

Antioxidant Enzyme Gene Polymorphisms in Japanese Migraine Patients with Medication Overuse Headache

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INTRODUCTION

Oxidative stress is characterized by increased reactive oxygen species activity and has been implicated in the development of many diseases such as ischemia-reperfusion injury, inflammation, and neurological diseases^[1-3]. It is generally accepted that the hydroxyl radical, a highly reactive form of oxygen, is responsible for the oxidant injury. It has been proposed that the hydroxyl radical is derived from the reaction of superoxide anion and hydrogen peroxide in the presence of iron [iron-catalyzed Haber-Weiss (Fenton) reaction]. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) are important antioxidant enzymes that protect cells against oxidative stress.

The activity of SOD, a radical-scavenging enzyme, is lower in migraine patients than in healthy controls; this suggests enhanced vulnerability to oxidative stress during migraine^[4]. Interestingly, nitric oxide (NO) metabolites and lipid peroxidation are increased during a migraine attack in platelets, in contrast to headache-free periods^[5]. Moreover, in chronic migraine patients, NO serum levels and SOD activity are decreased and serum peroxide levels are increased, in contrast to healthy controls^[6]. Thus, oxidative stress may be increased with increased frequency of headache in patients with migraine. Recently, it was shown that antioxidant capacity is lower in patients with medication overuse headache (MOH) compared to healthy headache-free subjects^[7]. Therefore, it is possible that an increase in

ABSTRACT

AIM: We investigated the association of an antioxidant enzyme gene polymorphisms and the medication overuse in migraine patients using cross-sectional method.

METHODS: In total, 47 migraine patients (6 males and 41 females; 36.4±10.3 years) and 22 medication overuse headache patients with migraine (1 male and 21 females; 39.6±9.9 years) participated in this study. The gene polymorphisms of superoxide dismutase (rs4880), catalase (rs1001179), and glutathione peroxidase-1 (rs1050450) were analyzed by polymerase chain reaction -restriction fragment length polymorphism methods.

RESULTS: No significant differences were observed in the genotype distributions of superoxide dismutase, catalase, and glutathione peroxidase-1 between migraine and medication overuse headache patients.

CONCLUSION: The results of this study showed no association between antioxidant enzyme gene polymorphisms and the complication of medication overuse headache in migraine patients.

oxidative stress may contribute to the aggravation of migraines due to medication overuse.

The polymorphisms of SOD (rs4880) and CAT (rs1001179) were known to be risk factors for migraine^[8]. In addition, SOD (rs4880)^[9] and glutathione peroxidase-1 (GPX1, rs1050450)^[10] polymorphisms have also been implicated in major depression which is recognized as a risk factor for the development of MOH in migraine patients^[11,12]. However, to the best of our knowledge, there have been no studies on the relationship between antioxidant enzyme gene polymorphisms and MOH. Therefore, we hypothesized that SOD, CAT, and GPX1 genes polymorphisms would modify the aggravation of migraines due to medication overuse.

Migraine patients are particularly prone to developing MOH^[11,13,14]. Although most MOH patients have migraine as the primary headache, not all migraine patients develop MOH. However, little is known about the factors that contribute to the complication of MOH in patients with migraine. In the present study, we focused on antioxidant enzyme gene polymorphisms such as SOD (rs4880), CAT (rs1001179), and GPX1 (rs1050450) and investigated the relationship between antioxidant enzymes genes polymorphisms and the complication of MOH in migraine patients.

METHODS

Subjects

We enrolled 47 migraine patients [6 males and 41 females: 5 with migraines with aura (MA), 36 with migraines without aura (MO), 6 with both MA and MO at different times; 36.4±10.3 years of age] and 22 MOH patients who had migraine (1 male and 21 females: 1 with MA and 21 with MO; 39.6±9.9 years of age) who were seen in an outpatient clinic of the Department of Neurology, Showa University East Hospital, Tokyo, Japan, between May 2010 and January 2011. These subjects were the same as those included in a previous study^[15]. The experience of depression is significantly more frequent in MOH patients than in migraine patients ($p < 0.001$)^[15]. The medications that were overused were combination analgesics in 14 patients (64%), analgesics in 9 patients (41%), and triptans in 2 patients (9%)^[15].

Migraines were diagnosed according to the *International Classification of Headache Disorders*, 2nd Edition (ICHD-II), 2004^[16]. We also confirmed by interview that migraine patients did not overuse headache medications. The revised ICHD-II criteria were used to diagnose MOH^[13]. MOH patients were questioned about their primary headaches by headache specialists. In addition, these headache specialists confirmed the primary headache according to the ICHD-II criteria after treating MOH. The subjects of the present study included not only patients with migraines but also patients with migraines and tension-type headaches; patients with tension-type headaches were excluded. We used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)^[17] to diagnose major depressive disorder.

All patients were Japanese. All patients who provided informed consent, including those with migraines and the subset with MOH, were enrolled in the study. We did not select patients in this study. This clinical study was approved by the Ethics Committee for Genome Research of Showa University.

Genotyping

Genomic DNA was extracted from whole blood using NucleoSpin® Blood QuickPure (NIPPON Genetics Co., Ltd., Tokyo, Japan). The gene polymorphisms of manganese superoxide dismutase (SOD, rs4880)^[18], catalase (CAT, rs1001179)^[19], and glutathione peroxidase-1 (GPX1, rs1050450)^[20] were studied. The polymorphism of each gene was determined by polymerase chain reaction (PCR)-restriction fragment length polymorphism (PCR-RFLP) methods. Primer sequences, restriction enzymes, and expected fragment sizes of the gene polymorphisms are shown in Table 1. The restriction enzyme-treated PCR fragments were run on 3% agarose gels and stained with ethidium bromide.

Statistical analysis

Categorical variables were analyzed by Fisher's exact test using Excel Statistics 2008 for Windows (Excel Toukei, Social Survey Research Information Co., Tokyo, Japan). A p value of ≤ 0.05 was considered statistically significant.

Table 1 Primers and restriction enzymes used for genotyping.

Polymorphism	Primer	Restriction enzyme	Product size (bp)
SOD (rs4880)	5'-GCT GTG CTT TCT CGT CTT CAG-3'	BsaWI	T: 167 and 40
	5'-TGG TAC TTC TCC TCG GTG ACG-3'		C: 207
CAT (rs1001179)	5'-TAA GAG CTG AGA AAG CAT AGC T-3'	SmaI	T: 185
	5'-AGA GCC TCG CCC CGC CGG ACC G-3'		C: 155 and 30
GPX1 (rs1050450)	5'-TCC AGA CCA TTG ACA TCG AG-3'	ApaI	T: 222
	5'-ACT GGG ATC AAC AGG ACC AG-3'		C: 170 and 52

Table 2 Genotype distributions of SOD, GPX and CAT genes polymorphisms.

		Total		Migraines		MOH		P value
		n = 69	%	n = 47	%	n = 22	%	
SOD rs4880	T/T	54	78.3	37	78.7	17	0.0	1.000
	T/C	15	21.7	10	21.3	5	22.7	
	C/C	0	0.0	0	0.0	0	77.3	
	T/T, C/C	54	78.3	37	78.7	17	77.3	
CAT rs1001179	T/T	0	0.0	0	0.0	0	0.0	1.000
	T/C	1	1.4	1	2.1	0	0.0	
	C/C	68	98.6	46	97.9	22	100.0	
	T/T, T/C	1	1.4	1	2.1	0	0.0	
GPX1 rs1050450	C/C	68	98.6	46	97.9	22	100.0	1.000
	T/T	2	2.9	2	4.3	0	0.0	
	T/C	14	20.3	9	19.1	5	22.7	
	C/C	53	76.8	36	76.6	17	77.3	
	T/T, T/C	16	23.2	11	23.4	5	22.7	1.000
	C/C	53	76.8	36	76.6	17	77.3	

RESULTS

The genotype distributions of polymorphisms of SOD (rs4880, T/T vs T/C plus C/C, $p=1.000$), CAT (rs1001179, T/T plus T/C vs. C/C, $p=1.000$), and GPX1 (rs1050450, T/T plus T/C vs C/C, $p=1.000$) genes were not significantly different between migraine patients and MOH patients (Table 2).

DISCUSSION

In the present study, no association was observed between polymorphisms of SOD (rs4880), CAT (rs1001179) and GPX1 (rs1050450) genes and the complication of MOH in patients with migraine.

Yanik *et al* reported that patients with major depression are exposed to oxidative stress^[21]. Stefanescu and Ciobica showed that the antioxidant enzyme activity is decreased and the levels of lipid peroxidation is increased in major depression^[22]. In addition, the polymorphisms of SOD (rs4880)^[9] and GPX1 (rs1050450)^[10] genes have also been implicated in major depression. Previous studies revealed a higher percentage of comorbidity with depression in MOH patients than in migraine patients^[11,12]. We also reported that the experience of depression is significantly more frequent in MOH patients than in migraine patients^[15]. In this study, however, we did not find an association between antioxidant enzymes genes polymorphisms and MOH.

We previously showed that methylenetetrahydrofolate reductase (MTHFR C677T, rs1801133) polymorphism contributes to the onset of MOH in patients with migraine^[15]. MTHFR is a key enzyme in homocysteine metabolism that acts by catalyzing the production of 5-methylenetetrahydrofolate from 5,10-methylenetetrahydrofolate^[23-25]. The T/T genotype of MTHFR C677T polymorphism, has been shown to decrease enzyme activity^[25]; thus, plasma homocysteine levels might be increased in T/T carriers in MOH patients. Furthermore, elevated homocysteine is known to promote oxidative stress^[26]. Therefore, it is possible that MTHFR gene polymorphism may be involved in oxidative stress in migraine patients with MOH. Interestingly, Gupta *et al* reported that oxidative stress continues even between headache episodes in migraine patients but not in patients with tension-type headache^[28]. This may be due to the different pathophysiological mechanisms of tension-type headache and migraine. Although this study did not find an association between polymorphisms in the investigated antioxidant enzymes genes and the complication of MOH in migraine patients, it is possible that other antioxidant enzymes genes polymorphisms may contribute to the aggravation of migraines by the overuse of medication. Further genetic studies are required to identify susceptible antioxidant enzymes genes that are associated with the complication of MOH in migraine patients. In addition, because the small sample size was a limiting factor in the present study, larger genetic studies are required to identify antioxidant enzymes genes polymorphisms that may be associated with the complication with MOH in migraine patients.

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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