Ischemic Stroke in Young Adults of South Asia

A.A. Razzaq,B.A. Khan,S.M. Baig (Section of Neurology, Department of Medicine, Aga Khan University Hospital, Karachi.)

Abstract

Objective: To study the risk factors, etiology and management of ischemic stroke in young adults in a South Asian population.
Methods: Retrospective study conducted at a large tertiary hospital in Karachi. One hundred and eighteen patients between fifteen and forty-five years admitted over a five year period with a diagnosis of ischemic infarct constituted the study population. The study variables included the full clinical spectrum, spanning historical, laboratory, radiological and outcome parameters.
Results: Forty-three percent of patients were hypertensive and 30% were diabetic. The combination of diabetes and hypertension was found in 19.5% of patients, intra-cranial and carotid artheroscierosis in 22% and embolism in 11% of the cases. The in-hospital mortality was 11%. The outcome was excellent in 27%, good in 50% and poor in 23% of patients.
Conclusion: The risk factors for artherosclerosis and the contribution of intra and extra-cranial artherosclerosis were found to be much higher than those from the Western Hemisphere (JPMA 52:417;2002).

Introduction

Ischemic stroke in young patients constitutes about 5% of all strokes[1-3]. The incidence varies from 11 to 20/100,000 in different studies[4,5]. During the past decade several studies have been carried out to define the clinical patterns and etiology of stroke in young patients, with strikingly different results. The main reasons for this wide variation include geographic differences, new diagnostic tools like trans-esophageal echocardiography and previously unknown etiologies such as anti-phospholipid antibody syndrome and disorders of inter-atrial septum[3,5].
An increasing number of studies have described the patterns of stroke in young Caucasian population[1,4]. Some of these studies have concentrated on investigation of incidence and others on the etiology of ischemic stroke in young patients. Very few articles have presented the full spectrum of disease in a single paper. Another reason for studying stroke in young adults is the lack of such data for the young population of South Asia. The population belt of Pakistan, India and Bangladesh is known to be homogenous, but unique in terms of demographic patterns and risk factors for cardiovascular disease[5]. This study was undertaken to define the risk factor profile, etiology and management outcomes of this disease in a developing country setting.

Patients and Methods

The study was conducted at the Aga Khan University Hospital, a private, tertiary care health center in Karachi, Pakistan. We retrospectively reviewed the medical records of all patients aged 15-45 years admitted with a diagnosis of ischemic stroke between November 1, 1992 to October 30, 1997. A total of 118 cases met the inclusion criteria. In all cases the diagnosis was established by excluding intracranial hemorrhage on the basis of computerized tomographic (CT) scan.

The study variables included data obtained from history and physical examination, results of laboratory and radiological investigations and outcome data. The historical data included information regarding age, gender, hypertension, diabetes, dyslipidemia, smoking, alcohol abuse, migraine and family history of ischemic heart disease. The radiologic investigations included carotid doppler, echocardiography, CT and MR scans and cerebral angiography. The laboratory investigations included hematocrit, sedimentation rate, anti-nuclear antibody, rheumatoid factor, anti-cardiolipin antibody, serum cholesterol and triglycerides. The outcomes data focused on duration of hospital stay, outcome at discharge and last outpatient follow-up. Due to the retrospective nature of the study, information on all of the above variables was not available in every case. Investigations were ordered by the treating physician on a case-by-case basis and tailored according to the diagnostic probabilities in each individual patient. Statistical analysis was carried out using the Statistical Program for Social Sciences.

Results

A total of 118 patients aged 15-45 years were admitted with a diagnosis of ischemic infarct over a five year period. They comprised 5% of 2,589 patients of all ages, admitted with a diagnosis of ischemic stroke during this period. The mean age of the group was 38 years. There were 76 males (64%) and 42 females (36%). About three quarters of the patients were in the 3 5-44 year age group. The rest were equally distributed among the 15-24 and 25-34 year age group.
The main risk factors for atherosclerosis in these patients were hypertension, diabetes and smoking. The neurological deficits were hemiplegia or hemiparesis, speech dysfunction and cerebellar dysfunction (Table 1).

Table 1. Distribution of cases by atherosclerosis risk factors (on history) and neurological deficits.

	No. (118)	%
Atherosclerotic risk factors		
Hypertension	51	30.5
Diabetes	36	30.5
Smoking	25	21.2
Hypercholesterolemia	15	12.7
Family history of heart disease	15	12.7
Alcohol	3	2.5
Neurological deficits		
Hemiparesis/hemiplegia	89	75.4
Speech dysfunction	48	41.5
Cerebellar dysfunction	14	11.9
Movement disorders	11	9.3
Gaze palsy	6	5.1

Investigations were ordered on a case-by-case basis. Therefore of the 118 cases included in the present study only 56.8% (n=67) underwent surface echocardiography and 38% (n=45) carotid doppler examination (performed with Toshiba triplex ultrasound scanner, which combines B-mode with color flow doppler). Of the 67 cases who underwent surface echocardiography, 51 (76%) cases showed no abnormality while the remaining cases had left atrial enlargement, valvular vegetations and wall motion abnormalities (Table 2). Of the 45 cases in whom carotid doppler was performed, 31(68.9%) patients had a normal scan. Varying degree of stenosis or ulceration of the carotid artery was found in 11 cases and information regarding degree of stenosis was not available for 3 of the 14 patients (Table 2).

Table 2. Distribution of cases by echocardiographic and carotid doppler examination.

Investigations	No.	%
Echocardiographic findings	67	
Normal	51	67
Wall motion abnormality	8	11.9
Left atrial enlargement	4	6
Thrombus	3	4.5
Valve vegetation	1	1.5
Carotid doppler findings	45	
Normal	31	69
Stenosis/ulceration		
Mild	5	11
Moderate	3	6.7
High	3	6.7
Type of plaque		
Soft	6	13

Laboratory investigations showed hypercholesterolemia in 18.8% and raised triglycerides in 19.6% cases. Of the 41 patients tested for presence of anticardiolipin antibody, a positive test was obtained in 9.7% cases.
The probable etiologies identified in 118 patients on the basis of physician diagnosis are summarized in Table 3.

Table 3. Etiology of stroke in 118 patients.

Etiology	No.	%
Undetermined	54	45.8
Intracranial atherosclerosis	17	14.4
Cardiac embolism	13	11
Non-atherosclerotic vasculopathy	10	8.5
Extracranial atherosclerosis	9	7.6
Other	8	6.7
Hematological abnormality (aCL)	4	3.4
Migraine	3	2.5

Seventeen (14.4%) patients were diagnosed to have probable intracranial atherosclerotic vasculopathy and 9 (7.6%) extra-cranial (carotid) atherosclerosis. Other etiologies included cardiac embolism, hematological abnormalities and migraine. In 54 (45.8%) etiology could not be determined. Other etiologies such as oral contraceptives and lacunar infarct accounted for six (5%) cases as shown in Table 3. Computerized topographic (CT) scan was performed in 108 patients. The findings are presented in Table 4.

Table 4. Distribution of cases by territory of infarct and cortical location on CT scan.

	No.	%
Territory of infarct	108	
Cortical	61	56.5
Internal capsule	11	10.2
Basal ganglia	9	8.3
Brainstem	7	6.5
Cerebellar	5	4.6
Thalamus	4	3.7
Lacunar	1	0.9
Normal	10	9.3
Cortical location	46	
Parietal	16	34.8
Temporo-parietal	9	19.6
Fronto-parietal	7	15.2
Occipital	6	13.0
Fronto-temporal	3	6.5
Frontal	3	6.5
Temporal	2	4.3

Approximately half of the patients (5 1.7%) had a cortical infarct. Internal capsule infarcts were found in 10.2% (n=11) and basal ganglia infarcts in 8.3% (n=9) and 11% (n=12) had posterior circulation infarcts. Information about size of infarct was available in 35 patients. Infarct size was categorized as small (<1.5 cm), medium (1.5-3 cm) and large (>3 cm). Small sized infarcts were found in 34.3% (n12), medium in 20.0% (n=7) and large in 45.7% (n16) of the cases. The pattern of lobar involvement was studied in patients undergoing CT scan. Information regarding lobar involvement was available in 46 patients. The largest number of infarcts were found in the parietal region (34.8%), followed by temporo-parietal, fronto-parietal, occipital, fronto-temporal, frontal and temporal (Table 4).
MRI scan was performed in 30 patients. Cerebral angiography was performed in only one patient due to fmancial constraints and was correlated with the high grade stenosis found on ultrasonography. The MR scan picked up a higher proportion of posterior circulation infarcts (Table 5).

Table 5. Location of infarct on MR scan.

	No.	%
Cortical	11	36.6
Lacunar	5	16.6
Brainstem	5	16.6
Basal ganglia	4	13.3
Cerebellar	2	6.6
Normal	2	6.6
Internal capsule	1	3.33

Cortical territory involvement sparing the deep structures was found in 11(36.6%) and lacunar infarct in 5 (16.6%) patients. The remaining patients had internal capsule and basal ganglia involvement. None of these patients had a thalamic infarct on MR scan. The MR scan was normal in 2 (6.6%) patients (Table 5).
The in-hospital mortality rate was 11% (n13). Predictors of mortality of young stroke patients

were analyzed at the bivariate level and statistical significance was tested with the help of tests for categorical data (Table 6). The low mortality could be a major reason for not achieving statistical significance with regard to variables such as hypertension and dyslipidemia. The movement disorders and the location but not the size of infarct were significant associated with the mortality in young patients with stroke (Table 6).

Table 6. Association of various clinical and radiological variables with stroke mortality.

Predictor	Dead (%)	Alive (%)	Significance (p)
H/o of hypertension			0.291
No	10.4	89.5	
Yes	11.7	88.2	
H/o of diabetes			0.339
No	13.4	86.6	
Yes	5.6	9.4	
H/o of smoking			
No	8.6	91.4	
Yes	20.0	80.0	
Size of infarct			0.142
Small	25.0	75.0	
Medium	0.0	100	
Large	6.3	93.6	
CT location			0.046
Cortical	14.6	85.2	
Lacunar	0.0	100	
Int. capsule	0.0	100	
Basal ganglia	0.0	100	
Thalamus	25.0	75.0	
Brain-stem	42.6	57.4	
Cerebellar	0.0	100	
Movement disorder			0.019
No	8.4	91.6	
Yes	36.4	63.6	

Long-term follow-up was available in about half the patients, as a large proportion of rural population was lost to follow-up. The mean duration of follow-up was 44 days. The neurological outcome on follow-up was excellent (no functional disability) in 15 (27%) patients. Twenty-seven (49%) patients had a good outcome (mild neuro deficit but not requiring assistance with activities of daily living, ADL) and 13 (23%) were unable to carry out ADL without assistance (poor outcome).

Discussion

We present our experience with 118 young ischemic stroke patients from South Asia. Several studies have recently focused on the causes of ischemic stroke in young patients (Table 7).

Table 7. Etiologies found in previous studies.

	Razzaq et al. Pakistan	Kristensen[1] Sweden	Bevan[3] US	Adams[4] US	Nencini[2] Italy
Atherosclerosis (intra/extra-cranial)	22.0	12.0	31.2	17.6	22.2
Non-atherosclerotic vascular disease	8.5	17.0	10.4	0.0	0.0
Cardiac embolism	11.0	35.0	35.4	17.6	22.2
Hematologic	3.4	8.0	16.7	0.0	0.0
Migraine	2.5	1.0	2.1	0.0	5.5
Others	6.7	5.0	0.0	0.0	22.0
Unknown	45.8	21.0	4.2	34.3	22.0

A group from Northern Sweden has emphasized the role of cardiac embolism in young stroke patients[1]. Patent foramen ovale was the pre-dominant underlying abnormality in these cases. Non-atherosclerotic vascular disease such as carotid and vertebral artery dissection have also been found to account for a substantial number of cases (10-15%)[2-5]. Hematologic abnormalities such as anti-cardiolipin antibodies and oral contraceptives together account for 5-10% of cases[1-7].

The prevalence of atherosclerotic disease in young stroke varies from 10-30% in different series[1,3]. This wide variation is due to 'differences in diagnostic criteria for atherosclerotic disease[4]. For example some authors have used cerebral angiography to' establish the diagnosis in each case, while others have accepted two or more risk factors as sufficient evidence for the presence of atherosclerosis[2-4].

The risk factors for atherosclerosis were studied in detail in order to defme their contribution to the etiology of young stroke. A history of hypertension was found in 43.2% patients, which is much higher than the figure of 15-20% in series from the Western Hemisphere[1,3,8,9]. Similarly, a history of diabetes was found in almost one third of these young patients, which is several fold higher than previously reported (3-10%)[3,9]. The combination of diabetes and hypertension has not been studied in young stroke and was found in 19.5% of our patients. The rates of smoking (2 1%) and a family history of heart disease (12%) were in agreement with previous reports from the Western Hemisphere[1-5]. The high prevalence of these risk factors for atherosclerosis may signify a shift of disease patterns in our population to the profile commonly seen in developed countries.

The salient laboratory parameters studied included hematology and lipid profiles, tests for autoimmune disease (ANA and Rh factor) and presence of anti-cardolipin antibodies. Despite of the high proportion of risk factors for atherosclerosis, the prevalence of hypercholesterolemia and hypertriglyceridemia was comparable to previous figures of 18-20% reported from the Western Hemisphere[3-5,9,10]. The presence of anti-cardiolipin antibody in 9.7% of those tested, signifies the importance of this etiologic subgroup in our population.

The surface echocardiogram was performed in 67 patients and indicated abnormalities in 16 patients. These included intracardiac thrombus, valve vegetation, left atrial enlargement and wall motion abnormalities. Congenital cardiac abnormalities were much less frequent than reported previously. Patent foramen ovale was considered to be an important etiology in a study from Northern Sweden[1], but we did not find a single case of this abnormality in our group. This reason for the absence of congenital cardiac abnormalities in this series is unexplained.

The carotid doppler was performed in 45 patients, of which 14 (31%) patients had stenosis or uleration of the carotid artery. The prevalence of carotid stenosis is much higher (0-15%) than the previous reports[1-3]. This coincides with the high contribution of atherosclerosis to the overall etiologic pattern in this study.

Among the total of 108 patients who underwent CT scan, the majority had pure cortical infarcts (57%), with basal ganglia and internal capsule involved in 8.3% and 10.2% of cases respectively. This is may be related to the predominant involvement of the carotid circulation by extra-cranial etiologies such as cardiac and carotid disease. Lacunar infarcts (0.9%) were found in a relatively small number of cases compared to other studies, reflecting the lesser contribution of small vessel disease in this group. The proportion of patients with vertebro-basilar infarcts (20%) was similar to other studies[1,5,7]. Several investigators have previously reported vertebral artery dissection as a major cause of ischemic stroke in young individuals[2-4]. Therefore a posterior circulation infarct in a young individual without an obvious cause merits cerebral angiography to rule out vertebral artery dissection. However, this etiology could not be investigated further in our series, due to unavailability of cerebral angiography in majority of the cases.

The size of infarct in young stroke patients has not been well studied previously[1-10]. In this study, we found nearly half of the infarcts to be large (>3 cm) in size (46%). This relatively high proportion of large infarcts may reflect the greater contribution of embolic causes, which affect the proximal trunks of major intra-cranial vessels leading to larger infarcts.

The etiology of ischemic stroke in this study was based on the probable diagnosis established by the attending physician keeping in view all available clinical data. This approach has been used by other investigators[3,4]. The comparison of our etiologic data with previous studies is presented in Table 7. The limited availability of cerebral angiography and trans-esophageal echocardiography may have significantly under-estimated the presence of cardiac and vascular

disease in our series. The overall contribution of extra and intra-cranial atherosclerosis was 22% which is higher than the previously reported figures of 10-20%. As mentioned earlier, cerebral arterography was not performed in the majority of cases. The diagnosis of extracranial vascular disease was based on the findings of carotid doppler ultrasonography and the presence of risk factors for atherosclerosis. Intracranial atherosclerotic vasculopathy was considered as the probable diagnosis in the presence of more than two risk factors and the exclusion of other possible etiologies. The contribution of cardiac embolism was 11%, which is much lower than the rates of 20-30% found in previous studies. As mentioned previously, abnormalities of inter-atrial septum such as patent foramen ovale have been reported to constitute the major cause of cardiac embolism in previous studies1. The complete absence of congenital cardiac abnormalities in our series is an unexplained finding.

The in-hospital mortality of 11% is similar to that reported in other series[1-5]. Long-term follow-up was available in about half the patients, as a large proportion of rural population was lot to follow-up. The mean duration of follow-up was one and a half months. There is little previous data regarding long-term outcome of young stroke patients. In this series the neurological outcome was excellent in 27% of patients (no functional disability). Almost half the patients (49%) had a good outcome (mild neurological deficit but not requiring assistance with activities of daily living, ADL) and about one fourth (23%) were unable to carry out ADL without assistance (poor outcome).

The analysis of mortality predictors has not been addressed in previous studies of young stroke[1-19]. The small number of dead patients may have obscured the statistical significance of several potential predictors. We found a significant correlation of abnormal spontaneous movements (such as chorea and hemiballismus) with mortality. This may be related to the deep location of these infarcts in the thalamus and basal ganglia. Brainstem location was found to be a significant predictor of mortality, due to probable involvement of cardio-respiratory centers. The size of the infarct on CT scan did not correlate significantly with mortality in our series.

In conclusion, this study emphasizes the dramatic shift of disease patterns in developing countries and highlights the increasing prevalence of risk factors for atherosclerosis. Intracranial and extracranial atherosclerosis together account for at least 20% of young stroke in this series, a figure much higher than reported previously from the Western hemisphere. The high rate of risk factors such as diabetes, hypertension and smoking indicate the need for population screening and education programs, targeted to the young population. The high prevalence of carotid stenosis in this series also adds to the evidence implicating atherosclerosis as a major causative factor of young stroke in this study.

References

1.Kristensen B, Maim J, Carlberg B. Epidemiology and etiology of ischemic stroke in young adults aged 18-44 years in Northern Sweden. Stroke, 1987;28:1702-9.
2.Nencini P Intizari D. Incidence of stroke in young adults in Florence, Italy. Stroke, 1988;19:977-81.
3.Bevan H, Sherma K, Bradley W. Stroke in young adults. Stroke, 1990;21 :382- 86.
4.dams HP, Kapelle U. Ischemic stroke in young adults. Arch. Neurol., 1995;52:491-95.
5.Siqueira JI, Santos AC, Fabio SR. Cerebral infarction in patients age4 15-45 years. Stroke, 1996;27:2016-19.
6.Dennis MS. Bum JP Sandercock PA. Long term survival after first ever stroke-The

Oxfordshire Community Stroke Project. Stroke, 1993;24:796-800.
7.Sorokin NR, Ronen R. Stroke in the young in Israel: incidence and outcomes. Stroke, 1996;27:838-41.
8.Marshall J. The cause and prognosis of stroke in people under 50 years. J.Neurol.Sci., 1982;53:473-88.
9.Hart RJ, Miller VT. Cerebral infarction in young adults. A practical approach. Stroke, 1983;14:l10-14.
10.Lisovoski F, Rosseau P. Cerebral infarction in young people.A study of 148 patients with early cerebral angiography. J. Nerol. Neurosurg. Psychiatry, 1991 ;54:576-79.
11.Biller J, Johnson MR. Adams HP Jr. Echocardiographic evaluation of young adults with non-hemorrhagic cerebral infarction. Stroke, 1986;17:608-12.
12.Van der Berg iSP, Limburg M. Ischeniic stroke in the young: influence of diagnostic criteria. Cerebrovasc. Dis.,1 993;3:227-30.
13.Guidetti D, Baratti M, Zucco R. Incidence of stroke in young adults in the Reggio Emilia area; Northern Italy. Neuroepidemiology, 1993;12:82-87.
14.Kittner SJ, McCarter RJ, Sherwin RW, et at. Black and white differences in stroke risk among young adults. Stroke, 1993;24: 1-15.
15.Bougoslavvy J, Pierre P. Ischemic stroke in patients under 45.Neurol. Clin., 1992;iO:113-24.
16.Hindfelt B, Nilsson 0. Brain infarction in young adults. Acta.Neurol.Scand., 1997;55:145-57.
17.Abraham J, Sherry G. Strokes in the young. Stroke, 1971;2:258-67.
18.Hilton-Jones D, Warlow CP. The causes of stroke in the young. J. Neurol., 1985;232:137-43.
19.Klein GM, Selland TP. Occlusive cerebrovascular disease in young adults. Can.J..Neurol..Sci., 1984;11:302-4.