

Low Frequency of Renal Artery Disease in Young Ischemic Stroke Patients

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Abstract-

Background: The frequency, associated risk factors and associated vascular disorders in renal artery disease have not been studied in young ischemic stroke patients.

Methods: From February 1999 to June 2006, we retrospectively reviewed a total of 152 younger ischemic stroke patients (≤ 50 y/o). Another 30 older ischemic stroke patients (age > 50 y/o) were randomly selected and studied as controls. All 182 patients received cerebral angiography and concomitant abdominal aortography. The extent of vascular stenosis was calculated for the renal, cerebral and coronary arteries. Vascular risk factors were also studied.

Results: Of the 152 younger patients, seven (4.6%) patients had renal artery disease including two (1.3%) with significant stenosis. There was no association between renal artery disease and vascular risk factors ($p > 0.05$). Patients with intracranial carotid and coronary artery disease had a significantly higher frequency of renal artery disease ($p < 0.05$).

Conclusion: Our results suggest that the frequency of renal artery disease is low in younger ischemic stroke patients. Intracranial carotid and coronary artery disease is associated with renal artery disease.

Key Words: Renal artery disease, Ischemic stroke, Young adult

Acta Neurol Taiwan 2008;17:11-16

INTRODUCTION

Atherosclerotic renal artery stenosis and fibromuscular dysplasia are the two primary and most common diseases of the renal artery and are associated with two common clinical symptoms, renovascular hypertension and ischemic nephropathy. Atherosclerotic renal artery

stenosis is more common and accounts for 90 percent of cases^(1,2). It is a progressive disease, particularly in older patients with diabetes or other manifestations of atherosclerosis, which causes loss of renal function⁽²⁾. Fibromuscular dysplasia appears in less than 10 percent of patients with renal artery disease and most commonly in females between ages 15 and 50^(2,3). The angiographic

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Received June 15, 2007. Revised July 11, 2007.
Accepted August 13, 2007.

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studies usually showed a beaded, aneurysmal pattern which predominately involved medium-size arteries. The etiology of fibromuscular dysplasia is not well understood, but genetics, hormonal factors and mechanical disorders have been proposed as risk factors.

The true frequency of renal artery disease in the general population is still unknown because detection mainly derives from autopsy or angiographic study, obviously impractical/unwarranted procedures in the presumably walking well. Previous studies on hypertensive populations revealed that the frequency of renal artery disease was lower than expected⁽⁴⁾. Recent studies have reported that the elderly and declared patients with coronary or peripheral vascular disease were prone to suffer from renal artery disease⁽⁵⁻⁸⁾. Stroke is a common manifestation of atherosclerotic disease, and autopsy data in stroke patients ≥ 40 years of age demonstrated that renal artery disease was commonly associated with stroke⁽⁹⁾. However, few studies ever mention the frequency and importance of renal artery disease in young stroke patients. Here, we investigate the frequency and the severity of renal artery disease in young ischemic stroke patients aged ≤ 50 years. The associations of renal artery disease with vascular risk factors and with cerebral and coronary artery diseases were also examined.

SUBJECTS AND METHODS

We retrospectively studied the frequency of renal artery disease in young ischemic stroke patients who were admitted to the Department of Neurology in our hospital from February 1999 to June 2006. All ischemic stroke patients age ≤ 50 years were advised to receive cerebral angiography to evaluate the possible underlying vascular anomaly. In addition, concomitant abdominal aortogram to evaluate/detect any renal artery disorders and concomitant coronary angiography for cardiac vessel disease were also suggested. Angiographic studies were not performed if the patient refused to give his/her consent, if the patient had poor renal function (creatinine level ≥ 2 mg/dL), or if there were other severe medical diseases. In total 60% of the young ischemic stroke patients underwent concomitant abdominal aortographic

study. For comparison purposes, another 30 older ischemic stroke patients (>50 y/o) were randomly selected and studied by neuroradiologists using the same protocol. Vascular risk factors such as hypertension, diabetes, serum lipid profile, smoking, and alcohol were also studied. This study was approved by the Human Study Institutional Review Board of our hospital.

Definitions of vascular risk factors

Hypertension (HT) was defined as being present when (1) the patient was previously diagnosed with HT by a clinician and/or (2) systolic blood pressure was ≥ 140 mm Hg and/or diastolic blood pressure was ≥ 90 mm Hg on two different occasions and/or the patient was receiving antihypertensive treatment. Diabetes mellitus was diagnosed if patients had elevated fasting plasma glucose (≥ 126 mg/dL) or was receiving treatment for diabetes. Cigarette smoking was defined as a risk factor when a subject reported smoking ≥ 10 cigarettes per day for more than six months before the stroke. Alcohol consumption was regarded as a risk factor when a subject regularly drank alcohol at a level of ≥ 30 g per day or ≥ 210 g per week for more than six months before the stroke. Hyperlipidemia was defined as a risk factor when the fasting blood cholesterol level was ≥ 200 mg/dL and/or triglyceride level was ≥ 150 mg/dL and/or patients were treated with fibrates or statins.

Angiographic study

Using standard procedures, digital subtraction angiography was used to study the blood vessels. To prevent contrast-induced nephropathy, all patients received adequate hydration at least one day before and one day after angiographic study. A nonionic contrast agent was used and the maximal dosage was restricted under 300 ml. The degree of arterial stenosis was assessed in the cerebral, coronary and renal arteries. The cerebral arteries were classified into extracranial carotid system, intracranial carotid system and vertebrobasilar system. The extracranial carotid system included the common carotid artery, external carotid artery, and the internal carotid artery below the cavernous segment. The intracranial carotid system included the internal carotid

artery above the cavernous segment and its intracranial branches. The vertebrobasilar system is composed of the vertebrobasilar artery and posterior cerebral artery. The diameter of any vascular stenosis was determined according to the North American Symptomatic Carotid Endarterectomy Trial criteria⁽¹⁰⁾. Renal artery disease was defined when there was evidence of renal artery stenotic lesions on the abdominal aortogram. Renal artery disease with $\geq 50\%$ diameter narrowing was regarded as significant stenosis. Diameter narrowing of $\geq 50\%$ stenosis in cerebral and coronary artery was regarded as significant artery disease.

Statistical analysis

SPSS 12.0 software was used for statistical analysis. The statistics were computed using chi-square or Fisher's exact test as appropriate. $P < 0.05$ was considered as statistically significant. Multiple logistic regression was used to assess the association of vascular lesions in patients with renal artery disease.

RESULTS

Characteristics of young versus older ischemic stroke patients

A total of 182 ischemic stroke patients underwent renal and cerebral angiographic studies. Among them, 152 patients were ≤ 50 years of age (age range = 18 to 50 years, mean \pm SD = 38 ± 7 years) and 30 patients were > 50 years of age (age range = 53 to 79 years, mean \pm SD = 68 ± 7 years). Of the 152 younger patients, brain infarction was seen in 144 patients and transient ischemic attack in eight. Stroke of other determined etiology (26%) was the most common subtype, while large artery atherosclerosis (12%) was the least common. Of the 30 older stroke patients, brain infarction was seen in 23 patients and transient ischemic attack in seven. The clinical characteristics of these young and older ischemic stroke patients were summarized in Table 1. The three most common vascular risk factors were hypertension (49.3%), cigarette smoking (46.7%) and hypertriglyceridemia (46.7%) in young ischemic stroke patients. Hypertension was significantly more common in the

older stroke group ($p = 0.038$).

Frequency of renal artery disease in young and older ischemic stroke patients

In the younger ischemic stroke patients, 145 patients (95.4%) had normal renal artery findings; however, seven patients (4.6%) had renal artery disease including two (1.3%) with significant stenosis. In the seven patients with renal artery disease, four (2.6%) were male including one (0.7%) with significant stenosis; five (3.3%) patients had unilateral renal artery disease (four on the right side and one left side) and two (1.3%) had bilateral involvement. The frequency of renal artery disease in different stroke subtypes was 15.0% in large artery atherosclerosis (three of the 20 patients), 6.8% in Moyamoya disease and artery dissection (two in 30 patients; total number of other determined etiology: 43), 4% in small-vessel occlusion (one in 26 patients), 3% in cardiac embolism (one in 29 patients) and 0 in undetermined etiology (0 in 26 patients).

In the older group of stroke patients, seven (23.3%) had renal artery disease including four (13.3%) with significant stenosis. In the seven patients with renal artery disease, six males had bilateral involvement and one female had unilateral disease. As shown in Table 1, older stroke patients had a higher frequency of renal artery disease as compared with the young stroke patients (23.3% vs. 4.6%, $p = 0.003$).

Table 1. The comparison of risk factors and renal artery disease in patients ≤ 50 years of age and > 50 years of age

Clinical characteristics	Age ≤ 50 years old (n=152)	Age > 50 years old (n=30)
Mean age	38 ± 7	68 ± 7
Male / female	112 / 40	24 / 6
Hypertension*	75 (49.3%)	21 (70.0%)
Diabetes mellitus	22 (14.5%)	8 (26.7%)
Hypercholesterolemia	55 (36.2%)	10 (33.3%)
Hypertriglyceridemia	71 (46.7%)	9 (30.0%)
Smoking	71 (46.7%)	15 (50.0%)
Alcohol	32 (21.1%)	5 (16.7%)
Renal artery disease*	7 (4.6%)	7 (23.3%)

*: $P < 0.05$ if compared between ≤ 50 y/o and > 50 y/o.

Cerebral and coronary artery disease in young ischemic stroke patients

All of the 152 young ischemic stroke patients received cerebral angiographic studies which revealed that 32 patients (21.1%) had $\geq 50\%$ intracranial carotid stenosis, 18 (12%) had extracranial carotid stenosis and 14 (9.2%) had vertebrobasilar stenosis. Four patients (three females and one male) had carotid fibromuscular dysplasia according to angiographic criteria but none had renal artery disease. A total of 129 young stroke patients received a coronary angiographic study. Among them, 27 patients (21%) had coronary artery disease, including 23 with one-vessel disease, one with two-vessel and three with three-vessel disease.

Comparisons between young ischemic stroke patients with and without renal artery disease

As shown in Table 2, there was no significant difference in vascular risk factors between patients with and without renal artery disease ($p > 0.05$). Patients with renal

Table 2. Risk factors of renal artery disease and its association with cerebral and coronary artery disease in 152 younger ischemic stroke patients

Renal artery disease	Yes n= 7 (%)	No n= 145 (%)	P
Male	4 (57.1)	108 (74.5)	0.308
Hypertension	5 (71.4)	70 (48.3)	0.273
Diabetes mellitus	2 (28.6)	20 (13.8)	0.267
Hypercholesterolemia	2 (28.6)	53 (36.6)	1.000
Hypertriglyceridemia	4 (57.1)	67 (46.2)	0.706
Smoke	4 (57.1)	67 (46.2)	0.706
Alcohol	1 (14.3)	31 (21.4)	1.000
Coronary artery disease*, ≥ 1 vessel	4 (66.7)	23 (18.7)	0.017
Intracranial carotid system ($\geq 50\%$)	4 (57.1)	28 (19.3)	0.036
Extracranial carotid system ($\geq 50\%$)	2 (28.6)	16 (11.0)	0.194
Vertebrobasilar system ($\geq 50\%$)	0 (0.0)	14 (9.7)	1.000

*Six patients with renal artery disease and 123 patients with normal renal artery received coronary angiography.

The statistics used were chi-square or Fisher's exact tests as appropriate.

artery disease had a significantly higher frequency of intracranial carotid and coronary artery disease than patients without renal artery disease ($p=0.036$ and 0.017 , respectively, Fisher's exact test). Multivariate logistic regression analysis showed that renal artery disease was significantly associated with intracranial carotid and coronary artery disease ($p=0.023$ and 0.022 , respectively).

DISCUSSION

Previous studies using autopsy findings indicated that renal artery stenosis was rarely seen in stroke patients aged 40-49 years⁽⁹⁾. In a Canadian study of patients with severe atherosclerosis (elsewhere), only 1% had $\geq 50\%$ renal artery stenosis⁽⁵⁾. However, a Japanese study found 4.7% of patients with Moyamoya disease had $\geq 50\%$ renal artery stenosis⁽¹¹⁾. Our results indicate that the frequency of renal artery disease and significant renal artery stenosis in young ischemic stroke patients is low (4.6% and 1.3%, respectively). It is likely that renal artery disease is not common in young stroke patients but may be related to certain disease entities.

Previous studies have shown that subjects reaching age 50 or more are prone to suffer from renal artery disease^(7,8,12). The frequency of renal artery disease ranged from 11% to 22% among elderly patients aged ≥ 50 years and increased in aging patients with generalized atherosclerotic disease^(7,8,12). In patients with other atherosclerotic vascular disease, the reported frequency of renal artery disease varied from 6% to 39%⁽¹³⁻¹⁵⁾. Our study showed that the presence of renal artery disease was sig-

Table 3. The association of renal artery disease to cerebral and coronary arteries using multivariate logistic regression analysis in 152 young ischemic stroke patients

Vascular territory	Odds ratio	95% confidence interval	P value
Coronary artery disease*, ≥ 1 vessel	8.70	1.50-50.38	0.023
Intracranial carotid system ($\geq 50\%$)	5.57	1.18-26.32	0.022
Extracranial carotid system ($\geq 50\%$)	3.23	0.58-18.01	0.584

*Six patients with renal artery disease and 123 patients with normal renal artery received coronary angiography.

nificantly higher in older ischemic stroke patients as compared to young ischemic stroke patients. It is possible that renal artery disease is age-dependent and advanced age is a major risk factor for renal artery disease.

Previous reports have found that old age, female sex, hypertension, renal insufficiency, coronary artery disease, peripheral vascular disease and cerebrovascular disease are possible risk factors for renal artery disease^(5,16-20). Diabetes mellitus, hypercholesterolemia, and smoking are regarded as predictors in an atherosclerotic population and atherosclerosis is a major cause of renal artery disease^(2,12,13). However, some studies indicated that the risk factors for atherosclerosis may not affect the presence of renal artery disease in atherosclerotic patients^(5,12). Harding et al.⁽¹²⁾ showed that hypertension did not predict significant renal artery disease, and renal artery disease could be common in normotensive patients. Our study of younger stroke patients shows that there was no significant association between the presence of renal artery disease and vascular risk factors.

It has been reported that less than 10% of renal artery disease is caused by renovascular fibromuscular dysplasia^(2,3). In patients with fibromuscular dysplasia, renal artery involvement is more common than carotid artery⁽³⁾. A previous study demonstrated that in the sixteen patients with carotid fibromuscular dysplasia, none had renal artery involvement⁽²¹⁾. In our study, there were four young ischemic stroke patients with carotid fibromuscular dysplasia but none had renal artery involvement. These findings suggest that the involvement of carotid or renal artery in fibromuscular dysplasia deserves further study.

Other previous studies found an increased number of significant carotid artery stenosis in patients with renal artery disease^(19,20). Renal artery disease was also demonstrated to be a frequent finding among patients with coronary artery disease^(5,6,13,14). Our study showed that intracranial carotid artery disease and coronary artery disease were significantly associated with renal artery disease. In our study, the frequency of renal artery disease is lower than our previously reported 12% of $\geq 50\%$ extracranial carotid stenosis, 9.2% of $\geq 50\%$ verte-

brobasilar stenosis and 21.1% of $\geq 50\%$ intracranial carotid stenosis⁽²²⁾ in young ischemic stroke patients. Thus, our study suggests that although artery disease such as atherosclerosis tends to involve vessels everywhere, renal artery involvement may be less common than cerebral and coronary artery involvement.

CONCLUSION

Our results suggest that the frequency of renal artery disease is low in young ischemic stroke patients. The association of renal artery disease is more commonly found in patients with intracranial carotid and coronary artery disease than with extracranial carotid and verte-brobasilar artery disease.

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