

Recurrence Rates Evaluation in Hemorrhagic and Ischemic Stroke after the First Attack in the Patients Admitted in the Razi Hospital

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Abstract: Stroke, positioning in the third place of the most fatal diseases produces instabilities and profound socio-economical as well as psychological problems for both individuals and society. These problems are intensified in recurrent stroke. Regarding the lack of relevant study on such a crucial field we carried out a research to find out of stroke recurrence and mortality and scrutinize the relevant risk factors. According to the previous reports the overall 17% rate of recurrence in stroke with the $p = 17\%$, $q = 0.83$, $z = 1.96$ we selected 300 patients (34-85 yr. old) who had been admitted in the neurology ward of Razi hospital for their first stroke (proven stroke) and after discharge of them they followed up monthly for 5 years over a period of 60 months from March 2000 to March 2005. Selection was randomly (simple randomized sampling) (150 ischemic and 150 hemorrhagic cases). In the cases that new signs or symptoms in favor of a new attack were detected and If clinically warranted brain CTscan or MRI were used for paraclinically approve the recurrence of stroke. The cumulative risk of occurrence among selected cases encompassing 56% male and 44% female was 32% to which males and females contributed 12 and 20%, respectively (67.5% female vs. 32.5% male, $p\text{-value}=0.00$). For initial stroke HTN (78%), smoking (43%) and HLP (26%) were the most probable risk factors attributable to the event. In recurrent stroke HTN (28%), HLP (11%), smoking (9%) and IHD (9%) were the most important factors. Mean time of the recurrence after the initial stroke was 5.3 ± 3.4 months. 21% of the patients with positive ischemic heart disease developed ischemic stroke (95% ischemic stroke, 5% hemorrhagic stroke, $p\text{-value} = 0.05$). Because of the fact that the mortality rates and disabilities with recurrent stroke are usually more vigorous than initial events, secondary prevention of stroke must be considered seriously. This study highlights the importance of strict hypertension, ischemic heart disease and hyperlipidemia control and cease of smoking.

Key words: Hemorrhagic stroke, ischemic stroke, stroke recurrence, risk factors

INTRODUCTION

After heart disease and all forms of cancer, stroke is the third leading cause of death in the United States, Canada, Europe, Australia and Japan (Hankey, 1999). It is the main cause of adult neurological disability and accounts for the greatest number of hospitalizations for neurological diseases and the most common cause of severe handicap, dependency and loss of social competence. Every year about 700,000 Americans experience a new or recurrent stroke; about 160,000 of these people die. Of the survivors, approximately one-third experiences another stroke within five years. The annual risk of dying after stroke is about 9%, which is approximately 2.3 times that of the general population, with an even higher risk of about 15% in the first year (Dennis *et al.*, 1993; Hankey *et al.*, 2000).

The patient who is recovering from a mild stroke or who had a mild disability, with recurrence of stroke long-term institutionalization and death probability increases.

Despite the fact that stroke recurrence is an important public health concern (Bauren *et al.*, 1994) there been no prospective studies in Iran focused on ischemic and hemorrhagic stroke recurrence and the information regarding stroke recurrence relationship with risk factors is scarce.

The purpose of this research, is to estimate the risk of the recurrence of ischemic and hemorrhagic stroke between two sex groups in patients admitted to Tabriz neurology center of Razi hospital and to compare it with previous studies conducted in other countries. This study also examines ischemic and hemorrhagic stroke recurrence and whether the type of the initial stroke influences the risk and type of further stroke.

Stroke recurrence not only may add to physical impairment and disability but may also increase mortality and length of hospital stay (Hier *et al.*, 1991). In addition, stroke recurrence may lead to vascular dementia or may be an important trigger for dementia in the elderly (Alter *et al.*, 1994; Hankey *et al.*, 1998).

The decline in stroke mortality and the increase in life expectancy of the population undoubtedly increase the number of persons at risk for recurrent stroke, stroke-related disability and the cost of medical care (Hier *et al.*, 1991).

MATERIALS AND METHODS

Form March 2000 to March 2005, 300 subject including (150 cases of ischemic Stroke and 150 cases of hemorrhagic stroke) of first-in-a lifetime Strokes admitted to Tabriz medical center of Razi hospital neurology ward were randomly identified and prospectively followed up face to face monthly over a period of twelve months.

The recurrences in both ischemic and hemorrhagic groups were evaluated and main influencing factors were determined. We determined rates of in-hospital hemorrhagic and ischemic stroke as well. All patients with stroke who were admitted to participating center prospectively documented, with respect to clinical and neurological parameters, medical history, results of technical and laboratory investigations, presumed etiology and follow-up investigations at 5 years.

Effects of sex, age and type of the initial stroke on recurrence were evaluated carefully. Mean time gap between the initial and recurrent stroke was calculated.

For the assessment of the survival and recurrences after stroke, following the careful sampling and collecting data from the primary sources and follow up program, SPSS 13.00 is used to analyze the patients, final data. Quantitative data provided as mean±standard deviation and qualitative data as numbers and frequencies and their percent (%). P-value higher than 0.05 was statistically considered significant.

For doing comparisons to find significant differences and relationships and also for estimation of correlation between defined variables, Pearson test, independent sample t-test and chi-square test were used. We made a separate analysis by Stroke types, sex groups, age, recurrence time and the risk factors and finally the results were compared with the findings of the previous studies in other centers.

Classification of stroke types (ischemic or hemorrhagic) was based on clinical and radiological (CT/MRI scan) findings. Risk factor details were obtained from hospital records and the patients self-report.

Recurrent stroke is defined as rapidly evolving clinical signs of focal disturbance of cerebral function lasting longer than 24 h or leading to death, with no apparent other cause than a vascular dysfunction, occurring at least 72 h after the onset of the first stroke. And these clinical situations were approved with Brain CT scan or MRI.

RESULTS

At the end of follow up of all 300 patients including 156 male patients (56%) and 144 female patients (44%), we observed ischemic stroke in 54% of males (27/50) and 46% of females (23/50) which produced no significant difference ($p_value > 0.05$). Females (62.5%) tolerated approximately twice as males (37.5%) recurrence.

There was no relationship between type and sex ($p_value > 0.05$), which means none of the stroke types studied here is predominant in any of the sexes compared to another.

Cumulative risk of recurrence was 32% (32 cases) for one year. The risk of hemorrhagic stroke among men and women was 18.8 and 18.8%, respectively but for ischemic the result was 18.8% for men and 43.8% for women, which shows a higher risk of recurrence for women with initial ischemic stroke. The recurrence numbers for the study period ranged form zero (without recurrence) to six. The mean time from the initial stroke was 5.3 +/- 3.4 months. There was no relationship between time of the recurrence and stroke ($p>0.05$) (Fig. 1 and 2).

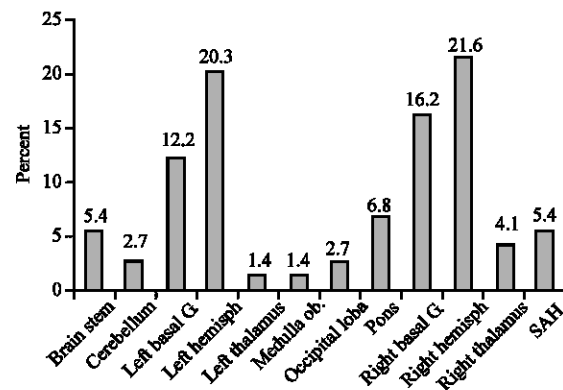


Fig. 1: Brian territories affected by stroke

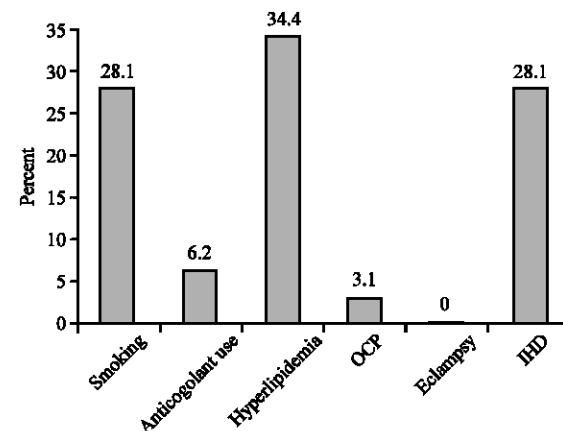


Fig. 2: Risk factor in intial stroke

Among 51 cases who had experienced recurrence, females were predominant in frequency (with 62.5% versus 37.5% of males, p -value = 0.011).

For initial stroke hypertension (78%) smoking (43%) and hyperlipidemia (26%) were the most probable risk factors attributable to the event. A positive history of IHD was found in 21% of the entire patients. For patients experiencing the recurrent stroke HTN accounting for the 87.5% of recurrent cases stays on top of the list but HLP (34.4%), smoking (28%) ischemic heart disease (28%) stay on second and third positions, respectively. The least important risk factors for recurrence were eclampsy (0%), OCP (3.1%) and a history of anticoagulant use (6.3%).

HTN and HLP were found in 6% of ischemia and 46% of hemorrhages. Among the patients with established HLP 11.5% were hemorrhagic and 88.5% were ischemic (p -value 0.00) i.e. Most of the hyperlipidemic patients were ischemic (23% versus 1% of hemorrhagic stroke). There was not a significant relationship between type of initial stroke and HTN (p -value = 0.114) which was the same for initial stroke. Approximately 21% of strokes were associated with IHD among which we found a significant relationship with the stroke types (hemorrhagic as well) (p -value < 0.05).

Most of the 143 cases with positive history of smoking (43%) were males (40% male and 3% female, p -value = 0.00) 24% of which culminating to hemorrhagic and 19% to ischemic without meaningful relationship (p -value = 0.210). Not necessarily smoking causes stroke with higher intensity (p -value = 0.195).

No relationship was found between smoking and mortality rate (p -value = 0.48).

Oral Contraceptive (OCP) use was positive in 18 female patients (13.6% of females populations, 11.4% ischemic versus 2.3% hemorrhagic, p -value = 0.10).

The majority of 21% of the patients with positive ischemic heart disease developed ischemic stroke (95% ischemic stroke, 5% hemorrhagic stroke, p -value = 0.00).

Eclampsy was positive in 2 women medical history. Hemorrhagic patients were free of IHD history. One of the cases of hemorrhagic stroke had a positive history of anticoagulant use.

Mean age of the subjects ranging from 34-85 was 61.86 ± 13.3 as a whole without significant difference between males and females (p -value = 0.312) that slightly increases among recurrent cases to mean age of 63.4 ± 17.1 . Mean ages of hemorrhagic (61.06 years) and ischemic strokes (62.66 years) shows no meaningful difference between types of initial strokes and there was no statistically meaningful relationship between age and recurrence time (p -value > 0.05).

Ninty five percent of males and females were in the range of 64.1 ± 12.5 and 58.9 ± 13.9 , respectively. As for initial stroke we did not observe meaningful relationship between age and type and age and sex (for both p -value = >0.05). Advancing age was neither significantly related to the initial nor the recurrent stroke.

At the end of the follow up program overall mortality rate was 6% mostly affecting females (4% females versus 2% of males, p -value = 0.21) of which 5% occurred in hemorrhagic and 1% in ischemic. 83% of the deaths identified in the age range of 60-75 years old.

Right hemisphere was involved in 45 cases (15%) showing roughly the same involvement for the left one with 48 cases (16%).

Recurrence time after initial stroke among the hemorrhagic stroke and ischemic stroke shows no difference (mean 4.58 ± 2.9 months vs. 5.82 ± 3.7 months, p -value > 0.05).

Twenty one, 48 and 31% of the patient had a mild, moderate and sever stroke, respectively but not meaningful relationship was found between type of the stroke and their severity (p -value > 0.05). We observed that the higher was the intensity of the initial stroke, was the probability of recurrence (p -value < 0.05).

DISCUSSION

Cumulative risk of recurrence in this study was 96 cases (32%) for 5 years and 24% annually while Most of the studies without our methodological limitations have given estimates of first-year stroke recurrence rates of between 4 and 17% and for each year 5% increases (Foulkes *et al.*, 1989; Wolf *et al.*, 1983; Sage *et al.*, 1983; Erikson and Olsson, 2001; Petty *et al.*, 2000; Prencipe *et al.*, 1998). In Framingham study authors reported that stroke recurrence rates range from 4-14% annually (Goldstein and Perry, 1992; Bovsen and Truelsen, 2000). R.L. Sacco in "The stroke Data Bank" and P. sandercock in "Very early prevention of stroke recurrence" reported that the estimates of early recurrences range from 1.2-9% of the cases (Mohr *et al.*, 2001; Sandercock and Tanglanakul, 1997). These variations may be related to methodological differences or differences in age, gender, or coexistent morbidities among the cohorts studied (Shi *et al.*, 1994).

There has been considerable variation in the stroke recurrence rates reported by stroke registries that have included both ischemic and hemorrhagic strokes (Minlai *et al.*, 1996; Elneihoum *et al.*, 1998; Hankey *et al.*, 1998; Mas *et al.*, 2001). Differences between studies looking at stroke recurrences seem to occur particularly in the first year after index stroke and may be explained by differences in definition of stroke recurrence.

This study confirms the important previous finding that the risk of stroke recurrence is higher in the immediate period (especially in the first year) after the index stroke (Minlai *et al.*, 1996; Elneihoum *et al.*, 1998; Hankey *et al.*, 1998; Mas *et al.*, 2001).

The mean time from the initial stroke was 5.3 +/- 3.4 months.

In keeping with the study carried out by Burn *et al.* (2003) and some other studies (Minlai *et al.*, 1996; Hankey *et al.*, 1998) in the present study we found significant differences in the recurrence rates by the types of stroke. (Ischemic 62.5% versus hemorrhagic 37.5%) but some other researches couldn't find enough statistical evidence for the differences (Apperlos *et al.*, 2003; Smaualsson *et al.*, 1996; Leonardi *et al.*, 2002; Friday *et al.*, 2002). In the "TOAST" study stroke subtype was not a predictor of recurrence (Yamamoto and Bogousslavsky, 1998).

As observed in previous studies, the present study supports the suggestion that people who suffer ischemic strokes have a much better chance for survival than those who experience hemorrhagic ischemic strokes (83.3 versus 16.7%). In one small study, however, survivors of hemorrhagic stroke had a greater chance for recovering function than those who suffered ischemic stroke. By the end of the study, 32% of the patients had a second stroke.

In a study by Hill on stroke recurrence in the year 2000 the recurrence rate for hemorrhagic stroke was 2.4% per year, whereas the Recurrence rate for ischemic cerebrovascular disease was 3.0% per year (Hankey *et al.*, 2003) that shows a higher recurrence rate for ischemic than that for hemorrhagic stroke which is compatible with what we identified but the lower figures can be contributed to the inequality of the situations in which the studies were carried out as for recurrence rate. More research must be done in this area with more standard methodology.

In the present study, the risk of recurrence for women with initial ischemic stroke is approximately two times as for men (62.5 vs. 37.5).

In contrast with initial stroke in which men are at higher risk than women (which is supported by other studies, in the present study women were in higher risk of recurrence (56 vs. 44).

In Keeping with Rochester, Minn study (Foulkes *et al.*, 1989) there was not significant sex difference matching the types.

Like as most of the previous studies risk factors such as HTN, HLP, IHD and smoking are associated with higher risks of recurrence (Baurm *et al.*, 1994). However, in Oxfordshire, no significant predictor was

found (Baurm *et al.*, 1994). For initial stroke hypertension (78%) smoking (43%) and hyperlipidemia (26%) were the most probable risk factors attributable to the event. A positive history of IHD was found in 21% of the entire patients. For patients experiencing the recurrent stroke HTN accounting for the 87.5% of recurrent cases stays on top of the list (as shown in other studies (Hier *et al.*, 1991; Mohr *et al.*, 2001) but HLP (34.4%), smoking (28%) and ischemic heart disease (28%) change their positions while in some studies IHD ranks the second (Hankey *et al.*, 1998).

As a result hypertension not only is the predominant factor in occurrence but also plays a main role in recurrence of the stroke, which is supported by the other studeies (Goldstein and Perry, 1992).

We found that most of the 43 cases with positive history of smoking were males (40 vs. 3%) most of which (~ 56%) culminating to hemorrhagic and rest (44%) to ischemic stroke.

The majority of the patients with ischemic heart disease developed ischemic stroke (95%).

Although stroke often is considered a disease of the elderly, 57% of strokes occurred in persons younger than 65 years, which is shown in some studies (Dennis *et al.*, 1993).

Dennis *et al.* (1993) on their Long-term survival study after first-ever stroke found the same result but it was not in coordination with a study by Jeffrey L Arnold, which found it 25%. It can be explained by result for ischemic stroke (Shi *et al.*, 1994). Another study shows 21% died by the end of the year (Petty *et al.*, 2000).

At the end of the follow up program overall mortality rate was 6% mostly affecting females (4% females versus 2% of males, p-value = 0.21) of which 5% occurred in hemorrhagic and 1% in ischemic. In the Northern Manhattan study, a cumulative mortality rate of 41% was observed in stroke patients (Foulkes *et al.*, 1989). In a shorter follow-up in 12 European hospital-based registers, the proportion of dead patients ranged from 12% in France to 41% in an UK center at 3 months (Minlai *et al.*, 1996).

We observed that right hemisphere was involved in 150 cases (15%) showing roughly the same involvement for the left one with 160 cases (16%). Our results concerning the relation between the risk of first recurrence and the site of brain lesion did not differ from some previous studies (Erikson and Olssen, 2001) in which no significant association between stroke location and recurrence was found.

Regarding the site of brain lesion identified by CT or MRI, rare studies compared locations of initial stroke with those of first recurrence.

One problem in the study of stroke recurrence is the difficulty in identifying recurrences, particularly when they occur shortly after the index stroke. Reliable detection of new neurological signs in a patient who has depressed consciousness or is paralyzed or bedridden is more difficult than in a recovered patient. Another difficult issue is to find the responsible determinants of recurrence, especially when the preventative treatment is the appropriate for the stroke subtype. The small size of the different recurrent stroke type is a major limitation in interpreting the results for the other stroke types.

CONCLUSION

The high risk of stroke after an initial stroke is now well understood. However, much remains to be learned about the best way to manage patients with these conditions.

The risk of cumulative stroke recurrence in our area was higher than those observed in most studies, but the risk of mortality was lower.

The risk of death or recurrence after stroke is profoundly influenced by hypertension, smoking and hyperlipidemia and ischemic heart disease.

Because of the fact that the mortality rates and disabilities with recurrent stroke are usually more than initial events, Secondary prevention of stroke must be considered seriously. This study highlights the importance of strict hypertension, ischemic heart disease and hyperlipidemia control and cease of smoking.

RECOMMENDATIONS AND SUGGESTIONS

It is proposed to consider cerebrovascular subtypes (lacunar, aterotrombotic and atherosclerosis) because recurrence and prognosis varies from one to another.

Study in more details in Iranian ethnic and racial groups.

Regarding the site of brain lesion identified by CT or MRI, rare studies compared locations of initial stroke with those of first recurrence. We propose to use imaging utilities after recurrences to see if they are from the same type or the sometimes change in nature.

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