Neurology Asia 2016; 21(4) : 311 – 316

Sex differences in large artery atherosclerotic stroke, a Korean study

Cindy W Yoon *MD*, Hee-Kwon Park *MD PhD*, Joung-Ho Rha *MD PhD*

Department of Neurology, Inha University School of Medicine, Incheon, Korea

Abstract

Background & Objective: Sex differences in cerebral atherosclerosis and subsequent stroke have not been thoroughly investigated and conflicting data exist. The aim of this study was to investigate sex differences in the risk factors and distribution of large artery atherosclerotic stroke in a Korean population. *Methods:* We included consecutive acute ischemic stroke patients with symptomatic extracranial atherosclerosis (ECAS) or intracranial atherosclerosis (ICAS) based on brain and vascular imaging who presented at our hospital between January 2011 and December 2015. We then compared risk factor profiles and the proportion of symptomatic ECAS and ICAS between men and women. *Results:* Eight hundred and forty four patients were enrolled during the study period. The proportion of ECAS in men was notably higher than in women (19.4% in men vs. 9.3% in women; $p < 0.001$). A multiple regression analysis showed that male gender was a factor favoring ECAS (vs. ICAS, odds ratio [OR], 3.554; 95% confidence interval [CI], 2.175-5.808; $p < 0.001$). Age (OR, 1.051; 95% CI, 1.031-1.072; $p = 0.001$) and hyperlipidemia (OR, 2.330; 95% CI, 1.538-3.529; $p < 0.001$) were also factors favoring ECAS. However, after stratification by sex, the association was only significant in men. *Conclusions:* There is a sex difference in the distribution of atherosclerotic stroke. Sex may be an effect modifier of the association between atherosclerotic risk factors and atherosclerotic distribution.

INTRODUCTION

Sex differences regarding strokes have become increasingly recognized. Epidemiologic studies reveal that strokes are more common among men but that women have more severe manifestations of the disease.[1] Sex differences may have implications for effective stroke prevention and treatment. Sex-specific guidelines have been developed for preventing stroke in women which includes recommendations on the stroke risk factors that are unique to and more common in women than men.[2] Sex differences relevant to antiplatelet treatment also have been reported.[3,4] With respect to ischemic stroke subtypes, women tend to have more cardioembolic strokes, while men have more lacunar and atherosclerotic strokes.[5,6]

Atherosclerotic stroke is one of the major causes of ischemic stroke. Cerebral atherosclerosis can be divided into extracranial atherosclerosis (ECAS) and intracranial atherosclerosis (ICAS). Little is known about sex differences in cerebral atherosclerosis and subsequent strokes due to conflicting data. Some studies have reported male predominance in ICAS,[7,8] whereas others have reported that women more commonly develop ICAS.[9-12] We aimed to investigate sex differences in the risk factors and distribution of large artery atherosclerotic stroke in a Korean population.

METHODS

We analyzed the data collected from patients admitted to Inha University Hospital with an acute ischemic stroke between January 2011 and December 2015. We included patients with an acute ischemic stroke that was considered to be caused by symptomatic ICAS or ECAS based on diffusion-weight imaging (DWI) and vascular imaging studies (magnetic resonance angiography, computed tomography angiography, or angiogram). An evident large artery atherosclerosis (LAA) according to the criteria outlined by the Stop Stroke Study Trial of Org 10172 in Acute Stroke Treatment (SSS-TOAST)[13] was considered as symptomatic ICAS or ECAS. Patients were excluded if they had cardioembolic sources[13] or other etiologies such as arterial dissection, moyamoya disease, or vasculitis.

We investigated vascular imaging findings of the relevant intra- and extracranial arteries, including the middle cerebral artery, anterior

Address correspondence to: Joung-Ho Rha, MD, PhD, Department of Neurology, Inha University School of Medicine, 7-206, 3-ga, Choong-gu, Shinheungdong, Incheon 400-103, Korea. Tel: +82-32-890-3418, E-mail: fc21@nate.com

cerebral artery, posterior cerebral artery, basilar artery, and the intra- and extracranial portions of the internal carotid artery (ICA) and the vertebral artery (VA). Stenosis of the extracranial ICA was measured using the North American Symptomatic Carotid Endarterectomy Trial method.[14] Intracranial stenosis was estimated according to the methods described in the Warfarin-Aspirin for Symptomatic Intracranial Disease study.[15] Stenosis ≥ 50% was considered significant.

Vascular risk factors, including hypertension (defined as receiving medication for hypertension or a blood pressure ≥ 140/90mmHg), diabetes mellitus (defined as the use of hypoglycemic agents, fasting blood sugar ≥ 126mg/dl, or glycosylated hemoglobin levels ≥ 6.5%), hyperlipidemia (defined as receiving cholesterol-reducing agents or an overnight fasting low-density lipoprotein ≥ 130mg/dl), and smoking habits were also analyzed.

All statistical analyses were performed using SPSS version 18 (IBM, Chicago, IL). We analyzed the differences between men and women using the chi-square test or Fisher's exact test for categorical variables and the Student's t-test or the Mann–Whitney U-test for continuous variables. Multivariate logistic regression analyses were performed to differentiate risk factors for ECAS from those for ICAS.

RESUTLS

During the study period, 2,234 patients were diagnosed with acute ischemic stroke. Of these, 844 (37.8%) patients were classified in the LAA group, 447 (20.0%) in the cardioembolism group, 359 (16.1%) in the small artery occlusion group, 446 (20.0%) in the undetermined group, and 138 (6.2%) in the other causes group.

Eight hundred and forty four patients classified as large artery atherosclerosis, including 520 men and 324 women, were analyzed. Compared with men, women were older (the mean ages for women and men were 70.0 and 64.9 years, respectively), had a higher prevalence of hypertension (71.6% vs. 64.2%; $p = 0.029$) and hyperlipidemia (58.6% vs. 46.8%; $p = 0.001$). Men were more likely to be current cigarette smokers than women (54.0% vs. 11.4%; $p < 0.001$). (Table1)

ICAS was more prevalent than ECAS in both men (ICAS 68.7% vs. ECAS 19.4% vs. ICAS + ECAS 11.9%) and women (ICAS 79.9% vs. ECAS 9.3% vs. ICAS + ECAS 10.8%). However, a significantly higher proportion of men had ECAS (19.4% in men vs. 9.3% in women; $p < 0.001$) (Fig. 1). There were no differences in distribution of ICAS and ECAS between men and women (Table 2).

In a multivariate logistic regression analysis excluding the patients with both ICAS and ECAS, the male gender was a factor favoring ECAS (vs. ICAS) (odds ratio [OR], 3.554; 95% confidence interval [CI], 2.175-5.808; $p < 0.001$) after controlling for age, hypertension, diabetes, hyperlipidemia, and smoking. Age (OR, 1.051; 95% CI, 1.031-1.072; $p = 0.001$) and hyperlipidemia (OR, 2.330; 95% CI, 1.538-3.529; $p < 0.001$) were also factors favoring ECAS (vs. ICAS). However, after stratification by sex, this association was only significant in men (Table 3). The percentage of ECAS increased with age in men but not in women (Fig. 2).

DISCUSSION

In our study, ICAS was more prevalent than ECAS in both men and women, confirming that ICAS causes stroke more frequently than ECAS in Asian populations. For unclear reasons, ECAS

Table 1: Characteristics of patients by sex

	Male (N=520)	Female (N=324)	*p*- value
Age, y, mean ± SD	64.9 ± 12.3	70.0 ± 12.1	< 0.001
Hypertension, N (%)	334 (64.2)	232 (71.6)	0.029
Diabetes mellitus, N (%)	187 (36.0)	138 (42.6)	0.059
Hyperlipidemia, N (%)	241 (46.8)	188 (58.6)	0.001
Smoking, N (%)	281 (54.0)	37 (11.4)	< 0.001
BMI, kg/m^2, median (IQR)	23.6 (21.6-25.9)	23.2 (20.9-26.1)	0.443

SD, standard deviation; IQR, interquartile range; BMI, body mass index

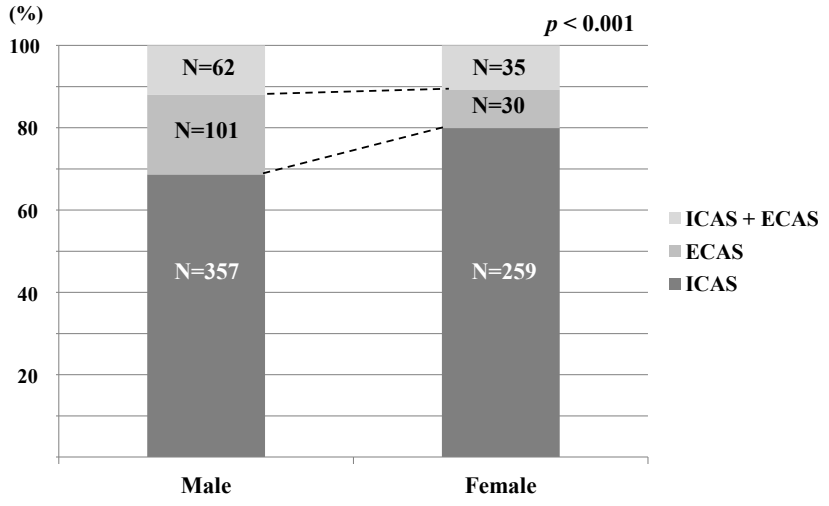

Figure 1. Percentage of male and female patients with symptomatic intracranial atherosclerosis (ICAS) and extracranial atherosclerosis (ECAS).

occurs more frequently in Caucasians, while ICAS is more common in Asian, Hispanic, and black patients.[16-18] Previous studies have shown that ICAS is responsible for ischemic stroke in 5 to 10% of white patients, whereas it may cause up to 33% of strokes in Asian, Hispanic, and black patients.[8,17,19]

Compared to the relatively consistent results on racial differences in ICAS and ECAS, the relationship between sex and cerebral atherosclerosis remains controversial. Several studies have reported female predominance in ICAS,[9-11] whereas others have reported that men are more likely to have ICAS than women.[7,8] In the present study, ICAS was more prevalent in women compared to men, and male gender was a factor favoring ECAS (vs. ICAS).

Along with male gender, increasing age was an independent risk factor for ECAS (vs. ICAS) in this study. Previous studies attempting to compare risk factors between ICAS and ECAS have shown inconsistent results. Most studies from East Asia have reported, as we have, that old age is a risk factor for ECAS,[9-11] while studies from the West

Table 2: Distribution of intracranial atherosclerosis (ICAS) and extracranial atherosclerosis (ECAS)

	Male	Female	*p*- value
Distribution of ICAS	*N = 419	*N = 294	0.251
Distal ICA	50 (11.9)	33 (11.2)	
MCA	205 (48.9)	141 (48.0)	
ACA	29 (6.9)	22 (7.5)	
PCA	32 (7.6)	24 (8.2)	
BA	53 (12.6)	39 (13.3)	
Distal VA	50 (11.9)	35 (11.9)	
Distribution of ECAS	*N = 163	*N = 65	0.584
Proximal ICA	140 (85.9)	55 (84.6)	
Proximal VA	23 (14.1)	10 (15.4)	

ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; VA, vertebral artery
*Including the patients with ICAS+ECAS

Table 3: Adjusted odds ratios for the presence of symptomatic extracranial atherosclerosis (ECAS) than intracranial atherosclerosis (ICAS) (before and after stratification by sex)

ECAS > ICAS						
	Before stratification by sex		After stratification by sex			
			Male		Female	
	Adjusted OR (95% CI)	*p*- value	Adjusted OR (95% CI)	*p*- value	Adjusted OR (95% CI)	*p*- value
Male	3.554 (2.175-5.808)	< 0.001*				
Age	1.051 (1.031-1.072)	0.001*	1.059 (1.034-1.083)	< 0.001*	1.029 (0.994-1.066)	0.105
Hypertension	1.005 (0.651-1.551)	0.983	1.346 (0.638-1.888)	0.623	0.732 (0.316-1.698)	0.468
Diabetes mellitus	0.856 (0.563-1.302)	0.467	1.016 (0.622-1.662)	0.948	0.529 (0.228-1.229)	0.139
Hyperlipidemia	2.330 (1.538-3.529)	< 0.001*	2.331 (1.442-3.770)	0.001*	1.737 (0.762-3.960)	0.189
Smoking	0.971 (0.613-1.536)	0.899	0.954 (0.578-1.575)	0.855	1.623 (0.548-4.811)	0.382

OR, odds ratio; CI, confidence interval
Adjusted OR; adjusted for all variables shown in this table
*$p < 0.05$

have suggested that ICAS develops later in life compared to ECAS.[20,21] Based on present and previous studies, racial differences could be an effect modifier of the relationship between aging and distribution of cerebral atherosclerosis.

We observed a potential interaction between age and sex in cerebral atherosclerosis. Old age was a risk factor for ECAS in men but not in women. Therefore, sex may be an effect modifier of the association between aging and the distribution of cerebral atherosclerosis. Although the mechanisms of this interaction are unclear, sex hormones may drive this difference. Previous studies have shown that low androgen levels are associated with the severity and progression of proximal ICA stenosis in elderly men.[22,23] Decreasing androgen levels in men may influence ECAS more than diminishing estrogen levels in women. Further research regarding the impact of sex hormones on cerebral atherosclerosis is needed to elucidate this hypothesis about female-male differences in cerebral atherosclerosis and related strokes.

Generally, hyperlipidemia is thought to be more closely related to ECAS than ICAS.[9,10,24,25] Our study confirmed this in the unstratified sample; however, after stratification by sex, this association was significant only in men. A previous study conducted in patients with proximal carotid stenosis showed sex-related differences in carotid plaque features and inflammation. Compared to men, women had a lower prevalence of thrombotic plaques and a lower concentration of inflammatory cells, despite a greater prevalence of hyperlipidemia.[26] Other preclinical and clinical studies have addressed different effects of male and female sex hormones on hyperlipidemia and atherosclerosis.[27-31] Our results, along with previous data, suggest that sex may modify the relationship between hyperlipidemia and cerebral atherosclerosis.

A major limitation to our study is that this was a single center study with a small cohort, which could limit the generalizability of our results. Validation in a multicenter study of a large population is needed. We did not collect data to further clarify our results, such as inflammatory markers or endogenous sex hormone levels. Some of the potential risk factors for atherosclerosis,

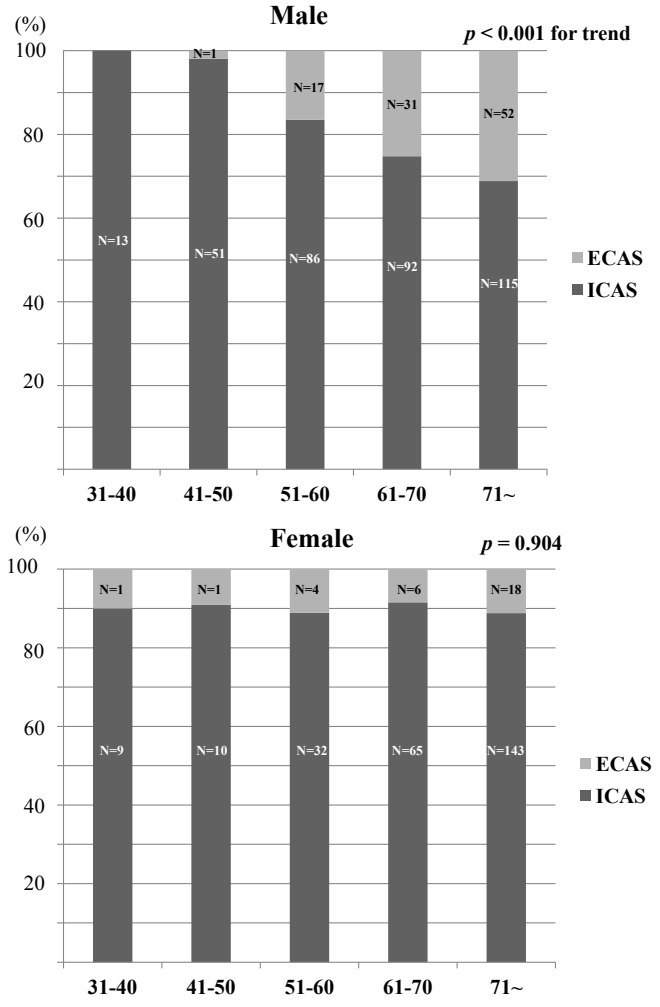

Figure 2. Percentage of patients with symptomatic intracranial atherosclerosis (ICAS) and extracranial atherosclerosis (ECAS) stratified by age (Excluding the patients with ICAS+ECAS).

including dietary habits and physical activity, were not evaluated in our study.

However, our study has important implications for stroke research. Most clinical stroke studies contain a majority of men, which skews the results. Based on our results, an appropriate sex-stratified analysis is needed in future clinical studies.

ACKNOWLEDGEMENT

This study was supported by an Inha University Research Grant (INHA-51372).

DISCLOSURE

Conflicts of interest: None

REFERENCES

1. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology a systematic review. *Stroke* 2009; 40:1082-90.
2. Bushnell C, McCullough LD, Awad IA, *et al*. Guidelines for the prevention of stroke in women a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45:1545-88.
3. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006; 295:306-13.
4. Stefania B, Valeria R, Marco P, Gaetano T, Flavia F. Impact of sex and gender on the efficacy of antiplatelet therapy: The female perspective. *J Atherosclerr Thromb* 2015; 22:109-25.
5. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology

of ischemic stroke subtypes according to TOAST criteria incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke* 2001; 32:2735-40.
6. Förster A, Gass A, Kern R, *et al*. Gender differences in acute ischemic stroke etiology, stroke patterns and response to thrombolysis. *Stroke* 2009; 40:2428-32.
7. Huang HW, Guo MH, Lin RJ, *et al*. Prevalence and risk factors of middle cerebral artery stenosis in asymptomatic residents in Rongqi County, Guangdong. *Cerebrovasc Dis* 2007; 24:111-5.
8. Wityk R, Lehman D, Klag M, Coresh J, Ahn H, Litt B. Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke* 1996; 27:1974-80.
9. Kim YD, Choi HY, Jung YH, *et al*. Classic risk factors for atherosclerosis are not major determinants for location of extracranial or intracranial cerebral atherosclerosis. *Neuroepidemiology* 2009; 32:201-7.
10. Kim JS, Nah H-W, Park SM, *et al*. Risk factors and stroke mechanisms in atherosclerotic stroke intracranial compared with extracranial and anterior compared with posterior circulation disease. *Stroke* 2012; 43:3313-8.
11. Lei C, Wu B, Liu M, Chen Y. Risk factors and clinical outcomes associated with intracranial and extracranial atherosclerotic stenosis acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2014; 23:1112-7.
12. Pu Y, Liu L, Wang Y, *et al*. Geographic and sex difference in the distribution of intracranial atherosclerosis in China. *Stroke* 2013; 44:2109-14.
13. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol* 2005; 58:688-97.
14. Njemanze P, Beck O, Gomez C, *et al*. North american symptomatic carotid endarterectomy trial. Methods, patient characteristics, and progress. *Stroke* 1991; 22:711-20.
15. Chimowitz M, Kokkinos J, Strong J, *et al*. The warfarin-aspirin symptomatic intracranial disease study. *Neurology* 1995; 45:1488-93.
16. Leung SY, Ng T, Yuen S, Lauder I, Ho F. Pattern of cerebral atherosclerosis in Hong Kong Chinese. Severity in intracranial and extracranial vessels. *Stroke* 1993; 24:779-86.
17. Sacco RL, Kargman D, Gu Q, Zamanillo M. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction the Northern Manhattan Stroke study. *Stroke* 1995; 26:14-20.
18. White H, Boden-Albala B, Wang C, *et al*. Ischemic stroke subtype incidence among whites, blacks, and hispanics the northern manhattan study. *Circulation* 2005; 111:1327-31.
19. Wong K, Huang Y, Gao S, Lam W, Chan Y, Kay R. Intracranial stenosis in Chinese patients with acute stroke. *Neurology* 1998; 50:812-3.
20. Solberg L, McGarry P. Cerebral atherosclerosis in Negroes and Caucasians. *Atherosclerosis* 1972; 16:141-54.
21. D'Armiento FP, Bianchi A, de Nigris F, *et al*. Age-related effects on atherogenesis and scavenger enzymes of intracranial and extracranial arteries in men without classic risk factors for atherosclerosis. *Stroke* 2001; 32:2472-80.
22. Debing E, Peeters E, Duquet W, Poppe K, Velkeniers B, Van Den Brande P. Men with atherosclerotic stenosis of the carotid artery have lower testosterone levels compared with controls. *Int Angiol* 2008; 27:135-41.
23. Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SW, van der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. *Circulation* 2004; 109:2074-9.
24. Uehara T, Tabuchi M, Mori E. Frequency and clinical correlates of occlusive lesions of cerebral arteries in Japanese patients without stroke. *Cerebrovasc Dis* 1998;8:267-72.
25. Caplan L, Gorelick P, Hier D. Race, sex and occlusive cerebrovascular disease: a review. *Stroke* 1986; 17:648-55.
26. Sangiorgi G, Roversi S, Zoccai GB, *et al*. Sex-related differences in carotid plaque features and inflammation. *J Vasc Surg* 2013; 57:338-44.
27. Mäkinen JI, Perheentupa A, Irjala K, *et al*. Endogenous testosterone and serum lipids in middle-aged men. *Atherosclerosis* 2008; 197:688-93.
28. Hatch NW, Srodulski SJ, Chan H-W, Zhang X, Tannock LR, King VL. Endogenous androgen deficiency enhances diet-induced hypercholesterolemia and atherosclerosis in low-density lipoprotein receptor-deficient mice. *Gend Med* 2012; 9:319-28.
29. Nathan L, Shi W, Dinh H, *et al*. Testosterone inhibits early atherogenesis by conversion to estradiol: critical role of aromatase. *Proc Natl Acad Sci* 2001; 98:3589-93.
30. Henriques TA, Huang J, D'souza SS, Daugherty A, Cassis LA. Orchidectomy, but not ovariectomy, regulates angiotensin II-induced vascular diseases in apolipoprotein E-deficient mice. *Endocrinology* 2004; 145:3866-72.
31. Bourghardt J, Wilhelmson AS, Alexanderson C, *et al*. Androgen receptor-dependent and independent atheroprotection by testosterone in male mice. *Endocrinology* 2010; 151:5428-37.