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Original Article

Risk factors associated with ischemic stroke: A case-control study

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ABSTRACT

Background & Aim: Stroke is the second common cause of deaths and the third common cause of disability-adjusted life years worldwide in 2010, so knowledge of risk factors within a certain country is an essential step in reducing the stroke rate and resulting disease burden .

Methods & Materials: This was a case–control study to determine and assess risk factors influencing ischemic stroke. In this study, 72 stroke patients hospitalized in Firoozgar Hospital of Tehran city for ischemic stroke from June 2012 to September 2013 were considered as a case group, and 72 individuals were selected as a control group that referred to the same laboratory of the hospital due to the causes other than risk factors for cardiovascular disease. The association between various risk factors such as history of cardiovascular disease, hypertension, diabetes mellitus, migraines, and stroke has been investigated. Multivariate regression analysis was implemented to estimate the odds ratio (OR) of each risk factor for stroke events.

Results: Findings showed that according to multivariate logistic regression, factors such as a history coronary heart disease (OR = 23.33, P = 0.002) and hypertension (OR = 6.9, P = 0.001), low high-density lipoprotein (HDL) (OR = 6.84, P < 0.001), history of coronary heart disease, and cerebrovascular disease in first degree relatives (OR = 4.18, P = 0.007), have been identified as a predictor of ischemic stroke.

Conclusion: Following this hospital-based study of Iranians, we demonstrated that among various risk factors, history of coronary heart disease, hypertension, as well as low HDL, and history of coronary heart disease and cerebrovascular disease in first degree relatives are the strongest independent predictors of stroke.

Introduction

Non-communicable diseases are reaching epidemic proportions worldwide, and affected people in different ages, socioeconomic classes, and nationalities. The diseases have had a major role in mortality and developing the disability worldwide so that are responsible for about 60% of all deaths in the world (1). Cardiovascular diseases, stroke, diabetes mellitus, cancer, and chronic respiratory disease are the major non-communicable diseases. Therefore, the identification and control of risk factors can be prevented about 40-50 percent of premature deaths caused by these diseases (2, 3).

Based on estimating the global burden of disease and studying risk factors (GBD, 2010), stroke is the second common cause of deaths and the third common cause of disability-adjusted life years worldwide in 2010. A systematic review of population-based studies

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from 28 countries on the incidence of stroke showed that over the last four decades, the incidence of stroke is rising in low- and middle-income countries while has declined 42% in high-income countries (4). The annual incidence of stroke was 15 million worldwide that one-third of these patients died, and one-third will be disabled. More than 85% of these deaths occur in low- and middle-income countries (5, 6). More than two-thirds of the global burden of stroke takes place in developing countries, and the mean age of patients is 15 years younger than in developed countries (7, 8). In the Middle East and North Africa, stroke has been increasingly a major health issue and it is estimated to be twice its mortality by 2030 (9, 10).

However, stroke is largely preventable, so knowledge of risk factors within a certain country is an essential step in reducing the stroke rate and resulting disease burden (11, 12).

Various risk factors - including modifiable such as hypertension, diabetes mellitus, smoking, infection, alcohol abuse, lack of exercise, and overweight and non-modifiable, such as age, sex, family history of diseases - play an important role in the incidence of ischemic stroke. Therefore, the main step is a reduction of the incidence and burden of stroke (13).

Individuals' awareness of signs and symptoms of stroke is important because of quick access to emergency medical services. On the other hand, lack of awareness leads to developing a huge obstacle in the rapid treatment of stroke patients and paying the high costs (14).

According to the above, and that changing the lifestyle in Iran (15), for example increasing consumption of unhealthy and fast foods, a sedentary lifestyle, smoking, and drugs, leads to an increased risk of non-communicable diseases like cerebrovascular atherosclerosis, this study aimed to determine risk factors related ischemic stroke.

Methods

This was a case–control study to determine and assess risk factors influencing ischemic stroke. In this study, 72 stroke patients hospitalized in Firoozgar Hospital of Tehran city for ischemic stroke from June 2012 to September 2013 were considered as a case group.

Ischemic stroke diagnosis was made by neurologist and confirmed by brain computerized tomography scan in patients. Inclusion criteria included the incidence of ischemic stroke for the first time, and exclusion criteria were as follows: patients with hemorrhagic stroke (caused by trauma or tumor), patients who died, or not able to respond due to lack of alertness or not having first degree relatives and aware of patient's conditions.

After coordination, and obtaining permission from the Research Council of Tehran University of Medical Sciences and the hospital, first a part of information such as tests and telephone numbers was extracted from medical records, then demographic information and risk factors were collected from patients in all age groups through telephone interviews. In cases in which the patient suffered from aphasia, or was unable to respond for any reason, required information was obtained from first degree relatives and aware of patient's conditions.

In this study, 72 individuals were selected as a control group that referred to the same laboratory of the hospital due to causes other than risk factors for cardiovascular disease. Then, demographic and clinical information obtained from those individuals through the face to face interview.

Data were analyzed using the STATA software package (Stata Corporation, College Station, TX, USA), and descriptive tests and logistic regression. The model building was performed using multivariable fractional polynomial algorithm, and the competing models were compared using Akaike information criteria, and multivariate regression analysis was used.

Results

Demographic and clinical characteristics of the subjects with ischemic stroke and controls are shown in table 1. There was an inverse association between the level of education and ischemic stroke odds ratio (OR) = 0.58 [95% confidence interval (CI): 0.42-0.81; P = 0.001].

Table 1. Demographic and clinical characteristics of the subjects with ischemic stroke and controls*

Characteristics	Case subjects (N = 72)	Controls (N = 72)
Age mean (SD)	58.3 (15.4)	48.1 (14.1)
Sex - Male	36 (50)	44 (61.1)
Marital		
Single	5 (6.9)	8 (11.1)
Married	54 (75)	58 (80.6)
Divorced	3 (4.2)	2 (2.8)
Widowed	10 (13.9)	4 (5.6)
Educational level		
Illiterate	21 (29.2)	4 (5.6)
Under diploma	25 (34.7)	26 (36.1)
Diploma	10 (13.9)	16 (22.2)
University education	16 (22.2)	26 (36.1)
Job		
Employee	7 (9.7)	13 (18.1)
Self-employment	15 (20.8)	11 (15.3)
Student	1 (1.4)	5 (6.9)
Householder	29 (40.3)	31 (43.1)
Retired	20 (27.8)	12 (16.7)
Smoking status		
Never smoking	46 (63.9)	59 (81.9)
Quit smoking	10 (13.9)	3 (4.2)
Current < 20 cigarettes a day	7 (9.7)	7 (9.7)
Current ≥ 20 cigarettes a day	8 (11.1)	3 (4.2)
Obesity (BMI)		
< 30 kg/m^2	44 (61.1)	53 (73.6)
≥ 30 kg/m^2	27 (37.5)	15 (20.8)
History of hypertension**		
Yes	42 (58.3)	8 (11.1)
No	30 (41.7)	64 (88.9)
History of diabetes***		
Yes	20 (27.8)	11 (15.3)
No	52 (72.2)	61 (84.7)
History of migraine		
Yes	5 (6.9)	11 (15.3)
No	67 (93.1)	61 (84.7)
History of cardiovascular disease N (%)****		
Yes	26 (36.1)	2 (2.8)
No	46 (63.9)	70 (97.2)
History of cardiovascular disease or stroke in first degree relatives		
Yes	39 (54.2)	16 (22.2)
No	33 (45.8)	56 (77.8)
Total triglycerides		
< 150	20 (27.8)	30 (41.7)
≥ 150	52 (72.2)	41 (56.9)
HDL cholesterol		
< 50 for female, < 40 for male	49 (68.05)	25 (34.7)
≥ 50 for female, ≥ 40 for male	23 (31.9)	47 (65.3)

*N (%), except where otherwise indicated, **History of hypertension was defined as (1) previously diagnosed by a physician or (2) receiving blood pressure-lowering treatment or self-reported history of hypertension, ***History of diabetes mellitus was defined as (1) previously diagnosed by a physician (prescribed treatment) or (2) on oral hypoglycemic agents or insulin, ****History of cardiovascular disease was defined as previously diagnosed by a physician (prescribed treatment), previous myocardial infarction, rheumatic valvular heart disease, and prosthetic heart valve were based on medical history or self-reported history of cardiovascular disease. HDL: High density lipoprotein, BMI: Body mass index, SD: Standard deviation

People who have quit smoking than the group that did not use it had 4.27 times greater risk of ischemic stroke OR = 4.27 (95% CI: 1.1-16.43; P = 0.030) (Table 2). The OR between obesity (1: ≥ 30, 0: < 30) and stroke was 2.16 (95% CI: 1.02-4.57; P = 0.040).

Table 2. Risk factors associated with ischemic stroke: Result

Risk factors	OR (95% CI)	P-value
Age	1.04 (1.02-1.07)	> 0.001
Gender	1.5 (0.81-3.04)	0.180
Education	0.6 (0.42-0.81)	0.001
Cigarette[*]		
2	4.2 (1.11-16.43)	0.034
3	1.2 (0.42-3.91)	0.660
4	3.4 (0.85-13.61)	0.080
BMI[**]	2.1 (1.02-4.57)	0.040
History of hypertension[***]	11.2 (4.68-26.77)	< 0.001
History of diabetes[$]	2.1 (0.93-4.85)	0.070
History of migraine	0.41 (0.13-1.25)	0.120
History of cardiovascular disease[&]	19.7 (4.47-87.38)	< 0.001
History of cardiovascular disease or stroke in first degree relatives	4.13 (2.006-8.52)	< 0.001
HDL cholesterol[@]	4.005 (2.002-8.01)	< 0.001
Total triglycerides[#]	1.9 (0.94-3.82)	0.070

[*]Cigarette: 1 (never smoking = baseline), 2 (quit smoking), 3 (Currently, fewer than 20 cigarettes a day), 4 (Now more than 20 cigarettes a day), [**]BMI: < 30 and ≥ 30, [***]History of hypertension was defined as (1) previously diagnosed by a physician or (2) receiving blood pressure-lowering treatment or self-reported history of hypertension, [$]History of diabetes mellitus was defined as (1) previously diagnosed by a physician (prescribed treatment) or (2) on oral hypoglycemic agents or insulin, [&]History of cardiovascular disease was defined as previously diagnosed by a physician (prescribed treatment), previous myocardial infarction, rheumatic valvular heart disease, and prosthetic heart valve were based on medical history or self-reported history of cardiovascular disease, [@]HDL cholesterol: High-density lipoprotein. HDL-C < 40 mg/dl in men or < 50 mg/dl in women as low, [#]Total TG: TG ≥ 150 mg/dl high, OR: Odds ratio, CI: Confidence interval, TG: Triglycerides

Migraine history and history of diabetes were not associated with ischemic stroke. Strong risk factors for stroke were history of coronary heart disease and hypertension [OR = 19.7 (95% CI: 4.47-87.38, P < 0.001) and OR = 11.2 (95% CI: 4.68-26.77, P < 0.001), respectively]. There was a positive association between a history of coronary heart disease or cerebrovascular disease in the first degree relatives and stroke, OR = 4.13 (95% CI=2.006-8.52, P < 0.001) the association between hypertriglyceridemia (1: ≥ 150, 0: < 150) and stroke tended to be significant, OR = 1.9 (95% CI: 0.94-3.82, P = 0.070) (Table 2). The OR between low high-density lipoprotein (HDL) [(1: < 50 for female, < 40 for male), 0: otherwise] was 4.005 (95% CI: 2.002-8.01; P ≤ 0.001). Figure 1 shows the OR for stroke between different levels of HDL compared to the baseline value of 68 (mg/dl).

The final multivariable logistic regression model is shown in table 3.

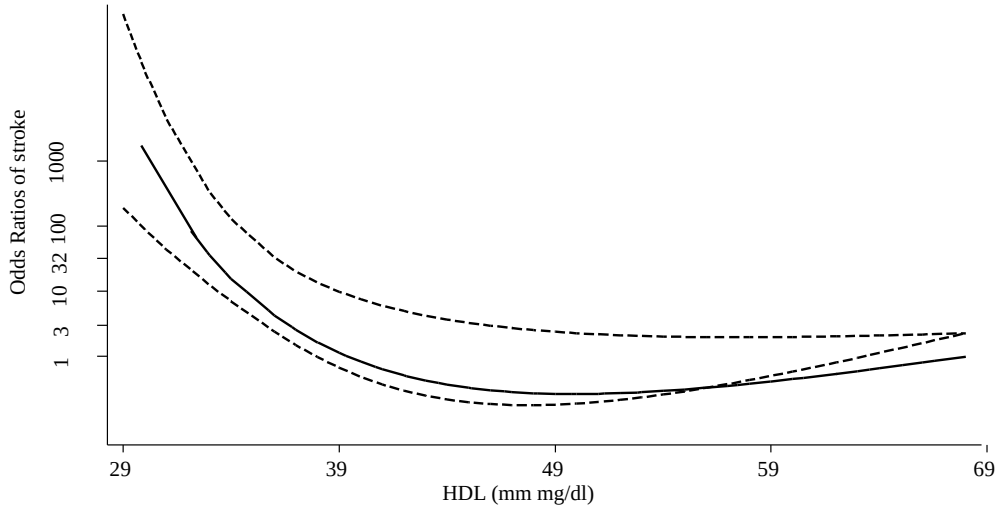

Figure 1. Relation between high-density lipoprotein and ischemic stroke in both sexes

Table 3. Risk factors associated with ischemic stroke: Result of multivariable logistic regression

Risk factors	OR (95% CI)	P-value
History of cardiovascular disease (CHD)	23.3 (3.06-177.48)	0.002
History of hypertension*	6.9 (2.12-22.50)	0.001
Low HDL**	6.8 (2.31-20.19)	< 0.001
History of cardiovascular disease or stroke in first degree relatives	4.1 (1.47-11.88)	0.007
Hypertriglyceridemia***	1.8 (0.6-5.78)	0.200

*History of hypertension was defined as (1) previously diagnosed by a physician or (2) receiving blood pressure-lowering treatment, **HDL cholesterol: High-density lipoprotein. HDL-C < 40 mg/dl in men or < 50 mg/dl in women: Low, ***TG ≥ 150 mg/dl: High. This model adjusted for age, sex, education, and cigarette. TG: Triglycerides, CHD: Coronary heart disease, OR: Odds ratio, CI: Confidence interval

Discussion

This study was conducted to determine the risk factors for ischemic stroke; our findings indicated that a history of coronary artery disease is known as the strongest risk factor. Bando et al. (16) also showed that persistent atrial fibrillation after mechanical mitral valve replacement is the most important risk factor for stroke. A case–control study done by O'Donnell et al. (17) reported heart problems associated with increased risk of stroke. Another study also showed similar results (18).

Unlike this study, in a population-based cohort study, by Fahimfar et al. (10), males are known as risk factors. Phillips et al. (19) stated that in South Australia there was not a significant difference between men and women in the younger group, but in the older group, 61% were men.

In a hospital case–control study, Chang et al. (20) determined that 20-40% of stroke is related to women 20-44 years with migraine. Oral contraceptive pills, high blood pressure, and smoking were increased factors of stroke in these female. However, in our study, such a relation was not observed; migraine prevalence is higher in younger age, while most strokes occur in older (21), so our small sample size, especially under the age of 49 years may be considered as proof of the inability of the study to show this relationship. There are studies which introduced diabetes as a risk factor for ischemic stroke (10, 22), but in this study, such an association was not seen due to a small sample size

Both univariate and multivariate logistic regression models showed that similar to other studies (8, 10, 19), a history of hypertension has significantly stronger association with stroke. Since blood pressure can be controlled using simple screening programs and non-drug approaches such as reducing salt intake without the need to complicated equipment specialized tools, control of the risk factor is the most important activity.

We found the inverse relation between education and ischemic stroke in univariate analysis that few studies have investigated the relationship.

Various studies, like our study, determined that overweight and obesity, especially abdominal obesity, have an additive effect on ischemic stroke (19, 23, 24), while a review study reported conflicting results (25). Furthermore, another study declared that there was not an association between body mass index and ischemic stroke while a direct relation was observed between waist-to-hip ratio and stroke (17).

Different studies have emphasized on the effective role of a history of coronary heart disease and cerebrovascular disease in first degree relatives on stroke, in particular in persons < 70 years. This is consistent with our study (26, 27).

Researchers showed that current smoking than no smoking use and quitting smoking have more chance to the incidence of stroke (17), while our findings also indicated that people who have quit smoking than the group that did not use it had 4.27 times greater risk of ischemic stroke. It is necessary to assess and evaluate the impact of number of cigarette and duration of quitting smoking on stroke.

Many studies like our study showed that the low level of HDL increases significantly the chance of stroke (8, 17, 28).

Findings of epidemiological studies have been inconsistent, with most studies failing to

identify an association between cholesterol and ischemic stroke. Some studies indicated no relation between triglyceride levels and stroke (10) while in some studies, hyper-triglyceridemia is known as a risk factor of ischemic stroke (28, 29), our study also showed that hyper-triglyceridemia, and stroke tended to be significant. The association between that our study has several potential limitations, including those inherent to a case–control design (e.g., selection bias and recall bias). In cases in which the patient suffered from aphasia, or was unable to respond for any reason, information was obtained from first degree relatives and aware of patient's conditions, reporting bias should be considered, but we made a concerted effort to overcome such anticipated biases by obtaining information in a standardized manner, In addition, review the medical records of patients through telephone interviews with the patient or first-degree relatives also have been trying to reduce reporting bias, especially.

We used controls from hospital-based sources. Ideally, controls would be drawn from the general population without the disease and come from community sources in the same catchment areas. Although our overall findings are consistent, hospital-based controls could underestimate the true association for some risk factors.

Conclusion

Following this hospital-based study of Iranians, we demonstrated that among various risk factors, history of coronary heart disease, hypertension, as well as low HDL, and history of coronary heart disease and cerebrovascular disease in the first degree relatives are the strongest independent predictors of stroke. Finally, we expect that this study can help to clarify the risk factors for ischemic stroke and can be used as a reference for future studies.

Conflict of Interests

Authors have no conflict of interests.

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