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Associations of OPRM1 A118G Gene Polymorphism with Pain Sensitivity and Opioid Dosage of Patients with Postherpetic Neuralgia

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KEYWORDS Gene. Herpes Zoster. Opioid. Pain. Polymorphism

ABSTRACT This study aimed to explore the associations of $OPRM_1$ A118G gene polymorphism with pain sensitivity and opioid dosage of patients with postherpetic neuralgia (PHN). According to the 3-month follow-up results, 103 PNH patients were enrolled as a PHN group, and 112 without PHN after herpes zoster were included as a non-PHN group. The factors affecting PHN occurrence were subjected to one-way analysis of variance and multivariate logistic regression analysis. The frequency distribution of GG, AG and AA genotypes in both PHN and non-PHN groups conformed to the Hardy-Weinberg equilibrium law ($P>0.05$). Initial treatment duration of more than 72 hours, severe acute pain and genotype GG were independent risk factors for PHN. Genotype GG exhibited significantly increased distribution frequency in mild, moderate and severe PHN groups. The 48-hour opioid dosage was highest in the patients with genotype GG ($P<0.05$). $OPRM_1$ A118G gene polymorphism causes individual differences in the pharmacodynamics of opioids in PHN patients.

INTRODUCTION

Herpes zoster (HZ) is an acute herpetic skin disease caused by reactivation of the varicella-zoster virus dormant in sensory ganglia, mainly manifested as unilateral papules and vesicles in zonal distribution and pain (Marra et al. 2020). It can be cured within 14 to 30 days in most cases, and pain disappears (Le and Rothberg et al. 2018). However, persistent pain still exists in some patients 3 months after the occurrence of HZ, which is referred to as postherpetic neuralgia (PHN) (Wang et al. 2020). As the most common complication of HZ, PHN has an incidence rate of about twenty percent in HZ patients aged over 50 years old and as high as fifty percent in those aged over 85 years old (Texakalidis et al. 2019). PHN leads to depression and physical disability, and persistent pain and abnormal sensation affect the quality of life (Du et al. 2021).

Acute and chronic pains are mainly treated by opioids, with the dosage varying among individuals (Okusanya et al. 2020). Numerous candidate genes related to drug metabolism have been reported, of which ì-opioid receptor gene ($OPRM_1$) has been studied extensively (Persson et al. 2019). $OPRM_1$ gene, which is located at 6q24-25, exon 1, encodes ì-opioid receptors (MORs) that are crucial target receptors for endogenous opioid peptides and opioid analgesics. The $OPRM_1$ gene polymorphism has been associated with the difference between the clinical responses of patients to opioids (Saiz-Rodríguez et al. 2021). At present, some single nucleotide polymorphisms (SNPs) in $OPRM_1$ gene have been confirmed, and A118G SNP is one of the most widely studied ones. Nevertheless, the associations of $OPRM_1$ A118G gene polymorphism with the pain sensitivity and opioid dosage of PHN patients remain largely unknown.

Objectives

The aim of this study was to provide a valuable reference for the gene-targeted therapy of PHN patients by exploring the relationships of $OPRM_1$ A118G polymorphism with the occurrence of PHN and the dosage of opioids.

MATERIAL AND METHODS

Subjects

This study has been approved by the ethics committee of the hospital, and written informed consent has been obtained from all patients. HZ

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patients treated in the pain clinic of the hospital from June 2019 to December 2020 were prospectively analysed, and whether they suffered from PHN was determined according to the 3-month follow-up results. A total of 103 PNH patients were enrolled as a PHN group, and 112 patients without PHN were included as a non-PHN group.

The inclusion criteria were set as follows:

1. Patients diagnosed as HZ in strict accordance with the expert consensus on diagnostic criteria in China
2. Those aged ≥50 years old
3. Chinese Han people

The exclusion criteria involved:

1. Patients with acute or chronic pain caused by other factors
2. Those with malignant tumours
3. Those with abnormal immune function
4. Those who were receiving or recently received immunosuppressive or cytotoxic therapy.

Main Reagents and Apparatus

dNTPs were provided by TaKaRa Biotech (Dalian) Co., Ltd. (China). Taq DNA polymerase, restriction enzyme and nucleic acid purification kits were purchased from Takara Biomedical Technology (Beijing) Co., Ltd. (China). Polymerase chain reaction (PCR) amplification system was bought from PE (USA). The other information of involved materials is mentioned below.

Pain Assessment and Dosage Data

The severity of acute pain and PHN was evaluated using the numerical rating scale (NRS) (Shafshak and Elnemr 2021). In detail, the patients described the severity of their pain with 11 numbers (0-10), and a larger number meant severer pain. 0 point, 1-3 point(s), 4-6 points, 7-9 points and 10 points indicated no pain, mild pain (without effects on sleep), moderate pain, severe pain (wake up with pain and unable to sleep) and sharp pain, respectively. Pain was initially scored before administration of analgesics. Then the patients were given corresponding analgesics such as oxycodone, tramadol, fentanyl transdermal patches and morphine based on individual differences in their medications and the European guidelines on opioid analgesia for cancer pain (Caraceni et al. 2012). The dynamic NRS score of less than or equal to 3 points was set as the standard for satisfactory PHN control. The opioid dosage was calculated according to the morphine equivalent daily dose (MEDD). In other words, the total dosage of opioids administrated during follow-up was converted into the total morphine equivalent dose (mg) divided by the total administration time (d) through the formulas: 200 mg/d tramadol (oral) = 30 mg/d oxycodone (oral) = 6 mg/d fentanyl (patches) = 20 mg/d morphine (intravenous/subcutaneous) = 60 mg/d morphine (oral).

Detection of $OPRM_1$ Gene Polymorphism

Venous blood (2 mL) was collected from patients, added into sodium citrate anticoagulant tubes (Thermo Fisher, USA) before the induction of anaesthesia, mixed well and stored at -80°C. Next, DNA was extracted using Resin-type™ genomic DNA extraction kit (Shanghai Saibaisheng Gene Technology Co., Ltd., China), and genotyping was performed by PCR-restriction fragment length polymorphism. The upstream primer was 5'-CAGTTGAACAGGGTGAATCTAGCG-3', and the downstream primer was 5'-CCGGCACTAGTACCTCCCTGA-3'.

The PCR system (20 μL) was composed of 1× PCR buffer, 2.0 mM Mg^{2+}, 0.2 mM dNTP, 1 U of HotStarTaq polymerase, 1 μL of sample DNAs and 1 μL of PCR primers. PCR procedure comprised of 96°C for 14 minutes, 12 cycles × (95°C for 21 s, 0.6-64°C/cycle for 40 seconds and 71°C for 1.6 minutes), 24 cycles × (93°C for 21 seconds, 58°C for 30 seconds and 71°C 1.6 minutes), 73°C for 3 minutes, and 4°C finally. The enzyme digestion reaction system contained 1× CutSmart Buffer, 1 U of Hpy188 I restriction endonuclease, and 5 μL of PCR product, which was added with ddH_2O to 10 μL and subjected to water bath at 37°C overnight. The digested products were diluted 10-fold and then loaded on 3730XL DNA analyser (Thermo Fisher, USA) for SNP typing.

Data Collection and Observation of Adverse Reactions

The basic information of patients was recorded, including age, gender, lesion site, duration of initial treatment, severity of acute pain, administration

of hormones and treatment course. Besides, the 48-hour opioid dosage, a 24-hour sleep quality score and state trait anxiety inventory (STAI) score were recorded (Kornilov et al. 2018; Kühlmann et al. 2018). The scale consisted of 20 items, including inversely and directly worded questions and punctuation. The scores ranged between 20 and 80 points, and a higher score indicated a higher level of anxiety.

Statistical Analysis

SPSS 19.0 software was used for statistical analysis, and the differences in genotypes and allele frequencies were compared by the χ^2 test among groups. All variables were expressed as frequency and mean ± standard deviation (‘x ± s), and the independent sample *t* test was employed to compare general characteristics such as age and gender among groups. P<0.05 indicated that a difference was statistically significant.

RESULTS

Genotypes

On the electropherogram of each genotype of $OPRM_1$, 1 and 2 were genotype GG, 3 and 4 represented genotype AG, and 5 and 6 corresponded to genotype AA (Fig. 1).

Hardy-Weinberg Equilibrium Test Results

In both PHN and non-PHN groups, the frequency distribution of GG, AG and AA genotypes (72, 36 and 9 versus 8, 28 and 67) conformed to the Hardy-Weinberg equilibrium law (P>0.05), suggesting that the sampled populations had comparable equilibrium (Table 1).

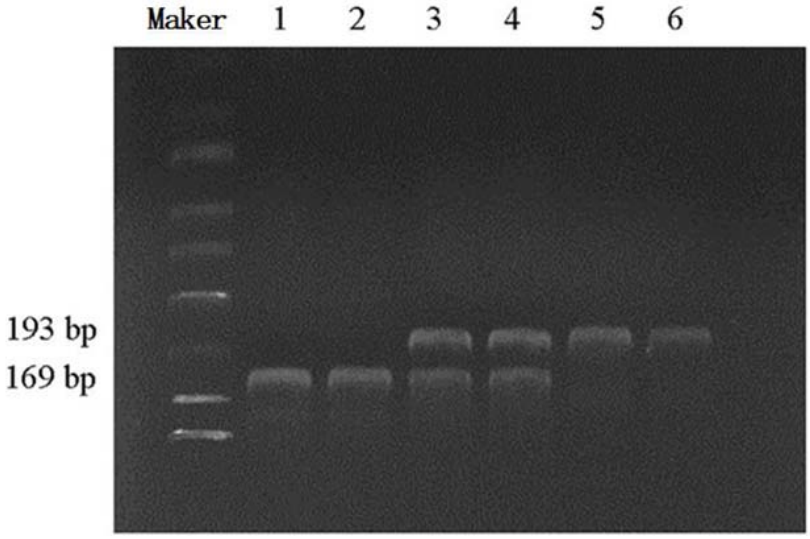

Fig. 1. Detection results at A118G restriction site in PHN patients. PHN: Postherpetic neuralgi

Table 1: Hardy-Weinberg equilibrium test results

Group	*AA*		*AG*		*GG*		χ^2	*P*
	Theoretical value	*Measured value*	*Theoretical value*	*Measured value*	*Theoretical value*	*Measured value*		
PHN (n=103)	9.3	9	36.4	36	71.6	72	1.264	0.351
Non-PHN (n=112)	67.1	67	28.2	28	7.9	8	0.569	0.584

PHN: Postherpetic neuralgia

Clinical Data

Age, initial treatment duration, acute pain severity, treatment course, genotype and allele frequency showed significant differences between the two groups (P<0.05), while no significant differences were found in gender, lesion site or administration of hormones (P>0.05) (Table 2). Therefore, the occurrence of PHN was affected by $OPRM_1$ A118G genotype and allele frequency.

Multivariate Logistic Regression Analysis Results of PHN

The factors with significant differences in one-way analysis of variance were included in multivariate logistic regression analysis. The results showed that initial treatment duration of more than 72 hours, severe acute pain and genotype GG were independent risk factors for PHN (P<0.05) (Table 3).

Distribution of Genotypes at the A118G Locus in Patients with Different Degrees of PHN

The PHN group was further grouped based on the severity of PHN (mild, moderate and severe), and the relationship between genotype and PHN severity was analysed. The distribution frequency of the GG genotype rose significantly in mild, moderate and severe PHN groups (8.82, 15.63 and 27.03 percent) (P<0.05) (Table 4).

Association Between Different Genotypes of $OPRM_1$ A118G and Opioid Dosage

A total of 69 patients taking opioid analgesics in the PHN group were selected, and the opioid

Table 2: Clinicopathological characteristics affecting PHN [n (percent)]

	PHN group (n=103)	*Non-PHN group (n=112)*	t/χ^2	*P*
Age (years old)			41.973	0.000
<50	6 (5.83)	50 (44.64)		
≥50	97 (94.17)	62 (55.36)		
Gender			0.009	0.925
Male	49 (47.57)	54 (48.21)		
Female	54 (52.43)	58 (51.79)		
Lesion Site			0.569	0.903
Face	19 (18.45)	23 (20.54)		
Trunk	27 (26.21)	28 (25.00)		
Arms and legs	21 (20.39)	26 (23.21)		
Multiple sites	36 (34.95)	35 (31.25)		
Initial Treatment Duration (h)			12.7345	0.002
<48	18 (17.48)	35 (31.25)		
≥48-72	15 (14.56)	28 (25.00)		
>72	70 (67.96)	49 (43.75)		
Acute Pain Severity			90.104	0.000
No pain	0 (0)	15 (13.39)		
Mild pain	3 (2.91)	31 (27.68)		
Moderate pain	6 (5.83)	35 (31.25)		
Severe pain	94 (91.26)	31 (27.68)		
Administration of Hormones			2.674	0.102
Yes	33(32.04)	48 (42.86)		
No	70(67.96)	64 (57.14)		
Treatment Course (d)			25.972	0.000
<14	91(88.35)	64 (57.14)		
≥14	12(11.65)	48 (42.86)		
Genotype			8.800	0.012
AA	53(51.46)	71 (63.39)		
AG	27(26.21)	32 (28.57)		
GG	23(22.33)	9 (8.04)		
Allele Frequency			6.055	0.014
A	60(58.01)	83 (73.84)		
G	43(41.99)	29 (26.16)		

PHN: Postherpetic neuralgia

Table 3: Multivariate logistic regression analysis results of PHN

Factor	*β*	*SE*	*Wald*	*P*	*OR (95% CI)*
Age	0.517	0.538	4.632	0.211	0.856 (0.469~2.952)
Initial treatment duration	1.178	0.539	7.102	0.003	1.971 (1.475~3.293)
Acute pain severity	2.804	0.670	8.403	0.001	2.295 (1.504~4.127)
Genotype	1.573	0.421	7.115	0.005	1.853 (1.306~3.195)

Assignment of independent variables: age: <50 years old=0, and e"50 years old=1, initial treatment duration: <48 h=0, 48-72 h=1, and >72 h=2, acute pain severity: no pain=0, mild pain=1, moderate pain=2, and severe pain=3, and genotype: AA=0, AG=1, and GG=2. CI: Confidence interval; OR: odds ratio; PHN: postherpetic neuralgia; SE: standard error.

dosage was converted using MEDD. The 48-hour opioid dosage rose in the patients with different genotypes in moderate and severe PHN groups in turn, which was highest in patients with the GG genotype (44.24 and 89.52 mg3.48^{-h}) (P<0.05). In addition, the sleep quality score and STAI score showed no significant differences in moderate and severe PHN groups (P>0.05) (Table 5). Thus, the opioid dosage should be elevated for the cases with GG genotype.

Table 5: Association between different genotypes of OPRM1 and opioid dosage

Genotype	*MEDD median (25-75 percent, mg48-h)*	*Sleep quality score*	*STAI score*
Moderate Pain			
AA	38.63(25.09~63.20)	2.69±0.47	41.66±8.37
GA	42.83(25.61~64.29)	2.73±0.52	39.64±7.11
GG	44.24(26.57~63.48)	2.79±0.49	42.67±9.08
t/χ2	5.205	1.417	0.232
P	0.018	0.346	0.824
Severe Pain			
AA	81.68(65.18~275.39)	2.71±0.44	38.55±5.14
GA	87.44(58.37~212.75)	2.16±0.37	40.80±9.42
GG	89.52(39.21~110.36)	1.83±1.15	37.29±7.13
t/χ2	7.039	1.174	0.680
P	0.001	0.413	0.658

MEDD: Morphine equivalent daily dose; STAI: state trait anxiety inventory

DISCUSSION

Neuralgia caused by herpes virus infection accounts for over twenty-five percent of all kinds of neuralgia, with an increasing incidence rate annually (Dai et al. 2020). PHN has an unclear pathogenesis, but peripheral sensitisation, central sensitisation and inflammatory reaction are the major causes (Lin et al. 2019). Currently, PHN is mainly treated with opioids, most of which exert an analgesic effect with $OPRM_1$ as a vital target, and such an analgesic effect is affected by the $OPRM_1$ gene polymorphism (Xu et al. 2015). In this study, the frequency distribution of the three genotypes of $OPRM_1$ A118G in PHN and non-PHN groups conformed to the Hardy-Weinberg equilibrium law, implying that $OPRM_1$ A118G reflected the general conditions of patients.

PHN may be affected by various factors including age, lesion site, initial treatment duration and treatment course (Forbes et al. 2016). In this study, PHN and non-PHN groups had significantly different age, initial treatment duration, acute pain severity, treatment course, and genotype and allele frequency. Besides, logistic regression analysis revealed that initial treatment duration of more than 72 hours, severe acute pain and genotype GG were independent risk factors for PHN. The administration of antiviral drugs as early as possible can suppress herpes virus to the maximum extent, and the patients given antiviral treatment within 72

Table 4: Distribution of genotypes at the A118G locus in patients with different degrees of PHN [n (percent)]

Genotype	*Mild pain (n=34)*	*Moderate pain (n=32)*	*Severe pain (n=37)*	χ^2	*P*
AA	24(70.59)	16(50.00)	12(32.43)	10.843	0.028
GA	7(20.59)	11(34.38)	15(40.54)		
GG	3(8.82)	5(15.63)	10(27.03)		

PHN: Postherpetic neuralgia

hours after skin lesions have a higher risk of PHN than that of the cases treated within 48 hours (Roth et al. 2010). Zhao et al. (2017) reported that severer acute pain indicated a higher risk of PHN, being consistent with the results of this study. PHN patients suffer from disappearance and fibrosis of the myelinated fibres of sensory ganglia, resulting in atrophy of the posterior horn of the spinal cord. The $OPRM_1$ polymorphism plays an important role in pain and pain-related phenotypes, and the A118G polymorphism has been most widely studied (Yu et al. 2019). De Capraris et al. (2011) demonstrated that patients with $OPRM_1$ 118A>G polymorphism exhibited different postoperative pain responses from those of the cases with wild-type genes, so the analgesic effects were different. Additionally, Matic et al. (2017) evaluated the relationship between $OPRM_1$ A118G gene polymorphism and opioid dosage in 243 patients with cancer pain, and found that the cases with AG and GG genotypes needed higher doses of analgesia. Chatti et al. (2017) found in 129 Tunisian patients with cancer pain that the morphine dose required for relieving pain was associated with the $OPRM_1$ A118G gene polymorphism. Besides, Reyes-Gibby et al. (2007) analysed 207 inpatients with cancer pain treated with morphine, and found that the patients with GG genotype required significantly more morphine than those with AA genotype. Moreover, Gong et al. (2013) reported that the $OPRM_1$ A118G gene mutation reduced the sensitivity of patients with cancer pain to opioids, then increasing the opioid consumption. In this study, the genotype GG was an independent risk factor for PHN, which is in line with the results of a previous literature (Forbes et al. 2016).

PHN is relieved mainly through the administration of opioids at present (Gudin et al. 2019). $OPRM_1$ genetic mutations can change the sensitivity of patients to opioids (Palada et al. 2018). To prove the difference between PHN severity and opioid dosage in patients with different $OPRM_1$ A118G genotypes, 69 patients who had moderate or severe pain and took opioid analgesics in the PHN group were herein selected. The 48-hour opioid dosage of patients with different genotypes significantly increased in moderate and severe PHN groups in turn, and that of patients with GG genotype was highest. Hence, the patients with a higher proportion of allele G in $OPRM_1$ expression were less sensitive to opioids, and the analgesic effect can be enhanced only by increasing the dose of analgesic drugs, being consistent with the findings of Saiz-Rodríguez et al. (2021). The binding force of opioid receptors to endogenous morphine-like substance β-endorphin in patients with GG type is three times that of the cases with AA type, and the number and activation of MORs are inhibited by $OPRM_1$ A118G gene locus mutations, ultimately attenuating the efficacy of opioids. Thus, the opioid dosage of patients with GG genotype should be raised to augment the analgesic effect (Mahmoud et al. 2011).

CONCLUSION

In conclusion, $OPRM_1$ A118G gene polymorphism is a genetic factor leading to individual differences in the pharmacodynamics of opioids in PHN patients.

RECOMMENDATIONS

It is of great significance to further explore the causes for the above-mentioned individual differences from transcription, translation, protein expression and other aspects in the future.

ABBREVIATIONS

MEDD: morphine equivalent daily dose
MOR: μ-opioid receptor
NRS: numerical rating scale
$OPRM_1$: μ-opioid receptor gene
PCR: polymerase chain reaction
PHN: postherpetic neuralgia
SNP: single nucleotide polymorphism
STAI: state trait anxiety inventory

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