Epidemiology of Stroke in Iran

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Abstract

Numerous hospital-based stroke registries have been developed in Iran during last decade. Khorasan Stroke Registry, Khorasan Posterior Circulation Stroke Registry, Khorasan Pediatric Stroke Registry and Khorasan Stroke in Young Adults Registry are among these published registries. Meanwhile, There is only one epidemiologically designed study of stroke in Iran and Middle East. Based on this standard epidemiologic study; The crude annual incidence rate of First Ever Stroke (FES) is 139 (95% CI, 128 to 149) per 100 000; for men, 144 (95% CI, 128 to 159), and for women, 133 (95% CI, 118 to 148). The incidence rates increases significantly with each decade of life and is similar in men and women. Subtypes of FES in 81.9% of patients is ischemic stroke, 12.7% is intracerebral hemorrhage, and 2.4% have subarachnoid hemorrhage. The crude annual incidence rate per 100 000 inhabitants is 113 (95% CI, 104 to 123) for ischemic stroke, 18 (95% CI, 14 to 21) for intracerebral hemorrhage and 3 (95% CI, 2 to 5) for subarachnoid hemorrhage. Ischemic strokes are occurring approximately 1 decade earlier in Iran than in other countries. [GMJ.2016;5(Supp. 1):3-9]

Keywords: Stroke; Epidemiology; Iran

Introduction

Hospital-based stroke registry is useful for understanding diverse clinical characteristics for stroke prevention strategies regarding stroke in the country. Stroke registry could also provide an excellent data bank for clinical research in stroke. The causes, clinical presentations, risk factors and outcomes of brain infarction are heterogeneous[1]. These factors are essential in determining initial stroke management. To treat stroke patient optimally related to geographical, racial or environmental differences[2]. Stroke registry makes valuable epidemiologic information about stroke and have influence on therapeutic and, the physician must identify the correct mechanism of stroke. Ischemic stroke is a complex entity with multiple etiologies and variable clinical manifestations[3]. A well-organized stroke data bank can help to provide much information and numerous insights into these problems. Variations in the distribution of stroke subtypes between stroke registries may be due to differences in patients population, classification criteria and the extent of diagnostic investigations[4,5]. Large stroke data banks provide the best available information for the diagnosis, clinicoradiological correlations and outcome of patients with cerebrovascular disease. In this review article we look to some published hospital-based stroke registries and one standard epidemiologic study of stroke in east of Iran.
Khorasan Stroke Registry (KSR)
The Khorasan Stroke Registry (KSR) established for evaluation of incidence, clinical manifestations, risk factors, topography and etiology of ischemic stroke in Southern Khorasan, Iran, during 2001-2005[6,7]. Consecutive stroke patients underwent a standard battery of diagnostic investigations by a stroke neurologist[8]. Topography and etiology of brain infarction determined by the Asian Stroke Criteria (ASC)[9,10].The incidence of ischemic stroke in Southern Khorasan based on the hospital-based registry is 43.17 cases per 100000 people per year[6,7]. 1392 ischemic stroke patients (738 females, 654 males) were evaluated in the KSR. Atherosclerosis consisted 53.6% of etiologies followed by uncertain causes (19.9%), cardioembolism (11.8%) and miscellaneous etiologies (2.9%)[6,7].11.7% of our patients had both atherosclerotic and cardioembolic mechanisms. The women were significantly more susceptible to stroke with atherosclerotic mechanism and miscellaneous etiology; P<0.001, P<0.001 respectively. Men were significantly more preponderant for stroke with uncertain cause, P<0.001. The distribution of stroke with cardioembolic mechanism was not significantly different based on gender (P=0.79). Distribution of stroke with atherosclerotic, cardioembolic and uncertain mechanisms was not significantly different based on small versus large vessel territory involvement (P=0.689, P=0.207, P=0.078, respectively)[6,7]. Stroke with miscellaneous etiology was found in large vessel territory infarcts, (P<0.001). The distribution of stroke with atherosclerotic and cardioembolic mechanisms was not significantly different between carotid versus vertebrobasilar territory involvement (P=0.371, P=0.297 respectively). Miscellaneous etiology was present in carotid territory infarcts (P=0.013). Stroke with uncertain causes was significantly more frequent in vertebrobasilar territory involvement (P=0.001). Rheumatic valvular disease was present in 44.8% of cardioembolic strokes and caused 4.31 preventable stroke cases per 100000 Persian 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%. 336 patients with intracerebral hemorrhage (189 females, 147 males) were evaluated in the KSR. The incidence of intracerebral hemorrhage in Southern Khorsan population is 10.43 cases per 100000 people per year[6,7]. Hypertension was extremely prevalent and is seen in 87% of these ICH cases. In terms of localization of ICH, 32% were putaminal, 29% lobar, 28% thalamic, 5% cerebellar, and 6% had a pontine location. During the first week after stroke 25.3% of ICH patients died in the hospital[6,7]. High frequency of atherosclerotic etiology in the KSR is the due to 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 Persian population[11].

Khorasan Posterior Circulation Stroke Registry (KPCSR)
Clinical information about stroke in the vertebrobasilar territory has lagged behind that for anterior circulation stroke[12]. Posterior circulation syndrome often has been attributed to hemodynamically significant vertebrobasilar arteries stenosis leading to low flow ischemia or penetrating artery disease[13]. KPCSR is the first reported posterior circulation stroke registry in Iran, which deals with clinical course and etiology of stroke based on the different topographies of the vertebrobasilar territory[13]. Consecutive patients with vertebrobasilar territory brain infarction admitted in Ghaem hospital, Mashhad enrolled in a prospective study during 2005-2007[13]. Diagnosis of ischemic stroke in the posterior circulation was made by a stroke neurologist based on the clinical manifestations and neuroimaging. The territory of infarct was determined by topographic maps of cerebrovascular territory. Vertebrobasilar territory infarcts were classified into five groups according to the location involved: brainstem, thalamus, cerebellum, cortical posterior cerebral artery and mixed categories[13]. All of the stroke patients underwent a standard battery of diagnostic investigations and etiology of ischemic stroke was determined by the Asian
Stroke Criteria[9,10]. The 72-hour stroke course determined as regressive, stable and deterioration. 302 Patients (147 females, 155 males) with mean age years 62.5; SD: 7.8 were investigated. Cortical posterior cerebral artery, thalamus, brain stem, cerebellum and mixed categories consisted 31.3%, 4.3%, 32.8%, 17.9% and 13.9% of the stroke topographies[13]. The influence of gender and age groups on distribution of infarct localization was not significant (P=0.65, P=0.127). Hypertension, hyperlipidemia, diabetes and smoking were found in 22.5%, 7.9%, 3.9% and 4.6% of the patients in isolation, and 37.4% of them had multiple stroke risk factors. Differences in frequency rate of risk factors among various stroke localizations were not significant (P=0.123). Atherosclerosis consisted 50.6% of etiologies in our patients followed by uncertain (25.5%), cardioembolism (12.5%), both atherosclerosis and cardioembolism (6.3%) and miscellaneous causes (4.6%) [13]. Atherosclerotic stenosis was found in 42 (10.6%) patients in KPCSR. The V1, V2, V3, V4, basilar and posterior cerebral artery stenosis were found in 26, 1, 1, 8, 4, and 2 patients respectively. Atherosclerosis was the most common etiology in age groups 60-69 and 70-79 years. Coexistence of atherosclerosis and cardioembolism was found in 50% of the patients aged 80-89 years. Uncertain etiology consisted 38% of stroke subtypes in patients younger than 50 years[13]. The distribution of stroke etiologies in age groups was significantly different (P=0.002). The effect of gender in frequency rate of stroke etiologies was not significant (P=0.271). The distribution of stroke etiologies based on its localization was not significantly different (P=0.421). Atherosclerosis was the most common etiology in all localizations of stroke in the posterior circulation. Rheumatic mitral stenosis consisted 34.2% of the cardioembolic mechanism in our patients. Atrial fibrillation was present in 50% of patients with cardioembolic mechanism in KPCSR. Stabilization consisted the most common early stroke course (57.7%) followed by deterioration (22.1%) and regression (20.2%)[13]. The effect of gender and age groups on distribution of course subtypes was not significant (P=0.121, P=0.081 respectively). The distribution of course subtypes was not significantly different based on the risk factors (P=0.606). The distribution of stroke course based on its etiologies was not significantly different (P=0.697). Mortality of our patients with posterior circulation stroke within the first week post event was 10.9%. Among patients with deteriorative course, 43.3% had atherosclerotic etiology and 35.8% of them had uncertain cause. A significant association between stroke localization in the vertebrobasilar territory and its course was not found, df=8, (P=0.901). In summary, Atherosclerosis consists the most common cause of posterior circulation stroke in Iranian patients based on our hospital-based registry. The cause of stroke in the posterior circulation could not reliably be derived from infarct topography.

**Khorasan Pediatric Stroke Registry (KPSR)**

Ischemic stroke is rarely seen in childhood. Congenital stroke may pass unrecognized by parents during early infancy, until the child starts crawling or walking[8]. At this stage asymmetry is noted or delay in the rate of acquired motor or cognitive skills is manifested. Stroke in children usually represents with acute onset hemiplegia. Recovery in children is more than adults because the developing brain has more plasticity[8]. Frequent striatocapsular involvement leads to more dystonic and choreathetotic sequelae in childhood strokes. The pediatric causes of stroke are quite different than adult causes[8]. Atherosclerosis is a rare cause of brain infarction in the children. Certain subgroups of children are at high risk of ischemic stroke; these include children with congenital heart disease, rheumatic valvar disease, sickle cell anemia, cancer, Moyamoya disease and Down syndrome. Homocystinuria, mitochondrial disease, prothrombotic states, migraine and trauma are among other causes of ischemic stroke in childhood and early adolescents[8]. A population based study was conducted for determination of incidence, clinical manifestations and etiology of pediatric ischemic stroke in Southern Khorasan, Iran, during 2002-2007[14]. In this province, every child...
with possible diagnosis of stroke is referred to stroke neurologist and routinely admitted in Pediatric division of Valie-Asr tertiary care hospital. The diagnosis of ischemic stroke was made based on the clinical presentation and brain imaging. All of the patients underwent a standard battery of diagnostic investigations[8]. Seventeen children with ischemic stroke (7 females, 10 males) with mean age of 5.5 years were evaluated[14]. The incidence of pediatric ischemic stroke in our province is 1.8 cases per 100000 child population per year[14]. Unilateral weakness was found in all of the patients. Ipsilateral extensor plantar response, heightened deep tendon reflexes, seizure, fever and altered consciousness were found in 41%, 35%, 47%, 35%, and 23% of the patients respectively. The onset of pediatric brain infarction in our registry was sudden in 35%, acute in 59% and subacute in 6% of cases[14]. The infarctions were localized in carotid territory in 88% of the cases. Meningoencephalitis induced vasculopathy consisted 23.5% of determined etiologies followed by Fallot tetralogy (11.8%), head trauma (11.8%), dehydration (11.8%), migraine (11.8%), and hypercoagulable state (5.9%). Twenty three percent of our pediatric patients had uncertain cause of stroke[14]. All of our pediatric stroke patients with infectious etiology were young children and half were referred from a rubral area in summer 2004. The polymerase chain reaction for herpesvirus, and tuberculosis and bacterial culture of cerebrospinal fluid was negative in these cases. Special virology facilities was not available. In-hospital mortality of our pediatric ischemic stroke patients was 11.7%[14]. The incidence and clinical characteristics of pediatric brain infarction in Iran is the same as other studies around the world. Meningoencephalitis induced vasculopathy is the most common determined etiology of pediatric ischemic stroke in Persian population.

Khorasan Stroke in Young Adults Registry (KSYAR)
Cardioembolism constituted 54% of all stroke etiologies in Persian young adults and rheumatic valvular heart disease was present in 32% of these cases and caused 2.5 preventable stroke cases per 100000 Persian young adults per year[15,16]. Evaluation of all age groups of Persian stroke patients revealed that frequency of cardioembolic mechanism of stroke in Iran is similar to other areas around the world, however rheumatic valvular disease and valvular fibrillation consists the most frequent sources of cardioembolism in Iran despite western countries[6,7,11]. Rheumatic mitral stenosis was found in 45% of Iranian cardioembolic stroke patients[15,16] and atrial fibrillation was present in 68% of these stroke patients with rheumatic mitral disease in whole age groups[15,16]. The incidence of rheumatic valvular disease in whole of our stroke patients was 9.3% and significantly higher in females[15,16]. The cause of this gender discrepancy is unknown. Early diagnosis and treatment of streptococcal throat infection and its complications including prevention of rheumatic valvular disease and its complications[3,11,17,18].

Epidemiologic designed study of stroke in Iran
The population denominator used in this study was obtained from a census conducted in October and November 2006[19]. This census is conducted every 10 years and is conducted with a door-to-door approach. The study was conducted in 3 different health districts of Mashhad, located in the province of Khorasan-Razavi, northeastern Iran. From November 21, 2006, for a period of 1 year, patients with recent stroke in the already defined study areas were identified[19]. The study area was delineated by the main boulevards in Mashhad. According to the 2006 census, the study population comprised 450 229 inhabitants. The only Neurology center in Mashhad is Ghaem Hospital, and all neurology emergency care is supplied at this hospital. Ghaem Hospital is 1 of the most important hospitals in the east of Iran. It is the referral hospital for eastern Iran. When a patient with stroke is admitted to another hospital, after having been incorrectly diagnosed with another condition, they will then be transferred to Ghaem Hospital as soon as their diagnosis of stroke is made. This occurs when the hospital does not have a neurologist. In addition, some hospitals have a policy not to admit stroke patients because
of the high associated mortality and morbidity and lengthy hospital stay. The other main hospital located in the study region is Hasheminejad Hospital, which has both internal medicine and neurosurgical wards. The 2 other smaller hospitals located within the region are 17 Sharivar (a welfare insurance hospital) and Imam Hosein (a military hospital). First-ever stroke (FES) is defined as a stroke occurring for the first time during a patient’s lifetime. Past history of stroke was determined by using all available information, including hospital records, information provided by patients, and family reports\[6,7\]. Neuroimaging was used to classify patients with definite FESs into Ischemic Stroke (IS), Intracerebral Hemorrhage (ICH), and Subarachnoid Hemorrhage (SAH) subgroups \[22-24\]. An undetermined stroke is a stroke for which a patient did not undergo CT scanning within 28 days of the onset of symptoms and an autopsy was not performed\[8\]. A possible stroke is considered as any acute episode of neurologic disturbance that is suggestive of stroke but for which there is insufficient information to establish whether the symptoms and duration (<24 hours or >24 hours) fully met the World Health Organization definition for definite stroke. “Possible” and “CT-only” strokes were not included in the incidence figures. Multiple sources were used to identify stroke patients, particularly those who were not admitted to hospital. The following methods were used. The medical records of all patients admitted to the 4 hospitals in the study area were examined every day by expert staff to determine any cases with stroke. All of these patients were visited by a member of the study team. Cases were included only if they lived in the study area. Two hospitals outside the study area were also contacted for potential cases, as it is possible that cases might have been seen at these hospitals. These cases were followed up in the same manner when a suspected stroke patient was identified. One of these, Imam Reza Hospital, is a main referral hospital with >800 beds, although there are no beds for either stroke or neurosurgery \[20\]. Faraby is a smaller welfare insurance hospital. One of the authors provided consultations for difficult neurologic cases, and patients with stroke were referred to the study in return. Despite a referral healthcare structure in Iran, there may be situations where people bypass a primary care contact and self-refer to specialists (private) and hospital outpatient clinics \[24\]. Therefore 35 neurologists in the study area were informed about the study and were asked to identify stroke patients who were not hospitalized. Death certificates and reports were reviewed on a monthly basis to identify non-hospitalized fatal stroke cases. For accurate estimation of nonhospitalized stroke patients, 980 trained health personels who had enough general knowledge about stroke participated in this study and were responsible for checking their neighborhoods for potential stroke cases. They were asked to refer any person with suspected symptoms of stroke. Each health personel was responsible for between 50 and 100 houses. Cases were eligible only if they had been resident within the defined geographic area for at least 1 year before the stroke. This latter criterion was used because Mashhad has a large number of temporary residents not included in census figures. Among 684 strokes four hundred ninety-one cases (71.8%) were admitted to hospital (92% in Ghaem Hospital and 8% in other hospitals), and 193 patients (28.2%) were managed in the community; these latter cases being mainly referred by volunteers and other neurologists. The main ethnic groups were Persian (82.5%), Turk (8.3%), Afghan (4.8%), Kurd (2.8%), Arab (1.2%), and other (0.4%). A final diagnosis of FES was made in 624 (91.2%) individuals, of whom 52.4% were men and 47.6% were women. The crude annual incidence rate of FES was 139 (95% CI, 128 to 149) per 100,000; for men, 144 (95% CI, 128 to 159), and for women, 133 (95% CI, 118 to 148) \[20\]. No strokes were found in children age <15 years. The incidence rates increased significantly with each decade of life and were similar in men and women. A CT scan was performed for 661 events (96.6%). We used MRI as the only form of imaging in another 5 cases. Autopsy was performed in 2 cases, for whom we also had a prior CT, for a definite diagnosis of stroke subtype. Consequently, imaging/autopsy was performed for 666 cases (97.4%) of events and for 614 cases (98.4%) of FES.
Pathologic subtypes of FES were classified in all 605 people who either had imaging within 28 days of stroke or had an autopsy examination: 511 (81.9%) patients had IS, 79 (12.7%) had ICH, and 15 (2.4%) had SAH. The crude annual incidence rate per 100,000 inhabitants was 113 (95% CI, 104 to 123) for IS, 18 (95% CI, 14 to 21) for ICH, 3 (95% CI, 2 to 5) for SAH, and 4 (95% CI, 2 to 6) for undetermined stroke [20]. When adjusted to the world and European populations, stroke incidence rates were greater than those of crude incidence rates [20, 25]. Incidence adjusted to the European population aged 45 to 84 years was greater in Mashhad than in all other “ideal” studies conducted since 1995, apart from that in West Ukraine, and was largely attributable to a greater incidence of IS. The incidence of ICH also appeared to be greater in Mashhad than in all other regions apart from Tbilisi, Georgia. Adjusted incidence rates for each subtype of stroke were similar between men and women. We found that the incidence of stroke, adjusted to the European population aged 45 to 84 years, in Mashhad, Iran, was greater than in most Western countries with the exception of the Ukraine. Incidence rates were even higher than those of Novosibirsk, Russia, a region known for its high incidence of stroke. Although population-based stroke studies are the best way to determine the real burden of stroke, these studies are scattered and have been performed mostly in developed countries. This is the first population-based study of stroke in a Middle East region that fulfills “ideal” criteria for a stroke incidence study. The incidence of stroke was higher than expected. Indeed, the incidence was approximately double that of the majority of “ideal” studies conducted in the last decade [20]. Importantly, the incidence of stroke was as high in women as in men. In a recent review of the differences between men and women, the overall incidence of stroke was 33% higher in men, apart from a few studies with small sample sizes and consequent low power. The reason for this difference between Iran and most other countries is unclear. Interestingly, although the adjusted incidence rates were high, the crude incidence rate of stroke was relatively low. Low crude incidence rates of stroke may occur when stroke incidence is low or when the source population is young; low crude incidence occurs in a young population because age is strongly associated with stroke incidence. However, despite the relatively young population in Mashhad, ISs are occurring approximately 1 decade earlier than in other countries. That is, a higher age-specific incidence is seen in younger age groups. This explains both the greater age-adjusted stroke incidence observed in Mashhad than in other countries and the fact that a low crude stroke incidence is present in a setting of a high age-adjusted stroke incidence.

Conclusion

Numerous hospital-based stroke registries have been developed in Iran in recent decade [8,26-29]. However, there is only one epidemiologic designed study of stroke in Iran and Middle East which was performed in North East of Iran and reported above. Incidence and prevalence studies of stroke could have influence in development of guidelines in stroke management [30].

References

17. Ghandehari K, Mouradian M. Rheumatic valvular disease and stroke in eastern Iran. PKJFM. 2004;8:2-5.