PRELIMINARY FINDINGS OF TASHKENT HOSPITAL BASED STUDY OF RISK FACTORS FOR DIFFERENT ISCHEMIC STROKE SUBTYPES

Khurshidakhon Abduboriyevna Rasulova

Tashkent Pediatric Medical Institute, Uzbekistan

ABSTRACT

Objective: To determine risk factors in different pathogenic subtypes of ischemic stroke in Tashkent hospital registry and to compare with the data of other stroke registers.

Design: Prospective observational study.

Participants: 300 adults aged 18 years or over who suffered first-ever acute ischemic stroke, of them, the data of 100 patients with atherothrombotic, lacunar and cardioembolic strokes were analyzed.

Main outcome measures: Mathematically significant differences and not significant differences but interesting from other point of view. Categorical variables are expressed as frequencies and percentages. Differences were regarded as statistically significant when the P value was less than 0.05 ($P < 0.05$).

Results: Of 100 patients with acute first-ever ischemic stroke at the median age of 62.63 ± 4.68 (interquartile range 25-92) years, 57% were men and 43% were women. Depending on aetiology and stroke subtype, all the patients were divided into three groups: 42 patients with atherothrombotic stroke, 41 – with lacunar stroke, and 17 patients with cardioembolic stroke. Atherothrombotic stroke developed often in people over 60 years old, while lacunar stroke prevailed at the younger age. Stroke cases increased in people over 51 years old. Although men were more likely to suffer strokes than women, stroke incidence was equal in both sexes with increasing of age (over 60 years old), especially in atherothrombotic stroke, testifying to that women live longer. Combination of cerebral atherosclerosis and hypertension was the most significant risk factor for stroke. Atherosclerosis was the main aetiological factor for ischemic stroke, independently of its pathogenic heterogeneity. Diabetes mellitus was an independent risk factor for all stroke subtypes, which in most cases worsened the course and outcome of stroke. Hypertension was the leader aetiological factor for lacunar stroke. In these patients, we also should consider the presence of other risk factors, e.g. severe large vessel obstructions, se-triglycerol ≥ 2 mmol/L, etc. Cardioembolic stroke developed mainly because of cardiac thrombosis and valve pathology, which were often associated with chronic diseases of other organs, worsening the course and outcome of stroke. Despite of high prevalence of myocardial infarction in men, women were more likely to develop cardioembolic stroke.

Conclusions: This study found simultaneous influence of many risk factors (multifactorial disease) in the development of ischemic stroke. The more course and influence of the underlying disease and risk factor, the higher stroke risk and severity, especially in the absence or inadequate previous therapy of underlying disease before the stroke index. We have noted a high prevalence of under-diagnosis of vascular risk factors at levels of primary and secondary care. We recommend for improved public awareness of vascular risk factors and better diagnostic and treatment facilities aimed at addressing those factors at levels of primary and secondary healthcare. Larger population-based studies may provide additional data on stroke incidence and outcome among Uzbeks.

UDC CODE & KEYWORDS

■ UDC: 616.831-005.1 ■ Ischemic stroke ■ Pathogenic heterogeneity ■ Risk factors

INTRODUCTION

In Uzbekistan, the annual number of new stroke cases is about 209/100,000 inhabitants (Azhieva, 2008; Gafurov, 2009; Sagatov et al., 2011), while this rate is 130 in France, 155 in Germany, 170 in the UK, 223 in Spain, 400 in Hungary (Bonita, 1992; Bogousslavsky, 2000; Aszalos et al., 2002), 231 in Ukraine, 500 in Russia, and 795 in the USA (AHA computation based on the latest available data) (calculated from overall incidence of stroke) (Bonita, 1992; Vereschagin et al., 2002; Feigin, 2005; Suslina et al., 2009; Go et al., 2013). Men are 1.25 times more likely to suffer strokes than women, yet 60% of deaths from stroke occur in women. Since women live longer, they are older on average when they have their strokes and thus more often killed (Bonita, 1992; NINDS, 1999). According to a recently epidemiologic study published in Catalonia (Spain) on acute stroke by Marrugat et al. (2007), the incidence rates in Catalonia are among the lowest in developed countries. The cumulative incidence rate of cerebrovascular diseases per 100,000 population was 218 (95% CI, 214-221) in men and 127 (95% CI, 125-128) in women. In Uzbekistan, among men stroke cases is about 1.95, while in women is 3.15/1000 inhabitants (Azhieva, 2008; Sagatov et al., 2011). Gafurov (2009) reported 44.6% of deaths from stroke, of them 5.1% at early hospitalization (first 6 hours) that is 3-fold lesser than in late stages (14.7%). Disability affects 42.2% of stroke survivors, and no more 10.2% stroke patients could save their employability.

Stroke is a heterogeneous disease with more than 150 known causes. Ischemic stroke accounts for approximately 80-90% of all strokes. There are various classification systems for acute ischemic stroke (Amarenco et al., 2009). The TOAST classification is based on clinical symptoms as well as results of further investigations; on this basis, a stroke is classified as being due to (1) thrombosis or embolism due to atherosclerosis of a large artery, (2) embolism of cardiac origin, (3) occlusion of a small blood vessel, (4) other determined cause, (5) undetermined cause (two possible causes, no cause identified, or incomplete investigation) (Adams et al., 1993; Landau et al., 2005).

<http://www.journals.cz>

Given the disease burden of stroke, prevention is an important public health concern. Straus et al. (2002) writes that primary prevention is less effective than secondary prevention (as judged by the number needed to treat to prevent one stroke per year). Recent guidelines detail the evidence for primary and secondary prevention in stroke (Mast, 1997; NINDS, 1999; Bogousslavsky, 2000; Goldstein et al., 2006; Furie, 2011; Lambert, 2011). Because stroke may indicate the underlying disease, it is important to determine risk factors for stroke. Unmodifiable risk factors include age (older), gender (male), race/ethnicity (black), and stroke family history. In contrast, other risk factors for stroke, like high blood pressure, atherosclerosis, diabetes, heart diseases, obesity, unhealthy diet, alcohol consumption, drug use, or cigarette smoking, etc., can be changed or controlled by the person at risk (modifiable risk factors). According to recent studies (Wolf et al., 1991; Suslina et al., 2009), the most powerful risk factors ("death quintet") are high blood pressure, elevated serum cholesterol level, low glucose tolerance, cigarette smoking, and hypertrophy of the left ventricle on ECG. Risk for stroke arises 8-fold, if the person has three of these five risk factors. Patients with all these factors have a risk of 33-35% to develop stroke.

Our aim was to determine risk factors in different pathogenic subtypes of ischemic stroke in Tashkent hospital registry and to compare with the data of other stroke registers.

Patients and Methods

The prospective observational study was done at the Central Clinical Hospital of "Uzbekistan Railways" Co., 1-clinic of Tashkent Medical Academy, Tashkent Clinical Hospital No.5, the Second Republican Clinical Hospital (Tashkent, Uzbekistan) between September 2009 to April 2014. Total three hundred consecutive acute first-ever ischemic stroke cases have been collected and analysed. The diagnosis was based on clinical evaluation, using the WHO criteria, and the diagnosis was confirmed by CT and/or MRI of the brain in all the patients confirming cerebral or brain stem infarcts. We included in the study only one hundred patients with the most frequent ischemic stroke subtypes (atherothrombotic, lacunar and cardioembolic) using the TOAST classification (Adams et al., 1993), Vereschagin-Suslina's criteria (Suslina et al., 2009) and computed program of the Russian National Stroke Center to determine subtypes of ischemic stroke (www.stroke-center.ru, 2004). According to these criteria, all stroke patients were divided into three groups: 42 patients with atherothrombotic stroke, 41 patients with lacunar stroke, and 17 patients with cardioembolic stroke. Exclusion criteria were (1) intracerebral hemorrhage, (2) previous stroke, (3) brain tumor, (4) severe systemic diseases, (5) stroke of other determined cause, (6) stroke of undetermined cause. 64 patients had been examined by MRI, and 14 by MRA.

The following set of data were considered: (1) age, (2) sex, (3) family history, (4) stress, (5) obesity (BMI of 30 kg/m² or greater), (6) physical inactivity, (7) working and living conditions, (8) nutrition, (9) onset and course of stroke, (10) previous TIA, (11) duration of underlying disease, (12) associated disease, (13) elevated serum triglycerol (≥ 2.0 mmol/L), (14) hypercholesterolaemia (serum cholesterol ≥ 5.3 mmol/L), (15) diabetes mellitus, (16) smoking, (17) alcohol consumption, (18) elevated haematocrit (HTC ≥ 0.5 ; repeatedly in condition of normovolaemia), (19) elevated platelet count (≥ 300 G/L), (20) ECG data, (21) functional status (measured using Scandinavian Stroke Severity Scale, Glasgow Coma Scale, Gusev-Skvortsova Stroke Scale).

The diagnosis of underlying disease was established if patients were already treated with appropriate therapy at the time of admission or diagnosed during the hospital stay using Doppler ultrasonography, daily monitoring of blood pressure, ECG, EchoCG, ophthalmoscopy, cerebral angiography (MRA), blood tests, and from previous medical documentations of the patients. We have considered onset of stroke from the beginning of appearance of first symptoms of stroke from the medical history, as well as course of stroke was estimated by patient's functional status investigated by Stroke Scales on admission to the hospital and in dynamics during hospital stay. Hypertension was defined as a previous physician diagnosis of hypertension or blood pressure readings consistently $\geq 140/90$ mmHg. Diabetes was defined as a previous physician diagnosis or fasting plasma glucose ≥ 7 mmol/L. Atherosclerosis was defined as a previous diagnosis or during our examination using Carotid Doppler ultrasound scanning performed on 67 patients. Abnormalities noted in the common and internal carotid arteries included intimal thickening, presence of atheromatous plaques, and carotid lumen stenosis. These were graded according to the Society of Radiologists in Ultrasound Consensus Conference recommendations (Grant et al., 2003).

Stress was considered when experiencing stressful life events (e.g., death of a spouse or a child, losing job, etc.) in the previous years before stroke. Sleep disorders in our patients were noted in medical history before stroke (usually as their complains). Because we had not performed special methods to study sleep disorders such as polysomnography, Epworth sleepiness scale, etc., we did not classified sleep disorders to apnoea, hypopnoea, etc.

We have regarded patients as smokers if they had smoked for 10 years or more or they were smoking in the last 5 years before their stroke. Beside the well known risk factors, drinking habits of our patients have also been registered. Alcohol consumption was estimated from the regular intake during the 2 years before the index stroke.

In groups of patients with different stroke subtypes, we determined the rate of risk factors and the results were compared with each other. Results of our data bank have been compared with those of other stroke registries.

In our study, we included not only the mathematically significant differences but also those that were not significant but interesting from other point of view. We applied the usual statistical methods for the analysis of the groups of patients created from different aspects. Categorical variables are expressed as frequencies and percentages. Differences were regarded as statistically significant when the P value was less than 0.05 ($P < 0.05$).

Results

The average age of the patients was 62.63 ± 4.68 (interquartile range 25-92) (mean $\pm$ SD) years old. Men were 57 and women were 43, thereby giving a male-to-female ratio of 1.32:1. Age at presentation was 54.8 ± 10.6 years in males and 62.5 ± 7.12 years in females, a difference that was statistically significant ($P < 0.05$). Depending on stroke subtype, the average age of patients with atherothrombotic stroke was 63.29 ± 2.82 (interquartile range 44-80) years old (52.4% men and 47.6% women);

PRELIMINARY FINDINGS OF TASHKENT HOSPITAL BASED STUDY OF RISK FACTORS FOR DIFFERENT ISCHEMIC STROKE SUBTYPES

in lacunar stroke - 61.46 ± 3.67 (interquartile range 30-80) years old (63.4% men and 36.6% women); in cardioembolic stroke - 63.82 ± 4.68 (interquartile range 25-92) years old (47.1% men and 52.9% women). Applied independent t-test showed non-significant difference of age between the groups ($P > 0.05$). Thus, men were more likely to develop ischemic stroke, especially lacunar stroke. Only cardioembolic stroke developed often in women. While stroke cases were observed at the age over 25 years old, the maximum frequency of the disease was marked after the age 50. In this case, lacunar stroke prevailed in younger age, cardioembolic stroke developed in older age. However, at the age older than 70 years old, all stroke subtypes developed in both sexes with equal frequency.

Hypertension in 89%, atherosclerosis in 73%, including their combinations in 36%, diabetes mellitus in 32%, and heart diseases in 36% were the most frequent aetiological factors in our stroke patients. Comparative analysis of the leader risk factors in pathogenic subtypes of ischemic stroke has shown prevalence of atherosclerotic lesions of head magisterial arteries (100%) in combination with hypertension (52.4%) and diabetes (40.5%) in atherothrombotic stroke. Among patients with lacunar stroke, hypertension was registered in 90.2%, followed by atherosclerosis in 29.3% and diabetes in 34.1%. Aetiological factors for cardioembolic stroke were thrombotic masses in heart diseases and cardiac dysfunctions in 94.1% ($P < 0.05$), associated with atherosclerosis (70.6%), hypertension (52.9%), and diabetes mellitus (17.6%) (Figure 1).

Figure 1: The leader aetiological factors of stroke pathogenic subtypes (%)

Note: H+A – Hypertension + Atherosclerosis

Source: Author

In cardioembolic stroke group, we have found the following high risk sources of embolus, according to classification of risk sources of cardiogenic embolism by Adams H.P. et al. (1993): constant form of atrial fibrillation in 35.3%, mitral stenosis+atrial fibrillation in 17.6%, dilatatory cardiomyopathy in 17.6%, which was associated with chronic alcoholism in 11.8%, akinesis of the left ventricle in 11.8%, artificial valve (5.9%). Medium risk sources were: heart failure in 5.9%, mitral insufficiency in 11.8%, paroxysmal form of atrial fibrillation in 35.3%. 23.5% of patients had suffered myocardial infarction in the last 5 years or more before their strokes. Atherosclerotic plaques of large vessels (including aorta in 5.9%), as well as platelet count $\geq 300/L$ in 11.8% ($P < 0.05$) could be embolism sources as well. Diabetes mellitus as independent cluster was observed in 17.6%. Simultaneously, epilepsy in 11.8% ($P < 0.05$), respiratory diseases in 11.8% ($P < 0.05$), and thrombocytopenia in a patient with alcohol abuse (5.9%) were registered in the cardiogenic embolism group (Table 1).

In lacunar stroke group, heart diseases were noted in 34.1% (of them, myocardial infarction in 2.4%), mostly angina pectoris in 24.4% ($P < 0.05$). It is interesting that obesity and se-triglycerol ≥ 2 mmol/L were the frequent risk factors in lacunar stroke as well, testifying to their independence on stroke subtypes ($P > 0.05$). Moreover, we think that diseases accompanied by overload and tension, like asthma, hemorrhoids, and hernia, as well as chronic renal and prostatic diseases, along with the other risk factors, could result in sharp increase of blood pressure and contribute to lacunar infarction on the background of systemic arterial defeat (Table 1). In this group of patients, we observed pure motor stroke in 23 (56.1%) of patients and sensorimotor stroke in 12 (29.3%) patients. The other 6 (14.6%) patients had pure sensory stroke, ataxic hemiparesis, and dysarthria-clumsy hand syndromes with equal frequency.

Figure 2 shows that hypertension was found in all stroke subtypes, but more often in lacunar stroke (95.1%). Men had hypertension more often than women did, and in many cases, it was diagnosed after their strokes. Although heart diseases and cardiac dysfunctions were the distinctive risk factors for cardioembolic stroke, it was interesting that myocardial infarction, which had occurred in 6 months or less before the stroke index, was observed in atherosclerotic stroke (11.9%). Although myocardial infarction had high frequency in men, cardioembolic stroke often developed in women. 25% patients, often men, with previous TIAs developed strokes during 5 years. Diabetes mellitus as an independent risk factor was registered in 34% patients, in most cases with duration of 5 years or more (22%), mostly in atherothrombotic stroke (28.6%). Dyslipidemia was the main risk factor in all stroke subtypes, especially in atherothrombotic stroke (52.4%). This risk factor trended to increase in men. Nutritional features in 41% resulted in obesity, hypertension, diabetes and atherosclerosis as well. Simultaneously four risk factors were registered in 28% of the patients. Physical inactivity was marked in 64%, often in men (36%) than in women (28%), and in all stroke subtypes (Figure 2).

Familial stroke risk was registered in 23% of cases, mostly in atherothrombotic stroke (26.2%) (Figure 2). Members of a family might have a genetic tendency for stroke risk factors, such as an inherited predisposition for hypertension or diabetes. The influence of a common lifestyle among family members could also contribute to familial stroke. In our study, familial stroke risk was higher in men (15%) than in women (8%).

Men were more likely to have harmful habits, like cigarette smoking and chronic alcoholism. Abstainers, moderate drinkers (alcohol intake ≤ 60 g/day) were 17% and heavy drinkers (alcohol intake ≥ 60 g/day) were 9%. Depending on intensity and duration of smoking, smokers had high risk to develop stroke, especially among the youth (15%). Among stroke patients with hypertension, caffeine intake (systemic coffee and tea intake ≥ 100 g/day) was noted in 45%. We could find drinking habits and long-term smoking in cardioembolic stroke, systemic caffeine intake in lacunar and atherothrombotic stroke subtypes, especially in men. Stress was one of the main risk factors for stroke (67%), often in men. Sleep disorders contributed to stroke in 49%, independently of sex.

PRELIMINARY FINDINGS OF TASHKENT HOSPITAL BASED STUDY OF RISK FACTORS FOR DIFFERENT ISCHEMIC STROKE SUBTYPES

Table 1: Risk factors and co-morbidities in different stroke subtypes (%)

Risk factors and co-morbidities	Total stroke patients (n=100)	Atherothrombotic stroke (n=42)	Lacunar stroke (n=41)	Cardioembolic stroke (n=17)
Heart diseases:	36	14.3 (6)	34.1 (14)	94.1(16)*
Angina pectoris	12	4.8 (2)	24.4 (10)*	0
Unstable stenocardia	1	0	2.4 (1)	0
Myocardial infarction	14	21,4 (9)	2.4 (1)	23.5 (4)
Dilatatory cardiomyopathy	4	0	2.4 (1)	17.6 (3)*
Mitral stenosis (rheumocarditis)	3	0	0	17.6 (3)*
Atrial fibrillation:	12	2.4 (1)	7.3 (3)	47.1 (8)*
Inconstant form	5	2.4 (1)	2.4 (2)	11.8 (2)*
Constant form	7	0	2.4 (1)	35.3 (6)*
Diabetes mellitus	34	40.5 (17)	34.1 (14)	17.6 (3)
Obesity and se-triglycerol ≥ 2 mmol/L	38	30.9 (13)	46.3 (19)	35.3 (6)
Cervical osteochondrosis	18	26.2 (11)	14.6 (6)	5.9 (1)
Parkinsonism	3	4.8 (2)	2.4 (1)	0
Epilepsia	3	2.4 (1)	0	11.8 (2)*
Dementia previous to stroke	1	0	0	5.9 (1)*
Peripheral artery diseases:	6	4.8 (2)	7.3 (3)	5.9 (1)
Aneurism of aorta	1	0	0	5.9 (1)*
Dissection of vertebral artery	1	2.4 (1)	0	0
Subclavian steal-syndrome	1	2.4 (1)	0	0
Varicose veins of legs	1	0	2.4 (1)	0
Venous thrombophlebitis of legs	2	0	4.9 (2)	0
Platelet count ≥ 300 /L	3	2.4 (1)	0	11.8 (2)*
Renal diseases	10	9.5 (4)	14.6 (6)	0
Gastrointestinal diseases	6	9.5 (4)	4.9 (2)	0
Respiratory diseases	5	2.4 (1)	4.9 (2)	11.8 (2)*
Prostatic diseases	2	0	4.9 (2)	0
Cataract	3	4.8 (2)	0	5.9 (1)
Bronchial asthma	1	0	2.4 (1)	0
Goiter	1	2.4 (1)	0	0
Abdominal hernia	1	0	2.4 (1)	0
Hemorrhoids	1	0	2.4 (1)	0
Chronic alcoholism	3	0	2.4 (1)	11.8 (2)*

Note: there is number of patients in brackets, * - significant differences between total stroke patients and stroke subtypes, $P < 0.05$

Source: Author

Duration of influence of the underlying factor and associated disease was higher in cardioembolic stroke (82.4%) than in lacunar (68.3%) and atherothrombotic ones (54.8%). This fact suggests that the main risk factor and underlying disease contribute to increase of severe vascular structural changes and thrombosis, as well as establishes connection between duration of influence of the main risk factor and stroke incidence (Figure 2).

Discussion

Many studies of risk factors for stroke that categorized strokes as ischemic or hemorrhagic have not subdivided ischemic stroke according to the different clinical or etiological subtypes. Most of stroke registries are not homogenous, e.g. Hamburg Stroke Data Bank includes not only strokes but also TIAs (Spitzer et al., 1998). Other registries include ischemic strokes only, e.g. Berliner Schlaganfall daten bank (Mast, 1997), Yonsei Stroke Registry (Lee et al., 2001), or San Diego stroke data bank (Rothrock, 1993). Some studies have compared the prevalence of risk factors between the different subtypes of ischemic stroke and have reported important differences in the frequency of established vascular risk factors. Our stroke data bank is a hospital based one.

In actuality, stroke strikes all age groups, however, older people have a higher risk for stroke than the general population and the risk for stroke increases with age. For every decade after the age of 55, the risk of stroke doubles, and two-thirds of all strokes occur in people over 65 years old. People over 65 also have a 7-fold greater risk of dying from stroke than the general population (Bonita, 1992; NINDS, 1999; Bogousslavsky, 2000; Straus et al., 2002; Goldstein et al., 2006; Furie, 2011; Go et al., 2013). In our series of acute ischemic stroke cases, people were over 51 years old. Relatively lesser number of patients was registered at the younger age group (25-40 and 41-50 years). In agreement with studies by Bonita (1992), Yip et al. (1997), Keong et al. (1998), NINDS (1999), Bogousslavsky (2000), Goldstein et al. (2006), Kim et al. (2006), Delbari et al. (2011), Alkali et al. (2013), Go et al. (2013), in our hospital based study, men had a greater risk for all stroke subtypes, especially for lacunar stroke. However, stroke incidence was equal in both sexes with increasing of age (over 60 years old), especially in atherothrombotic stroke, testifying to that women live longer. We assume that stroke in women occurred because of unhealthy diet and associated pathology. In men stroke occurred due to additional harmful habits (smoking, alcohol consumption) and stress.

PRELIMINARY FINDINGS OF TASHKENT HOSPITAL BASED STUDY OF RISK FACTORS FOR DIFFERENT ISCHEMIC STROKE SUBTYPES
Figure 2: Risk factors of ischemic stroke, depending on its pathogenic heterogeneity (%)

Source: Author

In this study, we investigated only the most frequent ischemic stroke subtypes, i.e. atherothrombotic, cardioembolic and lacunar strokes, which, according to Fisher (1991), Petty et al. (2000), Arboix et al. (2000, 2001), Vereschagin et al. (2002) and Suslina et al. (2009), account for about 34-50%; 22-30% and 20-45% of brain infarcts, respectively. Ischemic stroke of unusual cause subtype has not been included in the present study although representing up to 6% of the total of cerebral infarctions (Arboix et al., 2001). In studies by Kim et al. (2006), large-artery atherosclerosis was the most frequent subtype (42%), followed by small-vessel occlusion (27%), cardiogenic embolism (15%), undetermined etiology (15%), and other determined etiology (1.5%). In a prospective, comparative study between Malaysian and Australian hospital-based stroke registries conducted by Keong et al. in 1998, lacunar infarction was common in Malaysians, and cardioembolic stroke was common in Australians. There were significant differences in the risk factors for stroke with diabetes mellitus, smoking, hypercholesterolemia and hypertriglyceridemia more common in the Asian group, while the Caucasian group were older and had more atrial fibrillation.

We found hypertension to be the most prevalent risk factor for ischemic stroke (89%). This was consistent with previous studies by Yip et al. (1997), Bogousslavsky (2000), Arboix et al. (2000), Petty et al. (2000), Aszalos et al. (2002), Kim et al. (2006), Delbari et al. (2011), Sagatov et al. (2011), Kuwashiro et al. (2012), Alkali et al. (2013). According to Budapest Stroke Data Bank (1990-1996), hypertension was the most frequent risk factor but the case fatality rate was determined by the presence or absence of ischaemic heart disease (Aszalos et al., 2002). According to studies by Arboix et al. (2000), in 1473 consecutive ischemic stroke patients collected in a prospective stroke registry, hypertension was present in 52% of patients followed by atrial fibrillation in 27% and diabetes in 20%. Our findings are similar with reported previously. The other most frequent aetiological factors were atherosclerosis in 73%, including their combinations in 36%, diabetes mellitus in 32%, and heart diseases in 36%.

The pattern of risk factors associated with atherothrombotic stroke included atherosclerotic lesions of head magisterial arteries (100%) in combination with hypertension (52.4%) and diabetes (40.5%), and age (over 60 years old) that is similar with studies by Arboix et al. (2000), in which chronic obstructive pulmonary disease, hypertension, diabetes, transient ischemic attack, and age were risk factors for this stroke subtype. Although carotid stenosis is a cause of stroke, serum

cholesterol levels have not been associated with atherothrombotic stroke because no epidemiologic studies have properly looked for this association in this particular subtype of ischemic stroke. In previous cohort by Arboix et al. (2000), previous cerebral hemorrhage, hypertension, obesity, and diabetes were strong predictors of lacunar stroke, while in our study hypertension was registered in 90.2%, followed by atherosclerosis in 29.3% and diabetes in 34.1%. In the case of cardioembolic stroke, thrombotic masses in heart diseases and cardiac dysfunctions in 94.1% ($P < 0.05$), associated with atherosclerosis (70.6%), hypertension (52.9%), and diabetes mellitus (17.6%), as well as female gender. These results are similar to other studies (Adams et al., 1993; Rothrock, 1993; Mast, 1997; Keong et al., 1998; NINDS, 1999; Bogousslavsky, 2000; Aszalos et al., 2002; Goldstein et al., 2006; Kim et al., 2006; Arboix et al., 2000, 2004, 2010). In studies by Kim et al. (2006), risk factors included hypertension (71%), cigarette smoking (35%), diabetes mellitus (30%), history of previous stroke (22.7%), emboligenic cardiac diseases (20%), and hypercholesterolemia (11%). Hypertension was more common in patients with lacunar stroke than in those with other subtypes ($p < 0.05$), and the case-fatality rate was higher in patients with cardioembolic stroke than in those with other subtypes ($p < 0.01$).

In the case of lacunar stroke, pure motor stroke accounted for 56.1% that is consistent with studies by Melo et al. (1992), Arboix et al. (2004, 2010) reported that pure motor stroke is a reliable clinical test for diagnosing lacunar infarction.

Physical inactivity in our patients was prevalent in 64% of patients. In studies by Willey et al. (2009) it was found that only moderate- to vigorous-intensity exercise was associated with reduced stroke incidence, whereas light exercise (such as walking) showed no benefit.

While stress can be difficult to define, there are many studies showing a link between significant ongoing stress and increased risk of high blood pressure and cardiovascular events. Chronic stress leads to frequent smoking, chronic alcoholism, hypertension, etc. Stress could increase prolonged exposure to higher blood pressure and therefore promote damage to blood vessel walls, increase the risk of heart disease and atrial fibrillation, and it could predispose to atheroma, aneurysms and ischemic stroke. In addition, acute stressful events – such as death of a spouse or losing job – have been linked to heart attacks, and while there is no firm evidence that these can cause stroke. The adrenalin produced by stress can affect the blood platelets and promote clotting, possibly causing a blockage of arteries in or near the brain. Therefore, some sort of biological rationale suggests perhaps in acute stressful situations a person could be at risk of stroke. According to studies by Egido et al. (2012), compared with healthy age-matched individuals, stressful habits and type A behavior are associated with high risk of stroke. This association is not modified by gender. In our study, stress was one of the main risk factors in our cases (67%), especially in men and in atherothrombotic (76.2%, $P < 0.05$) and lacunar strokes (65.8%).

Sleep disorders contributed to stroke in 49%, independently of sex. We have not classified them as we did not performed special methods of study (e.g., polysomnography). In studies by Zhang et al. (2012), apnoea was defined as a complete cessation of airflow for ≥ 10 s. Hypopnoea was defined as a significant reduction in airflow ($> 50\%$) for ≥ 10 s or a moderate reduction in airflow for ≥ 10 s together with an arousal or oxygen. Obstructive sleep apnoea syndrome (OSAS) is characterized by repetitive episodes of upper airway obstruction during sleep with associated intermittent hypoxaemia, which affects $\geq 4\%$ of adult males and $\geq 2\%$ of adult females. It is widely accepted that repetitive nocturnal hypoxaemia in OSAS patients is associated with increased risk of stroke and cardiovascular disease. The underlying pathophysiology linking these disorders with OSAS has not been fully elucidated (Yaggi et al., 2005; Zhang et al., 2012).

Stroke subtyping can have different purposes, e.g. describing patients' characteristics in a clinical trial, grouping patients in an epidemiological study, careful phenotyping of patients in a genetic study, and classifying patients for therapeutic decision-making in daily practice. Regarding the 4 main categories of aetiologies of ischemic stroke (i.e. atherothrombotic, small vessel disease, cardioembolic, and other causes), the classification should reflect the most likely aetiology without neglecting the vascular conditions that are also found (Amarenco et al., 2009). For example, we found previous myocardial infarction in atherosclerotic stroke or small vessel disease (lacunar stroke) in the presence of severe large vessel obstructions. Therefore, we assume that each stroke subtype is also heterogeneous, depending on aetiological factor, as well as duration, severity and course of underlying disease.

There were a number of limitations to the present study. A major limitation of our study was its hospital-based design. The sample size was small and although the correlations were significant, they were often quite low, which could have been a chance finding. Population-based studies allow for complete case-ascertainment of stroke in the community, but such studies require huge financial resources and manpower. In our study, not all stroke patients in a defined area will present to the hospital. Minor strokes, deaths at home and other stroke subtypes will go undetected. Nonetheless, the diagnosis of all patients presenting to a hospital allows accurate subtyping of stroke.

Conclusion

Thus, in our hospital-based study, acute ischemic stroke cases increased after the age of 51. Men had a greater risk for all stroke subtypes, but greater risk for males was at the younger age (less than 61 years old), while women were generally older when they had their strokes and were more likely to die from them, since women tend to live longer. Although men were more likely to develop heart diseases, women had a higher risk for cardioembolic stroke, independently of age. Lacunar infarction (small vessel disease) prevailed at the younger age and was associated with angiopathy of hypertensive or diabetic origin, testifying to occurrence and increase of rate of hypertension and diabetes mellitus in younger people. Atherothrombotic stroke developed in people over 60 years old; however, its prevalence among patients of younger age was an evidence of manifestation of early atherosclerosis and its complications.

Ischemic stroke is multifactorial heterogeneous disease. Although there may not be a single genetic factor associated with stroke, genes do play the large role in the expression of stroke risk factors such as hypertension, heart disease, diabetes, and vascular malformations. Familial risk for stroke was higher in men, possibly, because of environmental factors, such as a common sedentary lifestyle or harmful habits, rather than hereditary factors. Atherosclerosis was the main aetiological factor for ischemic stroke, independently of its pathogenic heterogeneity. Diabetes mellitus was an independent risk factor for all stroke subtypes, which in most cases worsened the course and outcome of stroke.

Hypertension was the leader aetiological factor for lacunar stroke. In these patients, we also should consider the presence of other risk factors, e.g. severe large vessel obstructions, se-triglycerol ≥ 2 mmol/L, etc. Cardioembolic stroke developed mainly because of cardiac thrombosis and valve pathology, which were often associated with chronic diseases of other organs and worsened the course and outcome of stroke. Despite of high prevalence of myocardial infarction in men, women were more likely to develop cardioembolic stroke. However, cardiogenic embolism occurred with equal frequency in both genders when they had suffered myocardial infarction in the last 6 months or more before their strokes.

Given the large body of circumstantial evidence, best medical management for stroke includes advice on diet, exercise, lifestyle, smoking and alcohol use, as well as reduction of stress. Medication or drug therapy is the most common method of stroke prevention; carotid endarterectomy can be a useful surgical method of preventing stroke.

Stroke develops after simultaneous influence of many risk factors (multifactorial disease). The more course and influence of the underlying disease and risk factor, the higher stroke risk and severity, especially in the absence or inadequate previous therapy of underlying disease before the stroke index. Correction of risk factors is the most effective strategy for prevention of cerebrovascular diseases in a whole.

In conclusion, we have provided relevant data on the clinical profile of stroke in Tashkent hospitals. We have noted a high prevalence of under-diagnosis of vascular risk factors at levels of primary and secondary care. We recommend for improved public awareness of vascular risk factors and better diagnostic and treatment facilities aimed at addressing those factors at levels of primary and secondary healthcare. Smoking-cessation campaigns, aggressive control of hypertension and appropriate use of anticoagulant therapy could significantly reduce the current stroke burden in Uzbekistan. Larger population-based studies may provide additional data on stroke incidence and outcome among Uzbeks.

REFERENCES

1. Adams, H.P., Bendixen, B.H., Kappelle, L.J. (1993). Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*, 24(1), 35-41.
2. Alkali, N.H., Bwala, S.A., Akano, A.O., Osi-Ogbu, O., Alabi, P., Ayeni, O.A. (2013). Stroke risk factors, subtypes, and 30-day case fatality in Abuja, Nigeria. *Niger Med J.*, 54(2), 129-135.
3. Amarenco, P., Bogousslavsky, J., Caplan, L.R., Donnan, G.A., Hennerici, M.G. (2009). Classification of Stroke Subtypes. *Cerebrovasc Dis.*, 27, 493-501.
4. Arboix, A., Bechich, S., Oliveres, M., García-Eroles, L., Massons, J., Targa, C. (2001). Ischemic stroke of unusual cause: clinical features, etiology and outcome. *European Journal of Neurology*, 8(2), 133-139.
5. Arboix, A., Massons, J., García-Eroles, L., Targa, C., Comes, E., Parra, O. (2010). Clinical predictors of lacunar syndrome not due to lacunar infarction. *BMC Neurology*, 10:31 doi:10.1186/1471-2377-10-31
6. Arboix, A., Morcillo, C., García-Eroles, L., Oliveres, M., Massons, J., Targa, C. (2000). Different vascular risk factor profiles in ischemic stroke subtypes: a study from the "Sagrat Cor Hospital of Barcelona Stroke Registry". *Acta Neurol Scand.*, 102(4), 264-270.
7. Arboix, A., Padilla, I., Massons, J., García-Eroles, L., Comes, E., Targa, C. (2004). Clinical study of 222 patients with pure motor stroke. *J Neurol Neurosurg Psychiatry*, 75, 231-234.
8. Aszalos, Z., Barsi, P., Vitrai, J., Nagy, Z. (2002). Hypertension and clusters of risk factors in different stroke subtypes (an analysis of Hungarian patients via Budapest Stroke Data Bank). *Hum. Hypertension.*, 16, 495-500.
9. Azhieva, Z.B. (2008). Dynamics and prognosis of the incidence of cerebral strokes, according to registry of Nukus city. *J Neurology (Uzbekistan)*, 3-4, 44. In Russian.
10. Bogousslavsky, J. (2000). Risk factors and stroke prevention. *Cerebrovasc. Dis.*, 10 (3), 12-21.
11. Bonita, R. (1992). Epidemiology of stroke. *Lancet*, 339, 342-344.
12. Delbari, A., Salman Roghani, R., Tabatabaei, S.S., Rahgozar, M., Lokk, J. (2011). Stroke epidemiology and one-month fatality among an urban population in Iran. *Int J Stroke*, 6, 195-200.
13. Egidio, J.A., Castillo, O., Roig, B., Sanz, I., Herrero, M.R., Garay, M.T. (2012). Is psycho-physical stress a risk factor for stroke? *J Neurol Neurosurg Psychiatry*, 83(11), 1104-1111.
14. Feigin, V.L. (2005). Stroke epidemiology in the developing world. *Lancet*, 365(9478), 2160-2161.
15. Fisher, C.M. (1991). Lacunar infarcts: a review. *Cerebrovasc Dis.*, 1311, 320.
16. Gafurov, B.G. (2009). The rate and clinical structure of cerebral strokes in Uzbekistan, according to hospital registry. Report in Scientific Conference: Relevant problems in Surgery, Tashkent. In Russian.
17. Go, A.S., Mozaffarian, D., Roger, V.L., Benjamin, E.J., Berry, J.D., Borden, W.B., Bravata, D.M., Dai, S., Ford, E.S. (2013). Heart Disease and Stroke Statistics - 2013 Update. A Report From the American Heart Association. *Circulation*, 127, e6-e245.
18. Goldstein, L.B., Adams, R., Alberts, M.J. (2006). Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke*, 37(6), 1583-1633.
19. Grant, E.G., Benson, C.B., Moneta, G.L., Alexandrov, A.V., Baker, J.D., Bluth, E.I. (2003). Carotid artery stenosis: Gray-scale and Doppler US diagnosis – Society of Radiologists in Ultrasound Consensus Conference. *Radiology*, 229, 340-346.
20. Furie, K.L. (2011). Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 42, 227.
21. Keong, W., Jin, K., George, J., Tan, C.T., Biard, A., Donnan, G.A. (1998). A comparative study of stroke subtypes between Asians and Caucasians in two hospital-based stroke registries. *Neurol. J. Southeast Asia*, 3, 19-26.
22. Kim, J.T., Yoo, S.H., Kwon, J.H., Kwon, S.U., Kim, J.S. (2006). Subtyping of Ischemic Stroke Based on Vascular Imaging: Analysis of 1,167 Acute, Consecutive Patients. *J Clin Neurol.*, 2(4), 225-230.

PRELIMINARY FINDINGS OF TASHKENT HOSPITAL BASED STUDY OF RISK FACTORS FOR DIFFERENT ISCHEMIC STROKE SUBTYPES

23. Kuwashiro, T, Sugimori, H., Ago, T., Kamouchi, M., Kitazono, T. (2012). FSR Investigators. Risk factors predisposing to stroke recurrence within one year of non-cardioembolic stroke onset: the Fukuoka Stroke Registry. *Cerebrovasc Dis.*, 33(2), 141-149.
24. Lambert, M. (2011). AHA/ASA Guidelines on Prevention of Recurrent Stroke. *Am Fam Physician*, 83(8), 993-1001.
25. Landau, W.M., Nassief, A. (2005). Time to burn the TOAST. *Stroke*, 36, 902-904.
26. Lee, B.I., Heo, J.H., Kim, D.I. (2001). Yonsei Stroke Registry. *Cerebrovasc Dis.*, 12, 45-151.
27. Marrugat, J., Arboix, A., García-Eroles, L., Salas, T., Vila, J., Castell, C., Tresserras, R., Elosua, R. (2007). The estimated incidence and case fatality rate of ischemic and hemorrhagic cerebrovascular disease in 2002 in Catalonia. *Rev Esp Cardiol.*, 60, 573-580.
28. Mast, H. (1997). Assoziation von Hypertonie und Diabetes mellitus mit mikroangiopathischen Hirninfarktmustern. *Nervenarzt.*, 68, 129-134.
29. Melo, T.P., Bogousslavsky, J., van Melle, G. (1992). Pure motor stroke: a reappraisal. *Neurology*, 42, 789-798.
30. National Institute of Neurological Disorders and Stroke (NINDS) (1999). Stroke: Hope Through Research National Institutes of Health: http://www.ninds.nih.gov/disorders/stroke/detail_stroke.htm.
31. Petty, G.W., Brown, R.D.Jr, Whisnant, J.P., Sicks, J.D., O'Fallon, W.M., Wiebers, D.O. (2000). Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. *Stroke*, 31, 1062-1068.
32. Rothrock, J.F. (1993). An analysis of ischemic stroke in an urban southern California population *Arch. Intern. Med.*, 153, 619-624.
33. Sagatov, D., Rasulova, Kh., Madjidova, Y. (2011). Risk factors and prognosis of ischemic stroke in young patients in Uzbekistan. *Medical and Health Science Journal*, 5, 16-22.
34. Spitzer, K., Becker, V., Thie, A., Kunze, K. (1998). The Hamburg Stroke Data Bank: goals, design and preliminary results. *Neurol.*, 236, 139-144.
35. Straus, S.E., Majumdar, S.R., McAlister, F.A. (2002). New evidence for stroke prevention: scientific review. *JAMA*, 288(11), 1388-1395.
36. Suslina, Z.A., Varakin, Y.A., Vereschagin, N.V. (2009). Brain vascular diseases: Epidemiology. Pathogenic mechanisms. Prevention. Moscow, 352. In Russian.
37. Vereschagin, N.V., Suslina, Z.A. (2004). Determination of the probabilities of stroke subtypes: www.stroke-center.ru. In Russian.
38. Vereschagin, N.V., Varakin, Y.Y. (2002). Epidemiology of stroke in Russia. Book: Emergency states in neurology, 16-21. In Russian.
39. Willey, J.Z., Moon, Y.P., Paik, M.C., Boden-Albala, B., Sacco, R.L., Elkind, M.S. (2009). Physical activity and risk of ischemic stroke in the Northern Manhattan Study. *Neurology*, 73, 1774-1779.
40. Wolf, P.A., D'Agostino, R.B., Belanger, A.J., Kannel, W.B. (1991). Probability of Stroke: A risk profile from the Framingham Study. *Stroke*, 22, 312-318.
41. Yaggi, H.K., Concato, J., Kernan, W.N. (2005). Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med.*, 353, 2034-2041.
42. Yip, P.K., Jeng, J.S., Lee, T.K., Chang, Y.C., Huang, Z.S., Chen, R.C. (1997). Subtypes of ischemic stroke. A hospital-based stroke registry in Taiwan (SCAN-IV). *Stroke*, 28(12), 2507-2512.
43. Zhang, L., Zhuang, J.H., Peng, H. (2012). Correlation between endothelial dysfunction, Rho-associated protein kinase activity, C-reactive protein and obstructive sleep apnoea syndrome in male patients. *J Int Med Research*, 40, 2183-2190.