atherosclerotic plaques are local, non-continuous and occur in well-defined areas (such as the ICA bifurcation). Although all risk factors for atherosclerosis are systemic, it is interesting that ICAD risk factors differ in the anterior and posterior circulation.[30-32] Along with systemic risk factors, fluid dynamics and arterial geometry play a significant role in the progression of atherosclerosis, showing that the combination of local factors in vascular structures is equally important.[33] Previous studies have defined VAH as an independent risk factor for ICAD in the posterior circulation.[34] In our research, while VAH and hyperlipidaemia were not risk factors for anterior circulation, they were found to be independent risk factors for posterior circulation. The ROC analysis showed a VA diameter difference's cut-off value of 1.4 mm. Possible reasons for the occurrence of ICAD in the posterior circulation in patients with VAH may be increased pressure difference in the bifurcation areas, low blood flow velocity in the hypoplastic VA and prolonged contact of LDL with the lumen.[35]

In conclusion, our study detected ICAD in 172 (20%) patients. While the independent risk factors of anterior ICAD were HT and DM, the risk factors of posterior ICAD were HT, DM, hyperlipidaemia and VAH. The fact that our study detected posterior ICAD more frequently is a surprising result. The most significant limitation of our study is that it was retrospective and hospital-based. Our study was a CT angiography study, and patients who could not receive contrast material due to renal dysfunction were excluded. Another limitation of our study is excluding these patients since we could not determine the aetiology of significant vessel occlusions. Another limitation of our study is that whether ICAD is symptomatic or not was not evaluated. The parameters associated with atherosclerosis cannot be measured in vivo, so we recommend performing high-resolution MR angiography studies to examine blood flow parameters.

DISCLOSURE

Conflict of interest: None

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