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Full Length Research Paper

Glutathione S- transferase M1 and T1 gene polymorphisms in South Indian stroke patients

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Stroke is a multifactorial disease caused by the interaction of several genetic and environmental factors and a variety of risk factors such as blood pressure, diabetes, advanced age and smoking. Active cigarette smoking has been established as a major risk factor for coronary heart disease and for both ischemic and hemorrhagic stroke and the risk is particularly elevated in younger people. Glutathione S-transferases (GSTs) are the phase II enzymes that catalyze the conjugation of glutathione to a wide range of electrophiles and represent a protective mechanism against oxidative stress. So far no information has been provided regarding the role of GSTM1 and GSTT1 gene polymorphisms and ischemic stroke in Indian populations. So the present study is carried out to investigate the association between the GST M1 and T1 gene polymorphisms and the risk of stroke in a South Indian population. We genotyped 198 ischemic stroke patients and 162 age matched controls using multiplex polymerase chain reaction. Statistical analysis showed that the frequency of both wild and null genotypes of GSTM1 (OR = 0.91, p = 0.68) and GSTT1 (OR = 0.60, P = 0.077) did not differ significantly between control and stroke patients. Further analysis of GSTM1 and GSTT1 genotypes among male smokers and non smokers category of stroke patients and control subjects showed a protective role of GSTM1 wild type (OR = 0.44, p = 0.007) and GSTT1 wild type (OR = 0.36, p = 0.01) in smokers.

Key words: Glutathione S- transferase, ischemic stroke, gene polymorphism, South Indian population.

INTRODUCTION

Stroke is the rapidly developing loss of brain functions due to disturbance in the blood supply to the brain. This can be due to ischemia (lack of blood flow) caused by blockage (thrombosis, arterial embolism), or a hemorrhage (leakage of blood) (Sims and Muyderman 2009). More than two-thirds of the global burden of stroke is borne by developing countries, where the average age of patients with stroke is 15 years younger that in developed countries (Truelsen et al., 2001). Stroke is a multifactorial disease caused by the interaction of several genetic and environmental factors and a variety of risk factors such as blood pressure, diabetes, advanced age and smoking.

Oxidative stress is considered as one of the important mechanisms involved in neuronal damage due to ischemia in stroke patients (Leinonen et al., 2000). Glutathione-S transferases (GST) are phase II detoxification enzymes responsible for the metabolism of numerous xenobiotics and play a major cellular antioxidant role (Hayes and Strange, 2000). Men are 25% more likely to suffer stroke than women (National

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Institute of Neurological Disorders and Stroke, 1999). Active cigarette smoking has been established as a major risk factor for coronary heart disease and also for both ischemic and hemorrhagic stroke (Bolego et al., 2002; Aldoori and Rahman, 1998; Humphries and Morgan, 2002) and the risk is particularly elevated in younger people (Aldoori and Rahman, 1998; www.cdc.gov/ tobacco/ data_statistics/ sgr/ 2004/ index.html; Bonita et al., 2004). Several animal model and humans studies have showed a role of DNA damage in vascular diseases (Bridges et al., 1990; De Flora et al., 1997). According to a hypothesis, tobacco smoke induced DNA damage causes cell proliferation in the intima of arteries, and contributes to atherosclerotic plaque formation (Bridges et al., 1990). Cigarette smoke contains numerous carcinogens and has been shown to generate reactive oxygen species which induce oxidative damage in isolated DNAs (Leanderson and Tagesson, 1992). Studies indicate that smoking cessation may reduce oxidative DNA damage and also increase some DNA repairing mechanisms (Inoue et al., 2003).

GSTT1 and GSTM1 are the most extensively studied genes in the GST gene super family. Numerous genetic polymorphisms have been reported for GST genes. The genetic mutations in these genes may cause lack of functional enzyme (Dufour et al., 2005) or lead to either increased or reduced metabolic activity (Hung et al., 2003). In particular, two of the GST encoding genes, identified as GSTM1 and GSTT, have a null genotype in humans due to the deletions of both paternal and maternal alleles, resulting in lack of active proteins (Seidegard et al., 1998). According to their primary structure GST enzymes are divided into six classes such as alpha, mu, pi, sigma, theta, and zeta which encompass several genes and isoenzymes in humans (Board et al., 1997). The GSTM1 gene located on chromosome 1p13.3 (Pearson et al., 1993), codes for cytosolic GST μ class enzyme, and has a deletion polymorphism that results in the complete absence of functional gene product. The prevalence of the GSTT1 null genotype has been shown to vary between different ethnic groups. Both the GSTM1 and the GSTT1 null variants result in the lack of enzyme production.

GST polymorphisms have been associated with different diseases such as diabetes mellitus, hypertension, Parkinson's disease and rheumatoid arthritis (Yalin et al., 2007; Wang et al., 2006; Keladaa et al., 2003; Park et al., 2004). A study carried out in Chinese population showed protective role of GSTT1 wild genotype against type 2 diabetes (Wang et al., 2006). A study from Turkey could not find any association between GSTT1 and diabetes but GSTM1 null genotype was found to be significantly associated with the disease (Yalin et al., 2007).

So far, no information has been provided regarding the role of GSTM1 and GSTT1 gene polymorphisms and ischemic stroke in Indian populations. So, the present study was carried out to investigate the association between the GST M1 and T1 gene polymorphisms and the risk of stroke in a South Indian population.

MATERIALS AND METHODS

Study subjects

The study group comprised of 198 ischemic stroke patients (including both new and recurrent stroke patients) from the major hospitals of Hyderabad, Bhagwan Mahavir Medical Research Centre and Government Nizamia General Hospital of Andhra Pradesh, India. Patients with acute stroke were examined by a qualified stroke neurologist to confirm the diagnosis and the ischemic strokes were differentiated by computed tomography scans and magnetic resonance imaging. Classification of subtypes was done according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria (Meschia, 2002). Patients with hemorrhagic stroke were excluded from the study. The Institutional Ethics Committee approved this study and informed written consent was obtained from all the subjects who participated in the study. Information on demographic characteristics was collected using a standard questionnaire prepared especially for this purpose. Age matched control subjects (162) from the same socioeconomic background were selected for comparison. Smokers were defined as those reporting daily smoking. Ex-smokers and occasional smokers were classified as non-smokers. Information was also collected on the number of cigarettes smoked per day and duration of smoking. Risk factors including hypertension and diabetes were documented. Hypertension was defined according to Joint National Committee VI-VII, as a systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mm Hg based on the average of the 2 blood pressure measurements. Diabetes was diagnosed if fasting plasma glucose was >126 mg/dl in accordance with the American Diabetes Association (Diagnosis and Classification of Diabetes Mellitus, 2009).

Estimation of lipid profiles, DNA isolation and genotyping

6 ml of venous blood from each subject was collected. 4 ml was transferred to a plain test tube for serum and 2 ml was taken in an EDTA tube for DNA extraction. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) were estimated using a semiautomatic analyser (ERBA, CHEM-7, and Transasia Biomedicals, India) using commercial kits (ERBA). DNA was isolated by salting out method (Lahari et al., 1992). In brief, equal amount of Red blood cells (RBC) lysis buffer containing Triton-X was added to the whole blood sample, in-order to lyse the Red blood cells (RBC) and spinned to get the white pellet that consists of White blood cells (WBC). The so formed pellet was lysed with White blood cells (WBC) lysis buffer containing 10% SDS (sodium dodecyl sulfate), and then high molar concentration of NaCl was added consecutively to separate out the protein fraction. Finally, ice cold ethanol was added to get the DNA fibers which were separated and resuspended in TE buffer and stored at -20°C until the PCR (polymerase chain reaction) reaction was performed. The GSTM1 and GSTT1 gene deletions were analyzed simultaneously with multiplex PCR. Primers used to detect GSTM1 deletions were forward 5' - GAACTCCCTGAAAAGCTAAAGC - 3' and reverse 5'-GTTGGGCTCAAATATACGGTGG -3'. GSTT1 deletion was detected using forward 5'-TTCCTTACTGGTCCTCACATCTC-3' and reverse 5'-TCACCG GATCATGGCCAGCA-3'. 268 bp fragment of α-globin gene was used as internal positive control with

Table 1. General characteristics of the study group.

Variable	Stroke (n = 198)	Controls (n = 162)
	Mean (SD)	
Gender		
Males	142 (71.72)	86 (53.09)
Females	56 (28.28)	76 (46.91)
Age in years, mean (SD)	54.92 (11)	54.52 (11)
Body mass index (BMI) (kg/m^2)	27.02 (2.58)	22.23 (2.46)
Smoking status in men		
Never	34 (23.94)	6 (3.7)
Current	108 (54.55)	80 (49.38)
<15 pack-years	37 (34.26)	38 (47.5)
≥15 pack-years	71 (65.74)	42 (52.5)
Diabetes	62 (31.31)	47(29.01)
Hypertension	137 (69.19)	79(48.76)

Table 2. Lipid profiles of stroke patients and control subjects.

	Stroke (n = 198)	Controls (n = 162)	P value
	Mean (SD)		
Total cholesterol	238.5 (24.5)	164.6 (16.2)	0.0001
Triglycerides	109.6 (27.1)	98.5 (31.2)	0.01
Low density lipoprotein	185.5 (11.2)	93.6 (16.5)	0.0001
High density lipoprotein	35.6 (7.1)	43.4 (5.2)	0.0001
Very low density lipoprotein	37.6 (4.7)	31.7 (3.2)	0.0001

the following primers: Forward 5'-CAACTTCATCCA CGTTCACC-3' and reverse 5'-GAAGAGCCAAGGACAGGTAC-3'. The 50 µl incubation mixture consisted of 10 mM Tris-HCl, pH 8.3; 50 mM KCl; 0.2 mM of each dNTP; 2.0 mM MgCl2; 1.25 units *Taq* polymerase; 20 picomole of each primer; and 100 ng genomic DNA. Amplification was performed with an initial denaturation at 94°C for 5 min, 35 cycles were run with denaturation at 94°C for 1 min, annealing at 65°C for 1 min and extension at 72°C for 1 min. The products were analyzed on 2% agarose gel stained with ethidium bromide. Amplified 215 and 480 bp products indicated the presence of the GSTM1 and GSTT1 genes, respectively

Statistical analysis

Lipid profiles of ischemic stroke patients and controls were analyzed using Independent sample t-test. Association between genotypes and stroke was examined by using odds ratio (OR) with 95% confidence interval (CI) and chi square (χ^2) analysis. All the statistical tests were two sided, and were considered significant at p value < 0.05. Genotypic frequencies were calculated according to the number of different genotypes observed and the total number of genotypes examined. Yate's correction has been applied wherever necessary. Pack-years smoked was calculated to indicate cumulative cigarette dose and lighter and heavier smokers were categorized by the approximate 50th percentile pack-years value among controls, that is, <15 pack-years and >15 pack-years.

RESULTS

The percentage of males, hypertensives, diabetes, and smokers were more in patient group compared to controls (Table 1). Estimation of lipid profiles among stroke patient sand control subjects are shown in Table 2. The mean blood levels of lipids were high in stroke patients compared to controls suggesting a significant association (P<0.01)".

GSTM1 and GSTT1 polymorphism

In our case-control study, we genotyped GSTM1 and GSTT1 polymorphisms in 198 stroke patients and in 162 control subjects. The genotype frequencies of GSTM1

Table 3. Genotype distribution of the GSTM1 and GSTT1 polymorphisms in stroke and control subjects.

Genotype	Stroke (N = 198)		Controls(N = 162)		OR (95% CI)	P value
	No.	%	No.	%		
GSTM1 wild	107	54.04	91	56.17	0.91 (0.60-1.39)	0.6
GSTM1 null	91	45.96	71	43.83		
GSTT1 wild	157	79.29	140	86.42	0.60 (0.34-1.06)	0.07
GSTT1 null	41	20.71	22	13.58		
GSTM1 null/GSTT1 null	23	11.61	15	9.25	1.4 (0.70-2.96)	0.3
GSTM1 wild/ GSTT1 wild	89	44.95	84	51.86		
GSTM1 wild/ GSTT1 null	18	9.1	7	4.32	2.1 (0.82-5.43)	0.1
GSTT1 wild/ GSTM1 null	68	34.34	56	34.57		

P- value was calculated by χ^2 test with 2 x 2 contingency table and considered <0.05 as significant.

Table 4. Genotype distribution of the GSTM1 and GSTT1 polymorphisms among male smokers and non smokers' category of stroke patients and control subjects.

Genotype	Stroke	Control	OR	95% CI	P value
Smoker	108	80			
GSTM1 wild	42	47	0.44	0.24-0.80	0.007
GSTM1 null	66	33			
GSTT1 wild	83	72	0.36	0.15-0.86	0.01
GSTT1 null	25	8			
Non smoker	34	6			
GSTM1 wild	31	5	2.06	0.17-24	0.88*
GSTM1 null	3	1			
GSTT1 wild	33	6	2.75	0.08-91	0.58*
GSTT1 null	1	0			

* Yates corrected p value.

and GSTT1 polymorphisms among the patients and controls are shown in Table 3. The frequency of GSTM1 wild and null genotypes in stroke patients were 54.04 and 45.96% as against 56.17 and 43.83% in controls, while the frequency of GSTT1 wild and null genotypes were 79.29 and 20.71% in patients and 86.42 and 13.58% in controls, respectively. The results showed that the frequency of both wild and null genotypes of GSTM1 (OR = 0.91, p = 0.68) and GSTT1 (OR = 0.60, P = 0.077) did not differ significantly between control and stroke patients. Further analysis of GSTM1 and GSTT1 genotypes among male smokers and non smokers category of stroke patients and control subjects showed a protective role of GSTM1 wild type (OR = 0.44, p = 0.007) and GSTT1 wild type (OR = 0.36, p = 0.01) in smokers (Table 4).

DISCUSSION

This is the first study on the association of GSTM1 and GSTT1 gene polymorphisms with ischemic stroke in a South Indian population. We could not find any significant association between GSTM1 and GSTT1 gene polymorphism and stroke, while GSTM1 and GSTT1 wild type showed a protective role in smokers. GSTs are the phase II enzymes that catalyze the conjugation of glutathione to a wide range of electrophiles and represent a protective mechanism against oxidative stress (Ketterer, 1998) and involved in the pathogenesis of several chronic degenerative diseases (Meister, 1989). Members of the GST supergene family utilize a wide variety of products of oxidative stress as substrates; so, they have an important role in protection of cells from reactive oxygen species (Hayes and Strange, 1995). Smoking may affect the development of stroke by triggering oxidative stress (Agarwal, 2005), which leads to atherosclerosis according to the oxidative theory of atherogenesis (Steinberg et al., 1989). In 1908, Buerger observed a relationship between smoking and atherosclerosis and noted severe distal ischaemia among young male addicted smokers. In general ischemic stroke

occurs as a result of atherosclerosis in the carotid arteries and their branches (American Council on Science and Health, 2003). Cigarette smoking is known to contribute to the development of atherosclerosis which in turn has a higher risk of having stroke (Hankey, 1999). Turkanoglu et al. (2010) reported the role of GSTT1 and GSTM1 null genotypes together with hypertension in the pathogenesis of ischemic stroke. Similarly in a Korean population, GSTM1 null genotype was found to increase the risk of cerebral infarction (Kyung-Suk Moon et al., 2007), while GSTT1 null allele was associated with the risk of atherosclerosis (Salama et al., 2002). Study carried out by Xianglan et al. (2005) showed that women non smokers who lived with a husband who smoked had an elevated prevalence of stroke, and prevalence increased with the number of cigarettes and the duration of time that their husbands smoked. The relation between smoking and type of stroke, number of cigarettes smoked, and the effect of stopping was assessed by Framingham Heart Study for the first time and concluded smoking as a significant independent risk factor for stroke and specifically to brain infarction (Wolf et al., 1988). In our study, a high frequency of smokers was observed among stroke patients compared to controls. Shinton and Beevers showed that cigarette smoking independently contributed to the incidence of stroke: the greatest risk was of subarachnoid haemorrhage, followed by cerebral infarction (Shinton and Beevers, 1989).

GSTs have been shown to act as inhibitors of the Jun kinase pathway, which is an important signaling mechanism for the activation of cytoprotective genes (Adler et al., 1999). Human cytosolic GSTs have ethnic-dependent polymorphism frequencies. 20 to 50% of individuals do not express this enzyme due to a homozygous gene deletion, known as the null type allele of GSTM1 gene (Seidegard et al., 1998). The percentage of individuals who do not express this enzyme is higher in Caucasians and Asians than in Africans (Bailey et al., 1998; Roth et al., 2000). The *GSTT1* gene is located on chromosome 22, and 20 to 60% of individuals do not express the enzyme, also due to a gene deletion, known as the GSTT1*0 allele (Pemble et al., 1994). About 60% of Asians, 40% of Africans and 20% of Caucasians do not express this enzyme (Strange and Fryer, 1999). Studies carried out in South Indian women showed a significant association of GSTM1 null polymorphism and endometriosis (Roya et al., 2008). GST polymorphisms have also been associated with senile macular degeneration (Oz et al., 2006). Study carried out in Arab glaucoma patients showed a significant association of GSTM1/T1 polymorphisms with the disease (Khaled et al., 2008). GSTM1 gene polymorphisms were found to be associated with cardiac iron deposition in patients with beta-thalassemia major (Wu et al., 2006).

In our study, we did not observe any association between GSTM1 and GSTT1 gene polymorphism and ischemic stroke. However, GSTM1 and GSTT1 wild type showed a protective role in smokers.

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