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Short Communication

Catechol-O-Methyl Transferase Gene Polymorphisms in Japanese Patients with Medication overuse Headaches

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Abstract

We here in investigated whether dopamine-related gene polymorphisms were involved in the aggravation of migraines due to the overuse of medication. Polymorphisms in the catechol-O-methyltransferase (COMT, rs4680, rs2075507), dopamine-β hydroxylase (DBH, rs1108580, rs1611115, insertion/deletion (I/D)), noradrenaline (norepinephrine) transporter (NET, rs2242446), and α_{2B}-adrenaline receptor (ADRA2B, I/D) genes were studied. Forty-seven migraine patients (6 males and 41 females; 36.4 ± 10.3 years) and 22 medication overuse headache (MOH) patients (1 male and 21 females; 39.6 ± 9.9 years) who had migraines participated in this study. The geno type of each gene polymorphism was analyzed using polymerase chain reaction (PCR) or PCR-restriction fragment length polymorphism (RFLP) methods. Significant differences were observed in the genotypic distributions of rs2075507 (A/A vs. A/G plus G/G, $P = 0.012$) between migraine patients and MOH patients, but not in the other gene polymorphisms. The results of the present study revealed a correlation between the COMT gene polymorphism (rs2075507) and complication of MOH in patients with migraines.

ABBREVIATIONS

MOH: Medication Overuse Headache; MO: Migraine without Aura; MA: Migraine with Aura; DRD2: Dopamine D2 Receptor; COMT: Catechol-*O*-Methyltransferase; DBH: Dopamine-βHydroxylase; NET: Norepinephrine Transporter; ADRA2B: α_{2B}-adrenaline Receptor; I/D: Insertion/Deletion; ICHD-II: International Classification of Headache Disorders, 2nd Edition.

INTRODUCTION

Medication overuse headaches (MOH) are frequently reported in patients with migraines [1-3]. Although most patients return to the episodic migraine pattern following drug withdrawal, MOH markedly decreases the quality of life of these patients [1]. Furthermore, the incidence of co-morbidity with depression was shown to be higher in MOH patients than in migraine patients [3,4]. Therefore, the aggravation of migraines due to the overuse of medications needs to be prevented. The pathophysiology of migraines involves the neurotransmitter system including catecholamine such as dopamine, noradrenaline, and adrenaline. High dopamine levels have been detected in the platelets of patients with migraine without aura (MO), but not in those of patients with migraine with aura (MA) [5]. A previous study suggested that an increase in the release of dopamine from the brain and neurons played a role in the complication of MOH in migraine patients [6]. A high percentage of MOH patients were also found to have migraines as primary headaches [2,3], and initially had MO [1]. We also confirmed that 95% of MOH patients had MO as primary headaches, and demonstrated that a dopamine D2 receptor (DRD2) polymorphism (rs6275) contributed to the complication of MOH in migraine patients [7]. Since rs6275 is a silent mutation, this polymorphism may be in linkage disequilibrium with other functional mutations in the DRD2 gene. Thus, dopamine-related gene polymorphisms may be involved in the onset of MOH in migraine patients. In the present study, we focused on dopamine-related gene polymorphisms that are functional polymorphisms and/or are related to the pathogenesis of depression and/or migraines. We investigated the relationship between Catechol-*O*-methyltransferase (COMT, rs4680 [8,9], rs2075507 (previous name rs2097603) [10]), dopamine-β hydroxylase (DBH, rs1108580 [11], rs1611115 [12], insertion/deletion (I/D) [13]), noradrenaline(norepinephrine)

transporter (NET, rs2242446 [14]), and α_{2B}-adrenaline receptor (ADRA2B, -4825 I/D [15]) gene polymorphisms and the complication of MOH in migraine patients.

MATERIALS AND METHODS

Subjects

We enrolled 47 patients with migraines [six males and 41 females: five with migraine with aura (MA), 36 with migraine without aura (MO), and six with MA + MO; 36.4 ± 10.3 years of age] and 22 patients with MOH (one male and 21 females: one with MA and 21 with MO; 39.6 ± 9.9 years of age) who were admitted to the Department of Neurology in an outpatient clinic of the Showa University East Hospital, Tokyo, Japan between May, 2010 and January, 2011. These subjects were the same as those included in previous studies [7]. The incidence of depression was significantly higher in patients with MOH than in patients with migraine ($P< 0.001$) [7]. The medications that were overused were combination analgesics in 14 patients (64%), analgesics in nine patients (41%), and triptan in two patients (9%) [7].

Migraines were diagnosed according to the International Classification of Headache Disorders, 2nd Edition (ICHD-II), 2004 [16]. We also confirmed, via interviews, that patients with migraines did not overuse medications. The revised ICHD-II criteria were used to diagnose MOH [1]. Headache specialists asked MOH patients about primary headaches, and confirmed the primary headache after treating MOH, according to the ICHD-II criteria. Although the subjects of this 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) to diagnose major depressive disorder [17].

All patients were Japanese, and all who gave their informed consent, including those with migraines and patients with MOH, were enrolled in this study. The Ethics Committee for Genome Research of Showa University approved this clinical study.

Genotyping

Genomic DNA was extracted from whole blood using the NucleoSpin® Blood QuickPure kit (NIPPON Genetics Co., Ltd., Tokyo, Japan). COMT (rs4680 and rs2075507), DBH (rs1108580, rs1611115, and I/D), ADRA2B (I/D), and NET (rs2242446) gene polymorphisms were studied. Each gene polymorphism was determined as described previously [12-15,18,19]. These genotyping assays were performed on a maximum of 30 samples, plus a positive control. The primer sequences and restriction enzymes used to detect polymorphisms and their expected fragment sizes are shown in (Table 1). PCR products or restriction-enzyme-treated PCR fragments were run on 3% agarose gels and stained with ethidium bromide.

Statistical analysis

The genotype frequencies were tested using the public statistical web-tool http://www.oege.org/software/hwe-mr-calc.shtml for Hardy-Weinberg equilibrium (HWE). $P>0.05$ was considered not deviate from the equilibrium. Categorical variables were analyzed by the χ^2 test or Fisher's exact test using Excel Statistics (Excel Toukei) 2008 for Windows (Social Survey Research Information Co., Tokyo, Japan).Values of $P<0.05$ were considered significant.

RESULTS AND DISCUSSION

Table 2 shows the genotypic distributions in subjects. Only the genotype distribution of ADRA2B I/D polymorphism was not consistent with HWE in subjects ($P<0.05$). It may be due to methodological reasons (e.g., non-population-based study, small sample size). Significant differences were observed in the genotypic distributions of rs2075507 (A/A vs. A/G plus G/G, $P = 0.012$) between migraine patients and MOH patients (Table 2), but not in those of COMT rs4680 and other gene polymorphisms (Table 2). The odds ratio (A/A vs A/G plus G/G) was 2.597 (95% CI = 1.151-5.829). In the present study, a correlation was detected between the COMT gene polymorphism (rs2075507) and the complication of MOH in patients with migraines. To the best of our knowledge, there have been no studies on the relationship between COMT rs2075507 and migraine. In this study, we did not collect healthy control subjects, because the aim of this study was to investigate the involvement of dopamine-related gene polymorphisms in the aggravation of migraine by overuse of medications. Nunokawa *et al.* [20] reported that the distribution of rs2075507 polymorphism in Japanese healthy controls was A/A (53.9%), A/G (39.1%) and G/G (7.0%). Between subjects in this study and healthy controls in Nunokawa's study, the genotype distribution was not different (A/A vs. A/G and G/G, $P=0.478$). Therefore, COMT rs2075507 might not be involved in the onset of migraine. The frequency of co-morbidity with depression was previously shown to be higher in MOH patients than in migraine patients [3,4]. We also confirmed that the incidence of depression was significantly higher in MOH patients than in migraine patients [7]. A relationship was previously found between COMT rs2075507 and major depression disease [10]. This SNP causes an A to G substitution in the P2 promoter region and the A-allele has frequently been detected in patients with major depression disease [10]. However, in the present study, the A-allele of COMT rs2075507 was more common in patients with migraines than in patients with MOH. A previous study suggested that an increase in the release of dopamine from the brain and neurons played a role in the complication of MOH in migraine patients [6]. Other studies reported that the G-allele of rs2075507 reduced COMT activity in lymphocytes [21]. In the present study, COMT activity appeared to be low because the A/G and G/G genotypes of rs2075507were enhanced in MOH patients. Furthermore, although the G/G genotype of rs4680, another functional polymorphism of COMT, was slightly lower in patients with MOH than in patients with migraine (G/G vs. G/A plus A/A, $P=0.100$), the G-allele of rs4680 is known to enhance COMT activity [21]. Thus, extracellular dopamine levels may be enhanced in MOH patients due to low COMT activity. Additionally, we previously reported that a polymorphism in the dopamine D2 receptor (rs6275) was associated with the complication of MOH in migraine patients [7]. Therefore, multiple factors, dopamine-related gene polymorphisms, appear to be involved in the aggravation of migraines due to the overuse of medication. However, the sample size was the primary limitation of this study. Future studies using a larger number of samples must be undertaken to elucidate the relationship between dopamine-related gene polymorphisms and MOH.

CONCLUSION

The results of this study revealed a correlation between the COMT gene polymorphism (rs2075507) and the complication of MOH in patients with migraines.

Table 1: Primers and restriction enzymes used for genotyping.

Polymorphism		Primer	Restriction enzyme	Product size (bp)	Reference
COMT	rs4680	5'-TCG TGG ACG CCG TGA TTC AGG-3'	NlaIII	A: 40, 81 and 96	18
		5'-AGG TCT GAC AAC GGG TCA GGC-3'		G: 81 and 136	
	rs2075507	5'-TAG TAA CAG ACT GGC ACG AA-3'	HindIII	A: 350	19
		5'-GTT CAA AGG GCA TTT ATC ATG-3'		G: 74 and 276	
DBH	rs1108580	5'-TCC TTC ATG CCT GGA GCC CAG TGC TTG TCT-3'	EcoNI	G: 38 and 169	13
		5'-GAC AGG AAA GGT ACT ATG ACA TTG GCA CAG-3'		A: 207	
	rs1611115	5'-GGA GGG ACA GCT TCT AGT CC-3'	HhaI	T: 131	12
		5'-CAC CTC TCC CTC CTG TCC TCT CGC-3'		C: 22 and 109	
	I/D	5'-GCA AAA TAC AGG CAC ATG CAC C-3'	-	I: 276	-
		5'-GTC AGC GAG ATG GGG AGG TGG A-3'		D: 257	
NET	rs2242446	5'-CCA TTT GGG GCA GGC GAA AGT-3'	Sty I	T: 176	14
		5'-CGC TGA CGG GAC GCA GGG TTC CCA GCC AAG-3'		C: 30 and 146	
ADRB2	I/D	5'-ACG TGT AGA GGA AGA GGA AGG-3'	-	I: 212	15
		5'-CGT TCG GCA ATG TCT GGA ATA C-3'		D: 200	

Table 2: Genotype distribution of gene polymorphisms.

			Subjects		Migraine		MOH		
			n=69	(%)	n=47	(%)	n=22	(%)	*P* value
COMT	rs4680	G/G	23	33.3	19	40.4	4	18.2	
		G/A	37	53.6	23	48.9	14	63.6	
		A/A	9	13.0	5	10.6	4	18.2	
		G/G	23	33.3	19	40.4	4	18.2	0.100
		G/A, A/A	46	66.7	28	59.6	18	81.8	
	rs2075507	A/A	34	49.3	28	59.6	6	27.3	
		A/G	28	40.6	16	34.0	12	54.5	
		G/G	7	10.1	3	6.4	4	18.2	
		A/A	34	49.3	28	59.6	6	27.3	0.012*
		A/G, G/G	35	50.7	19	40.4	16	72.7	
DBH	rs1108580	A/A	53	76.8	35	74.5	18	81.8	
		A/G	16	23.2	12	25.5	4	18.2	
		G/G	0	0.0	0	0.0	0	0.0	
		A/A	53	76.8	35	74.5	18	81.8	0.558
		A/G, G/G	16	23.2	12	25.5	4	18.2	
	rs1611115	T/T	1	1.4	0	0.0	1	4.5	
		T/C	25	36.2	16	34.0	9	40.9	
		C/C	43	62.3	31	66.0	12	54.5	
		T/T	1	1.4	0	0.0	1	4.5	0.319
		T/C, C/C	68	98.6	47	100.0	21	95.5	
	I/D	I/I	20	29.0	12	25.5	8	36.4	
		I/D	37	53.6	27	57.4	10	45.5	
		D/D	12	17.4	8	17.0	4	18.2	
		I/I	20	29.0	12	25.5	8	36.4	0.355
		I/D, D/D	49	71.0	35	74.5	14	63.6	

NET	rs2242446	T/T	23	33.3	15	31.9	8	36.4	
		T/C	34	49.3	23	48.9	11	50.0	
		C/C	12	17.4	9	19.1	3	13.6	
		T/T	23	33.3	15	31.9	8	36.4	0.715
		T/C, C/C	46	66.7	32	68.1	14	63.6	
ADRA2B	I/D	I/I	20	29.0	17	36.2	3	13.6	
		I/D	42	60.9	27	57.4	15	68.2	
		D/D	7	10.1	3	6.4	4	18.2	
		I/I	20	29.0	17	36.2	3	13.6	0.086
		I/D, D/D	49	71.0	30	63.8	19	86.4	

*:p<0.05

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