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RISK FACTORS IN INDIVIDUALS WITH A FAMILIAL HISTORY OF ISCHEMIC STROKE

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ABSTRACT

Stroke is one of the most important causes of morbidity and a chief cause of fatality. A positive parental history of stroke, via the heritable factors including hypertension, dyslipidemia and diabetes, can contribute to increased chances of developing stroke. In addition, ethnicity, age, heredity and gender also have been recognized as indicators of stroke-risk. The present study was conducted in a low socioeconomic area of Karachi. It involved 66 adult, first degree relatives of patients who had a stroke and were compared with individuals with no positive family history of stroke. Several non-modifiable, modifiable and potentially modifiable risk factors were taken into account with the help of a structured questionnaire, and biochemical estimations. Result showed that there was a high prevalence of risk factors in the middle and lower socioeconomic groups eventually leading to stroke. As compared with control there was a significant increase in triglyceride levels, and systolic and diastolic blood pressures ($p<0.05$) whereas, a significant decreased blood glutathione concentrations and HDL levels ($p<0.05$) in the test group. In subjects with a familial history of stroke, there are a number of potentially modifiable risk factors, like high triglyceride levels, low HDL, hypertension and smoking associated with an increased incidence of stroke. Conclusively, the protective and precautionary measures in the present study for the persons at high risk for stroke could be implemented and future studies can be carried out to understand whether the management of risk factors can be beneficial to avoid stroke.

KEY WORDS: Familial, heritable, ischemic, stroke, risk factors.

INTRODUCTION

Stroke is an emergent cerebro-vascular incident that can cause permanent brain damage, functional impairments, adult disability and death. According to the National Institute of Neurological Disorders and Stroke, 2009 (Lloyd-Jones *et al*., 2009), it is the second most prevalent cause of death worldwide. Stroke is a sudden disturbance in blood flow to the brain resulting in a rapidly developing loss of brain functions. The blockage or bleeding of vessel is followed by the damage of surrounding areas in a very short time, as a result, those affected areas of the brain become dysfunctional leading to Hemiplegia (inability to move one or more limbs on one side of the body), receptive and expressive aphasia (inability to understand or formulate speech) and homonymous hemianopsias (inability to see one side of the visual field) (Donnan *et al*., 2008). Strokes can be classified as ischemic and hemorrhagic stroke. Ischemic strokes occur due to interruption of the blood supply because of thrombosis or embolism whereas; rupture of and/or aberrant vasculature is the characteristic feature of hemorrhagic strokes. Ischemia accounts for about eighty percent of both the types of stroke. Studies concerning epidemiology of the hazards related to stroke appear to be extremely essential for averting stroke. Several modifiable and non modifiable hazardous factors pertaining to stroke have been indicated (Naz *et al*., 2009). Elevated cholesterol, atrial fibrillation, high blood pressure, diabetes, increased age, earlier stroke or transient ischemic attack (TIA), and smoking are the major ones. Aging increases the risk for stroke by affecting other functions most importantly the cardiovascular system. The probability of developing stroke becomes twice for each consecutive decade past 55 years of age (Brown *et al*., 1996; Wolf *et al*., 1992). Hypertension appeared to be a chief causative agent involved in cerebral infarction as well as intra-cerebral hemorrhage (Fields *et al*., 2004; Wolf *et al*., 1991). Smoking can increase mean blood pressure, rate of heart, cardiac index and thrombus generation in small and narrow arteries. Chronically it also enhances the load of atherosclerosis and can decrease arterial distensibility. All these affects contribute to enhanced stroke risk (Burns *et al*., 2003; Kool *et al*., 1993; Silvestrini *et al*., 1996). Atherogenic risk factors predominantly obesity, dyslipidemia, and hypertension are among the most prevalent risk factors in diabetic patients that predispose them to the risk of developing stroke. Atrial fibrillation is a common finding in aged people and it has been suggested that one fourth of the strokes are due to atrial fibrillation in old aged persons i.e. having equal to or more than 80 years of age (Wolf *et al*., 1991). There is an obvious relationship between dyslipidemia and the risk of ischemic stroke in both men and women. The risk of developing stroke appears to be dependent on the elevated cholesterol and low levels of HDL (Leppälä *et al*., 1999; Lindenstrom *et al*., 1994).

Several studies have shown that ischemic stroke is at least in part, a heritable disease (Flossmann *et al*., 2004; Hassan *et al*., 2000). There are some evidences that increased stroke- risk is associated with both paternal and maternal history of stroke (Kiely *et al*., 1993; Welin *et al*., 1987). This is due to the inheritance of stroke risk factors as well as susceptibility to the effects of such risk factors. Environmental factors and lifestyle also appeared to be important factors in population based studies (Liao *et al*., 1997). Hence it can be hypothesized that the risk of stroke for a person can be influenced by his family history of stroke via genetic or environmental factors or their combined effects. Although several studies have found positive family history of stroke as a risk in the offspring, the available family study data is insufficient and published data is limited and inconsistent (Boysen *et al*., 1988; Carrieri *et al*., 1994; Kiely *et al*., 1993;

Marshall, 1973; Welin *et al*., 1987). The purpose of this study was to test whether a positive family history influences an individuals' chance of having stroke in later years of life by determining the presence of certain risk factors associated with the disease.

Methodology: This prospective observational study was conducted in the Department of Physiology, University of Karachi. Subjects particularly of young age groups were randomly selected from different areas of Karachi. The subjects were explained about the purpose of the study and informed consent was obtained from the research participants. The decided inclusion criteria comprises of the presence of a positive family history of stroke whereas, those already afflicted by the disorder were excluded from the study. Demographically similar community controls were used. A structured questionnaire was prepared in accordance with the objectives of the study. A detailed history regarding modifiable risk factors like smoking, hypertension, diabetes, cardiovascular problems, use of contraceptives in case of female subjects, and use of other medications like aspirin or warfarin were specifically asked. Thorough physical examination included height, weight, waist and hip circumference and blood pressure by sphygmomanometer. BMI and waist to hip ratio were calculated using standard methods given by the World Health Organization 1989 (Shah *et al*., 1989). Total body weights of the individuals were measured after wearing light cloths in kg. Height, in metres, was also measured. BMI was computed by dividing the weight of the subjects in kg to the squared height in meters. The subjects were placed in different categories of BMI in accordance with the Asian cut-offs (Mascie-Taylor and Goto, 2007). Waist to hip ratio was calculated by measuring the waist to hip circumference in inches, using measuring tape to distinguish between central obesity and upper body obesity. Subjects were categorized as hypertensives by using JNC VII Criteria (Chobanian *et al*., 2003). Those with blood pressure > 140/90 were categorized as hypertensive. Blood samples were collected from the subjects and control groups after at least 12 hour fast and plasma was separated using heparin as anticoagulant. Plasma glucose concentration was determined by O-toluidine method (Winckers and Jacobs, 1971).

The subjects were categorized as diabetics if their fasting blood glucose levels were more than 126 mg/dl. Plasma cholesterol and triglyceride levels were measured using enzymatic kit (Clonital Italy). Serum HDL-C level was measured by Dextran Sulphate Mg (II) method, using enzymatic kit (QCA, France). Serum LDL-C concentration was determined with polyvinyl sulfate method using enzymatic kit (QCA, France). Blood GSH level was also measured (Beutler *et al*., 1963). Hyperlipidemia was considered present with elevated total cholesterol and triglyceride levels above or equal to 200mg/dl, whereas HDL levels below 40mg/dl and LDL-cholesterol more than or equal to 150mg/dl. Sample size being computed based on the chosen confidence limits (95% confidence interval).

RESULTS

All experimental groups were matched for age distribution. Mean age was 23.5±1.07 years in control subjects and 33.31±1.84 in the test group. Male to female ratio in the study was found to be 1:6 for the control group and 1:1.44 in the test group. 7.14% individuals in the control group and 59.09% in the test group were married. Both groups belonged to low and middle socioeconomic status and none belonged to upper class. Mean body mass index in the subjects of test group was higher than the control group (Table 1) which was significant ($p>0.05$). As compared with the control group the values of systolic and diastolic blood pressures were significantly high ($p>0.05$) in the test group.

Table 1. Cardiovascular parameters of the study participants.

Variable	Control	Subjects with a positive familial history of stroke
BMI (kg/m2)	20.68 ± 0.64	23.32 ± 1.04*
SBP (mmHg)	110.42 ± 1.82	124.13 ± 5.57*
DBP (mmHg)	74.78 ± 1.81	83.77 ± 3.00*
WHR	0.79 ± 0.02	0.85 ± 0.01

* p-value < 0.05

Data presented as mean ± S.D.

Abbreviations: BMI, Body mass index; SBP, Systolic blood pressure; DBP, diastolic blood pressure; WHR, waist to hip ratio

Discussion

A familial history of stroke serves as a risk factor for ischemic stroke although the exact mechanism is not clear but the presence of certain conditions like diabetes and obesity, environmental and behavioral factors like smoking and hypertension, life styles such as physical inactivity and direct effect of a single gene on the risk of stroke at a young age or the combination of environmental, behavioral and genetic factors in certain families may contribute to the development of ischemic stroke (Hassan *et al.,* 2000). Several modifiable and non modifiable risk factors for stroke are well documented and among them high blood pressure and dyslipidemia are the most frequent risk factors (Khan *et al*., 2009; Khealani *et al*., 2014). Those individuals having familial inheritance of these conditions are at a risk for developing stroke in future. The presence of environmental and life style factors such as higher sodium and higher-fat diet, lower physical activity and lower socio economic status act as contributors in causing stroke together with the

genetic factors (Marshall, 1973). In high income countries the preventive strategies are of better value than that in under developed countries, this has played an important role in the less prevalence of stroke in high-income countries (Khealani *et al*., 2014). Gender, age, race, heredity and ethnicity have been recognized as indicators of risk for stroke. Even though these factors are non-modifiable but their existence helps to figure out those who are at greater risk, facilitating prophylactic treatment for the prevention in high risk group (Boysen *et al*., 1988; Carrieri *et al*., 1994; Herman *et al*., 1983; Kiely *et al*., 1993; Marshall, 1973; Welin *et al*., 1987). In our study we observed the presence of several risk factors in individuals with parental stroke history. Considerable evidences suggest that around sixty to eighty percent of the ischemic strokes are attributed to high blood cholesterol, cigarette smoking, persistent raised blood pressure, diabetes mellitus and carotid stenosis (ischemic stroke with atherosclerosis); valvular heart disease and atrial fibrillation (ischemic stroke of cardiac origin) (Hankey, 2006).

Hypertension is the major causal risk factor for all principal pathological & etiological subtypes of ischemic stroke (Khealani *et al*., 2014). The association between elevated blood pressure and increased occurrence of stroke has been established in some prospective studies (Droste *et al*., 2003; Moulin *et al*., 1997). Significant elevation of the systolic (31.81%) as well as diastolic (22.72%) blood pressure was observed in the study participants (Table 1). It is well recognized that hypertension prevails in families, suggesting a genetic basis. In fact genes have been identified for several syndromic forms of hypertension (Gavras *et al*., 1997; Karet *et al*., 1996). The relationship between family history of stroke and hypertension has been confirmed by various studies and probably the genetic susceptibility to hypertension in an individual to a certain extent may also increase the heritability of ischemic stroke (Casas *et al*., 2004; Flossmann *et al*., 2005; Schulz *et al*., 2004). Ederle and Brown, (2006) found that high blood pressure accounts for about 35-50 percent of stroke risk. Other epidemiological studies suggest that by reducing only 5 to 6 mm Hg of systolic, and 2 to 3 mmHg of diastolic blood pressure can reduce the chance of both ischemic and hemorrhagic stroke to 40 % (Whisnant *et al*., 1996).

Hypertension, along with another important risk factor, diabetes, often co-exists and increases the susceptibility for coronary artery disease. Patients afflicted by diabetes are 2-3 times more prone to develop stroke, and they frequently have hyperlipidemia and hypertension. In the current study, diabetes was present in 22.72% (Fig. 1) which is similar to other studies having range from 20.3% to 41% (Awada *et al*., 1999; Robinson *et al*., 2001). The mechanism of production of stroke due to diabetes may be due to cerebrovascular atherosclerosis, cardiac embolism or rheological abnormalities (Biller *et al*., 1993). It has been demonstrated that elevated blood glucose concentration greatly enhances the strength and degree of subsequent brain damage. High blood pressure and poor glycemic control are associated with higher incidence of cerebral infarction (Kameyamai *et al*., 1994).

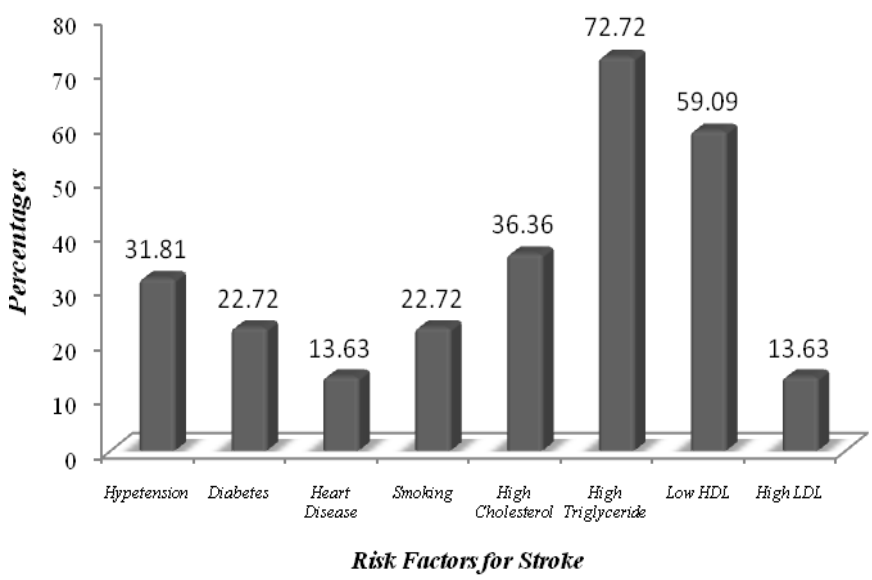

Fig. 1. Prevalence of Potential Risk Factors in the Subjects Having Positive Family History of Stroke.

Hypercholesterolemia has been variably associated with ischemic stroke (Khan *et al*., 2009; Rathore *et al*., 2013). Elevated triglycerides and a decline in the levels of HDL cholesterol, which usually exist together, are essential risk factors for ischemic stroke and among patients with heart disease (Grundy, 1999). Hypercholesterolemia leads to rapid atherosclerosis and risk of cardiac and cerebral ischemia. Use of statins can lower cholesterol and reduce incidence of stroke (Hebert *et al*., 1997). Statins have antiatherogenic effect rather, simply cholesterol lowering effect. They also exert effect on atherosclerotic plaque stability. However, the findings of a recent study done to evaluate the frequency of hypercholesterolemia in stroke patients suggest some contradictory results. Another study suggests a very weak relationship between hypercholesterolemia as a common risk factor and stroke (Saeed *et al*., 2015). Our data shows the high occurrence of hypercholesterolemia (36.36%) in the subjects having positive family history of stroke (Fig. 1).

Table 2. Lipid profile of the study participants.

Parameters	Control	Subjects with a positive familial history of stroke
Total cholesterol (mg/dl)	163.57 ± 5.67	153.62 ± 15.56
Triglyceride (mg/dl)	169.91 ± 5.67	313.04 ± 28.21*
HDL-C (mg/dl)	48.55 ± 3.14	35.30 ± 4.59*
LDL-C (mg/dl)	81.05 ± 4.80	77.03 ± 12.1

* p-value < 0.05
Data presented as mean ± S.D.
Abbreviations: HDL-C, High density lipoprotein; LDL-C, Low density lipoprotein

Table 3. Glucose and glutathione levels of the study participants.

Parameters	Control	Subjects with a positive familial history of stroke
Fasting glucose (mg/dl)	91.09 ± 4.62	92.76 ± 8.66
Glutathione (nmol/gm of Hb)	0.50 ± 0.19	0.26 ± 0.17*

* p-value < 0.05
Data presented as mean ± S.D.

Furthermore, triglyceride was particularly high and HDL was significantly low as compared to controls (Table 2). Life style and dietary habits have the potential of more than having stroke risk. Diets rich in trans fats, saturated fat and cholesterol can elevate the amount of lipids in blood. Diets with excess calories can lead to obesity and accounts as a risk factor for stroke as it affects circulatory system particularly central obesity which weakens the vessels. In our subjects, body weight was higher as compared to the control group but BMI was slightly but not significantly higher than the control group. Evidences from some other studies also suggest that android fatness but not the BMI alone is a key risk factor for the development of stroke (Mascie-Taylor and Goto, 2007). In a meta-analysis, done on obese and overweight stroke patients, to evaluate the influence of BMI on mortality that was stroke-specific, clearly it was concluded that the risk of mortality due to stroke is reduced with an elevated BMI (Bagheri *et al*., 2015). Obesity has an atherogenic effect which is suggestive of the pathophysiologic process attributed to the augmented risk related to cerebro-vascular ailment (Garrow *et al*., 1991).

Following the incident of stroke, the role played in brain damage by oxidative stress is very crucial. Study has shown that immediately after the acute stroke of ischemic etiology, there is a buildup of oxidative stress indicated by sudden low levels of antioxidant enzymes (Afshari *et al*., 2015; Milanlioglu *et al*., 2015). GSH in its reduced form can directly act for the removal of superoxide, nitric oxide, hydroxyl and carbon radicals (Gandhi and Abramov, 2012). In our study blood glutathione concentrations in subjects were low ($p<0.05$) as compared to control groups (Table 3), which suggests a buildup of oxidative stress. It has been suggested that enhanced oxidative stress may be a consequence of cerebral ischemia (Afshari *et al*., 2015; Milanlioglu *et al*., 2015).

Smoking serves to be the most crucial risk factor leading to stroke. Approximately 22.72% of our study participants possessing a positive family history of stroke were smokers as well (Fig. 1). The chance of developing ischemic stroke could be doubled owing to cigarette smoking in a clear dose-effect manner (Shinton and Beevers, 1989). An elevated level of fibrinogen (Dintenfass *et al*., 1975), platelet adhesiveness (Mehta *et al*., 1982), and reduced cerebral blood flow (Rogers *et al*., 1983) probably occurring as a consequence of cigarette smoking, are thought to be the important culprits, elucidating the mechanism by which smoking can increase the chances of developing ischemic stroke. All of these factors contribute to the formation of atheroma attributed to smoking (McGill *et al*., 1979; Whisnant *et al*., 1990). There is some evidence of clustering of risk factors in smokers, for instance a smoker is more likely than a nonsmoker to have hyperlipidemia and hypertension (Luria, 1991).

Several case-series studies have revealed the most common adjustable vascular risk factors for stroke. Among these factors, hypertension was found to be the most important adjustable vascular risk factor. Ischemic heart disease (IHD) was present in 9-46% whereas atrial fibrillation was found in approximately 12% of patients with stroke (Khealani *et al*., 2008). IHD a well-known risk factor for stroke was present in 13.63% of our study subjects (Fig. 1).

Waist-to-hip ratio (WHR), used for the evaluation of abdominal obesity (Lee *et al*., 2015; Oliveira *et al*., 2015), appears to be one of the main hazardous factors for all types of stroke. Moreover, having increased waist-to-hip ratio along with other risk factors including familial history of diabetes, frequent alcohol intake, cardiac problems and psychological stress and/or depression, all contribute to the risk of first stroke (Oliveira *et al*., 2015). Our data showed a slightly elevated waist-to-hip ratio of the stroke patients as compared to the controls (Table 1). Furthermore, WHR is found to be more reliable parameter in predicting sub-clinical atherosclerosis as compared to BMI and waist circumference alone (Lee *et al*., 2015). Genetic predisposition alone or along with exposures pertaining to culture and environment, as well as lifestyle factors including diets rich in fats & sodium, less physically active routine, low socio-economic status and the interplay between factors pertaining to environment and genetics can be attributed to the vulnerability of an individual for the familial spread of stroke (Liao *et al*., 1997).

CONCLUSION

The key findings of the present study, lead us toward the conclusion which suggests that, the individuals who have a positive family history of stroke, either maternal or paternal, may exhibit certain relevant risk factors that may predispose them to develop ischemic stroke in future. Hence, proper awareness should be provided to such individuals in order to make them modify their lifestyle and have a healthier life.

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