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Review Article

Etiology and Risk Factors of Ischemic Stroke in Elderly versus Younger Patients

Mahmoud Abdelhafiz ,
Ayman Gamea, Mennatallah Helmy , Islam El-Malky

*Department of Neurology, Faculty of Medicine – South Valley University, Qena, Egypt.

Abstract

Background: Identification of risk factors and causes of stroke is the key to optimizing treatment and preventing recurrence. Our aim is identifying risk factors and possible causes of ischemic stroke in young and old patients. A single-center prospective cohort study conducted in Qena University Hospital, Egypt. enrolled 1000 hospitalized patients with ischemic stroke from January 2022 to December 2023. Patients were divided into young (18- < 50 years) and old (≥ 50 years) groups. Clinical, imaging and laboratory data were compared to identify risk factors in each group.

Results: 146 (14.6%) were under 50 years, while 854 (85.4%) were over 50. The mean age is 63.4 ± 12.7 years; 495 (49.5%) are males. Smoking, hypertension and diabetes more predominant in the old group 411 (48.1 %) (p-value < .016); 657 (76.9 %) (p-value < 0.001); 413 (48.3 %) (p-value < 0.001) respectively. Large vessel atherosclerosis and small vessel occlusion are more predominant in the old group (p-value < 0.001). However, cardio embolism is more predominant in the young population (p-value < 0.001).

Conclusions: Our study verified frequencies of embolic sources as potential etiology for ischemic stroke, particularly in young population. Early screening and recognition of cardio-embolic sources in young populations could help in stroke prevention.

Key Words: Imaging, Laboratory, Young versus Old, Stroke

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Corresponding Author: Mahmoud Abdelhafiz.

E-mail: ahmed.elsaman@med.sohag.edu.eg

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Introduction

Stroke is the second leading cause of death worldwide. In 2022, the World Health Organization (WHO) reported that ischemic stroke affects 7.6 million people annually, with a prevalence of 77 million (997/100,000) across all age groups. Of these, 57% are women, 367/100,000 are between the ages of 15 and 49, 648/100,000 are under the age of 70, and the rate of ischemic stroke in young adults is 19%.⁽¹⁾ The prevalence of stroke within the US population escalates with age: 2.7% for individuals aged 20, 6% for those over 60, and 13% for those above 80 years. Every year, about 800 000 new or recurrent stroke cases.⁽²⁾ Most studies have used the age range of approximately 18 to 50 years to characterize ischemic stroke in young adults.⁽³⁻⁵⁾ The etiologies of ischemic stroke in young patients differ from those of old patients, and the clinical data in the population of young adults with stroke has been the subject of many studies. The results of the many research studies vary about the etiology, stroke subtypes, and risk factors for ischemic stroke in young individuals.⁽⁶⁾ However, the cause of stroke cannot be determined in approximately 30% of patients, even with a thorough etiological work-up. A common mistake is diagnosing cryptogenic stroke in patients with incomplete or delayed etiological investigations.⁽⁷⁾

In our research, we aim to focus on the etiological diagnosis of stroke in young adults and compare it to the old population on the basis of TOAST classification, imaging, and laboratory evaluation.

Methods

One thousand patients with acute ischemic stroke who were hospitalized in the neurology department, between January 2022 and December 2023 were included in our prospective cohort study. . We use the following formula to calculate the sample size for our study: $N = Z^2(1-P)P/D^2$, where Z is the standard normal variance = 1.96 at 95% confidence interval, the absolute standard error that can be tolerated = 0.05, and P is the prevalence = 50%, so the minimal sample size required is $n = (1.96)^2 / 4(0.05)^2 = 384.16$. The patients then were divided into two age groups: Group (1) consisted of patients ages 18-<50 years, and Group (2) consisted of patients ages (> or = 50 years).

Patients with transient ischemic attack, hemorrhagic stroke, venous sinus thrombosis, <18 years, or with stroke mimics as migraine and epilepsy were excluded from the study. Before inclusion in the study, written informed consent was obtained from all patients

Laboratory findings, such as complete blood count, cholesterol, low-density lipoprotein, triglycerides, prothrombin time and concentration, and INR (international normalized ratio), were ordered for both groups; brain imaging as DWI (diffusion-weighted image) and MRI (magnetic resonance image) by using 1.5 tesla Siemens MRI and MRA for anatomical localization of ischemic occlusive lesion and intracranial vessels; carotid vascular duplex with Philips iU22 and 9–3 MHz linear array transducer to assess intimal medial thickness and atheroma thickness, ulceration, motility, bleeding, cysts, and calcification; cardiac examinations by 12-lead electrocardiography and transthoracic echocardiography. Trans esophageal echocardiography (TEE) and transthoracic echocardiography with bubble study were performed in cases without a prominent cause of ischemic stroke, especially in the young age group. Certain laboratory analyses in the case of young age group such as anti-thrombin 3, protein C, and protein S. Ischemic stroke patients were classified into four subgroups according to The Etiological Trial of Organization in Acute Stroke Treatment (TOAST).⁽⁸⁾ which includes the following subtypes: small vessel occlusion (SVO): subcortical or brainstem <1.5 cm lacunar infarct with no cerebral cortical impairment; large artery atherosclerosis (LAA): significant stenosis >50% ulceration or occlusion due to atherosclerosis in the proximal arteries; Cardio embolic (CE): High risk as atrial fibrillation, mechanical prosthetic valve, recent myocardial infarction <4 weeks, infective endocarditis with vegetation, dilated cardiomyopathy, and intra-cardiac thrombus included the left atrial/atrial appendage and ventricular thrombus and left ventricular a kinesis, and medium risk is old myocardial infarction (4 weeks–6 months), mitral stenosis without atrial fibrillation, patent foramen oval, congestive heart failure, non-bacterial thrombotic endocarditis, atrial

septal defect, mitral valve prolapse, and atrial flutter, and undetermined (UD) or cryptogenic.

SPSS software, version 21, was used to analyze all the data. Frequency and percentage and Pearson's chi-squared test, or Fisher's exact test, were used for qualitative data. The mean, standard deviation, and student t-test were used for quantitative data, and odds ratios and 95% confidence intervals of the causes of ischemic stroke were estimated for young adults in reference to non-young adults by logistic regression analysis. P-values less than 0.05 are considered significant.

Results:

The mean age of studied population is 63.4 ± 12.7 years (range: 18–91 years). 146 (14.6%) are < 50 years, while 854 (85.4%) are ≥ 50 years. 495 (49.5%) are males, clinical characteristics of the

participants are demonstrated in **Table 1**. Anatomical localization of the brain lesions, carotid artery measurements, and cardiac findings in young versus old patients are all demonstrated in **Table 2**, while routine laboratory findings are demonstrated in **Table 3**. Risk factors for ischemic stroke are demonstrated in **Table 4**. According to TOAST classification, large vessel atherosclerosis was recorded in 17 (11.6%) young versus 166 (19.7%) old patients (OR: 1.101, 95% CI: 0.598-2.028, p-value: < 0.001), and small vessel disease in 30 (20.5%) young versus 240 (28.1%) old patients (OR: 1.262; 95% CI: 0.743-2.143, p-value = 0.002), while cardio embolism in 69 (47.3%) of young versus 135 (15.5%) old patients (OR: 4.974, 95% CI: 3.106-7.966, p-value: < 0.001). UD 30 (20.5%) of young versus 313 (36.6%) old patients.

Table (1): Clinical characteristics of the study participants

	< 50 years (N = 146)	≥ 50 years (N = 854)	95 % C.I	P-value
Smokers	62 (42.5%)	411 (48.1 %)	(1.08-2.31)	0.016
Hypertensive	58 (39.7%)	657 (76.9 %)	(3.27- 6.97)	< 0.001
Diabetic	39 (26.7%)	413 (48.3 %)	(1.37-3.09)	< 0.001

Table (2): Neuroimaging and echocardiographic results

			Age				95 % C.I	P-value
			< 50 years (N = 146)		≥ 50 years (N = 854)			
DWI & MRI brain	ACA		0	0%	16	1.9%	(0.83-0.87)	0.095
	MCA		98	67.1%	476	55.7%	(0.49-0.89)	0.01
	PCA		20	13.7%	138	16.2%	(0.73-2.01)	0.451
	Lacunar		30	20.5%	240	28.1%	(0.7-2.14)	0.002
Carotid Doppler	I.M.T	Mean ± SD	(1.28 ± 0.9)		(1.77 ± 0.8)		(0.33-0.65)	< 0.001
		< 2 mm	126	86.3%	618	72.4%	(1.46-3.94)	< 0.001
		≥ 2 mm	20	13.7%	236	27.6%		
	Stenosis	No	129	88.4%	688	80.6%	(0.59-2)	< 0.001
		Yes	17	11.6%	166	19.4%		
ECG & TTE	Medium risk embolic source		31	21.2%	376	44%	(1.91-4.43)	< 0.001
	High risk embolic source		69	47.3%	135	15.5%	(3.1-7.96)	< 0.001

ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery; MRI: Magnetic resonance image; DWI: diffusion weighted imaging; ECG: electrocardiogram. TTE: Transthoracic echocardiogram; IMT: intima media thickness; CI: confidence interval; N.B: p-value < 0.05 is considered significant

Table (3): Laboratory characteristics of the study participants

	< 50 years (N = 146) Mean $\pm$ SD	$\geq$ 50 years (N = 854) Mean $\pm$ SD	95 % C.I	P-value
W.B.Cs	8.3 $\pm$ 3.2	9.5 $\pm$ 4.0	(0.49 -1.87)	< 0.001
Haemoglobin	13.7 $\pm$ 1.5	13.1 $\pm$ 1.9	(0.27- 0.93)	0.001
Platelets	296.0 $\pm$ 76.3	268.1 $\pm$ 88.9	(12.5- 43.1)	< 0.001
PT	12.4 $\pm$ 1.1	12.6 $\pm$ 1.7	(0.08- 0.48)	0.161
PC	94.0 $\pm$ 10.2	91.6 $\pm$ 14.0	(0.04- 4.7)	0.054
INR	1.1 $\pm$ 0.5	1.08 $\pm$ 0.17	(0.01-0.06)	0.243
Cholesterol	168.6 $\pm$ 48.4	187.1 $\pm$ 53.5	(9.22- 27.7)	< 0.001
Triglycerides	110.0 $\pm$ 86.1	128.3 $\pm$ 79.9	(4.18- 32.5)	0.011
LDL	28.3 $\pm$ 18.5	29.0 $\pm$ 14.5	(2.01- 3.31)	0.632

WBCs : white blood cells; **PT**: Prothrombin time; **PC**: Prothrombin concentration;

INR: international normalized ratio. **LDL**: low density lipoprotein

N.B: p-value < 0.05 is considered significant.

Table (4): Risk factors according to TOAST criteria

Risk Factor	< 50 (N = 146) N & %	$\geq$ 50 (N = 854) N & %	P-value	Risk Factor	< 50 (N = 146) N & %	$\geq$ 50 (N = 854) N & %	P-value
Vasculitis	1 (0.6%)	0 (0%)	0.35	Atrial septal defect	3 (2%)	0 (0%)	0.18
Carotid stenosis (<50%)	3 (2%)	70 (8.1%)	< 0.001	Cardiomyopathy	0 (0%)	3 (0.3%)	0.16
Carotid stenosis (>50%)	17 (11.6%)	166 (19.4%)	< 0.001	Endocarditis	0 (0%)	0 (0%)	
Carotid dissection	1 (0.6%)	0 (0%)	0.36	Valvular heart disease	59 (40.4%)	13 (1.5%)	< 0.001
Patent foramen ovale	7 (4.7%)	11 (1.2%)	0.18	Left atrial thrombus	6 (4.1%)	15 (1.7%)	0.09
Congestive heart failure	1 (0.6%)	5 (0.5%)	0.45	Small-vessel occlusion	30 (20.5%)	240 (28.1%)	0.16
Myocardial infarction <4 wk	5 (3.4%)	17(1.9%)	0.08	Anti-thrombin 3	1 (0.6%)	0 (0%)	0.35
ventricular thrombus	2 (1.2%)	0 (0%)	0.23	Protein S deficiency	0 (0%)	0 (0%)	
Atrial fibrillation	1 (0.6%)	87 (10.1%)	< 0.001	Protein C deficiency	0 (0%)	0 (0%)	
Ischemic heart disease	14 (9.5%)	360(42.1%)	0.03	Anti-cardio-lipin	2 (1.3%)	0 (0%)	0.27

Discussion

Many studies investigate risk factors of ischemic stroke in young patients; however, there are few studies that compare risk factors to older patients. Our research has a point of strength: this study is a large, prospective cohort study. Therefore, with a large number of patients, subgroup analysis between sex and stroke subtypes could be evaluated. In our results, the proportion of strokes in young patients to all cases with strokes is 14.6%, which is higher than in Western countries (5-10%) but slightly less than in developing countries (19-30%).⁽⁹⁾

By applying regression analysis Smoking, hypertension, and diabetes are risk factors for stroke in young and old patients; however, hypertension and diabetes are statistically significant risk factors in the old population.

We found that there is no significant difference between patients $\leq$ 50 years and patients $>$ 50 years as regards ACA and PCA territory infarction lesions, but a significant difference in MCA territory and lacunar infarction (p-value = 0.01 and p-value = 0.032), respectively. Lacunar infarction is more common in old patients in contrast to MCA territory infarction, which is more common in

young. Increased incidence of lacunar infarction in old age might be due to vascular risk factors. As regards the explanation of MCA territory infarction in the young, this might be due to more cardioembolic sources of ischemic stroke in this group, which is different from the Chinese population, where intracranial stenosis is more common in the young age group.⁽¹⁰⁾ But **Lee**, in another meta-analysis, detected that the risk of MCA infarction is increased with age.⁽¹¹⁾ However, cardio embolism and different ethnicities might be possible reasons for our results; Egypt still has a high prevalence of RHD in young-age patients.⁽¹²⁾

Intima media thickness (IMT) was markedly greater in those over 50 (1.77 ± 0.8 mm) than under 50 (1.28 ± 0.9 mm), p -value < 0.001 , and 19.4% of patients over 50 had carotid stenosis, compared to 11.6% under 50; p -value = 0.024. However, **Saxena** found higher IMT in stroke patients (0.77 ± 0.36 mm) when compared to controls (0.56 ± 0.13), $p < 0.001$, but the difference persisted across all age groups (20–40, >40–<60, and >60 years).⁽¹³⁾ Also, a Norwegian study investigating stroke in young patients aged 15–44 concluded that there is a 20% ICA-IMT increase compared to controls, and the only factor related to the increase of ICA-IMT is the age.⁽¹⁴⁾

Our choice to study the etiology of stroke in both groups by the application of TOAST classification, as ASCOD classification has limited added value because it only distinguishes arterial dissection from the other determined causes.⁽¹⁵⁾ Although the IPSS categorization might help the investigation of potential risk factors like smoking, migraines, and oral contraceptive use in young patients. The TOAST, on the other hand, has distinct categories for cardioembolism and large and small vessel diseases.⁽⁸⁾

Cardiac sources of emboli were determined in 69 (47.3%) and 135 (15.5%) young versus old patients, respectively. The higher risks for cardiac emboli in young patients were rheumatic and prosthetic valve diseases, whereas IHD was more prevalent in old patients (p -value < 0.001). In harmony with our findings, many Asian studies found that CE as an etiology for stroke was higher in young patients, as in Korea (35.2%).⁽¹⁶⁾ and Japan (54.1%).⁽¹⁷⁾ While,

in another Western study, LAA and CE were the predominant subtypes.⁽¹⁸⁾

However, this is against other Asian studies where CE and LAA prevalence were less than SVO in the young population, such as the multicenter Japanese study.⁽⁶⁾ and the Chinese study, where the percentage of SVO was 30.7%.⁽¹⁹⁾ The higher burden of cardiovascular risk factors, higher sodium intake, and genetic factors among Asian populations may all contribute to the predominance of SVO in young patients.

In the Middle East region, we could find the high prevalence of CE in Qatar (36.1%)⁽²⁰⁾ and the low prevalence of CE in Turkey (9%) and Tunisia (19%), where atrial fibrillation, mitral stenosis, and mitral valve replacement were the predominant risk factors, while undetermined causes were (58.4%) and (40%), respectively.^(21, 22)

Statistically significant increases of WBCs (9.5 ± 4.0), CHOL (187.1 ± 53.5), TG (128.3 ± 79.9), and VLDL (29 ± 14.5) and decreases of HGB (13.1 ± 1.9), PLTs (268.1 ± 88.9), and PC (91.6 ± 14) in patients > 50 years when compared with patients ≤ 50 years, although there was no statistically significant difference as regards PT and INR. Our data confirm that age differences may have different cerebrovascular risk factors and stroke etiologies. Outlining these distinctions could aid in the development of preventive strategies.

Our study has some limitations, including incomplete work-up, as a transesophageal echocardiography or intracranial vascular imaging of all the studied population potentially might lead to underestimation of patent foramen ovale, and possible other embolic sources might not have been identified. Furthermore, screening tests are inadequate for some rare genetic and hematologic disorders; this might overestimate the undetermined etiology. So, further research investigating these risk factors is advisable.

Conclusions

Few studies compare risk factors for ischemic stroke in young and old populations; our study verified frequencies of embolic sources, especially valvular heart disease, as a potential etiology for ischemic stroke, particularly in the young population. Diabetes, hypertension, and carotid

stenosis are potential risk factors in the old population. Early screening and recognition of cardioembolic sources and risk factors could help in stroke prevention. However, detailed, correct etiological classification is essential for future studies.

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