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White Matter Lesions, Risk Factors, and Etiological Classification in Young versus Old Cerebral Infarction Patients: A Retrospective Study

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Objective: To compare the differences in risk factors and etiological classification between cerebral infarction in young patients and elderly patients, and explore the correlation between cerebral infarction in young patients and white matter lesions (WMLs).

Methods: Sixty young patients with cerebral infarction and 142 elderly patients with cerebral infarction were included. The distributions of risk factors such as hypertension, diabetes, heart disease, smoking status, alcohol consumption status, migraine status, and WMLs in the two groups were carefully investigated and statistically analyzed.

Results: According to the univariate analysis, the proportions of males, obese patients, patients with migraine, and patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) in the young group were significantly greater than those in the elderly group. Hypertension, heart disease, and hyperhomocysteinemia were significantly more common in the elderly group than in the young group. According to the TOAST classification, the incidence of stroke of undetermined etiology in the young group was greater than that in the elderly group, whereas the incidence of large-artery atherosclerosis (LAA) in the elderly group was greater than that in the young group. Binary logistic regression analysis revealed that male sex, migraine status, and obstructive sleep apnea-hypopnea syndrome were independently associated with cerebral infarction in young adults, whereas hypertension, heart disease, and hyperhomocysteinemia were independently related to cerebral infarction in elderly individuals. In addition, the incidence of WMLs in the migraine group of young cerebral infarction patients was significantly greater than that in the nonmigraine group.

Conclusion: Compared with those in elderly patients with cerebral infarction, the risk factors for cerebral infarction in young patients are relatively controllable. Furthermore, more methods are needed to determine the etiology of unexplained cerebral infarction in young patients. WMLs are thought to have a relatively high incidence in young patients with cerebral infarction and are significantly associated with migraine.

Keywords: cerebral infarction, white matter lesions, young people, risk factors, migraine

Introduction

Cerebral infarction refers to a syndrome characterized by local blood supply disruption to the brain, resulting in ischemia and hypoxia that lead to necrosis and softening of brain tissue, subsequently causing corresponding neurological deficits.[1] Cerebral infarction in the young population is rare, accounting for only approximately 5% of the total stroke population, however, when it occurs in young people, it is extremely harmful to families and society.[1] In recent years, the incidence of stroke in young people has been increasing annually, accounting for 10–14% of all strokes, with an increase in incidence of up to 40%.[2] The incidence of stroke in young people is increasing, and disabling and fatal stroke can cause immeasurable losses to families. Therefore, investigating the causes and risk factors for stroke in young people is

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particularly important, but stroke in young people has its own special characteristics compared with stroke in elderly people.[3]

There have been many studies on the risk factors for stroke in young people, and hypertension, diabetes mellitus, hyperlipidemia, adverse lifestyle factors, and familial inheritance are all risk factors for stroke in young people.[4–6] However, few studies have investigated the relationship between cerebral WMLs and stroke in young people.

In this study, we investigated the correlation between cerebral infarction and cerebral white matter lesions (WMLs) in young people and compared the risk factors and etiological typing of cerebral infarction in old people by using relevant statistical methods on 60 young people's strokes collected from two stroke centers and the control of 142 old people's strokes selected randomly to comprehensively analyze the differences between young people's cerebral infarction and old people's cerebral infarction and provide a basis for the prevention and treatment of young people's cerebral infarction. These findings provide a basis for the prevention and treatment of cerebral infarction in young people.

Method

Patients with acute cerebral infarction who were hospitalized at the Second Affiliated Hospital of Nanchang University and Fengxin County People's Hospital between September 2021 and December 2023 were selected. All patients met the diagnostic criteria for stroke in China[7] and were confirmed to have ischemic stroke by cranial magnetic resonance. All the information comes from a complete medical information system. All patients had complete biochemical indices, such as blood pressure, blood glucose, blood lipids, homocysteine, coagulation indices, c-reactive protein (CRP), thyroid function, and other biochemical indices, and were also examined with transcranial Doppler ultrasonography and cranial magnetic resonance angiography; additionally, some of the patients underwent CT angiography imaging and angiography with vascular subtraction imaging. Patients suspected of having other causes of stroke underwent dynamic electrocardiography, cardiac ultrasound, immuno-antibody profile, coagulation index, or genetic testing. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University and Fengxin County People's Hospital.

All patients were investigated for the presence or absence of hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease, smoking, alcohol consumption, obesity, and more than a dozen other possible risk factors for stroke in young people who have been confirmed by other studies. The history of migraine was in accordance with the headache classification and diagnostic criteria of the International Headache Society,[8] which determines whether all investigators have a history of migraine. Patients underwent 3T cranial magnetic resonance imaging, and the presence of WMLs was determined by two imaging physicians, with conflicts referring to a third, more senior imaging physician. All factors were defined as "0 for absence and 1 for presence". The two groups of patients were compared.

All patients were typed by TOAST using imaging, biochemical parameters, and other relevant tests to compare the etiologic characteristics of the two groups, and some patients for whom no clear cause could be found after several tests or who had a combination of several possible causes were categorized as unexplained. There are five subtypes: large-artery atherosclerosis (LAA), cardioembolism (CE), small-artery occlusion (SAO), stroke of other determined etiology (SOE), and stroke of undetermined etiology (SUE).

Statistical analysis was performed using IBM SPSS Statistics V.25.0 software. Quantitative data were examined to determine if they conformed to a normal distribution, a *t*-test was used for conformity, and nonparametric tests were used for data that did not conform to a normal distribution. Qualitative information was tested using the x^2 test, and chi-square tests for patients less than 5 years old were performed using Fisher's exact test. Independent risk factors were obtained by including univariate indicators in binary logistic regression. All two-sided tests were used, with $P < 0.05$ indicating a statistically significant difference.

Results

In the present study, 60 young stroke patients younger than 45 years of age and 142 elderly stroke patients who were randomly selected using a random number table were ultimately included. Among the 60 young patients, 42 (70%) were male and 18 (30%) were female; the mean age was 40.78±5.38 years. Among the 142 elderly patients, 72 (50.7%) were male, and 70 (49.3%) were female. The average age was 69.43±9.93 years. In comparison, the

male composition ratio of the young group was significantly greater than that of the elderly group ($p < 0.05$). The baseline information is detailed in Table 1.

In the young cerebral infarction group, among the more than ten risk factors identified, the top risk factors were hyperlipidemia, hypertension, cerebral WMLs, hyperhomocysteinemia (Hcy), diabetes mellitus, and migraine. The top risk factors for elderly individuals were hypertension, hyperhomocysteinemia, hyperlipidemia, cerebral WMLs, diabetes mellitus, and smoking. The risk factors for hypertension, heart disease, hyperhomocysteinemia, obesity, migraine, and obstructive sleep apnea-hypopnea syndrome (OSAHS) were compared between the two groups. The proportions of individuals with obesity, migraine, and OSAHS in the young group were significantly greater than

Table 1 Comparison of the General Conditions of the Two Groups and Univariate Analysis

Variable		Youth (*n*=60)	Elderly (*n*=142)	X^2/t	*P*
Mean age (SD), years		40.78±5.38	69.43±9.93	26.41	<0.001
Gender	Male	42	72	6.387	0.011
	Female	18	70		
High blood pressure	No	26	24	15.821	<0.001
	Yes	34	118		
Diabetes	No	45	95	1.300	0.254
	Yes	15	47		
Atrial fibrillation	No	59	139	Fisher	>0.999
	Yes	1	3		
Heart diseases	No	59	124	5.999	0.015
	Yes	1	18		
High blood fat disease	No	16	52	1.871	0.171
	Yes	44	90		
Cigarette smoking	No	48	104	1.035	0.309
	Yes	12	38		
Drinking wine	No	50	123	0.370	0.543
	Yes	10	19		
High HCY	No	34	50	7.993	0.005
	Yes	26	92		
Obese	No	55	142	Fisher	0.002
	Yes	5	0		
Migraines	No	46	136	17.263	<0.001
	Yes	14	6		
OSAHS	No	55	141	6.076*	0.014
	Yes	5	1		
High uric acid	No	52	121	0.073	0.787
	Yes	8	21		
White matter lesions	No	32	66	0.793	0.373
	Yes	28	76		
Medical history of tumor	No	60	136	1.352*	0.245
	Yes	0	6		
TOAST type	LAA	5	30	Fisher	0.043
	CE	1	3		
	SAO	38	89		
	SOE	0	1		
	SUE	16	19		

Note: *Calibrated cardinality.

Abbreviations: HCY, homocysteinemia; OSAHS, Obstructive Sleep Apnea Hypoventilation Syndrome; LAA, Large-artery atherosclerosis; CE, Cardioembolism; SAO, Small-artery occlusion; SOE, Stroke of other determined etiology; SUE, Stroke of undetermined etiology.

those in the elderly group. Hypertension, heart disease, and hyperhomocysteinemia were significantly more common in the elderly group than in the young group ($p < 0.05$). Patients with cerebral infarction were analyzed according to TOAST, and the three most common etiological factors were SAO, LAA, and SUE. The three most common etiological factors in the young group were SAO, SUE, and LAA, and the three most common etiological factors in the elderly group were SAO, LAA, and SUE. The one-way analysis of the etiological factors in the two groups revealed that the difference was statistically significant ($p < 0.05$), and the observational analysis revealed that the young group had a greater percentage of SUE than did the elderly group, while the elderly group had a greater percentage of LAA than did the young group. LAA was greater in the younger group than in the younger group. The specific analysis is shown in Table 1.

Risk factors with *P* values less than 0.1 in the univariate analysis were included in the binary logistic regression analysis, which revealed that sex (male), migraine status, and OSAHS status were independently associated with the occurrence of cerebral infarction in young people, whereas hypertension, heart disease, and hyperhomocysteinemia were independently associated with the occurrence of cerebral infarction in old people. Except for the analysis of obesity and etiology, the results were basically consistent with those of the univariate analysis. The results of the specific analysis are shown in Table 2.

Among the 14 young patients with cerebral infarction accompanied by migraine, 12 had cerebral WMLs. Sixteen of the 46 patients in the group without migraine had cerebral WMLs. The incidence of cerebral WMLs in the migraine group was significantly greater than that in the nonmigraine group ($p < 0.05$). The specific values analyzed are shown in Table 3.

Among the 6 elderly patients with cerebral infarction accompanied by migraine, 2 had cerebral WMLs. Among the 136 patients in the group without migraine, 74 had cerebral WMLs. The difference in the incidence of cerebral WMLs between the migraine group and the nonmigraine group was not statistically significant (p=0.552). The specific values analyzed are shown in Table 4.

Table 2 Binary Logistics Regression Analysis of Risk Factors of Cerebral Infarction Patients in Two Groups

Variable	*OR*	95% CI	*P*
Gender (male)	2.309	1.019–5.230	0.045
High blood pressure	0.304	0.132–0.699	0.005
Heart diseases	0.089	0.009–0.889	0.039
High HCY	0.338	0.156–0.732	0.006
Migraines	−13.155	3.374–51.286	<0.001
OSAHS	12.229	1.229–121.662	0.033

Abbreviations: HCY, homocysteinemia; OSAHS, Obstructive Sleep Apnea Hypoventilation Syndrome.

Table 3 Comparison of Cerebral White Matter Occurrence in the Migraine and No Migraine Groups of Young Cerebral Infarction Patients (n, %)

Variable	n	%
Migraine group (n=14)	12	85.714
No migraine group (n=46)	16	34.782
X^2		11.187
P		<0.001

Table 4 Comparison of Cerebral White Matter Occurrence in the Migraine and No Migraine Groups of Elderly Patients with Cerebral Infarction (n, %)

Variable	n	%
Migraine group (n=6)	2	33.333
No migraine group (n=136)	74	54.412
X^2		0.354*
P		0.552

Note: *Calibrated cardinality.

Discussion

In the present study, we found that cerebral WMLs were not significant in either univariate or multivariate regression and were not considered a risk factor for stroke in young adults. However, because the incidence of cerebral white matter in the elderly population is significantly greater than that in the young population, we believe that the role of cerebral WMLs should not be ignored after the absolute interference caused by age is considered. In young people with cerebral infarction, white matter and migraine are closely related.

In recent years, the incidence of stroke in young people has increased, resulting in immeasurable losses to families in the event of disability and death. Therefore, exploring the causes and risk factors for stroke in young people is particularly important, but stroke in young people has special characteristics compared with stroke in elderly people.[3] Previous studies[9] have shown that the proportion of men with stroke among young adults is significantly greater than that among older adults, which is consistent with the findings of the present study and may be related to social pressure and poor lifestyle habits among men. However, the present study did not find any significant difference between bad lifestyle habits, such as smoking and drinking, and the elderly group, thus, bad lifestyle habits are clearly a significant risk factor for both the young and the elderly groups. Therefore, good living habits are beneficial at any age.

With many scholars studying the etiology and pathogenesis of stroke in young people, it is generally recognized that the risk factors include genetic factors, hypertension, hyperlipidemia, diabetes, smoking and drinking and other unhealthy habits.[10–13] However, this study revealed several risk factors not found in previous studies; obesity, migraine, and OSAHS were significantly more common in this group than in the elderly group. Obesity can cause a series of diseases, such as hyperlipidemia, hypertension, and diabetes, so it is urgent to control the weight of young people. Previous studies have shown that OSAHS is an independent risk factor for cerebrovascular disease,[14] and one study revealed that OSAHS may be a risk factor for intracranial vascular stenosis in young people.[15] This may be related to the multisystem functional impairment of the organism caused by repeated intermittent hypoxia/reoxygenation and hypercapnia accompanying OSHAS. In contrast, cerebral atherosclerosis is a pathological process caused by endothelial damage and is characterized by chronic inflammation of blood vessels, which ultimately causes early-onset cerebral arterial stenosis in the young population.[16]

Many studies have concluded[17] that migraine is closely associated with cerebral infarction in young people and is considered to be an aura of cerebral infarction, but its specific pathophysiologic mechanism is not clear. However, the association between migraine and cerebral WMLs has been confirmed in several studies, and it is believed that the frequency, severity, and occurrence of such attacks may aggravate cerebral WMLs.[18–21] In the present study, we also found that the rate of combined cerebral WMLs was significantly greater in young patients with cerebral infarction in the presence of migraine than in patients with cerebral infarction in the nonmigraine group. In this study, migraine status was confirmed to be a risk factor for cerebral infarction in young adults, but there was no significant difference in cerebral WMLs between young adults and older adults. The prevalence of cerebral WMLs reaches more than 70% in the population over 50 years of age and more than 95% in the population over 80 years of age, and the prevalence is less than 10% in the general population of young people, excluding those with genetic or pathological cerebral WMLs.[22] According to the results of the present study, the incidence of cerebral WMLs in young patients with cerebral infarction without migraine was significantly lower than that in elderly patients with cerebral infarction, so it can be assumed that

the relatively high incidence of cerebral WMLs in young people with cerebral infarction is significantly associated with the occurrence of migraine. Although the results of this study are the same as those of previous studies,[23] although cerebral WMLs do not appear to have a statistically significant relationship with young cerebral infarction, their incidence in young cerebral infarction patients is greater than that in the general young population, and they are related to the development of migraine headache, which provides a strong basis for the active prevention and treatment of migraine headache.

The etiologic typing of cerebral infarction according to the TOAST differed significantly from that reported in previous studies. One study revealed that the three most common cerebral infarctions were SUE, SAO, and LAA. There is also a different view, with LAA, SAO, and SOE in the top three.[24] In this study, we found that the three most common WMLs in the young group were SAO, SUE, and LAA, which is consistent with the high rate of cerebral WMLs found, but there were more unexplained types of WMLs, which may be related to underdiagnosis. For example, patients with mild cerebral infarction in their youth refused to improve appropriate tests, such as protein C, S or immunological tests. The main reasons for the differences in etiology are thought to be related to the patients' willingness to refine the relevant tests, the means of examination and investigator selection bias.

In our study, nearly 50% of young patients with cerebral infarction presented with cerebral WMLs, which was significantly greater than that of the normal population of the same age, although the specific mechanism by which cerebral WMLs lead to cerebral infarction in young people is not clear. However, patients with cerebral WMLs exhibit severe retinal microangiopathy, in addition to increased endothelial permeability of the corresponding vessels, which is considered to be highly susceptible to ischemia associated with small retinal arteries.[25] Since the retina is an extension of the mesencephalon and both have the same vascular origin during embryonic development,[26] the ophthalmic artery originates from the internal carotid artery, and both have the same vasoregulatory process,[26–30] it is believed that cerebral WMLs within the brain are highly susceptible to ischemia of the small intracranial arteries. This also explains why small artery occlusion is the main type of cerebral infarction in young people.

The findings of this study are reliable and supported by other research, providing robust evidence for the prevention of cerebral infarction in adolescents.[31] There are several limitations to this study: 1. This study focused solely on imaging-based WMLs, neglecting other magnetic resonance information, such as ischemic regions, responsible vessels, and infarct size; 2. The sample size remains insufficient, and the incidence of migraines and WMLs in elderly patients with cerebral infarction is very low; 3. Although the incidence of WMLs did not reach statistical significance in this study, the incidence of WMLs was significantly greater in affected adolescents than in healthy youths, necessitating further investigation into their pathophysiological mechanisms. Moving forward, we hope that further research will delve into the fundamental aspects of adolescent cerebral ischemia, identifying molecular differences from cerebral ischemia in older patients.

Conclusion

In conclusion, obesity, migraine, OSAHS, and WMLs are more common in young patients with cerebral infarction than in older patients with hypertension, heart disease, hyperhomocysteinemia, and heart disease. These factors are relatively easy to control and resolve, which provides strong evidence for the prevention of cerebral infarction in young people. We should limit oil and fat intake, control body weight, maintain good living habits, eradicate the causes of OSAHS and control symptoms, and prevent the recurrence and worsening of migraine in young people to alleviate cerebral leukoencephalopathy and eliminate the risk factors for cerebral infarction. However, it is still difficult to achieve precision in the study of the etiology of cerebral infarction in young people, and it is hoped that there will be more and better means to clarify the etiology in the future.

Data Sharing Statement

All relevant data are described within the paper. Deidentified data can be requested. Data can be requested by all interested researchers, who can be contacted via the corresponding author.

Ethics Approval and Consent to Participate

The research data in the study was retrieved from the the second affiliated hospital of Nanchang University Database. The datasets were fully de-identified and there were no patient identifiers, therefore, informed consent was not required from all participants. The research was approved by ethics committee of the second affiliated hospital of Nanchang University (No. [2016] 096), including the waiver of the need for informed consent. All authors confirm that the research was conducted in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have declared no conflicts of interest.

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