Central Asian Journal of Medical Sciences
CAJMS

Original Article

Cent Asian J Med Sci. 2016 Nov;2(2): 143-152.

Comparative Study of Ischemic Stroke in Patients Aged Above and Below 50 Years Admitted to a Tertiary Care Hospital in Ulaanbaatar

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Submitted: July 27, 2016
Revised: August 21, 2016
Accepted: September 1, 2016

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Objectives: The aim of this study was to compare characteristics of ischemic stroke between young (20-49 years) and old (50-89 years) patients undergoing investigations and treatment according to one common protocol in a tertiary hospital. **Methods:** This hospital-based prospective study included 90 young and 130 old patients with acute ischemic stroke. Data regarding the etiology of the stroke, diagnostic test results and degree of functional improvement of patients were examined during their observation. **Results:** Common causes for stroke in the young patients were current smoking (53.3%), heavy alcohol consumption (51.1%), cardiac embolism (36.0%), migraine with aura (25.5%), infective diseases (15.6%), and oral contraceptive use (14.4%). Leading causes for ischemic stroke in old patients were the conventional risk factors such as hypertension (75.4%), atherosclerosis (66.9%), and diabetes mellitus (26.9%). Most of the young stroke patients demonstrated good functional outcomes, at the time of discharge (71.1%) and at three weeks (86.6%) according to the Rankin Scale. **Conclusion:** There are significant differences between young and old patients with ischemic stroke regarding to risk factors, etiological subtypes and improvement of functional deficits associated with the stroke.

Keywords: Stroke, Cerebral Ischemia, Young Adult

Introduction

Ischemic stroke in young people can be devastating in terms of loss in productive years and its impact on a young person's life, their families, and society in general. As will be outlined in this article, some causes of stroke are more frequent in adults under 50 years of age compared to older populations. A recent report of the WHO MONICA Project documented that stroke

incidence varied from 48 to 240 per 100,000 people aged 45 to 54 years in 10 countries involved [1-4]. In the United States the average annual incidence rates of all strokes under the age of 55 years was 113.8 per 100,000, while that for cerebral infarction was 73.1 per 100,000 [2-3]. More than 10% of patients with cerebral infarction were 55 years or younger [3-5]. Almost two thirds of the global burden of stroke is borne by those in developing countries [4, 9, 14]. Data from yearly statistical reports on morbidity and mortality in Mongolia show that young adults account for approximately 20-26% of all stroke patients [6] as opposed to 10-13% in Western countries [9, 14, 18].

Several studies have shown that risk factors and etiology differ between young and elderly patients. Cardioembolic stroke, migraine and cerebral vasculopathy are frequently reported among young adults [5, 7, 9] whereas traditional risk factors such as large-artery atherosclerosis, diabetes and dyslipidemia are usually less frequent [3, 6]. Furthermore, etiological subtyping also varies according to nationality and geographical distribution [23]. It is important to define the etiological factors in young stroke patients in order to prevent recurrences. However, effective stroke prevention in the young cannot be attempted until the risk factors are clearly documented. Despite its substantial socioeconomic impact, there remains a lack of literature regarding the etiological subtyping and risk factors for ischemic stroke in young Mongolians. There have not been many comparisons between young and old patients treated and investigated in a tertiary center. This study was conducted in order to compare risk factors, etiological subtypes and severity of functional deficits in ischemic stroke between young (under 50 years) and old (above 50 years) Mongolian patients according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification developed by the American Heart Association which is based on multi-center trials [3].

Materials and Methods

1. Data collection

All consecutive patients with acute ischemic stroke admitted to the Stroke Unit, Department of Neurology, First State Central Hospital, Ulaanbaatar, Mongolia from October 2014 to July 2016, were prospectively observed and registered in a database (The Ulaanbaatar Stroke Registry Center). During this period out of 944 patients admitted for strokes (ischemic and hemorrhagic), 220 (23.3%) were selected patients with acute ischemic stroke according to inclusion criteria. Etiological and clinical classification of ischemic stroke was analyzed by dividing the cohort into two age groups which included 90 young patients (20-49 years) and 130 old patients (50-89 years).

Specific definition of "young stroke" is lacking. Some authors consider "young stroke" to pertain to individuals under 45 years and others under 50 years age [27, 28]. Hence, this paper uses methods from a review of hospital-based studies conducted in a Western and Asian countries on characteristics of ischemic stroke which included patients above and below 50 years of ages for comparative analysis regarding differences of risk factors, etiological subtypes and short-term outcome of stroke between age groups [9, 17, 19, 28].

Ischemic stroke was defined in accordance with the Baltimore-Washington Cooperative Young Stroke Study Criteria comprising neurological deficits lasting more than 24 hours because of ischemic lesions or transient ischemic attacks where computed tomography (CT) or magnetic resonance imaging (MRI) showed infarctions related to the clinical findings [9]. All patients had CT or MRI and magnetic resonance angiogram (MRA). Isolated acute ischemic lesions on CT or MRI were defined as lacunar infarctions if they were <1.5 cm in size and located as subcortical or in the brainstem. All other acute ischemic lesions were defined as non-lacunar infarction. Non-lacunar infarctions included subcortical and brainstem infarction (≥ 1.5 cm in size), cortical infarction, mixed cortical and subcortical infarction, and cerebellar infarction. Leukoaraiosis was defined as the presence of hypodense periventricular abnormalities on MRI (T2).

Blood pressure, body mass index and serum biochemistry on admittance were registered. Diagnostic workup included electrocardiography (ECG), echocardiography, and duplex sonography of neck vessels. The National Institute of Health Stroke Scale (NIHSS) was used to assess stroke severity score (0 = no stroke; 1-4 = minor stroke; 5-15 = moderate stroke; 16 = moderate to severe stroke; 17-42 = severe stroke). NIHSS measurements were performed on admittance and discharge, also at 21 days after stroke onset. Likewise, the Modified Rankin Scale (mRS) score and Barthel Index (BI) were obtained on discharge and at 21 days after stroke onset.

Risk factors including hypertension, smoking, alcohol use, diabetes mellitus, heart disease, migraine, vasculopathies were registered upon admittance. Hypertension was defined as prior

use of antihypertensive medication. Current smoking was defined as smoking at least 15 cigarettes per day. Diabetes mellitus was considered present if the patient was on glucose-lowering diet or medication. Heart diseases were considered present if diagnosed by a cardiologist any time before stroke onset. Atrial fibrillation required ECG confirmation any time prior to stroke onset. A history of prior cerebral infarction was registered. Old infarctions on CT or MRI were registered, including both clinically silent and symptomatic infarctions. Etiology was determined by Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [3], performed by a neurologist. Clinical classification was based on the Oxfordshire Community Stroke Project scale which includes lacunar syndrome, partial anterior circulation syndrome, total anterior circulation syndrome, and posterior circulation syndrome [11]. Internal carotid artery (ICA) stenosis was defined as a percentage of area reduction in neurosonology, graded from 30–49%, 50–69%, 70–99%, to occlusion. Calculation was performed using the ultrasound software (iU22, Philips, Amsterdam, Netherlands).

2. Data analysis

The recorded data was statistically analyzed for the percentage, mean and standard deviation of all variables. Logistic regression was performed to analyze the effect of the two age groups (young or old patients) on discharge and at day 21 adjusting for sex and NIHSS score on admission. The mRS score of 0–2 versus 3–6 was used as the dependent variable. SPSS (IBM, Armonk, NY, USA) version 16.0 for Windows was used for all statistical analyses. A p-value of <0.05 was considered statistically significant.

3. Ethical statement

Ethical approval was obtained from the Ethical Review Board of the Mongolian National University of Medical Sciences. Each patient signed a consent form before being involved in the study. The investigator maintained confidentiality of research data.

Results

From the 220 patients included in the study, 90 (40.9%) were 20–49 years old (mean age 38.5 ±5.6) and 130 (59.1%) were 50–89 years old (mean age 65.4 ±7.8). The proportion of males was higher among both groups by the age decades and overall the proportion of males was 61.1% in the young and 70.0% in the old patients (Table 1, Figure 1).

Table 1. Demography of young (n = 90) and old (n = 130) patients with cerebral infarction (n = 220)

Variable	Young patients	Old patients	p-value
Age (mean ±SD)			
Overall	38.5 ±5.6	65.4 ±7.8	
Males	34.3 ±4.5	63.7 ±6.7	
Females	37.8 ±6.8	68.4 ±5.6	
Sex (n (%))			
Males	55 (61.1)	91 (70.0)	
Females	35 (38.9)	39 (30.0)	0.05
Marital status (n (%))			
Married	57 (63.3)	75 (57.7)	0.30
Employment status (n (%))			
Employed	67 (74.4)	27 (20.8)	0.001

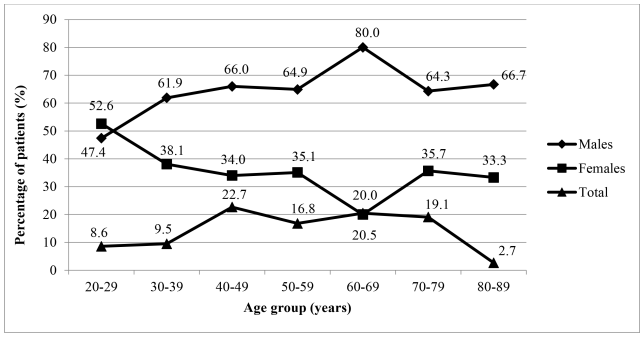

Figure 1. Age and sex distribution of young and old patients with cerebral infarction.

The leading conventional causes for stroke in the young and old groups were different as shown in Table 2: hypertension (38.9% vs. 75.4%), atherosclerosis (31.1% vs. 66.9%), current smoking (53.3% vs. 37.8%), long-term heavy alcohol consumption (51.1% vs. 12.3%), and diabetes mellitus (6.7% vs. 26.9%). Another relatively common cause was cardiac embolism (27.7% vs. 28.5%) under which the young and old groups could be further subdivided into valvular heart diseases (36.0% vs. 16.2%), atrial fibrillation (24% vs. 35.1%), cardiomyopathies (12.0% vs. 24.3%), coronary artery disease (12% vs. 24.3%), atrial septal defect (8% vs. 0%), atrial myxoma (4.0% vs. 0%), and patent foramen ovale (4% vs. 0%). Among the specific etiologies for young stroke patients were migraine with aura (25.5% vs. 12.2%), infective diseases including tuberculosis, syphilis, varicella zoster virus (15.6% vs. 0.8%), and oral contraceptive use (14.4 vs. 0%) as shown in Table 3.

Table 2. Comparison of conventional risk factors of ischemic stroke in young (n = 90) and old (n = 130) patients

Risk factors	Young patients (n (%))	Old patients (n (%))	p-value
Hypertension	35 (38.9)	98 (75.4)	0.001
Large and small artery atherosclerosis	28 (31.1)	87 (66.9)	0.05
Heart diseases	25 (27.7)	37 (28.5)	0.001
Diabetes mellitus	6 (6.7)	35 (26.9)	0.064
Dyslipidemia	23 (25.6)	40 (30.8)	0.07
Obesity	33 (36.7)	32 (24.6)	0.06
Current smoking (≥15 cigarettes per day)	48 (53.3)	34 (37.8)	0.001
Alcohol use (≥60 g/day)	46 (51.1)	16 (12.3)	0.073
Prior stroke or transient ischemic attack	4 (4.0)	10 (16.2)	0.001

Table 3. Comparison of specific risk factors associated with ischemic stroke in young (n = 90) and old (n = 130) patients

Specific risk factors	Young patients (n (%))	Old patients (n (%))	p-value
Migraine with aura	23 (25.5)	11 (12.2)	0.001
Infective diseases (tuberculosis, syphilis, varicella-zoster virus)	14 (15.6)	1 (0.8)	0.004
Oral contraceptive use	13 (14.4)	0	
Pregnancy and puerperium	9 (10.0)	0	
Arterial hypotension	7 (7.8)	3 (3.1)	0.005
Vessel dissection	6 (6.7)	2 (1.5)	0.001
Hypoplasia of cerebral arteries	6 (6.7)	5 (3.8)	0.063
Prothrombotic disorder	5 (5.6)	0	
Cerebral venous thrombosis	5 (5.6)	0	
Cerebral vasculopathies	4 (4.4)	3 (2.3)	0.001
Moyamoya arteriopathy	3 (3.3)	0	

The remaining rare risk factors which were more prevalent in the young group were vessel dissection (6.7% vs. 1.5%), hypoplasia of cerebral arteries (6.7% vs. 3.8%), prothrombotic disorder (5.6% vs. 0%), cerebral venous thrombosis (5.6% vs. 0%), and non-atherosclerotic vasculopathies including these conditions most frequently in the young patients. Large-artery atherosclerosis was less frequent among young patients: 14.4% vs. 25.4% (Figure 2).

The most common TOAST subtype was undetermined (24.4% vs. 12.3%) and cardiac embolism (23.3% vs. 21.5%),

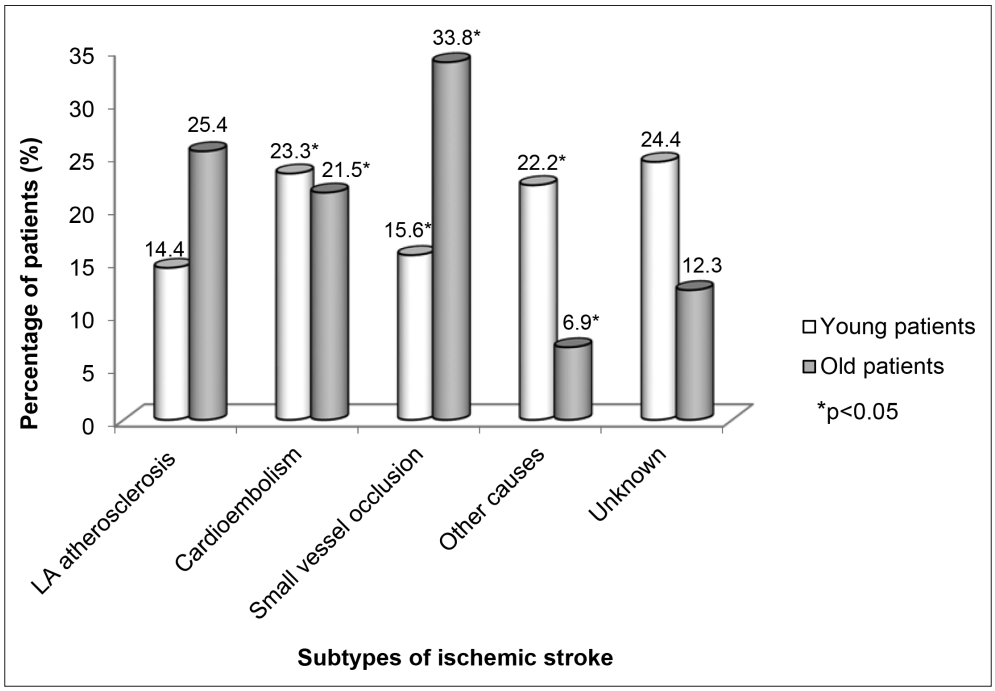

Figure 2. Proportions of TOAST subtypes of ischemic stroke according to young and old groups. LA = large artery

moyamoya arteriopathy (7.7% vs. 2.3%). The study shows that young patients with ischemic stroke appeared to have multiple etiologies as evidenced by having 2-3 risk factors (38.9%).

Upon multivariable logistic regression analysis, significant variables were hypertension, atrial fibrillation, migraine and smoking and atrial fibrillation emerged as an independent risk factor of young stroke with adjusted odds ratio of 5.16 (95% confidence interval: 1.34-21.16).

Cardiac embolism was found in similar proportions in both groups (27.7% vs. 28.5%) and included rheumatic heart disease, and paroxysmal atrial fibrillation, or combinations of followed by other determined cause (22.2% vs. 6.9%), and small vessel occlusion (15.6% vs. 33.8%) as seen in Figure 2.

The etiological classification was also analyzed by two groups according to age (20-49 and 50-89 years). The 20-49 year age group had small predominance of patients with cardioembolic stroke (23.3%). When data was analyzed according to gender and ages, young women are more likely to have cardioembolism and other rare specific factors, and men are more likely to have large-artery and small-artery disease, and both sexes presented with other various determined causes.

Table 4. Signs and symptoms of ischemic stroke in young (n = 90, 40.9%) and old (n = 130, 59.1%) patients

Signs and symptoms	Young patients (n (%))	Old patients (n (%))
Headache	25 (27.8)	13 (14.4)
Consciousness abnormality	11 (12.2)	44 (33.8)
Hemiparesis	68 (75.6)	118 (90.8)
Facial-brachial type paresis	75 (83.3)	87 (66.9)
Sensory disturbances	29 (32.2)	80 (61.5)
Speech slurring	22 (24.4)	54 (41.5)
Hemianopsia	10 (11.1)	25 (19.2)
Diplopia	6 (6.6)	10 (7.7)
Vertigo	28 (31.1)	20 (15.4)
Vomiting	26 (28.9)	11 (8.5)

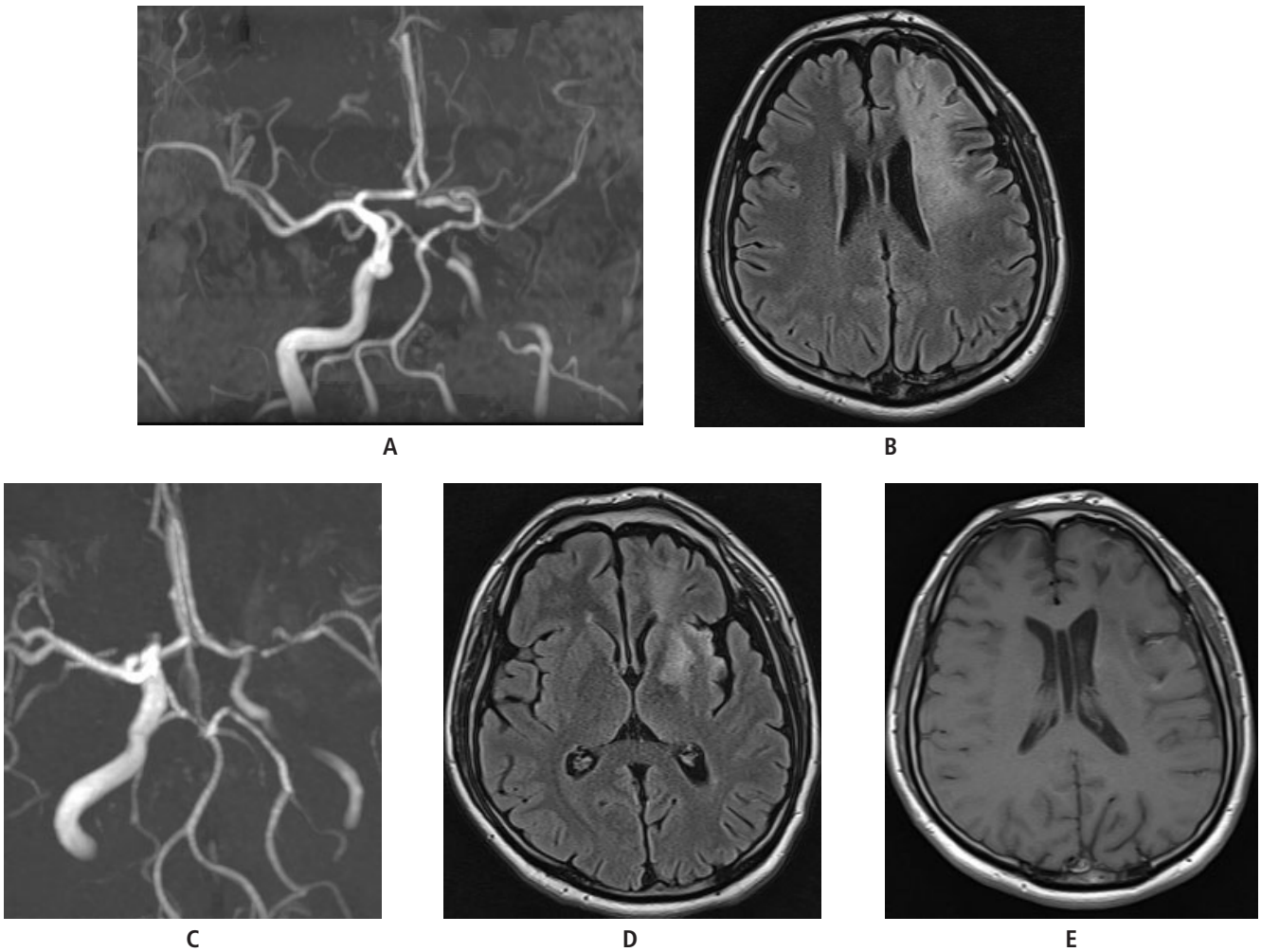

Figure 3. MRA from a 24-year-old man with diagnosis of ischemic stroke in the left MCA (middle cerebral artery) territory due to moderate stenosis of left ICA (internal carotid artery) above bifurcation with right facial-brachial type hemiparesis. **(A)** On day of admittance, MRA showed marked stenosis of left ICA with significant reducing blood flow in MCA; **(B)** MRI T2-weighted scan showed large infarct in the left frontotemporal area; **(C, D)** 11 days later, anterior circulation of cerebral flow was restored and foci of infarction were significantly diminished; **(E)** 21 days later, foci of infarction disappeared and the patient had considerable improvement his functional motor deficits (mRS 1-2 points), the patient returned to his work and was included in the control for secondary prevention of strokes.

On comparing the clinical features of presentation of young adults with that of elderly, it was found that headache, vertigo, vomiting, and facial-brachial type paresis are more common in young adults, whereas altered consciousness, speech abnormality, and sensorimotor hemiparesis are most common in old patients (Table 4).

On admittance, the NIHSS score of stroke severity was similar in both groups. Outcome on day 11 (or on discharge) and on day 21 was different between in both groups regarding NIHSS score (5.3 vs. 6.2 on day 11; 3.3 vs. 5.4 on day 21) and mRS score 0-2 (71.1% vs. 60.0% on day 11; 86.6% vs. 66.2% on day 21), and mean Barthel index (75.6% vs. 63.8% on day 11; 88.9% vs. 73.8% on day 21) according to the time of examination. These findings showed the significant improvement of neurological functions among the young patients. The mortality rates for young versus old groups differed significantly on day of discharge (7.8% vs. 11.5%). Logistic regression showed that mRS score 0–2 versus 3–6 was correlated with MRI scan findings on admittance (odds ratio 1.28, 95% confidence interval: 1.24–1.33), and at 11 and 21 days later (Figure 3; Table 5).

Discussion

Our study showed that the proportion of males was higher among the young and old groups of stroke patients. The predominance of males was also noted in other studies of cerebral infarction among young adults [6-8]. Accumulation of traditional risk factors probably starts earlier in males than in females.

Most traditional risk factors were less frequent among young stroke patients with exception of hypertension. It has been shown that hypertension is a considerable risk factor for young patients with cerebral infarction compared to matched controls [9, 19, 29]. In our study, the proportion of current smoking and alcohol consumption were clearly higher among the young compared to the old patients group. The frequency of diabetes mellitus was higher in elderly ischemic stroke patients than the young patients. In relation to stroke subtypes and etiology, young Mongolian adults with ischemic stroke have relatively high proportions of small artery occlusion (15.6%) and larger artery atherosclerosis (14.4%) than that recorded in studies carried out in other Asian countries [19, 28, 29]. Atrial fibrillation was the dominating

Table 5. Functional characteristics of ischemic stroke in young (n = 90) and old (n = 130) patients

Scores	Young patients (n (%))	Old patients (n (%))	p-value
On admission			
NIHSS[a]	6.8	7.3	0.001
At day 11			
NIHSS[a]	5.3	6.2	0.003
mRS 0-2	64 (71.1)	78 (60.0)	0.001
mRS 3-5	19 (21.1)	37 (28.5)	0.05
mRS 6	7 (7.8)	15 (11.5)	0.064
Barthel Index	68 (75.6)	83 (63.8)	0.001
At day 21			
NIHSS[a]	3.3	5.4	0.001
mRS 0-2	78 (86.6)	86 (66.2)	0.001
mRS 3-5	5 (5.6)	29 (22.3)	0.05
mRS 6	7 (7.8)	15 (11.5)	0.06
Barthel Index	80 (88.9)	96 (73.8)	0.001

[a]Mean stroke severity by NIHSS score: 0 = no stroke; 1-4 = minor stroke; 5-15 = moderate stroke; 16 = moderate to severe stroke; 17-42 = severe stroke.

cardiac source among older patients but was infrequent among young adults. In young adults the dominating heart disorders were rheumatic heart disease with and without valve disorders. This matches with the findings in other studies [7, 19]. Many studies show that migraine is a cause of stroke in young adults encounters in up to 20% of patients [5, 24]. Our result indicates that migraine with aura is likely related to ischemic stroke in up to 25.5% among young patients compared to old patients. Cervical artery dissection was 7.8% in young patients, which is the other rarest cause among the young patients and is mostly located in unilateral ICA. Frequency of patients with unknown etiology has small differences between other studies, accounting for 31–62% in young patients [23, 24] and in our stroke patients account for 24.4% overall in this category.

The distribution of infarctions in the anterior and posterior circulation was similar between young and old patients. The frequency of posterior circulation infarction was lower than in some other studies including young patients [21, 22]. We believe that this reflects better diagnostic precision in this study because most patients underwent MRI. Frequent MRI may also explain that we found a higher frequency of leukoaraiosis in old patients compared to recent studies [16-17]. In our study, 15.6% among the young versus 33.8% among the old patients had leukoaraiosis.

There was no difference with respect to severity of neurological deficits on admittance between young and old patients. There were large differences between two groups concerning the three-week outcome which showed beneficial effect for young stroke patients. At 11 day and 21 the mRS score of 0-2 was more prevalent in the young versus the old (71.1% vs. 60.0% at day 11, 86.6% vs. 66.2% at day 21), and mortality rate of young versus old patients (7.8% vs. 11.5% at day 11). The Barthel Index indicating the functional improvement also was significantly higher among young patients (88.9%) than old patients (73.6%) on multivariate analyses. This may indicate that young adults in our investigation endure cerebral ischemia better than old patients concerning short-term outcome, which is similar to recent observation made by Swiss and Norwegian groups [8, 17, 24]. The marked differences in stroke subtypes and etiology underscore the importance of conventional risk factors in urban areas of Mongolia [6]. Possible reasons to explain the above findings include poor compliance to treatment as well as predisposition factors to hypertension, heart diseases and diabetes with greater propensity to develop stroke complications. Further studies are warranted to confirm our findings and elucidate the reasons behind the alarming proportions of premature atherosclerotic cerebrovascular disease in young Mongolian patients.

This is one of the largest studies making a hospital-based direct comparison between ischemic stroke patients under 50 years and above 50 years admitted to a tertiary center, which we consider to be one of its advantages. All patients underwent investigations and treatment according to one common protocol. Another benefit was the frequent use of neuroimaging methods (MRI and MRA) which promotes high diagnostic precision. However, there are some limitations. First, using the TOAST and Baltimore-Washington Cooperative Young Stroke Study Criteria may complicate comparison with other studies using other criteria such as the World Health Organization criteria. Second, we might have missed some patients with untreated hypertension, atrial fibrillation or diabetes, especially in the young patient group. We plan to register the outcome of ischemic stroke at 6-12 months, which would give a complete impression about the patient's outcome in the different groups. Since this 6-12 month data was not included in this study, we might have missed few patients with, for example, atrial fibrillation or carotid stenosis. Stroke in young people requires a different approach to investigation and management than stroke in the elderly given differences in the relative frequencies of possible underlying causes. The results show the need for persistent management of conventional risk factors and proper patient investigation to determine specific etiology and subtyping of stroke in Mongolia. However, specificity is high in our study due to the frequent use of MRI and MRA. It seems evident that young patients may have an improved long-term outcome compared to old patients.

In conclusion, there are significant differences between young and old patients with ischemic stroke regarding to risk factors, etiological subtypes and improvement of functional deficits associated with the stroke. However, severity of stroke on admittance is similar but short-term outcome is different among young and old patients with relatively rapid improvement of functional deficit in young stroke patients compared to old ones.

Conflict of Interest

The authors state no conflict of interest.

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