

Early Ischemic Stroke Presentation in Pakistan

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ABSTRACT: Introduction: There are no studies from Pakistan that describe stroke presentation rates or factors associated with early or delayed presentation. This is important to know because current clinical protocols limit the use of recombinant tissue plasminogen activator (rtPA), the only available therapy for acute ischemic stroke, to a three-hour window from symptom onset. **Methods:** All patients aged 14 years or above with acute ischemic stroke of ≤ 48 hours duration were prospectively identified from the Aga Khan University Stroke Data Bank over a 22-month period ending May 2001. **Results:** 269 ischemic stroke patients presented within 48 hours of stroke onset. 55 out of 269 (21%) presented within first three hours and 110 out of 269 (41%) within first six hours. Unawareness of treatment options ($p < 0.001$) and inappropriate diagnosis and field triage ($p = 0.005$) were associated with delayed presentation. Small vessel occlusion or lacunar stroke in the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) ischemic stroke subtype was associated with delayed presentation ($p = 0.047$) and cardioembolic stroke was associated with earlier presentation ($p = 0.048$). Stroke severity assessed with the National Institutes of Health Stroke Scale at a cut off score of ≥ 15 was not associated with earlier time to presentation at three hours ($p = 0.114$) but there was some tendency at six hours ($p = 0.097$). **Conclusions:** The rate of early stroke presentation in a Pakistani tertiary care facility is comparable to certain developed countries. To increase the proportion of patients who can benefit from thrombolytic therapy, programs need to be instituted to increase public awareness of treatment options for stroke and expedited referral by the primary care provider.

RÉSUMÉ: Consultation précoce dans l'accident vasculaire cérébral ischémique au Pakistan. Contexte : Il n'y a pas d'étude au Pakistan décrivant les taux de consultation dans l'accident vasculaire cérébral (AVC) ou les facteurs associés à une consultation précoce ou tardive. Ce sont des informations importantes à cause des limites actuelles des protocoles cliniques pour l'utilisation de l'activateur du plasminogène recombinant (rt-PA), le seul traitement disponible pour l'AVC ischémique aigu. Ce traitement doit être administré en dedans de 3 heures du début des symptômes. **Méthodes :** Tous les patients âgés de 14 ans et plus, présentant un AVC ischémique aigu de moins de 48 heures, ont été identifiés de façon prospective dans la banque de données de l'AVC de l'Université Aga Khan sur une période de 22 mois se terminant en mai 2001. **Résultats :** Deux cent soixante-neuf patients atteints d'un AVC ischémique ont consulté dans les 48 heures du début des symptômes. Cinquante-cinq d'entre eux (21%) ont consulté dans les trois premières heures et 110 (41%) dans les six premières heures. La méconnaissance des options thérapeutiques ($p < 0,001$) et un diagnostic et un triage inappropriés ($p = 0,005$) étaient associés au retard à consulter. Dans l'essai clinique TOAST (Trial of ORG 10172 in Acute Stroke Treatment) sur les sous-types d'AVC, une occlusion d'un vaisseau de petit calibre ou un AVC lacunaire était associé à une consultation tardive ($p = 0,047$) et l'AVC cardioembolique était associé à une consultation plus précoce ($p = 0,048$). La sévérité de l'AVC évaluée au moyen du National Institutes of Health Stroke Scale avec un point de coupe de 15 et plus n'était pas associée à une consultation plus précoce dans le groupe qui avait consulté en dedans de 3 heures ($p = 0,114$), mais on notait une tendance en ce sens dans le groupe qui avait consulté en dedans de 6 heures ($p = 0,097$). **Conclusions :** Le taux de consultation précoce chez les patients présentant un AVC aigu dans les hôpitaux de soins tertiaires au Pakistan est comparable à celui de certains pays industrialisés. Il faudra établir des programmes d'information pour que le public soit au courant des options thérapeutiques dans l'AVC et de l'importance d'une référence rapide par le personnel médical de première ligne.

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Recombinant tissue plasminogen activator (rtPA) is the only available therapy for acute ischemic stroke. Current clinical protocols limit its use to a three-hour window from symptom onset. The role of thrombolytic therapy between 91 and 180 minutes after stroke onset remains highly controversial. However, studies have shown that rtPA given within six hours of stroke reduced death or dependency (i.e. more patients alive and independent) at three to six months, and this was statistically significant in favor of treatment.¹⁻⁴ Late presentation continues to be a primary cause of exclusion from thrombolytic therapy

among stroke patients. The data for stroke presentation has not been reported from Pakistan.

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This study presents the results of the hospital based Aga Khan University Stroke Data Bank evaluating stroke patients admitted to a large tertiary care medical center. In this observational study, we report the exceptionally large proportion of stroke patients presenting to the Emergency Department of a tertiary-care hospital in Karachi, Pakistan, within three hours of symptom onset and consequentially, a substantial difference in the number of patients eligible for thrombolytic therapy compared to published data from other countries.⁵⁻¹⁵ (Table 1)

MATERIALS AND METHODS

Study Design and Setting

This historical cohort was conducted from August 1999 to May 2001 at the Neurology Department of the Aga Khan University Hospital, Karachi, Pakistan. The Aga Khan University Hospital is a major tertiary care health facility, which caters to a large urban population of approximately 15 million.

Sample Selection

All acute stroke patients over the age of 14 years presenting to the Emergency Department from August 1999 to May 2001 were eligible to be enrolled in the Aga Khan University Stroke Data Bank. There were two patients who were <18 years-of-age, one presented >36 hours and the other <3 hours post onset. Patients with subarachnoid, subdural or epidural hemorrhage and transient ischemic attack (TIA) were excluded from the Data Bank. Any patient with an in-hospital stroke was also excluded. Acute stroke was defined according to the WHO criteria as a rapidly evolving focal or global neurological deficit with symptoms leading to death or lasting >24 hours due to a vascular etiology.¹⁶ Causes other than stroke were ruled out by brain imaging and other diagnostic studies. The diagnosis of stroke was verified by a neurologist, and a head CT scan was performed in all cases.

Table 1: International stroke presentation rates

| | Study Setting | Study Design | Population Characteristics | Median Prehospital Delay & Range/min | % presenting < 3 hours | % presenting < 6 hours |
|--|--|---|--|--------------------------------------|----------------------------|---------------------------|
| <i>Rosnagel et al</i> Ann Emerg Med 2004;44: 476-483 | Germany | Multicentre Prospective Cross-sectional | N=558 IC: Acute Stroke with onset < 7 days | 151 (5 - 9590) | N/A | N/A |
| <i>Harraf et al</i> BMJ 2002; 325:17-21 | UK & Dublin | Multicentre Prospective Observational | N=739 IC: Acute Stroke | 360 (108-1152) | 37 | 50 |
| <i>Barber et al</i> Neurology 2001 Apr 24; 56(8):1015-20 | Calgary, Canada | Multicentre Prospective | N=1168 IC: Acute Ischaemic Stroke | N/A | 27 | N/A |
| <i>Morris et al</i> Stroke 2000; 31:2585- 2590 | Genentech Stroke Presentation Survey, USA | Multicentre Prospective | N=1207 IC: Acute Stroke with onset <24 hours, age ≥ 18 years | 156 (72-378) | 56 | 75 |
| <i>Chang et al</i> Stroke 2004; 35:700- 704 | Taiwan | Prospective | N=196 IC: Acute Stroke with onset < 48 hours | 335 (112-860) | 26 | N/A |
| <i>Casetta et al</i> Neuroepidemiology 1999;18:255-264 | Italy | Prospective | N=760 IC: Acute Stroke | 210 | 41 | |
| <i>Vemmos et al</i> Cerebrovascular Diseases 2000; 10:133-141 | Athens | Prospective | N=1042 IC: Acute Stroke | N/A | 46 | N/A |
| <i>Derex et al</i> Stroke 2002;33:153 | France | Prospective | N=166 IC: Acute Stroke | 245 | 29 | 75 |
| <i>Streifler et al</i> Neuroepidemiology 1998;17:161-166 | Israel | Prospective | N=216 IC: Acute Stroke | N/A | 18 | 54 |
| <i>Leopoldino et al</i> Arq Neuropsiquiatr. 2003 Jun; 61(2A):186-7 | Brazil | Prospective | N=50 (59 for all) IC: Acute Ischaemic Stroke | 1126 (for all acute) | 26 (28 for all strokes) | 30 (32 for all stroke) |
| <i>Srivastava et al</i> Neurol India 2001;49:272-6 | India | Prospective | N=110 IC: Acute Stroke with onset < 72 hours | 460 | 25 | 49 |

IC=Inclusion Criteria

Table 2: Characteristics of patients with ischemic stroke presenting within 48 hours. (n=269 unless stated otherwise)

| Variables | | Frequency (Percent) | <3 hours | |
|---|--|------------------------------|---------------------|---------|
| | | | Frequency (Percent) | P value |
| Age | Mean(±Standard deviation); Median | 61 (±13.316) years; 62 years | | 0.804 |
| | ≤50 | 50 (18.6%) | 11 (22.0%) | |
| | 51-60 | 81 (30.1%) | 19 (23.5%) | |
| | 61-70 | 82 (30.5%) | 15 (18.3%) | |
| | ≥71 | 56 (20.8%) | 10 (17.9%) | |
| Sex | Male | 174 (64.7%) | 32 (18.4%) | 0.258 |
| | Female | 95 (35.3%) | 23 (24.2%) | |
| Socio-economic Status (n=259) | Upper | 67 (25.9%) | 14 (20.9%) | 0.973 |
| | Middle | 163 (62.9%) | 32 (19.6%) | |
| | Lower | 29 (11.2%) | 6 (20.7%) | |
| Education (n=156) | Illiterate | 32 (20.5%) | 4 (12.5%) | 0.600 |
| | Primary | 26 (16.7%) | 7 (26.9%) | |
| | Matric | 26 (16.7%) | 5 (19.2%) | |
| | Intermediate | 20 (12.8%) | 4 (20.0%) | |
| | Graduate | 42 (26.9%) | 5 (11.9%) | |
| | Postgraduate | 10 (6.4%) | 1 (10.0%) | |
| Transport problem | | 19 (7.1%) | 3 (15.8%) | 0.773 |
| Patient unawareness of treatment options | | 56 (20.8%) | 2 (3.6%) | <0.001 |
| Inappropriate diagnosis and field triage | | 57 (21.2%) | 4 (7.0%) | 0.005 |
| Financial problem | | 5 (1.9%) | 1 (20.0%) | 1.000 |
| Ischemic Stroke Subtype | Large Vessel Atherosclerosis | 67 (24.9%) | 15 (22.4%) | 0.649 |
| | Small Vessel Occlusion or Lacunar Stroke | 120 (44.6%) | 18 (15.0%) | 0.047 |
| | Cardioembolic Stroke | 21 (7.8%) | 8 (38.1%) | 0.048 |
| | Stroke of Other Determined Cause | 11 (4.1%) | 4 (36.4%) | 0.244 |
| | Stroke of Other Undetermined Cause | 50 (18.6%) | 10 (20.0%) | 0.931 |
| NIHSS score | ≤15 (mild-moderate) | 216 (80.3%) | 40 (18.5%) | 0.114 |
| | > 15 (severe) | 53 (19.7%) | 15 (28.3%) | |
| Prior stroke | | 56 (20.8%) | 13 (23.2%) | 0.564 |
| Prior transient ischemic attack (TIA) | | 20 (7.4%) | 4 (20.0%) | 1.000 |
| Coronary artery disease | | 73 (27.1%) | 17 (23.3%) | 0.481 |
| Myocardial infarction | | 37 (13.8%) | 11 (29.7%) | 0.132 |
| Diabetes mellitus | | 106 (39.4%) | 17 (16.0%) | 0.148 |
| Hypertension | | 164 (61.0%) | 33 (20.1%) | 0.869 |
| Hyperlipidemia | | 52 (19.3%) | 11 (20.0%) | 0.888 |
| Atrial fibrillation | | 7 (2.6%) | 2 (28.6%) | 0.634 |
| Congestive heart failure | | 10 (3.7%) | 4 (40.0%) | 0.125 |
| Rheumatic heart disease | | 5 (1.9%) | 2 (40.0%) | 0.271 |
| Currently smoker | | 34 (12.6%) | 6 (17.6%) | 0.665 |
| Former smoker | | 56 (20.8%) | 13 (23.2%) | 0.564 |

Data Collection and Methods of Measurement

The time of stroke onset was defined as the time when symptoms of stroke first occurred. If symptoms were first noted on awakening, onset was defined by when last observed to be normal.

Patients were worked up according to an established clinical stroke pathway, and investigations included neuroimaging (CT or MRI), electrocardiogram, transthoracic echocardiogram, complete blood count, coagulation profile, serum electrolytes, blood urea nitrogen, creatinine, urine detailed report, and carotid Doppler ultrasonography. Selected patients underwent transesophageal echocardiogram with bubble contrast, 24 hours holter monitoring and work up for hypercoagulable state. All patients were evaluated by a consultant neurologist, and the data was collected by neurology house staff on a standardized precoded data entry form. The data was collected in real time during the patient's hospital stay, and the patient's discharge was the end point for the purpose of this study.

Statistical Analyses

The quantitative data is presented in mean with standard deviation or median as appropriate. Univariate analysis was carried out to assess factors influencing the outcome (delay in presentation) using Chi square and student's *t* test. Association of categorical variables with outcome was performed with Pearson χ^2 or Fisher exact test as appropriate and association between quantitative variables and outcome was performed with student's *t* test.

SPSS (Statistical Package for the Social Sciences) version 15.0 for Windows was used for all calculations.

RESULTS

During the 22 month period, there were 596 patients enrolled in the AKU (Aga Khan University) Stroke Data Bank. Of these, 393 patients suffered from ischemic stroke and 126 were diagnosed with a primary intracerebral hemorrhage. Twenty-seven patients were considered not to have suffered a stroke (22 TIA, two psychogenic symptoms and one metabolic encephalopathy presenting as a stroke). An additional 50 patients with subarachnoid hemorrhage were enrolled, but excluded from analysis.

Our study focuses on the ischemic stroke group. Despite excluding "late presenters" from geographically remote regions and neighboring countries, 269 of the total 393 ischemic stroke patients (68.4%) presented within the first 48 hours of stroke onset. In this group, there were 174 (64.7%) men and 95 (35.3%) women with a male to female ratio of 1.83. The mean age was 61 years (± 13.32) with median of 62 years (Table 2). 55 out of 269 ischemic patients (20.4%) presented within 0-3 hours and 110 out of 269 (40.9%) within 0-6 hours (Table 3). The median time to presentation after stroke onset was 7 hours (420 minutes) i.e. 51.4% patients presented within 0-7 hours.

The most common reasons that patients reported for delay in presentation were unawareness of treatment options ($p < 0.001$), and inappropriate diagnosis and field triage ($p = 0.005$) (Table 3). There were no symptom recognition delays reported. In ischemic stroke subtype according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria¹⁷, small vessel occlusion or

lacunar stroke was associated with delayed presentation ($p = 0.047$) and cardioembolic stroke was associated with earlier presentation ($p = 0.048$) whereas there was no association with large vessel atherosclerosis, stroke of other determined cause and stroke of other undetermined cause. Stroke severity measured with the National Institutes of Health Stroke Scale at a cut off score of ≥ 15 was not associated with earlier time to presentation at 3 hours ($p = 0.114$) but there was some inclination at 6-hours ($p = 0.097$). There was also no association with age, sex, literacy, socioeconomic status, transport problems, financial problems, prior stroke, transient ischemic attack and other comorbidities including diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, atrial fibrillation, congestive heart failure and rheumatic heart disease.

DISCUSSION

Karachi, with a population of over 15 million, is the largest city in Pakistan. Being a developing nation, with the increasing problems of the developed world, it endures a double burden of disease.¹⁸ Stroke is a common clinical problem in Pakistan, accounting for 6.4% of all hospital admissions in two major hospitals in Karachi.¹⁹ The single prevalence study on a single ethnic community within Pakistan reports a prevalence rate of 4.8%²⁰ which is alarmingly high. However, the results of this study should be interpreted with caution as a non-validated questionnaire was used. There are no community incidence data available from Pakistan.

In a country where stroke rehabilitation centers are numbered and the fallout of stroke is devastating, early aggressive tissue salvage therapy is crucial. A substantial delay in the presentation of acute stroke was expected. However, our study shows that almost a quarter of the patients presented within the first three hours of stroke onset and as many as 40% within six hours. These percentages are comparable to internationally published data⁵⁻¹⁵ from more developed nations. The hospital net is nationwide and the university has a nursing program covering Afghanistan. It is not uncommon for patients to be brought in

Table 3: Hours between stroke onset and hospital presentation

| Hours | Frequency (Percent) | Cumulative Percent |
|-------|---------------------|--------------------|
| < 3 | 55 (20.4%) | 20.4% |
| 4-6 | 55 (20.4%) | 40.9% |
| 6-12 | 68 (25.3%) | 66.2% |
| 12-24 | 62 (23%) | 89.2% |
| 25-48 | 29 (10.8%) | 100% |
| Total | 269 (100 %) | |

from geographically remote regions and from neighboring countries. Thus we excluded all "late presenters" from the analysis. Despite these conditions, 269 out of 393 (68.4%) presented within 0-48 hours.

Patient awareness of stroke symptoms was not associated with early presentation to hospital as reported in several studies.²¹⁻²³ Attention to factors that go beyond symptom awareness such as education regarding new stroke treatments options and the limited time interval for effective therapy may increase the proportion of patients arriving within the first hours after stroke onset.^{12,24,25} These observations are also illustrated in our study that unawareness of treatment options was associated with significant delay to hospital presentation ($p < 0.001$). The longest phase of delay is reported to be the time from symptom recognition to the decision to seek medical care.²⁵ Awareness of treatment options may play an important role in deciding to seek medical care apart from other factors and, therefore, may become a potent factor in reducing this longest phase of delay.

If physicians were contacted, the patients were often inappropriately triaged leading to delays ($p=0.005$) as described in the literature.^{15,25-27} This underscores the need to set mechanisms in place at the general practitioners level to expedite diagnosis and referral to the organized stroke centers.

Small vessel occlusion or lacunar stroke according to the TOAST ischemic stroke subtype presented late ($p=0.047$) whereas cardioembolic stroke presented early ($p=0.048$). Late presentation in lacunar strokes might be attributed to milder stroke symptoms and low threat perception by the patient. Lacunar stroke was also the most common subtype of ischemic stroke presentation (44.6%) (Table 2) as reported previously in AKU Stroke Data Bank.¹⁹ However there was no association found with large vessel atherosclerosis, stroke of other determined cause and stroke of other undetermined cause.

Stroke severity assessed with the National Institutes of Health Stroke Scale (NIHSS) was not associated with early admission to hospital at 3 hours ($p=0.114$) but there was some tendency at 6 hours ($p=0.097$) at a cut off score of NIHSS >15 . Stroke severity has been shown to be associated with early arrival in many^{13,21,25-28} but not all studies²⁹⁻³¹. All patients should seek immediate medical attention irrespective of the severity of stroke as every third stroke patient with mild to moderate symptoms may deteriorate with increased risk of morbidity and mortality.³²

Age, sex, literacy, socioeconomic status, prior stroke or transient ischemic attack did not show any association with the time interval of arrival, neither did the risk factors for stroke including hypertension, diabetes mellitus, dyslipidemia and smoking along with the other comorbidities including coronary artery disease, atrial fibrillation, rheumatic heart disease and congestive heart failure as reported in several studies.^{8,23,25,28,29,33}

The socio-cultural profile of Pakistan differs from that of the western world. Despite the furious pace of change and modernization that has occurred in Pakistan over the last several years, the traditional extended family still forms the basic unit of society. This ensures that the elderly are constantly under observation, which may enable rapid recognition of stroke onset in this setting despite the lack of literacy.

Stroke recognition and reporting in this region is unexpectedly early, facilitated by the extended family system. Effective programs are needed to benefit patients from

thrombolytic therapy including increasing public awareness of treatment options for stroke, seeking immediate medical attention despite mild to moderate symptoms and expediting diagnosis and referral by the primary care giver.

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