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A Cyclooxygenase 2 Gene Polymorphism is a Risk Factor for the Complication of Medication Overuse Headaches in Patients with Migraines

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Abstract

We determined whether cyclooxygenase-2 (COX-2) gene polymorphisms were involved in the aggravation of migraines due to the overuse of medication. Polymorphisms in the COX-2 (rs20417, rs689466) gene were examined. Forty-seven patients with migraine (6 males and 41 females; 5 with migraines with aura (MA), 36 with migraines without aura (MO), 6 with MA + MO; 1 with MA and 21 with MO; 36.4 ± 10.3 years) and 22 patients with medication overuse headache (MOH) (1 male and 21 females; 39.6 ± 9.9 years) who had migraines participated in this study. The genotypes of each polymorphism were analyzed by polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) methods. No significant differences were observed in the genotypic distributions of rs20417 (C/C + G/C vs. G/G, p=0.220) between migraine patients and MOH patients. The frequencies of the rs689466 G/G genotype were significantly higher in patients with MOH than in patients with migraines (G/G vs. A/A+A/G, p=0.008). Furthermore, the frequencies of the rs689466 G/G genotype were significantly higher in patients with MOH who had migraines without aura (MO) than in patients with MO (G/G vs. A/A+A/G, p=0.001). The results of this study showed that the COX-2 polymorphism (rs689466) was independently related with the complication of MOH in patients with MO.

Key words:

Medication Overuse Headache; Migraine; Polymorphism; Cyclooxygenase-2

Introduction

Migraine patients are susceptible to developing medication overuse headaches (MOH) due to the overuse of medication [1-3]. Moreover, 56.8% of migraine sufferers use over-the-counter medicine (combination analgesics) alone [4], and 85.1% of MOH patients overuse combination analgesics [2]. Although most patients return to the episodic migraine pattern after drug withdrawal, the complications of MOH markedly decrease the quality of life of patients [1]. Furthermore, in contrast to migraine patients, the percentage of comorbidity with depression in MOH patients is higher [3-5]. Therefore, it is important to prevent the complications of MOH in patients with migraines.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen have been used to treat headaches in patients with migraines. NSAIDs inhibit cyclooxygenase (COX) and reduce the production of prostanoids such as prostaglandin I_2. However, the overuse of these drugs can cause MOH [6-8]. Martelletti et al. showed that COX-2 was up-regulated in migraine patients [9]. Dasdemir et al. also reported that a COX-2 polymorphism (rs689466) was a risk factor for migraines without aura (MO) [10]. Additionally, MOH patients who have migraines as the primary headache initially had MO [1]. Therefore, rs689466 may contribute to the pathogenesis of not only MO, but also MOH. However, to the best of our knowledge, there have been no studies on the relationship between COX-2 gene polymorphisms and MOH.

Therefore, we conducted the present study to investigate the relationship between COX-2 gene polymorphisms and MOH.

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 MA + MO; 36.4 ± 10.3 years) and 22 MOH patients (1 male and 21 females; 1 with MA and 21 with MO; 39.6 ± 9.9 years) who were admitted to the Department of Neurology in the outpatient clinic of Showa University East Hospital, Tokyo, Japan, between May, 2010 and January, 2011. These patients had participated in a previous study, in which the incidence of depression was shown to be significantly higher in MOH patients than in migraine patients ($p<0.001$) [11]. The duration of migraine history was not significantly different between migraine patients (16.5 ± 13.0 years, n=44) and MOH patients (20.39 ± 12.7, n=19, p=0.276). The overused medications were combination analgesics in 14 patients (64%), analgesics in 9 patients (41%), and triptans in 2 patients (9%) [11]. Migraines were diagnosed according to the International Classification of Headache Disorders, 2nd Edition

(ICHD-II) in 2004 [12]. We also confirmed with an interview that the migraine patients in the present study had not previously overused medication. The revised ICHD-II criteria were used for the diagnosis of MOH [1]. Headache specialists asked MOH patients about primary headaches, and confirmed primary headaches after the recovery of patients from MOH, according to the ICHD-II criteria. Although the subjects included in the present study were not only patients with migraines, but also patients with migraines and tension-type headaches, patients with tension-type headaches only were excluded from this study. We used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) to diagnose major depressive disorder [13].

All patients were Japanese. We enrolled all patients with migraines and patients with MOH who provided informed consent for this study, and did not select patients. The Ethics Committee for Genome Research of Showa University approved this clinical study.

Genotyping

The determination of COX-2 gene polymorphisms (rs20417 and rs689466) was performed by a polymerase chain reaction (PCR)-based method in accordance with Dasdemir et al. [10]. The sense oligonucleotide primer for rs20417 was 5'-AGG CAG GAA ACT TTA TAT TGG- -3', and the antisense primer was 5'-ATG TTT TAG TGA CGA CGC TTA-3'. PCR products were digested for 10-12 h at 37°C with Aci I. The 309 bp fragment indicated the presence of the C allele (no Aci I restriction site) and the 209 bp and 100 bp fragments indicated the presence of the G allele (presence of Aci I restriction site). The sense oligonucleotide primer for rs689466 was 5'-CCC TGA GCA CTA CCC ATG AT-3', and the antisense primer was 5'-GCC TTC ATA GGA GAT ACT GG-3'. PCR products were digested for 10-12 h at 37°C with Pvu II. The 273 bp fragment indicated the presence of the A allele (no Pvu II restriction site) and the 220 bp and 53 bp fragments indicated the presence of the G allele (presence of the Pvu II restriction site).

The PCR products or restriction enzyme-treated PCR fragments were run on 3% agarose gels and stained with ethidium bromide.

Statistical analysis

We applied univariate analysis using unpaired Student's t test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables. Statistical significance was accepted at the $p < 0.05$ level. The analysis was performed using Excel Statistics (Excel Toukei) 2008 for Windows (Social Survey Research Information Co., Tokyo, Japan).

Results

No significant differences were observed in the genotypic distributions of rs20417 (C/C + G/C vs G/G, p=0.220) between migraine patients and MOH patients (Table 1). The frequencies of the rs689466 G/G genotype were significantly higher in patients with MOH than in patients with migraines (G/G vs. A/A + A/G, p=0.008; Table 1). As shown in Table 2, the frequencies of the rs689466 G/G genotype were significantly higher in patients with MOH who had MO than in patients with MO (G/G vs. A/A + A/G, p=0.001).

		Subject		Migraine		MOH		
		n=69	(%)	n=47	(%)	n=22	(%)	P value
rs20417	C/C	1	1.4	0	0.0	1	4.5	
	G/C	12	17.4	7	14.9	5	22.7	
	G/G	56	81.2	40	85.1	16	72.7	
	C/C, G/C	13	18.8	7	14.9	6	27.3	0.220
	G/G	56	81.2	40	85.1	16	72.7	
rs689466	A/A	21	30.4	13	27.7	8	36.4	
	A/G	34	49.3	29	61.7	5	22.7	
	G/G	14	20.3	5	10.6	9	40.9	
	A/A, A/G	55	79.7	42	89.4	13	59.1	0.008*
	G/G	14	20.3	5	10.6	9	40.9	

*p<0.05, MOH: Medication Overuse Headache

Table 1: Distribution of Genotype Frequencies for COX-2 Polymorphisms.

		Subject		MO		MOH		
		n=57	(%)	n=36	(%)	n=21	(%)	P value
rs689466	A/A	18	31.6	10	27.8	8	38.1	
	A/G	28	49.1	24	66.7	4	19	
	G/G	11	19.3	2	5.6	9	42.9	
	A/A, A/G	46	80.7	34	94.4	12	57.1	0.001*
	G/G	11	19.3	2	5.6	9	42.9	

*p<0.05; MOH: Medication Overuse Headache; MO: Migraine Without Aura

Table 2: Distribution of Genotype Frequencies for COX-2 Polymorphism between MO patients and MOH patients who had MO.

Discussion

The present study was the first to demonstrate that the COX-2 rs689466 polymorphism contributed to the complications of MOH in patients with migraines, especially MO, and G/G genotype carriers appeared to be more susceptible to the aggravation of migraines by the overuse of medications.

A high percentage of MOH patients initially have MO [1]. In this study, although the difference was not significant, we found that MOH patients who had MO as primary headaches were slightly more common than MO patients in the migraine group. Furthermore, the frequency of comorbidity with depression was higher in MOH patients than in migraine patients [3-5]. We also confirmed that the prevalence of depression was significantly higher in MOH patients than in

migraine patients. Among the 22 patients with MOH, 64% overused combination analgesics, a finding that is similar to those of Imai et al. [2] and Kanki et al. [3]. Although the sample size in this study was small, the background of subjects appears to be coincident with those found in previous studies.

The COX-2 rs689466 polymorphism is located in a core c-MYB recognition sequence in the COX-2 promoter region, and the DNA/c-MYB complex binds to the rs689466 A allele, but not to the rs689466 G allele [14]. Furthermore, a previous study showed significantly lower transcriptional activity and mRNA levels in the rs689466 G allele than in the rs689466 A allele, both in vitro and in vivo [14]. Therefore, the expression of this enzyme may have been lower in individuals carrying the rs689466 G allele in the MOH group.

The G/G genotype in rs689466 has been related to the pathogenesis of MO [10], but not depression [15]. The results of the present study suggest that the G/G genotype in rs689466 is a risk factor for MOH in patients with migraine. Moreover, this is a risk factor for the complication of MOH in patients with MO. Although migraine patients may be complicated by MOH in the future, a significant difference was observed in COX-2 rs689466 between the MO and MOH groups in this study. Therefore, we showed that rs689466 may be one of the risk factors contributing to the aggravation of MO due to the overuse of medications. Since the sample size is the biggest limitation of the study, future studies with a larger sample must be undertaken to elucidate the relationship between rs689466 and MOH in more detail.

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