Khorasan Stroke Registry: Analysis of 1392 Stroke Patients

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Background: The hospital-based stroke registry is useful for understanding diverse clinical characteristics of stroke related to geographical, racial, or environmental differences.

Methods: The Khorasan Stroke Registry was established for evaluation of incidence, clinical manifestations, risk factors, topography, and etiology of ischemic stroke in Southern Khorasan, Iran, during 2001 – 2005. Consecutive stroke patients underwent a standard battery of diagnostic investigations by a stroke neurologist. Topography and etiology of brain infarction was determined based on the Practical Iranian Criteria classification.

Results: The incidence of ischemic stroke in Khorasan population is 43.17 cases per 100,000 people per year. During a 5-year period 1,392 ischemic stroke patients (738 females, 654 males) were evaluated in the Khorasan Stroke Registry. Atherosclerosis constituted 53.6% of etiologies followed by uncertain causes (19.9%), cardioembolism (11.8%), and miscellaneous etiologies (2.9%). Eleven point seven percent of our patients had both atherosclerosis and cardioembolic mechanisms. Rheumatic valvular disease was present in 44.8% of cardioembolic strokes and caused 4.31 preventable stroke cases per 100,000 Iranian population per year. Hypertension and history of ischemic cerebrovascular events were the most frequent risk factors, 53.1% and 22.3% respectively. In-hospital mortality of our ischemic stroke patients was 7.3%.

Conclusion: High frequency of atherosclerotic etiology in the Khorasan Stroke Registry is because of its classification criteria, which does not separate small vessel territory infarcts as a different etiologic subtype. Rheumatic valvular disease is an important cause of stroke in Khorasan population.

Keywords: Etiology • incidence • rheumatic • stroke

Introduction

No large hospital-based stroke registries have been published from Iran or the Middle East region. Because of this lack of information, we decided to perform two simultaneous studies of strokes. The first was a population-based study of stroke in Iranian young adults.1 We now report the second study, a hospital-based stroke registry designed to collect information regarding clinical presentations, neuroimaging data, and etiology of stroke in Iranian patients.

The causes, clinical presentations, risk factors, and outcome of brain infarction are heterogeneous.2 These factors are essential in making decision for initial management of stroke.2 A well-organized stroke data bank can help to provide much information and numerous insights into these problems. The diagnosis of etiologies in stroke guides decisions regarding secondary prevention in current practice.3 Variations in the distribution of stroke subtypes between stroke registries may be due to differences in patient population, in classification criteria, and the extent of diagnostic investigations.3 To treat optimally the stroke patients, the physician must identify the correct mechanism of stroke. Ischemic stroke is a complex entity with multiple etiologies and variable clinical manifestations. Rheumatic fever is an important cause of mitral and aortic valve disease in developing countries.1

Ischemic stroke is a complication of rheumatic
valvular disease. Prevention of rheumatic fever and its complications is inadequate in the developing countries.1

Patients and Methods

This population based study was carried out in Southern Khorasan province in Iran with 682,000 population (49.6% females, 50.4% males). In this province, any patient with possible diagnosis of stroke is referred to a stroke neurologist and is routinely admitted in Valie-Asr Tertiary Care Hospital in Birjand. Patients were diagnosed as having stroke were examined by an emergency stroke team and admitted to the Neurology Unit, which has 16 beds for patients who develop acute stroke. Our unit is the only neurology unit in the entire county (682,000 inhabitants), which has no other medical clinic dealing with neurological disease.

Consecutive patients with various severity of stroke were hospitalized. A signed informed consent was obtained from the patient or his/her first degree relatives. Excluded patients were; those with head trauma and subarachnoid hemorrhage, nonhospitalized patients, those who died before admission or evaluation by stroke neurologist or refused to sign the informed consent.

Data on demographics, clinical findings, stroke onset, 48-hour stroke course, and investigations of these patients were prospectively saved in the Khorasan Stroke Registry (KSR) data bank during 2001 – 2005. This stand alone database is kept in a SPSS software version 9.

The type of stroke onset was categorized as sudden, fluctuating, and progressive. The 48-hour stroke course was determined as regressive, stable, or deteriorative. Clinical findings were systematically evaluated; e.g., motor and sensory deficits classified as complete or partial. Cognitive disturbances, aphasia, hemineglect, visual deficit, seizure, headache, altered consciousness, and lacunar syndromes were recorded. The diagnosis and etiologic investigations of stroke was made by a stroke neurologist. Stroke was defined as an ischemic focal neurological deficit that persisted at least for 24 hours.1

All of the patients who developed ischemic stroke had one or more control brain computed tomography (CT) 48 hours after the stroke. Magnetic resonance imaging (MRI) was performed in patients with inconclusive control CT for stroke localization. Territorial location of infarct was determined by topographic maps of cerebrovascular territories in brain CT.5 Territorial involvement of supratentorial infarcts categorized as middle cerebral artery (MCA), anterior cerebral artery (ACA), Internal Carotid Artery (ICA), anterior choroidal artery, and anterior and posterior borderzone territories. The MCA branches included cortical, deep, and both.5 Vertebrobasilar territory infarcts were classified into four groups according to the involved location: brainstem, thalamus, cerebellum, and posterior cerebral artery (PCA).

Secondary hemorrhagic transformation of brain infarction and leukoaraiosis were evaluated. All of the patients who developed ischemic stroke underwent a standard battery of etiologic investigations.6 These investigations did not differ in various subtypes of ischemic stroke and included electrocardiography (ECG), blood electrolytes, complete blood count, coagulation profile, fasting blood sugar and lipid profile, duplex sonography of supra-aortic trunks, transcranial doppler, and transthoracic echocardiography. A 24-hour Holter monitoring was obtained in patients with history of syncope and/or palpitation with non-diagnostic ECG. Transeosophageal echocardiography was performed in those in whom transthoracic echocardiography was nondiagnostic despite high suspicion of cardioembolism. Three serial blood cultures were requested for any stroke patient with fever and heart murmur or valvular vegetation detected by echocardiography. Brain magnetic resonance imaging and angiography was performed in suspected arterial dissection, arteriovenous malformation, or aneurysm. Cardiac enzymes were measured when history or echocardiographic evidence of recent myocardial infarction was present.

An extended coagulation profile including detection of serum levels of antithrombin III, protein C, and protein S was requested in young adult patients without identifiable cause of stroke who had personal or family history of venous thrombosis, in patients with multiple unexplained strokes, and in those with abnormalities on routine screening coagulation tests.5 Antinuclear and anticardiolipine antibodies tests were requested in patients with cryptogenic stroke who had personal or family history of venous thrombosis, recurrent miscarriage, thrombocytopenia, cardiac valve vegetations.
livedo reticularis, or raised sedimentation rate. The sedimentation rate and VDRL tests were requested in patients with suspected vasculitis. These different levels of assessment is a standard protocol in diagnostic evaluation of stroke patients and does not influence the diagnoses. Holter monitoring, transesophageal echocardiography, and MRI were performed in 20%, 14% and 24% of the patients respectively. Blood culture, extended coagulation profile, and vasculitis profile were done in 8%, 10%, and 10% of the patients respectively. For nonhospitalized ischemic stroke patients brain CT, blood chemistry, and lipid profile were requested. Transthoracic echocardiography and carotid doppler were performed whenever possible in this group of patients. Because of incomplete diagnostic investigations nonhospital-ized patients were excluded from the study and were followed up in stroke clinic. However this group of patients were considered in calculation of real incidence of ischemic stroke in the province.

Hypertension was defined as using antihypertensive medication or detecting two blood pressure values (at least 1 week apart) of >140/90 mm/Hg. Those patients who took antidiabetic medication or had a fasting blood glucose >126 mg/dL were defined as having diabetes mellitus. Hypercholestrolemia was assumed as using lipid lowering medication or fasting cholesterol >200 mg/dL. Patients who smoked more than 5 cigarettes per day in the recent year were defined as smoker. Low mobilty was defined as walking less than 5 kilometers or half an hour per day. Obesity was calculated based on the body mass index, and consumpion of oral contraceptives in recent 2 years was considered as a risk factor in females. History of stroke in parents, and siblings diagnosed by neurologist or internist was also taken. Etiologic and topographic diagnosis of brain infarction was made based on the Practical Iranian Criteria (PIC) classification. Brain infarction was categorized as small or large vessel territory infarct. MRI is not often indicated in stroke patients, and is not available in many tertiary care centers especially in developing countries. The PIC imaging criteria relies on brain CT ≥ 48 hours of stroke onset.

Fisher exact, Pearson Chi-Square, and t-tests were used for statistical analysis and P < 0.05 was considered as significant. The results were compared based on the gender and territorial involvement (carotid versus verteobasilar and small versus large vessel territory) of brain infarction. Incidence is defined as the number of new cases of a disease that came into existence within a certain period of time per specified unit of population. The population at midpoint in the time period was picked up to represent the average population at risk. In this prospective study, 6.82 x 100,000 was used as person-years denominator in the calculation of cumulative incidence rate.

**Results**

During a 5-year period 1392 patients (738 females, 654 males; mean age 65.61; SD: 17.48) who developed ischemic stroke were investigated. All of these patients were residents of Southern Khorasan province in the east of Iran with 682000 population. The mean age of women and men with ischemic stroke was 65.83; SD = 14.59 and 67.70; SD = 13.73 respectively (t = 1.211, P = 0.227). All of the hospitalized patients signed informed consent. Forty-eight nonhospitalized patients were ineligible for the study. Thirty-two patients died before admission or evaluation by a stroke neurologist. Incidence of ischemic stroke in hospitalized patients was 40.82 cases per 100,000 people per year.

The incidence was calculated as: A/B = 40.82.

A = number of new cases of ischemic stroke in population per year; 1392/5 = 278.40.

B = population/100,000; 682,000/100,000 = 6.82.

The real incidence of ischemic stroke including 80 other stroke patients was calculated as; A/B = 43.17% or 294.40/6.82 per 100,000 population, where A is the whole number of new cases of ischemic stroke per year. These 80 ischemic stroke patients consisted 48 nonhospitalized and 32 early expired stroke patients.

Table 1 represents clinical characteristics and risk factors of the patients who developed ischemic stroke. Table 2 represents the neuroradiological findings of the patients with brain infarction. At least two neuroimaging examinations were performed in 88% (n = 1225) of the patients. Territorial infarcts were found in 64% (n = 892), a small deep infarct in 19.5% (n = 272) and a borderzone territory infarct in 4.6% (n = 64) of the patients. The left side was involved in 54.8% (n = 763) and 10.3% (n = 144) of the patients died in the hospital during the first week after the stroke. Total MCA territory was involved in 60% of the deceased patients. Brain herniation, aspiration
was found in 63% of women and 42% of men with cardioembolism were causes of death in 60%, 20%, 4%, pneumonia, myocardial infarction, and pulmonary embolism were causes of death in 60%, 20%, 4%, and 4% of the patients, respectively.

Hypertension as the most common risk factor was found in 63% of women and 42% of men with stroke, which had a significant difference ($\chi^2 = 15.231$, df = 1, $P < 0.001$). The effect of gender on frequency rate of other vascular risk factors was not significant. Table 3 demonstrates the distribution of various stroke etiologies based on gender and cerebrovascular territory involvement. The mean age of patients with atherosclerosis, cardioembolism, atherosclerosis plus cardioembolism, uncertain, and miscellaneous subtypes of stroke were 67.2, 56.5, 61.3, 60.1, and 38.4 years, respectively.

Rheumatic valvular disease (RVD) was found in 10.6% of the patients. It was present in 44.8% (147/328) of patients with cardioembolic mechanism and in 63.5% (101/159) of patients with atrial fibrillation. RVD caused 4.31 preventable stroke cases per 100,000 population per year. This incidence was calculated as; $\frac{A}{B} = 32.40/6.82$ per 100,000, where $A$ is the number of new cases of ischemic stroke due to RVD per year, and $B$ is the population per year. The number of RVD cases in the community was calculated as; $\frac{A}{B} = 32.40/6.82$, where $A$ is the number of new cases of ischemic stroke due to RVD per year, and $B$ is the population per year. This incidence was calculated as; $\frac{A}{B} = 32.40/6.82$ per 100,000, where $A$ is the number of new cases of ischemic stroke due to RVD per year, and $B$ is the population per year.

Table 3. Distribution of various ischemic stroke etiologies based on gender and cerebrovascular territory involvement in the KSR.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>No. (%)</th>
<th>Females</th>
<th>Males</th>
<th>LVT</th>
<th>SVT</th>
<th>CT</th>
<th>VBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>746 (33.6)</td>
<td>411 (55.7)</td>
<td>335 (51.2)</td>
<td>547 (54.5)</td>
<td>198 (51)</td>
<td>429 (54.4)</td>
<td>85 (50.6)</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>165 (11.8)</td>
<td>72 (9.8)</td>
<td>93 (14.2)</td>
<td>125 (12.4)</td>
<td>43 (11.1)</td>
<td>97 (12.3)</td>
<td>14 (8.3)</td>
</tr>
<tr>
<td>Ant + Cardio</td>
<td>163 (11.7)</td>
<td>104 (14.1)</td>
<td>59 (9)</td>
<td>104 (10.4)</td>
<td>58 (15)</td>
<td>92 (11.7)</td>
<td>20 (11.9)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>278 (19.9)</td>
<td>116 (15.7)</td>
<td>162 (25)</td>
<td>188 (18.7)</td>
<td>89 (22.9)</td>
<td>142 (18)</td>
<td>49 (29.2)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>40 (2.9)</td>
<td>35 (4.7)</td>
<td>5 (0.7)</td>
<td>40 (4)</td>
<td>0 (0)</td>
<td>28 (3.6)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Total (%) 1392 (100) 738 (100) 654 (100) 1004 (100) 388 (100) 788 (100) 168 (100)

*Patients with multiple strokes in both carotid and vertebrobasilar territories and patients with no ischemic lesion in brain tomography were not considered in analysis of stroke etiologies based on the territorial involvement; **CT = carotid territory; LVT = large vessel territory; **VBT = vertebrobasilar territory; SVT = small vessel territory.
rheumatic mitral disease in our cardioembolic stroke patients. Rheumatic mitral stenosis and severe rheumatic mitral regurgitation are accepted cardioembolic etiologies based on the PIC classification.

Lacunar syndrome was present in 392 patients. Lacunar or small vessel territory infarct was found in CT of 272 (69.4%) patients with lacunar syndrome. Of the other 120 patients with lacunar syndrome, 53 (13.5%) patients had no ischemic lesion on CT and 67 (17.1%) patients had large vessel territory infarct. Topography of brain infarction in our 392 patients with lacunar syndrome is illustrated in Table 5.

Small vessel territory infarcts were found in 212 (27%) patients with carotid and 53 (31%) patients with vertebrobasilar territory involvement ($\chi^2 = 0.581, df = 1, P = 0.446$). Small vessel territory was involved in 28.7% of women and 26.9% of men with brain infarction ($\chi^2 = 0.145, df = 1, P = 0.703$).Vertebrobasilar territory was involved in 17% of women and 20% of men with brain infarction ($\chi^2 = 0.465, df = 1, P = 0.495$). Distribution of stroke with cardioembolic mechanism was not significantly different based on the gender ($\chi^2 = 0.071, df = 1, P = 0.790$). Women were significantly more susceptible for stroke with atherosclerotic mechanism ($\chi^2 = 13.923, df = 1, P < 0.001$), and miscellaneous etiology ($\chi^2 = 21.727, df = 1, P < 0.001$), while men were significantly more preponderant for stroke with uncertain causes ($\chi^2 = 18.331, df = 1, P < 0.001$).

Migraine induced stroke consisted 70% of miscellaneous causes of brain infarction in our patients. Distribution of stroke with atherosclerotic, cardioembolic, and uncertain mechanisms was not significantly different based on the small versus large vessel territory involvement; ($\chi^2 = 0.160, df = 1, P = 0.689$), ($\chi^2 = 1.606, df = 1, P = 0.207$), ($\chi^2 = 3.116, df = 1, P = 0.078$) respectively. Stroke with miscellaneous etiology was found in large vessel territory infarcts ($\chi^2 = 15.916, df = 1, P < 0.001$). Distribution of stroke with atherosclerotic and cardioembolic mechanisms was not significantly different between carotid and vertebrobasilar territory involvement; ($\chi^2 = 0.801, df = 1, P = 0.371$), ($\chi^2 = 1.087, df = 1, P = 0.297$) respectively. Miscellaneous etiology was present in carotid territory infarcts ($\chi^2 = 6.150, df = 1, P = 0.013$). Stroke with uncertain causes was significantly more frequent in vertebrobasilar territory involvement ($\chi^2 = 10.760, df = 1, P = 0.001$). The mean age and standard deviation of patients with small versus large vessel territory involvement was 66.53; SD = 15.02 versus 66.78; SD = 13.91, $t = 0.148, P = 0.880$.

### Discussion

The epidemiological aspects of ischemic stroke are well recognized in population-based stroke...
registries. Incidence of ischemic stroke in our county is 43 and in northern Iran is 33 per 100,000 population.12 This difference may be because of some methodologic limitations in the study conducted in northern Iran.12 Accurate subtyping of cerebral infarction, precise mechanism, clinical patterns, and outcomes are only evaluated in hospital based stroke registries.3

Our hospital is the only one in our province to have a neurology unit, which deals with stroke patients. This helped to minimize selection bias, maximize accuracy in stroke diagnosis, and allowed uniform evaluation of patients with brain infarction. Admittedly, evaluation of outcome in our stroke patients was short term. The mortality rate in our series would be more if the evaluation time was more extended.13

Among Italian patients who developed ischemic stroke, 9.7% died in hospital.13 Hypertension and smoking were the most prominent risk factors of stroke followed by mild internal carotid artery stenosis in Chinese stroke patients.14 An incidence study of stroke from Rochester, Minnesota, recorded hypertension prior to stroke in 74% of patients with brain infarction.15 Prevalence of hypertension and stroke mortality has increased in Iran and southern Asia in recent decades.16 Hypertension is the most common risk factor in our patients. In comparison of stroke risk factors between Pennsylvanian men and women, hypertension was present in 48% of men and 32% of women with stroke.17 Hypertension was significantly more frequent in our female patients. The reason for this finding is not absolutely certain. Females may benefit from a less effective antihypertensive treatment.

All of the stroke registries include transient ischemic attack (TIA) as a risk factor for ischemic stroke. Because TIA and brain infarction have the same pathophysiology and mechanism and share the same prevention strategies, it would be acceptable to consider the history of brain infarction as a stroke risk factor. History of ischemic cerebrovascular events including TIA and brain infarction was present in 22.4% of our patients. A population-based prospective cohort study of patients with TIA or minor stroke was conducted in the Oxford area.18 The estimated risk of recurrent stroke at 3 months was 17.3% after TIA and 18.5% after minor ischemic stroke.18

Cardiac risk factors for stroke were present in almost 40% of our patients. However cardioembolic mechanism alone was found in 11.7% of our patients and coexisted with atherosclerotic mechanism in another 11.9% based on the PIC classification. The reason for this difference is our criteria for etiologic classification of brain infarction. Cardioembolic strokes represented 14% of Stroke Data Bank,19 and 20% of Lausanne Stroke Registry.20 Almost half of the cardioembolic strokes in developed countries is secondary to non-valvular atrial fibrillation. And only 7.6% of them is due to RVD.21 RVD is a common cause of stroke in Iran22 and other developing countries.23 Cardiac disease was found in 23% of Ethiopian stroke patients, and valvular heart disease constituted 40% of all heart diseases in the stroke patients.24 RVD was found in 44.8% of our patients with cardioembolic mechanism and constituted 59.7% of cardioembolic strokes in our young adult population.1 All of our young adult stroke patients with atrial fibrillation had rheumatic valvular disease,1 while RVD was found in 63.5% of our stroke patients with atrial fibrillation in all age groups. This comparison reveals that RVD is a very important etiology of stroke in all age groups of Khorasan population.

In Japanese population, lacunar infarction was the most common subtype of ischemic stroke,25 17% of our patients with lacunar syndrome had a large vessel territory infarct. While lacunar syndromes often appear in patients with lacunar or small deep infarcts, they are not infrequent in patients with large vessel territory involvement in whom microangiopathy is neither the only nor the most common cause of infarction. In the Oxford Stroke Registry, small vessel disease was not associated with hypertension or diabetes.26 Cardioembolic mechanism was present in 26.1% of our patients with small vessel territory infarct. 20% of patients with small deep infarcts had atrial fibrillation in Besancon Stroke Registry.27 In the German Stroke Data Bank, cardioembolism was the most common cause (25.6%) of stroke followed by large artery atherosclerosis (20.9%) and microangiopathy (20.5%).28 The PIC classification categorizes large artery atherosclerosis and microangiopathy as atherosclerotic mechanism, which increases the amount of this subtype. In Hallym Stroke Registry, large vessel atherosclerosis constituted 42% of etiology in Korean stroke patients.29 Miscellaneous etiology was infrequent in the KSR, Oxford, and German Stroke Data Banks.26, 28

Stroke of uncertain etiology constituted 20% of KSR, 30% of Stroke Data Bank,19 and 40.6% of
the Yonsei Stroke Registry. The table compares the frequency of stroke etiologies in KSR with other stroke registries. Distribution of stroke mechanism was significantly different between men and women in the KSR. The most male preponderance was present in strokes with uncertain etiology in women in the KSR. The reason of this finding is unknown. In the Oxford and German Stroke Data Banks, large vessel atherosclerosis was more strongly associated with the male sex. Women were more susceptible for stroke with atherosclerotic mechanism in the KSR, which may be due to a significantly higher frequency of hypertension in females. In the KSR, 87.5% of stroke with miscellaneous etiology was found in females. The reason for this gender effect could be female susceptibility to migraine, which constituted 70% of miscellaneous causes of stroke in our patients. The Athens Stroke Registry, and Besancon Stroke Registry analysed the distribution of risk factors, etiologic subtypes, and clinical presentations according to exact infarct location. The KSR is designed for analysis of etiologic distribution based on the carotid versus vertebrobasilar territory involvement and small versus large vessel territory infarcts.

The incidence of ischemic stroke in Khorasan population is similar to other stroke registries. Hypertension and history of ischemic cerebrovascular events are the most frequent stroke risk factors in the KSR. RVD is a very important cause of brain infarction in Khorasan population.

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References

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