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Original Article

Insulin resistance and elevated C-reactive protein among first-degree relatives of ischemic stroke patients

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ABSTRACT

Background: Family history is one of the non-modifiable risk factors for ischemic stroke. Atherosclerosis and thrombosis are the two major mechanisms for cardiovascular disease and stroke. Screening of family members is an important method to identify individuals at risk. Therefore, this study was planned to assess the atherosclerotic risk factors in first-degree relatives of patients with ischemic stroke.
Methodology: Case group included 40 first-degree relatives of ischemic stroke patients between 30 and 50 years of age. Forty age and gender matched apparently healthy subjects without major risk factors were recruited as controls. Their blood samples were analysed for routine biochemical parameters, Fasting Insulin, high sensitivity C-reactive protein and Homocysteine.
Results: First-degree relatives showed dyslipidemia (High total cholesterol, elevated Low Density Lipoprotein and elevated Non-High Density Lipoprotein), hyperinsulinemia and insulin resistance compared to controls. They had high levels of high sensitivity C-reactive protein ($p = 0.045$). There was positive correlation between fasting insulin and Homeostasis Model Assessment of Insulin Resistance with high sensitivity C-reactive protein among first-degree relatives.
Conclusion: First-degree relatives of ischemic stroke patients exhibited hyperinsulinemia, Insulin resistance and dyslipidemia. Insulin resistance, a low grade inflammatory state that leads to increased C-reactive protein which triggers the development of atherosclerosis. So screening for insulin resistance and dyslipidemia in first-degree relatives of ischemic stroke patients may help in preventing adverse vascular events.

1. Introduction

Cerebrovascular accident is the most common cause of death next to Myocardial infarction and cancer. Stroke accounts for 41% of deaths as per ICMR report. According to WHO Step wise approach to stroke surveillance protocol, the incidence of stroke was 148 per 1,00,000 populations in India [1]. The prevalence of stroke in India was 203/100,000 populations. The incidence of stroke was 1.7 times higher in males than females [2].

Indians suffer due to stroke in a relatively younger age (≥60 years) compared to western population (≥65 years) [3]. This is due to the development of metabolic risk factors at young age. Insulin resistance (IR) along with other metabolic risk factors led to cardiovascular diseases and stroke. Hence, it is very important to identify the population who are at high risk for the development of adverse vascular events to control the metabolic risk factors in them.

Ischemic stroke tends to aggregate in families, with a positive family history adding a relative risk of stroke 1.3–1.8 times [4]. Familial risk assessment is an important method for identifying individuals at risk and can influence appropriate screening and prevention strategies. A study by Choi et al. showed that history of stroke in sibling was strongly associated with a risk of developing stroke in future than positive parental history. They mentioned that family history of ischemic stroke was an absolute risk factor for the development of cerebrovascular diseases [5]. Thus, it can be assumed that family history of stroke will increase the chance for the development of atherothrombotic disease. However, there is no complete information regarding these risk factors in first-

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degree relatives of ischemic stroke patients in India. Therefore a prospective study was carried out to analyse the risk factors in first-degree relatives of patients with ischemic stroke.

2. Materials and methods

This case-control study was conducted in the Department of Biochemistry along with Department of Medicine, Jawaharlal Institute of Post graduate Medical Education and Research (JIPMER), Puducherry, India. The study was approved by JIPMER research committee and Institute Ethics sub-Committee.

2.1. Patients and control subjects

Forty first-degree relatives of ischemic stroke patients (11 siblings and 29 off-springs) between the age group 30 and 50 years were recruited in the study during 2011–2012. The diagnosis of stroke in the patients was confirmed from the clinical records and non-contrast cranial Computed Tomography scan. Forty age and gender matched apparently healthy subjects without family history of ischemic stroke, diabetes, hypertension and coronary artery diseases were recruited as controls. Smokers, alcoholics and pregnant women were excluded from the study groups. A written informed consent was obtained from all study subjects.

2.2. Assessment of risk factors

Body mass index (BMI) was calculated using the formula, weight in kilograms divided by height squared in meters. The blood samples were collected from the first-degree relatives between 3rd and 6th day of hospitalisation of stroke patients. Six millilitres of blood was collected from the study subjects after overnight fasting and the samples were analyzed for glucose, lipid profile, urea, creatinine, uric acid, homocysteine, high sensitivity C-Reactive Protein (hs-CRP), and fasting insulin.

2.3. Estimation of biochemical parameters

Concentration of serum glucose, urea, creatinine, uric acid, total cholesterol (TC), triglycerides (TGL), High density lipoprotein (HDL) were estimated by auto analyzer (Olympus AU 400, Germany) using commercially available reagent kits (Agappe diagnostics, Kerala, India). Very Low Density Lipoprotein (VLDL) levels were calculated by dividing the triglyceride concentration by 5. Low Density Lipoprotein levels were derived by Friedwald's formula, LDL-c = Total cholesterol − {HDL-C + VLDL-C} [6].

The level of homocysteine and fasting insulin was measured by ADVIA CENTAUR (Siemens, USA) using chemiluminescence technology [7]. Insulin resistance was assessed by Homeostasis Model Assessment of Insulin resistance (HOMA − IR). It was expressed as a product of insulin (mU/L) and glucose (mmol/L) levels divided by 22.5. The level of high sensitivity C- reactive protein (hs-CRP) was estimated using Enzyme Linked Immuno Sorbent Assay (ELISA) kit (APC Diagnostics Biochem, Canada Inc) [8].

3. Statistical analyses

The normality of the data was checked by Kolmogorov Smirnov test. Values of height, weight, fasting glucose, uric acid, total cholesterol, triglycerides, HDL, VLDL, Non HDL cholesterol, and Atherogenic index had normal distribution and expressed as mean ± standard deviation. Non Gaussian data like BMI, urea, creatinine, LDL −c, LDL/HDL ratio, TC/HDL ratio, TGL/HDL ratio, Non HDL/HDL ratio, fasting insulin, HOMA-IR, homocysteine and hs-CRP were expressed as median with range. Independent student's *t*-test and Mann Whitney *U* test were used to compare variables between first-degree relatives and healthy subjects accordingly. Correlation analysis of normally distributed data was done using Pearson's correlation and Spearman's correlation analysis was done for non-normal data. A p value of <0.05 was considered as statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 20.

4. Results

4.1. Demographic and routine biochemical parameters

The demographic and clinical characteristics of two groups are showed in Table 1. This study included 40 first-degree relatives and 40 age and gender matched apparently healthy subjects among which 25 males and 15 females in each group. It shows that all the anthropometric parameters between the study groups were comparable ($p > 0.05$). There was no significant difference in age, gender and BMI between two groups.

As shown in Table 1, the mean value of fasting glucose among first-degree relatives was 4.2 ± 0.63 mmol/L and among the healthy controls it was 3.9 ± 0.43 mmol/L. This difference was statistically significant ($p < 0.043$). There were no significant difference ($p > 0.05$) in the concentrations of urea, creatinine and uric acid between two groups.

4.2. Total lipid profile and lipid ratios

Lipid profile data of study subjects were shown in Table 2. Total cholesterol, LDL cholesterol and Non HDL cholesterol levels were significantly higher in first-degree relatives of ischemic stroke patients than controls. This difference was statistically significant ($p < 0.05$). Atherogenic index of plasma (AIP) was calculated as log (TG/HDL) [9]. The levels of LDL/HDL ratio and TC/HDL ratio were

Table 1
Comparison of demographic, clinical characteristics and routine biochemical parameters between first-degree relatives and healthy controls.

Variables	Controls (n = 40)	First-degree Relatives (n = 40)	p value
Age(years)	40 ± 3	41 ± 4	0.32
M/F	25/15	25/15	matched
Height(cm)	165.4 ± 6.19	164.3 ± 7.81	0.49
Weight(kg)	65.90 ± 5.04	66.33 ± 8.78	0.79
BMI (kg/m^2)[a]	25.36 (20.98–30.67)	26.2 (18.2–35.5)	0.18
Fasting Glucose (mmol/L)	3.9 ± 0.43	4.2 ± 0.63	0.043*
Urea Nitrogen (mmol/L)[a]	0.22 (0.1–0.7)	0.26 (0.1–0.9)	0.13
Creatinine (μmol/L)[a]	53.04 (44.2–88.4)	61.9 (35.4–265.2)	0.24
Uric acid (μmol/L)	256.1 ± 77.9	263.8 ± 76.3	0.66

Values are expressed as mean ± SD.
* Statistically significant.
[a] Data was analysed by Mann Whitney *U* test and expressed as median (range).

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