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Case Report

Orexin Receptor Gene Polymorphisms in Japanese Migraine Patients with Medication Overuse Headache

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Abstract

Patients with migraine disease are known to be complicated with medication overuse headache. Although it has been shown that orexin-1 receptor (HCRTR1, rs2271933) and orexin-2 receptor (HCRTR2, rs2653349) gene polymorphisms are contributed the pathophysiology of migraine, the relationship between these polymorphisms and medication overuse headache (MOH) is unknown. Therefore, we hypothesized that HCRTR1 and HCRTR2 gene polymorphisms may modify the aggravation of migraines due to medication overuse. To test this, we analyzed the orexin-related gene polymorphisms (rs2271933 and rs2653349) in migraine and MOH patients. The study population consisted of 69 patients including 47 migraine patients (mean age 36.4 ± 10.3 years, 6 males and 41 females) and 22 MOH patients (mean age 39.6 ± 9.9 years, 1 male and 21 females) who had migraines. HCRTR1 and HCRTR2 were analyzed by polymerase chain reaction (PCR)-restriction fragment length polymorphism (PCR-RFLP) methods. No significant differences were observed in the genotype distributions of HCRTR1 (rs2271933, C/C *vs*. C/T plus T/T, $p = 0.656$) and HCRTR2 (rs2653349, A/A plus A/G *vs*. G/G, $p = 1.000$) between migraine and MOH patients. The results of this study showed that the orexin-related gene polymorphisms are not identified as the contributing factors to the aggravation of migraines due to the overuse of medications.

Keywords: Medication Overuse; Migraine; Polymorphism; Orexin Receptor

Introduction

Migraine patients are particularly known to be complicated with medication overuse headache (MOH) [1-3]. Furthermore, 56.8% of migraine sufferers were found to use over-the-counter medicine alone [4]. Although MOH is known to be caused by triptan, ergotamine, opioid, and/or analgesic overuse in patients with headache [1], previous report showed that 85.1% of MOH patients overused combination analgesics [2]. It was known the increased levels of orexin-A (hypocretin 1) in the cerebrospinal fluid of chronic migraine and MOH patients [5]. Orexin-A is involved in the control of feeding and sleep behavior in the hypothalamus; therefore, it may contribute to the aggravation of migraines due to medication overuse.

Orexin-A binds to the orexin-1 receptor (HCRTR1) and orexin-2 receptor (HCRTR2), while orexin-B, another type of orexin, only binds to HCRTR2. Between migraine patients and controls, the genetic distribution of HCRTR1 (rs2271933) and HCRTR2 (rs2653349) was significantly different [6,7]. On the other hand, the genotypic and allelic frequencies of rs2653349 in HCRTR2 were similarly distributed between migraine patients and controls in another report [8]. Thus, previous studies have attempted to elucidate the relationship between orexin-related gene polymorphisms and migraine, whereas, that between orexin-related gene polymorphisms and MOH remains unknown. Therefore, we hypothesized that HCRTR1 and HCRTR2 gene polymorphisms may modify the aggravation of migraines due to medication overuse.

In the present study, we focused on orexin-related gene polymorphisms such as HCRTR1 and HCRTR2 and investigated the relationship between orexin-related gene polymorphisms and the complication of MOH in migraine patients.

Methods

Subjects

We enrolled 69 patients, including 47 migraine patients (mean age 36.4 ± 10.3, 6 males and 41 females) and 22 MOH patients (mean age 39.6 ± 9.9, 1 male and 21 females) with migraine who were admitted to an outpatient clinic of the Department of Neurology, Showa University East Hospital, Tokyo, Japan, between May 2010 and January 2011 [9].

Migraines were diagnosed according to the *International Classification of Headache Disorders, 2nd Edition* (ICHD-II), 2004 [10]. We also confirmed by interview that migraine patients did not overuse headache medications. The revised ICHD-II criteria were used to diagnose MOH [1]. MOH patients were questioned about their primary headaches by headache specialists. In addition, after treating MOH, primary headache was confirmed by these headache specialists using the ICHD-II criteria. Although 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) [11] to diagnose major depressive disorder.

All patients were Japanese. They gave their informed consent, including those with migraines and the subset with MOH, were enrolled in this study. This study was conducted under approval of the Ethics Committee for Genome Research of Showa University.

Genotyping

Genomic DNA was extracted from whole blood using NucleoSpin® Blood Quick Pure (NIPPON Genetics Co., Ltd., Tokyo, Japan). Gene polymorphisms in the orexin-1 receptor (HCRTR1, rs2271933) and orexin-2 receptor (HCRTR2, rs2653349) were studied [12]. Polymorphisms in each gene were determined by polymerase chain reaction (PCR) and PCR-restriction fragment length polymorphism (PCR-RFLP) methods. The primer sequences, restriction enzymes, and expected fragment sizes of the gene polymorphisms are shown in Table 1. The PCR products or 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 ≤ 0.05 was considered statistically significant.

Results

Forty seven 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; aged 36.4 ± 10.3] and 22 MOH patients who had migraine (1 male and 21 females: 1 with MA and 21 with MO; aged 39.6 ± 9.9) were enrolled in this study. Moreover, the incidence of depression was significantly higher in MOH patients than in migraine patients ($p < 0.001$). The overused drugs were combination analgesics in 14 patients (64%), analgesics in 9 patients (41%), and triptans in 2 patients (9%). The HCRTR1 (rs2271933) and HCRTR2 (rs2653349) genotype frequencies of this study are listed in Table 2. The genetic distribution of HCRTR1 was not different between migraine and MOH patients (C/C *vs*. C/T plus T/T, $p = 0.656$). Moreover, no significant difference was observed in the genotype distribution of polymorphism in the HCRTR2 (A/A plus A/G *vs*. G/G, $p = 1.000$) gene between migraine and MOH patients.

Table 1. Primers and restriction enzymes used for genotyping.

Polymorphism		Primer	Restriction enzyme	Product size (bp)
HCRTR1	(rs2271933)	5'-ATT CCG GGA GCA GTT TAA GG-3'	BccI	T: 142 and 138
		5'-GAC TGA AGC CAC AGC CTT TC-3'		C: 280
HCRTR2	(rs2653349)	5'-AGA GAA AAT GGA AGC CCC TG-3'	BccI	A: 330
		5'-AGT CAT CTG GCC TGA CAA GG-3'		G: 205 and 125

Table 2. Genotype distribution of gene polymorphisms.

Table 2 Genotype distribution of gene polymorphisms

		Subjects		Migraine		MOH		
		n = 69	(%)	n = 47	(%)	n = 22	(%)	*P* value
HCRTR1	C/C	6	8.7	5	10.6	1	4.5	
rs2271933	C/T	25	36.2	18	38.3	7	31.8	
	T/T	38	55.1	24	51.1	14	63.6	
	C/C	6	8.7	5	10.6	1	4.5	0.656
	C/T, T/T	63	91.3	42	89.4	21	95.5	
HCRTR2	A/A	0	0.0	0	0.0	0	0.0	
rs2653349	A/G	6	8.7	4	8.5	2	9.1	
	G/G	63	91.3	43	91.5	20	90.9	
	A/A, A/G	6	8.7	4	8.5	2	9.1	1.000
	G/G	63	91.3	43	91.5	20	90.9	

Discussion

It is widely understood that orexin regulates sleep/wakefulness states. Orexin knockout mice, a model of human narcolepsy, have the characteristics of rapid eye movement (REM) sleep dysregulation [13]. Sleep problems such as difficulty in falling asleep, mid-sleep awakenings, early morning awakenings, and nonrestorative sleep are known to be more frequent in chronic migraine than in episodic migraine patients [14]. Moreover, we previously identified sleepiness and excess sleep as major triggers in MOH patients rather than in migraine patients [15]. However, in the present study, no relationship was observed between orexin receptor gene polymorphisms (rs2271933 and rs2653349) and the complication of MOH in migraine patients. Since increased levels of orexin-A have been detected in the cerebrospinal fluid of MOH patients [5], further genetic studies are needed to identify the relationship between other orexin-related gene polymorphisms and the aggravation of migraines due to medication overuse.

In the present study, we did not collect data from healthy control subjects because the aim was to determine the involvement of orexin receptor gene polymorphisms in the aggravation of migraines due to the overuse of medications. Ahmed et al. previously reported that the distribution of HCRTR1 (rs2271933) and HCRTR2 (rs2653349) gene polymorphisms in healthy Japanese controls was T/T in 55%, C/T in 37%, and C/C in 8%, and G/G in 89%, A/G in 11%, and A/A in 0%, respectively [16]. No significant differences were observed in genotype distributions between the subjects in the present study and the healthy controls in the study by Ahmed et al. (C/C vs. C/T+T/T, p=0.872, and A/A+A/G vs. G/G, p=0.625). Furthermore, the administration of the orexin receptor antagonist filorexant was not effective for migraine prophylaxis [17]. Therefore, the orexin system may not be related to migraines.

Conclusion

Orexin-related gene polymorphisms were not identified as the contributing factors to the aggravation of migraines due to the overuse of medications in the present study. However, since the sample size was the biggest limitation of this study, future studies with larger samples need to be undertaken in order to elucidate the relationship between orexin-related gene polymorphisms and the complication of MOH in migraine patients.

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Masakazu Ishii, Masaaki Ishibashi, and Hirotaka Katoh contributed equally to this work.

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