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Original Article

Hypertension, diabetes, metabolic syndrome, inflammation and the risk of stroke

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ABSTRACT

After coronary heart disease (CHD) and cancer of all types, stroke is the third commonest cause of death worldwide. Prospective, population-based, observational studies show a continuous, positive relationship between hypertension and risk for stroke. Diabetes and metabolic syndrome were more frequent among the patients with stroke. Inflammation with presence of serum markers such as high-sensitivity C-reactive protein (hsCRP) is an important predictor of atherosclerotic disease, coronary risk and stroke, particularly in patients with hypertension and diabetes. The role of inflammation (as reflected by hsCRP) and the combined effect of hypertension, diabetes and metabolic syndrome in the prediction of risk of stroke are less defined. The present study was therefore designed to evaluate the association of hypertension, diabetes, metabolic syndrome and inflammation, in the prediction of risk of stroke. Hundred patients were recruited for the study, of which, fifty belongs to control and fifty were test group. For the entire study population hsCRP, sugar level, hypertension and lipid profiles were measured. Considerable variability was found between control and test group. Consequently, detection of inflammation is very important in stroke patients with hypertension and diabetes, in order to determine the possible risk factors and stratify post stroke patients into risk groups.

1. Introduction

Stroke is a non–communicable disease of increasing socioeconomic importance in ageing populations. Although internationally stroke has shown a tendency to decrease [1], it is still the third leading cause of death and an important cause of hospital admission and long-term disability in most industrialized countries [2]. Thus, early identification of those at increased risk of stroke should represent a significant contribution to health Improvement so that interventions can be targeted to those most likely to benefit. Numerous observational studies have demonstrated unequivocally a powerful association of hypertension, diabetes and metabolic syndrome with risk for stroke. Recent data have shown that high-sensitivity CRP (hsCRP) may be a stronger predictor of myocardial infarction (MI) and ischemic stroke than low-density lipoprotein (LDL) cholesterol [3]. At the same time, recent guidelines have emphasized that the highest risk of an incident stroke event was found among subjects who had both hypertension and diabetes. The present study was therefore designed to evaluate the association of inflammation, hypertension, diabetes and metabolic syndrome in the prediction of risk of stroke.

2. Materials and Methods

2.1. Patients

The total number of patients included in this study was 100. At the time of admission or entrance all patients responded to a standardized questionnaire covering many personal details (such

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as smoking habit, alcohol intake, physical activity, food habit, family history, and medical information) organised by trained interviewers. The study population consisted of 50 patients (test group) with a mean age of 59.26±9.7 years; the control group included 50 patients with mean age of 55.1±6.4 years.

2.2. Biochemical parameters and Assay

Samples for the analysis of lipid profile were obtained in the fasting state. The venous blood samples were drawn into pyrogen-free blood collection tubes without additive. The serum was collected after centrifugation at 3500 rpm for 3 minutes and then stored at in a refrigerator until analyzed. Samples were collected from the lab for further analysis. Total cholesterol (TC) and triglycerides (TG) were assayed by routine enzymatic methods using an auto analyser. High-density lipoprotein (HDL) cholesterol was measured using the same enzymatic method after precipitation of the plasma with phosphotungstic acid in the presence of magnesium ions. For cost reasons, LDL cholesterol values have long been estimated using the Friedewald formula: [TC] - [total HDL cholesterol] - 20% of the TG value = estimated LDL cholesterol. The VLDL cholesterol is estimated as one-fifth of the TG. The concentration of hsCRP was measured in serum by the latex-enhanced immunoturbidimetric method.

2.3. Statistical Analysis

Statistical analysis was performed with SPSS 12 statistical software package. Data were recorded on a pre-designed proforma and managed on spreadsheet. All the entries were checked for any error. Descriptive statistics for quantitative variables were computed by mean and standard deviation. Means in the two groups were compared by Student's t-test. In this study, $p<0.05$ has been considered as statistically significant.

3. Results

Clinical characteristics of study patients are given in Table 1. Stroke risk factors including smoking, obesity, hypertension and diabetes had a higher prevalence in the test group than in control. The percentage of the study population over 65 years were 6% and 32%in control and test group respectively. Smoking was significantly higher in test group (18%) than control (8%). Obesity (body mass index (BMI) 30 kg/m) was s significantly higher in test group (6%) than control (2%). Physical inactivity was slightly higher in test group than in control (90% and 88% respectively. 8% in control and 30% in test group were affected by metabolic syndrome. Of the people examined 32% in control and 56% in test group had blood pressure (BP) levels of 140 or 90 or higher. The prevalence of hypertension was higher in test group than control. The mean BP was significantly higher in test group ($p< 0.001$) than control. The occurrence of hypertension was significantly higher in people aged 50 years and over in control (28%) and test group (52%). In control 10 males and 6 females and in test group 19 males and 9 females were suffered from hypertension.

Table 1. Clinical characteristics of the study subjects (Non-modifiable and modifiable risk factors)

	Control (n=50	Test group (n=50)
Non-modifiable risk factors		
Age	55.0±86.4	59.2±69.7
Age >65	3(6%)	16(32%)
Sex M/F	29/21	31/19
Cigarette smoking	4(8%)	9(18%)
Obesity	1(2%)	3(6%)
Physical inactivity	44(88%)	45(90%)
Modifiable risk factors		
Hypertension	16(32%)	28(56%)
Hypertension (M/F)	10/6	19/9
Hypertension age >50	14(28%)	26(52%)
Hypertension + High hsCRP	8(16%)	25(50%)
Diabetes	11(22%)	20(40%)
Diabetes (M/F)	7/4	14/6
Diabetes age >50	18(36%)	16(32%)
Diabetes + High hsCRP	6(12%)	17(34%)
Hypertension + Diabetes /Age >50	3(6%)	12(24%)
Hypertension + Diabetes	4(8%)	16(32%)
Atherogenic dyslipidemia	1(2%)	1(2%)
Metabolic syndrome	4(8%)	15(30%)
Hypercholesterolemia	10(20%)	13(26%)
Hypertriglyceridemia	16(32%)	25(50%)
Low-HDL cholesterolemia	20(40%)	22(44%)
High-LDL cholesterolemia	6(12%)	10(20%)

History of diabetes was significantly higher for test group (40%) ($p< 0.02$) than for control (22%). The occurrence of diabetes was significantly higher in people aged 50 years and over in control (36%) and test (32%). In control 7 males and 4 females and in test group 14 males and 6 females were suffered from diabetes. The occurrence of diabetes and hypertension were significantly higher in people aged 50 year and over in control (6%) and in test group (24%).

Table 2 summarizes the biochemical parameters examined in serum samples of all patients divided according to the groups. All biochemical parameters are expressed in mean and standard deviation. Patients generally had moderate to high elevated levels of

lipid risk factors or markers such as, TC, TG, LDL cholesterol, low levels of HDL cholesterol in the test groups than the control. The patients had significant higher concentration of mean hsCRP levels in test group ($p< 0.001$) when compare with the healthy control group. The mean value of control group is found to be 0.9±0.4 and in test group 2.2±1.4. The prevalence of hsCRP in patients suffered from diabetes found to be in control (12%) and in test group (34%). The occurrence of hsCRP in hypertension found to be in control (16%) and in test group (50%).

Table 2. Baseline mean level of the biochemical parameters examined in serum samples of all the patients

	Control (n=50	Test group (n=50)
Systolic BP	123.8 11.6	133.6 16.6
Diastolic BP	81.2 7.7	85.4 9.1
High-sensitivity C-reactive protein	0.9 0.4	2.2 1.4
Glucose	114 20.9	128 36.7
Total cholesterol	166.0 30.8	181.6 27.9
Triglycerides	137.7 71.3	151.8 51.1
High-density lipoprotein cholesterol	40.1 6.8	41.1 7.7
Low-density lipoprotein cholesterol	98.9 26.9	110.5 28.7
Very low-density lipoprotein cholesterol	27.8 14.8	30.2 10.2

4. Discussion

Most epidemiological studies have confirmed that BP is among most important single risk factors of stroke in all ethnic groups [4, 5]. There is good evidence that BP contributes to the development of atherosclerosis and ischemic brain infarction. In general, 35-75 per cent of the stroke patients, depending on study material and methods, have been found to have elevated BP. The variation can mostly be explained by the different definitions of elevated BP. Hypertension has also been noted to be an important risk factor for recurrent stroke. The association between BP and stroke mortality is strong and direct, and the absolute risk of stroke mortality associated with high BP increases with age [6].

In the Multiple Risk Factor Intervention Trial (MRFIT) in 1973-75, 12-year mortality was determined for 5,163 men age 35-57 years who reported taking medication for diabetes and 3,24,815 men without a history of diabetes [7]. The risk of mortality from stroke was increased 2.8-fold among those with diabetes, even after adjusting for age, race, income, and cardiovascular risk factors. The risk of stroke mortality was greatest for nonhemorrhagic stroke (RR 3.8) than for subarachnoid (1.1) or intracranial hemorrhage (1.5) [8]. In the Nurses Health Study (NHS), the risk of stroke and cardiovascular disease (CVD) was determined in 1,16,177 female registered nurses who were free of CHD, stroke, and cancer at baseline [9]. There was an 8-year follow up during 1976-84. Sixteen nonfatal and eight fatal stroke cases were reported in the 1,483 women with diabetes, and 167 and 68 cases, respectively, among the nondiabetic women. The age-adjusted risk of stroke for diabetic versus nondiabetic women was 4.1. The risk was similar for fatal (5.0) and nonfatal (3.8) strokes. The Copenhagen City Heart Study (CCHS) evaluated 3,015 men and 3,501 women age 55-84 years [10].

This study indicated that both hypertension and diabetes were independently associated with an increased risk of the incidence of stroke. The analyses from another Finnish study [11] and the UK Prospective Diabetes Study (UKPDS) [12] have demonstrated that hypertension or an increase in systolic BP (SBP) were independently associated with an increased risk of stroke in the diabetic patients. Therefore, it may possible that the increased risk of stroke usually seen in hypertensive subjects may sometimes be related not only to the hypertension itself but also to diabetes.

Although subjects with hypertension are more likely to develop type 2 diabetes [13], and hypertension is very common in patients with type 2 diabetes [14], two studies [15, 16] assessed the joint effect of hypertension and type 2 diabetes on the stroke risk in the general population. A Japanese study analyzed the relation between diabetes and the risk of ischemic stroke stratifying for the hypertension status and BMI [15] and found that the excess risk of ischemic stroke associated with diabetes was primarily observed in nonhypertensive subjects or those with high BMI but not in hypertensive subjects or subjects with low BMI. The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) determined the RR of ischemic stroke attributable to diabetes, hypertension, or both [16]. It indicated that the risk of stroke attributable to a history of both diabetes and hypertension was substantially greater than for either condition alone, in keeping with the present study results.

The presence of metabolic syndrome has been associated with an increased risk of prevalent stroke in the existing literature. In the National Health and Nutrition Examination Survey among 10,357 subjects [17], the prevalence of metabolic syndrome was significantly higher in persons with a self-reported history of stroke (43.5%) than in subjects with no history of vascular disease (22.8%). Metabolic syndrome was independently associated with stroke history in all ethnic groups and in both sexes. The association between metabolic syndrome and stroke has been confirmed in other populations integrated by elderly subjects, and the frequency of metabolic syndrome has been reported to be significantly higher in patients with a history of atherothrombotic or nonembolic ischemic stroke [18, 19]. This association supports the clinical use of the metabolic syndrome in the identification of subjects who are at an increased risk of experiencing a stroke. Long-term follow-up population-based studies have demonstrated that healthy individuals with the metabolic syndrome are at a markedly increased risk for major cardiovascular events, including stroke, and cardiovascular mortality [20, 21].

High concentrations of hsCRP have been shown to be associated with increased risk of developing cerebrovascular disease. However, ischaemic brain injury is characterised by acute local inflammation and raised CRP concentration [22], as well as increases in other inflammatory cytokines [23]. Moreover, raised concentrations of CRP have crucial prognostic implications in patients with acute ischaemic stroke [24, 25]. The major risk factors for stroke and CVD, such as smoking, diabetes, and hypertension, are associated with higher hsCRP levels [26, 27]. These relationships could potentially explain the associations that have been found between hsCRP level and stroke or mortality. In a recent prospective cohort study found that baseline serum hsCRP level was an independent predictor for future ischemic stroke and all-cause mortality in an apparently healthy population. It is interesting that these results were obtained in the Japanese population, which has a lower median hsCRP level than Western populations [28, 29].

5. Conclusion

This study point out that hypertension, diabetes, metabolic syndrome and inflammation were proven as independently associated with an increased risk of the incidence of stroke. The highest risk of an occurrence of stroke event was found among subjects who had both hypertension and diabetes with elevated levels of hsCRP.

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