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Evaluation of The Impact of Hypocretin Receptor 1 rs2271933 Polymorphism on Sleep Components in Chronic Migraine Patients with Poor Sleep Quality: A Subgroup Analysis

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ABSTRACT

Introduction: Long-reported dual comorbidity between migraine and sleep disorders suggests that some gene variations may play a role in this relationship. Our previous study found an association between poor sleep quality and the G allele of the hypocretin receptor 1 (HCRTR1) rs2271933 gene in patients with chronic migraine (CM). This study aimed to examine the relationship of this gene with some sleep parameters.

Methods: The present study was designed cross-sectional in the Mersin University Neurology Clinic between January 2000 and February 2018. Patients aged 18–75 years with CM according to the International Classification of Headache Disorders-3 (ICHD-3) criteria were included. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate the sleep quality of the patients. Patients were divided into two groups according to PSQI scores <6 or ≥6. Genotyping was performed for the HCRTR1 rs2271933 gene.

Results: Among the 100 patients with CM, only the data of those (n=67) with poor sleep quality were included in this study. The mean age of patients was 40.9±11.8%, and the female rate was 89.6%. We detected that increasing the time to fall asleep (p=0.369) and the rate of poor sleep quality (p=0.461) and also shortening sleep duration (p=0.016) with the increase of G allele carrier of HCRTR1 rs2271933 gene.

Conclusion: As the G allele carrier of the HCRTR1 rs2271933 gene increased, a shorter sleep duration was observed. This finding may contribute to studies on the physiological roles of orexins.

Keywords: Chronic migraine, HCRTR1 rs2271933, poor sleep quality, sleep duration, sleep latency

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INTRODUCTION

Many epidemiological studies have revealed a positive relationship and a vicious cycle between migraines and sleep disturbances (1,2). Poor quality or insufficient sleep may trigger migraine attacks (3), while migraine attacks may affect sleep quality and cause sleep disturbances to increase and endure (4). This relationship between migraine and sleep disorders suggests the shared common pathophysiological mechanisms (5,6). According to some studies, environmental and genetic factors have almost equal influence on the development of both migraine and sleep disorders (7–9).

Hypocretin (HCRT) (or orexin) is a crucial molecule for genetic baseline research, as it plays an important role in both the sleep-wake cycle and pain modulation (10–12). Hypocretins and their receptors are neuropeptides synthesized in hypothalamic neurons (13). The HCRT system includes the neuropeptide donors HCRT-1 and HCRT-2 (orexin-A and -B, respectively), and their G-protein coupled receptors [HCRTR1 (OX1R) and HCRTR2 (OX2R), respectively] (14). The intense projections of HCRT to noradrenergic, serotonergic, dopaminergic, cholinergic, and gamma-aminobutyric acid (GABA) ergic /glutamatergic regions of the brain suggest that it may also play a role in neuropsychiatric disorders (15). Krystal et al. reported that GABA secretion may decrease, and oppositely, orexin activation may increase at night in patients suffering from insomnia. Their study demonstrated that orexinergic peptide levels in dogs' cerebrospinal fluid (CSF) increased by up to 70% after 24 hours of sleep deprivation (16). This finding suggests that sleep deprivation

Highlights

- **Most chronic migraineurs suffer from poor sleep quality.**
- **The sleep latency is more prolonged in G allele carriers of the HCRTR1 rs2271933 gene.**
- **G allele carriers of the HCRTR1 rs2271933 gene have a shorter sleep duration.**

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may affect the orexinergic system and that increased orexin activity may impair wakefulness. In fact, another study reported that orexin antagonist caused sleep symptoms in humans by both objective and subjective measurement methods (17).

Many genetic polymorphisms have been identified in the HCRTR1 gene. The HCRTR1 gene variant (rs2271933, G1222A) in exon 7 leads to amino acid substitution (Ile408Val) (18), and A allele carrier has been associated with 1.4-fold risk of migraine (19). Oliveira et al. found no difference between the patients with insomnia and the control group consisting of healthy individuals regarding the G1222A polymorphism of the HCRTR1 gene (20). Similarly, Tang et al. asserted that increased plasma orexin-A levels in patients with insomnia were associated with the course and severity of insomnia but were not associated with pre-orexin and orexin receptor gene polymorphisms (one variation (rs2271933) in the OX1R gene and one variation (rs2653349) in the OX2R gene) (21). On the contrary, according to our previous study, the G allele carriers of the HCRTR1 rs2271933 gene were associated with poor sleep quality in patients with chronic migraine (CM) (22). In another study comparing patients with major depressive disorder and healthy individuals, a correlation was found between the HCRTR1 rs2271933 gene and Pittsburgh Sleep Quality Index (PSQI) scores (23).

Considering all this, the functional significance of this common HCRTR1 rs2271933 gene variant remains unclear. There is a limited number of studies investigating the effect of genetic polymorphism of HCRTR1 on sleep in migraineurs. This study aimed to determine the potential effects of genetic variance of the HCRTR1 gene on sleep parameters in patients with CM who have poor sleep quality.

METHODS

Subjects and design of the study

This study is a subgroup analysis of research that was conducted as a cross-sectional. Patients aged between 18–75 years were included in the study on a voluntary basis., The patients were admitted to the Neurology Clinic of Mersin University between January 2000 and February 2018 and were diagnosed with definite CM according to the International Classification of Headache Disorders-3 (ICHD-3) criteria (24).

Patients with CM were questioned with PSQI for sleep disturbances and divided into two groups according to their PSQI scores <6 (CM with good sleep quality) or ≥6 (CM with poor sleep quality). Besides, the time of going to bed (8:00 PM-9:00 PM /9:00 PM-10:15 PM /10:15 PM-12:30 AM /12:30 AM-01:45 AM /1:45 AM-3:00 AM) and getting up (5:00 AM-6:30 AM /6:30 AM-7:45 AM /7:45 AM-9:45 AM /9:45 AM-11:00 AM /11:00 AM-12:00 NOON) were categorized according to the Morningness-Eveningness Questionnaire Self-Assessment Version (MEQ-SA). In addition, some factors that may affect sleep characteristics in the participants, such as shift work, smoking, alcohol consumption, and their sleeping and waking hours were questioned.

The blood samples of patients were taken for the HCRTR1 rs2271933 genotyping (details are given below).

In the previous study, we compared patients' demographic data with poor and good sleep quality (22). This study focused on the relationship between the HCRTR1 rs2271933 genotypes and sleep parameters in CM patients with poor sleep quality. Furthermore, we examined this relationship in patients who carry or do not carry the G allele of the HCRTR1 rs2271933 gene.

The study received approval from the Mersin University Rectorate Clinical Research Ethics Committee. All participants provided informed consent to take part in the study. The informed consent process followed the principles outlined in the Declaration of Helsinki, which is a set of ethical guidelines for medical research involving human subjects. Additionally, the study was supported by the Mersin University Faculty of Medicine, Individual Research Project Unit (Project No: 2018-2-AP4-2932).

Questionnaires

The Pittsburgh Sleep Quality Index

The PSQI is a widely used self-report questionnaire that evaluates sleep quality over one month. Its primary purpose is to establish a standardized measure for gathering consistent information about individuals' subjective sleep habits (25–28). The questionnaire comprises 19 items, further grouped into seven components. Completing the questionnaire usually takes approximately 5 to 10 minutes. The Turkish reliability and validity checks of PSQI were already done by Agargun et al. (1996) (29).

The seven components of the PSQI are as follows:

i) Sleep quality: This component assesses an individual's overall perception of their sleep quality, ranging from very good to very bad; *ii) Sleep latency:* It measures the time it takes for a person to fall asleep after going to bed. This component provides insights into how quickly individuals can transition from wakefulness to sleep; *iii) Sleep duration:* This component involves recording the total time spent sleeping, including both nighttime sleep and daytime napping; *iv) Habitual sleep efficiency:* It calculates the percentage of time an individual spends asleep while in bed. This component determines how efficiently one utilizes their time in bed for sleep; *v) Sleep disturbances:* It examines the frequency of various sleep disruptions, such as waking up during the night, experiencing difficulties in breathing or snoring, having bad dreams, or using the bathroom; *vi) Use of sleeping medication:* This component evaluates the frequency of using sleep aids or medication to initiate or maintain sleep; *vii) Daytime dysfunction:* It assesses the level of daytime impairment caused by sleep-related issues, including problems with energy levels, daytime sleepiness, difficulties in concentration, and overall daytime dysfunction.

Each item within the questionnaire is scored on a scale ranging from 0 to 3, with 3 representing the most negative response. The component scores are then summed up to yield a global PSQI score, which ranges from 0 to 21. Pittsburgh Sleep Quality Index global score lower than 6 (<6) indicates healthier sleep quality, whereas a score higher than 6 (≥6) often indicates poor sleep quality.

Morningness-Eveningness Questionnaire Self-Assessment Version

The MEQ-SA is a self-assessment questionnaire used to determine an individual's chronotype, which refers to their preference for morning or evening activities based on their circadian rhythm (30). The MEQ-SA helps assess whether a person's biological clock produces peak alertness in the morning, evening, or somewhere between. The standard MEQ-SA comprises 19 multiple-choice questions with four or five response options. The questions cover various aspects of sleep habits, alertness, and preference for different times of the day. Once all the questions are answered, the responses are scored, and a composite score is calculated. This composite score reflects the degree to which the individual favors morningness or eveningness. The Turkish reliability and validity checks of MEQ-SA were already done by Agargun et al. (2007) (31).

Genotyping

Genomic DNA was extracted from 10 ml of EDTA anticoagulated whole blood by using The PureLink™ Genomic DNA Mini Kit (Thermo Cat No: K182002, USA). The polymorphism of the HCRTR1 gene was genotyped using TaqMan SNP Genotyping assays (Applied Biosystems, Thermo cat No: 4351379) and TaqMan Genotyping Master Mix II (Thermo cat No:

4440038). Genotyping was performed using LightCyler 480 II Real-Time PCR (Roche). The polymerase chain reaction (PCR) was performed in a 20-µl reaction mixture and a 96-well Real-Time PCR System (Bio-Rad Laboratories, Hercules, CA, USA). The reaction mixture included 5 µl genomic DNA, 1 ml of primer-probe assay (for the HCRTR1 [rs2271933; https: //www. ncbi. nlm. nih. gov/snp/rs2271933] (32), TaqMan SNP Genotyping Assay, C__15961465_10) Thermo, USA). The amplification protocol was as follows: initial denaturation at 95°C for 10 min, followed by 40 cycles of 95°C for 15 s (denaturation), 60°C for 60 s (annealing), and 40°C for 30 s (cooling).

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) program version 22.0 premium software. Descriptive statistics were used to describe the study population characteristics. Quantitative variables were expressed as mean ± standard deviation (SD), and qualitative variables were expressed as frequency and percentage values. The Shapiro–Wilk normality test was used to test the normality of the distribution of quantitative data. The independent samples t-test was used to compare normally distributed continuous variables, whereas the Mann–Whitney U and Kruskal–Wallis H-tests were used for variables not normally distributed. Pearson chi-square and Fisher's exact tests were used to compare categorical variables and frequencies of occurrence. Bonferroni-corrected p-value (0.05/3; p <0.016) was considered significant for migraine genotype subgroups comparisons in Pearson chi-square. When the results between the comparisons were statistically significant, the parameter in the chi-square boxes that created the significance was determined according to the adjusted values; a value of ≥2 was considered as significant.

RESULTS

Among the 100 patients with CM, only the data of those (n=67) with poor sleep quality (PSQI score ≥6) were included in this subgroup analysis study. The comparison of sociodemographic and genotype characteristics of CM patients with poor and good sleep quality has already been compared in our previous study, thus the full data comparison is not presented here once again (22). The mean age of chronic migraine patients with poor sleep quality was 40.9±11.8, and 89.6% were female. The age of migraine onset was 27.2±10.4. Aura and autonomic findings in patients were reported at 34.3% and 70.1%, respectively. 43.3% of patients continued smoking, 3.3% were left. Also, 25% of them consumed alcohol. 12.3% of patients were working as a shift. The genotype distribution of the HCRTR1 rs2271933 gene among patients with CM was as follows; 25% of the patients had the AA, 30% had the AG, and 45% had the GG genotype. The genotype and allele distribution of the HCRTR1 rs2271933 gene among CM patients with poor sleep quality is given in Table 1. Furthermore, we presented the genotype distribution of the HCRTR1 rs2271933 gene in terms of age and gender among CM patients with poor sleep quality in Table 1.

The sleep latency was longer than 30 minutes in 75% of our patients with CM with the HCRTR1 rs2271933 gene. The time to fall asleep was 32.9±20.50 min in the patients with the AA genotype, 33.2±35.19 min with the AG genotype, and 48.9±48.48 min with the GG genotype sleep latency increased as the G allele carriers increased. However, this was not statistically significant (p=0.369).

The time spent in bed was 7.6±1.69 hours in patients with the AA genotype, 7.2±1.27 hours with the AG genotype, and 7.4±1.55 hours with the GG genotype. There was no significant difference regarding time spent in bed between these three genotypes (p=0.803). In addition, there was no difference between genotypes of the HCRTR1 rs2271933 gene regarding the times of going to bed (p=0.378) and getting up (p=0.638).

Total sleep time showed insignificant differences between the patients with variants of HCRTR1 rs2271933 genotypes; it was 6.8±1.27 hours in the patients with the AA genotype, whereas 5.9±1.99 hours in patients with the AG genotype and 6.5±1.78 hours with the GG genotype (p=0.285). The proportion of patients with bad (both fairly and very) subjective sleep quality was 13.4%, 20.9%, and 37.3% among the HCRTR1 rs2271933 gene's AA, AG, and GG genotypes, respectively. The ratio of bad sleep quality seemed to increase with the G allele carrier, but also, it was also not statistically significant (p=0.461).

The distribution of the HCRTR1 rs2271933 gene polymorphisms in patients with CM who have poor sleep quality according to the seven subcomponents used in calculating the PSQI score is shown in Figure 1. Of these, only the sleep duration seemed significantly shorter among patients with G alleles (p=0.044). However, it was also insignificant after the Bonferroni correction due to three subgroups (p<0.016). When we evaluated patients with CM who carried G allele or not separately, G allele carriers of the HCRTR1 rs2271933 gene had significantly shorter sleep duration than solely AA genotype carriers (p=0.016). While none of the patients with the AA genotype had a sleep duration of less than 5 hours, 25% of the patients with the AG or GG genotype had a sleep duration of less than 5 hours.

There was no significant difference between the patients with AA, AG, and GG genotypes of the HCRTR1 rs2271933 gene in terms of some sleep parameters such as waking up at midnight or early in the morning (p=0.505), getting up to use the bathroom (p=0.475), not breathing comfortably (p=0.767), feeling too cold (p=0.782), feeling too hot (p=0.205), having bad dreams (p=0.661), having pain while asleep (p=0.165), and loud coughing or snoring (p=0.501).

There was no difference between the patients with AA, AG and GG genotypes of the HCRTR1 rs2271933 gene regarding daytime dysfunction (p=0.949) and using sleep medication (p=0.549).

Table 1. Distribution of genotypes of HCRTR1 rs2271933 polymorphism in terms of age and gender, and the distribution of genotype and allele frequencies of the HCRTR1 rs2271933 polymorphism in CM patients with poor sleep quality

	HCRTR1 rs2271933					p value*
	Genotypes			Alleles		
	AA	AG	GG	A	G	
Age (mean ± SD)	36.6±10.66 (20–51)	44.5±12.05 (22–71)	39.9±11.71 (21–63)			0.211[a]
Gender (F/M) (n)	11/1	20/3	29/3			0.880[b]
PSQI Scores ≥6 n (%)	12 (17.9)	23 (34.3)	32 (47.8)	47 (35.1)	87 (64.9)	

a: Kruskal Wallis test; b: Pearson chi-square; CM: Chronic migraine; Hardy Weinberg equilibrium: 0.40; HCRTR1: Hypocretin 1; PSQI: Pittsburgh sleep quality index; *p <0.016 (according to Bonferroni correction: p=0.05/3=0.016)

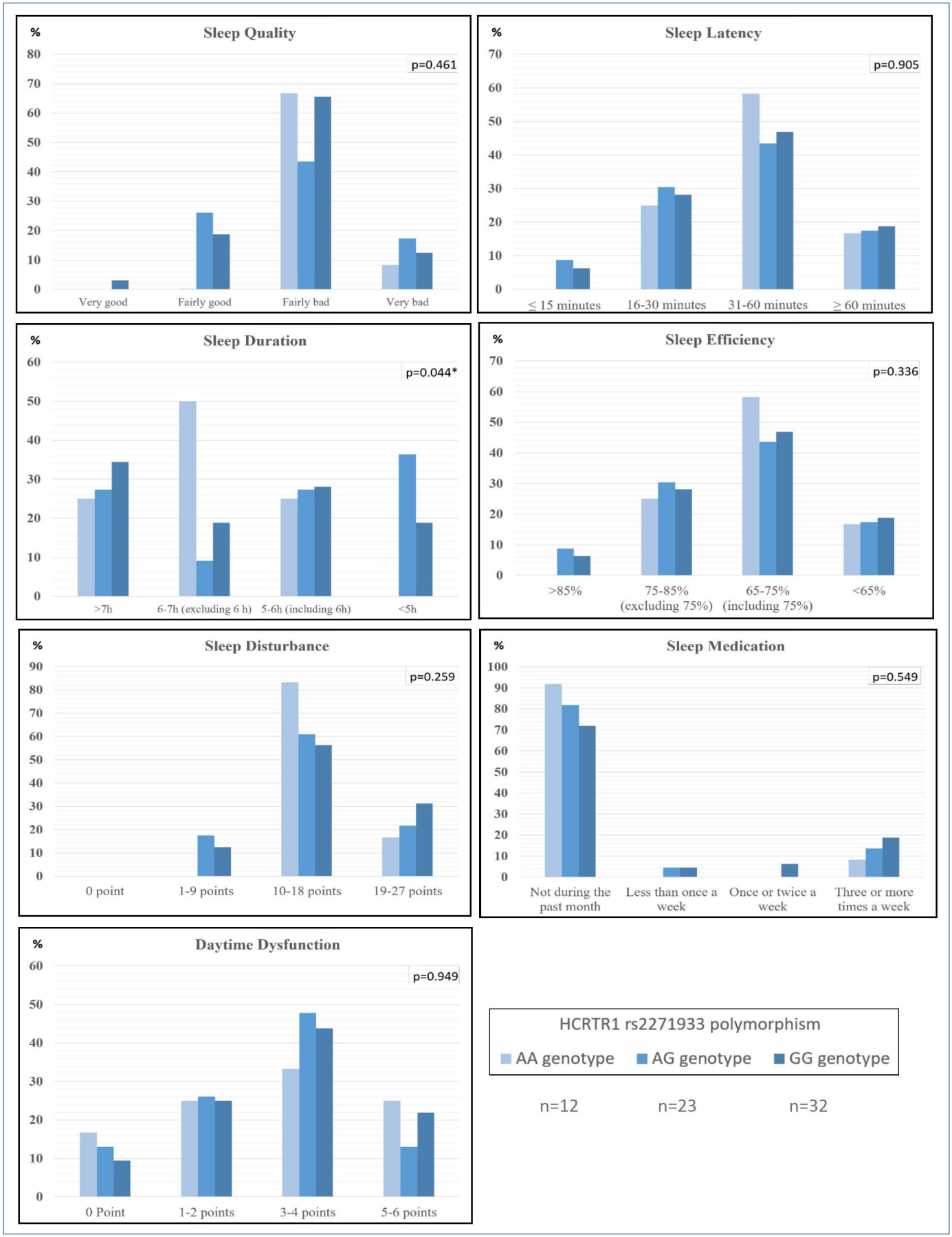

Figure 1. Distribution of the genotypes of the HCRTR1 rs2271933 polymorphism in seven subcomponents of the PSQI in CM patients with poor sleep quality (CM: Chronic migraine; h: hour; HCRTR1:Hypocretin receptor 1; PSQI: Pittsburgh sleep quality index; *Bonferroni-corrected p-value was calculated according to number of subgroups (0.05/3; p <0.016) in Pearson chi-square.)

The majority of the patients (70.1%) had a bed/room partner. According to the data obtained from the bed/room partner, no difference was found between the patients with the genotypes of HCRTR1 rs2271933 gene in terms of loud snoring (p=0.352), twitching or jerking in the legs while sleeping (p=0.861), disharmony and confusion during sleep (p=0.938).

DISCUSSION

The effect of genetic polymorphism of the HCRTR1 rs2271933 gene on poor sleep quality was investigated in patients with CM in this study. No significant differences were found between HCRT1 rs2271933 gene genotypes in sleep parameters including sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, daytime dysfunction and sleep medication intake (Figure 1). In addition, we compared these sleep parameters between the patients who carry or do not carry the G or A allele of the HCRTR1 rs2271933 gene. We found that G allele carriers of the HCRTR1 rs2271933 gene had significantly shorter sleep duration than solely AA genotype carriers.

Almost half of the migraineurs suffer from insufficient sleep, especially the sleep quality is reported to be more impaired in patients with CM than in those with episodic migraine (EM) (33,34). Our previous study also demonstrated poor sleep quality almost in 70% of patients with CM (22). Here in this study, we compared the subjective sleep quality between the subgroups of HCRTR1 rs2271933 gene AA, AG, and GG genotypes, but we did not find a statistically significant difference (Figure 1).

Lateef et al. found that difficulty initiating sleep is seen 2.2 times more frequently in patients with migraine when compared to healthy controls (35). In line with this, the sleep latency was also longer than 30 minutes in three of four patients with CM in our study. However, when we evaluated whether there was a difference between genotypes, we did not find a significant difference in sleep latency between the three subgroups.

Sleep duration is a complex parameter to evaluate, which can change according to genetic factors (up to 41%), changing lifestyles, and needs (33,36). A population-based study in Spain; showed that migraine is more common in people who sleep less than 8 hours a day. This finding suggests a link between insufficient sleep duration and migraine occurrence (37). In contrast, Jiyoung et al. reported that mean sleep duration did not differ between migraineurs and non-migraine headaches, but they reported that the need for sleep was higher in patients without CM or EM (33). It is known that migraineurs try to alleviate their headaches through sleep (38). In addition, Jiyoung et al. did not distinguish between EM and CM in the study (33). However, according to another study, sleep duration is shorter in patients with CM compared to patients with EM (2). These findings suggest the relationship between the alteration of sleep characteristics by the chronicity of migraine. This condition makes us think about the alteration of sleep characteristics by the chronicity of migraine. Our study found no significant relationship regarding sleep duration between the HCRTR1 rs2271933 gene AA, AG, and GG genotypes (Figure 1). However, in other subgroup analysis, we found that the sleep duration decreased among the patients with the G allele carrier (p=0.016). Interestingly, there was no difference between genotypes regarding time spent in bed.

Sleep efficiency can be affected by many factors (39). It was reported that migraine patients were 2.8 times more likely to have trouble sleeping and 2 times more likely to wake up early in the morning compared to healthy individuals. (35). Furthermore, Kelman et al. noted that patients suffering from CM have more problems with falling and staying asleep than those with EM (2). We evaluated whether there was an association between the CM patients with different genotypes of the HCRTR1 rs2271933 gene regarding going to bed and getting up times, but there was no significant difference. Other factors affecting sleep efficiency are snoring and breathing problems during sleep. In some studies, snoring is reported to be a risk factor for conversion from EM to CM (40). Some research showed that apnea and snoring increased in chronic headaches (41). In this study, we evaluated the parameters for sleep efficiency, such as falling asleep within 30 minutes, waking up in the middle of the night or early in the morning, having to get up to use the bathroom, not being able to breathe comfortably during sleep, feeling too cold, feeling too hot, having bad dreams, having pain during sleep, coughing or snoring loudly during sleep between the CM patients with genotypes of the HCRTR1 rs2271933 gene. However, we could not find a significant difference supporting the effect of HCRTR1 gene polymorphism.

Recent studies have shown significantly higher concentrations of hypocretin-1 in patients with drug overuse headaches and CM (42). Conversely, some authors suggested that the hypocretinergic system may have a complex role in the motivational state and addiction behaviors to drug abuse (19). Therefore, we wanted to investigate whether there is any effect of HCRTR1 gene polymorphism on sleep medication uptake. However we found no significant difference between AA, AG, and GG genotypes in patients with CM.

Daytime dysfunction is a vital sleep problem that includes some issues, such as low energy levels, daytime sleepiness, and difficulty concentrating (43). Daytime fatigue is reported to be 2.6 times higher in migraine patients (35). Seidel et al., on the contrary, noted that the ratios of fatigue and daytime sleepiness were not different in migraine from controls (44). These different results may be due to the intricacy of the patients' sleep problems. Therefore, we examined whether the HCRTR1 gene polymorphism affects daytime dysfunction parameters, but we could not obtain a significant result between the carriers of AA, AG, and GG genotypes.

In animal studies, HCRTR1 gene expression in the hypothalamus was found to be significantly higher in females compared to males (45). Yet, in humans, orexin levels do not vary significantly in different sexes and ages (46). Though, this condition can cause some sleep problems. For instance, it was shown that older individuals with insomnia are more likely to have higher levels of orexin-A (21). However, underlying genetic relationships are still obscure. This study did not find a significant difference between the genotypes of the HCRTR1 rs2271933 gene and the patients with CM who have poor sleep quality regarding age and gender. Similarly, in a study investigating the HCRTR1 rs2271933 gene polymorphism in insomnia patients, no significant difference was found in terms of gender (20).

Poor sleep quality, daytime sleepiness, insomnia, restless legs syndrome, and parasomnias are commonly described sleep disorders in migraineurs (47). Insomnia within these symptoms is three times more common among migraine sufferers than in the general population. In addition, compared to EM, patients with CM have a shorter night sleep and frequent problems in falling and staying asleep (2). Studies that focused relationship between these comorbidities have revealed that sleep disorders are polygenic disorders that may result from the synergy of genetic and environmental factors (8). This also makes it priceless to investigate genetic polymorphisms and their relationships with sleep. Thus, this study concentrated on the genetic relationship of poor sleep quality in patients with CM.

Strengths of the study

As much as we know, this study is the first to evaluate the relationship between sleep quality and the HCRTR1 G1222A gene polymorphism in patients with CM. Another important strength of the study is that a more stratified study population was created compared to previous studies by selecting patients with CM.

Limitations of the study

Our study has some limitations:

1. Although the PSQI is a widely used tool for assessing sleep quality, it is based on patients' self-reports. Findings may be misrepresented, exaggerated, or minimized. This can also change the final scores.

2. The difficulties in identifying temporal associations are due to a relatively small sample size and a need for more functional studies of the HCRTR1 G1222A.

3. Parameters such as sleep latency, total sleep duration, and quality have not been evaluated objectively by methods such as actigraphy or polysomnography.

Many factors, such as phenotypic characteristics, sample size, selection of polymorphisms, and population stratification, are difficulties in genetic association studies. We could not find a relationship between the HCRTR1 rs2271933 gene polymorphism and many components of PSQI parameters in our study. However, the ratio of patients with a shortening sleep duration was significantly higher among the HCRTR1 rs2271933 gene G allele carriers. Though some of the findings are exciting, it remains to be confirmed in different populations, in larger sample groups where clinical features are more rigidly stratified, and in combination with other polymorphisms involved in the mechanism of hypocretin synthesis and release. Furthermore, understanding the genetic basis of the relationship between migraine and sleep disorders will provide more information about the pathogenesis of both diseases, as well as allow the development of new diagnostic tests and personalized treatment strategies.

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Ethics Committee Approval: The informed consent process followed the principles outlined in the Declaration of Helsinki, a set of ethical guidelines for medical research involving human subjects. The study received approval from the Mersin University Rectorate Clinical Research Ethics Committee. Additionally, the study was supported by the Mersin University Faculty of Medicine, Individual Research Project Unit (Project No: 2018–2-AP4–2932).

Informed Consent: All participants provided informed consent to take part in the study.

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