COMTval158met Gene Polymorphism Correlation with Prenatal Anxiety and Labor Analgesia

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ABSTRACT This study investigates the correlation between COMTval158met gene polymorphism and prenatal anxiety and labor analgesia. Venous blood of 97 pregnant women was collected for the COMTval158met gene polymorphism analysis through reaction-restriction fragment length polymorphism method. Habitat modification *score* (*HMS*) and The *Symptom Checklist-90* (SCL-90) was applied to analyze the maternal anxiety status 1d before labor. The pain threshold and pain tolerance threshold were measured by Pain Threshold Machine. The average age, body weight, and gestational age among the three groups had no statistical difference ($P>0.05$). Habitat modification *score* and Hamilton Anxiety Rating Scale (HAM-A) score varied significantly between groups ($P>0.05$). The anxiety value, pain threshold, and pain tolerance were significantly different among groups ($P>0.05$). The polymorphism of the COMTval158met gene can affect maternal pain sensitivity and tolerance, which is associated with maternal antenatal anxiety and labor analgesia.

INTRODUCTION

As a normal physiological process, childbirth is a strong and persistent stimulus for mothers (Qingquan and Xuzhong 2016). Pregnant women's psychology and physiology have received more and more attention to the transformation of modern medical models (Wang et al. 2016). Because most of the labor is accompanied by pain, pregnant women often suffer from tremendous prenatal stress in terms of physiology and psychology, resulting in a variety of negative emotions. Among them, the prevalence of prenatal anxiety in pregnant women is rather high (Barcelona et al. 2016). As one of the most common mental disorders in prenatal women, antenatal depression is closely related to labor analgesia, which seriously threatens the delivery process and postpartum maternal and child health, and hinders the postpartum recovery

process (O'Donnell et al. 2017). Therefore, it is of great significance for maternal and infant health to seek the factors affecting prenatal anxiety and labor analgesia and intervene in responding to them. Studies have shown that the occurrence of affective disorder and the sensitivity of the human body to pain is closely related to genetic factors (Ren et al. 2019; Li et al. 2016). Catechol-O-methyltransferase (COMT) is a kind of metabolic enzyme that can regulate a variety of neurotransmitter activities, and is associated with a variety of mental disorders, and has a certain regulatory effect on human pain sensitivity (Gonzalezcastro et al. 2016). However, the association of COMT val158met gene polymorphism with prenatal anxiety and labor analgesia is not clear. Therefore, this study explored the relationship between COMTval158met gene polymorphism to prenatal anxiety and labor analgesia by comparing the maternal of different COMT genotypes.

METHODOLOGY

Subjects and Sample Size

This study was conducted at Luzhou Maternal and Child Health Care Family hospital of Luzhou City, Southwest China, China which is

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mostly populated with the Luzhou Han ethnic group. Using the sample calculation method margin of error of 5 percent, the sample size was determined before the commencement of the study. A total of 97 pregnant women admitted to the maternity department in Luzhou Maternal and Child Health Care Family hospital for delivery from March 2015 to August 2017 were selected, aged 21 to 34 years. Inclusion criteria: (1) full-term single-fetal primipara; (2) no fetal distress, amniotic fluid abnormalities and other obstetric complications; (3) no acute and chronic pain; (4) can fully understand the Hamilton anxiety scale (HAMA) (Wang et al. 2019) and the mental health symptoms self-rating scale (SCL-90) (Carrozzino et al. 2019) content. Exclusion criteria: (1) taking anti-anxiety and analgesic drugs within one month before delivery; (2) cardiac insufficiency; (3) history of allergy to anesthesia and analgesic drugs. The study was submitted to the Medical Ethics Committee of Luzhou Maternal and Child Health Care Family hospital and approved. All maternity and family members fully understood the research process and content, and voluntarily signed informed consent.

DNA Extraction

EDTA anticoagulated blood was used for DNA extraction, and 5 ml of all maternal venous blood, was centrifuged for 5 min in a low-temperature high-speed centrifuge (Beckman Coulter, Model: Allegra 64R) within 1 h after collection, and the red blood cell lysate was added in the lower turbid liquid to complete lysed erythrocyte. Proteinase K and leukocyte lysate were added and mixed thoroughly, and placed in a constant temperature water bath (Changzhou Wanhe Instrument Manufacturing Co., Ltd., Type: HH-601) at 37 °C for 12 h. The DNA was extracted following the method as described earlier in the literature (Ghatak et al. 2016). The DNA floc was suctioned with a glass needle, washed with 75% ethanol, dried in a 23 ° C environment, and then dissolved in TE buffer and placed in a refrigerator at 4 ° C for use.

Polymorphism Detection of COMTval158met Gene

PCR-restriction fragment length method was applied to classify the COMTval158met gene, and HMS and SCL-90 scale was used to evaluate the maternal anxiety status 1 day before labor. PCR primer sequence: downstream 5,-CTGCT-GAGGAGGATAAAGTGC-3, upstream 5,-GGATCGTGGATTACGCTCGG-3, the amplified product fragment was 117 bp. According to the operating instructions of the real-time PCR kit (Swiss Roche), the primers were added, followed by pre-denaturation, denaturation, annealing renaturation, and extension. The reaction conditions were 95 ° C for 5 min, 93 ° C for 1 min, 55 ° C for 1 min, and 70 ° C for 1.5 min. A small amount of amplified product was taken for agarose gel electrophoresis, and the electrophoresis band was monitored by a gel imager (Shanghai Qinxiang Scientific Instrument Co., Ltd., Type: GenoSens 1850), and the size of the amplified product was compared. Enzyme cut buffer and restriction enzyme was added to 15 ìl of the amplified product, and the reaction was carried out for 6 h at 37 ° C. The digested product was subjected to polyacrylamide gel electrophoresis, and the result was evaluated by a gel imager. Genotyping: A/A type was a mutant homozygote, A/G type was a mutant heterozygote, and G/G type was a wild type homozygote. Enzyme digestion results showed that the A/A type was not cut and the length was 117 bp; the A/G type was 19 bp, 98 bp, and 117 bp; the G/G type was 19 bp and 98 bp.

Analgesic Method

When the cervix was opened to 2~4 cm, the mother was taken to the left lateral position, and after skin preparation and draping were completed, the epidural anesthesia was injected into the second and third lumbar intervertebral punctures with 0.15 ìg/Kg remifentanil. Upon completion, the lumbar puncture needle was removed and the catheter was properly fixed. The epidural catheter was connected to an analgesic pump with a 0.5 ìg/ml sufentanil and 0.1% ropivacaine mixture instilled. Mothers were informed to seek medical staff for help if the pain was found.

Observation Indicators

COMTval158met genotype and allele distribution; general data, prenatal anxiety score, pain threshold and pain tolerance of different gene group mothers; the amount of drug use in the analgesic pump and frequency of help during

maternal delivery. The pain threshold tester was utilized (Beijing Yaou DePeng Technology Co., Ltd., Type: DP -EP601C) to determine the maternal pain threshold and pain tolerance threshold, and drug dosage used in the analgesic pump and the frequency of call for help during delivery were recorded.

Statistical Methods

Statistical analysis was performed with SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± SD. Student's t-test was used for comparisons. Categorical data were analyzed with the Chi-square test. $P < 0.05$ was defined as statistically significant.

RESULTS

General Information of COMTval158met Genotype and Allele Distribution Frequency of Mother and Comparison with Maternal Age, Weight, and Gestational Age

The distribution frequency of COMTval158met genotype in 97 women was: 14.43 percent for A/A type, 39.18 percent for A/G type, and 46.39 percent for G/G type; the distribution frequency of COMTval158met allele A was 34.84 percent, allele G distribution was 65.16 percent, and the allelic distribution was consistent with the law of genetic balance. There were 14 cases, 38 cases and 45 cases of A/A group, A/G group, and G/G group, respectively. Body weight for each genotype was comparable and gestation la age varied between

38 to 39.16 years. Hence, there was no significant difference in the average age, weight, and gestational age of the three groups. The difference was not statistically significant ($P>0.05$) (Table 1).

Table 1: General information of different genotypes of mothers

Groups	n	Age (years)	Body weight (kg)	Gestational age (weeks)
A/A group	14	25.74±3.67	67.20±7.59	38.63±0.91
A/G group	38	26.32±3.51	68.19±7.62	39.05±0.74
G/G group	45	25.93±3.71	67.56±7.35	39.16±0.86
F		0.18	0.12	2.22
P	0	0.835	0.889	0.114

This table shows the association of different genotpye with the other indicators as shown. P and f value was calculated and p<0.05 was considered to be significant.

Comparison of Maternal Anxiety Symptoms among Genotypes

The HMS scores and terror emotions in the A/A group and the A/G group weregreater than those in the G/G group, and the HAMA scores in the A/A group were significantly higher than those in the A/G group, and the difference was statistically significant ($P<0.05$). Among mental disease only horror and anxiety score between group varied significantly and A/A group had a score greater than that of G/G group, and the difference was statistically significant ($P<0.05$); the other scores were not significantly different among the three groups ($P>0.05$) (Table 2).

Table 2: Comparison of maternal anxiety symptoms among genotypes

Items	Gene type			F	P
	A/A n=14	A/G n=38	G/G n=45		
HAMA score	32.74±6.51[#*]	27.15±4.82[#]	23.97±3.12	21.7	<0.001
SCL90 score					
Mental disease	2.13±0.72	2.25±0.69	2.18±0.71	0.18	0.833
Paranoid	2.81±0.90	2.76±0.84	2.68±0.87	0.16	0.853
Horror	2.37±0.72[#]	2.21±0.53[#]	1.90±0.63	4.44	0.014
Hostility	2.28±0.54	2.20±0.61	2.17±0.58	0.19	0.829
Anxiety	2.84±0.77[#]	2.60±0.64	2.31±0.71	3.78	0.026
Depression	2.48±0.85	2.39±0.57	2.37±0.63	0.16	0.855
Interpersonal relation	2.57±0.74	2.61±0.72	2.52±0.57	0.19	0.824
Obsession	2.81±0.93	2.64±0.69	2.76±0.86	0.33	0.721
Somzatization	2.43±0.91	2.50±0.77	2.43±0.83	0.08	0.919

HAMA and SCL scores respective to genotypes. Note: compared with G/G group, [#] P"ÿ0.05; compared with between groups, [*] P"ÿ0.05

Comparison of Pain Threshold and Pain Tolerance Threshold of Maternal Genotypes

The pain threshold and pain tolerance threshold of A/A group were significantly lower than those of A/G group and G/G group, and the difference was statistically significant ($P<0.05$); the There was no significant difference in maternal pain threshold and pain tolerance between A/G group and G/G group ($P>0.05$) (Table 3). Overall pain threshold and tolerance varied significantly among the group with p-value of 0.008 and 0.015 respectively.

Table 3: Comparison of pain threshold and pain tolerance threshold of maternal genotypes (mA)

Groups	n	Pain threshold	Pain tolerance
A/A group	14	1.53±0.84[#]	4.47±1.14[#]
A/G group	38	1.98±0.63	5.14±1.06
G/G group	45	2.18±0.64	5.48±1.17
F		5.12	4.41
P	0	0.008	0.015

Pain threshold and pain tolerance threshold of maternal genotypes. Note: compared within groups,[#] $P<0.05$

Comparison of Maternal Analgesia Effect of Each Genotype

The number of drugs use and the frequency of help-seeking in A/A group aswas significantly higher than those in A/G group and G/G group, and the frequency of help-seeking in A/G group was significantly higher than that in G/G group, and the difference was statistically significant ($P<0.05$) (Table 4). That indicates drug dosage

Table 4: Comparison of maternal analgesia effect of each genotype

Groups	n	Drug dosage (ml)	Frequency of call for help (times)
A/A group	14	57.32±7.48[#]	11.54±2.06[#*]
A/G group	38	52.71±7.33[#]	9.74±1.88[#]
G/G group	45	47.85±7.79	6.94±1.71
F		9.73	43.83
P	0	<0.001	<0.001

Each genotype was compared based on maternal analgesia. [#] $P<0.05$; compared within groups, [*] $P<0.05$

and frequency of call had a significant effect on maternal analgesia with p-value <0.001.

DISCUSSION

Prenatal anxiety is commonly seen in primiparas. Due to a lack of childbirth experience, primiparas are always concern about childbirth pain, their fetal health. Prenatal anxiety varies in duration, and some women are afflicted throughout the pregnancy and delivery process (Pickles et al. 2016). Prenatal anxiety can increase the frequency and severity of vomiting in pregnant women, and even lead to miscarriage. Besides, anxiety can promote adrenaline secretion in pregnant women, induce metabolic acidosis, thus resulting in fetal distress; it can also cause autonomic dysfunction, leading to weak uterine contractions during labor and further dystocia (Liu 2016; Kingston et al. 2015). Pain in labor can consume more time, endanger maternal and fetal health, and increase the incidence of perinatal complications (Xiao et al. 2019). Studies have shown that the severity of anxiety is directly proportional to pain sensitivity and inversely proportional to pain tolerance (Karkal et al. 2016). Labor analgesia is a widely used method for alleviation of labor pain, but its analgesic effect varies among different pregnant women.

COMT is a catecholamine-like substance metabolizing enzyme that exerts its physiological effects mainly in the brain. By inhibiting the methylation of S-adenosylmethionine, COMT inactivates catecholamine neurotransmitters such as dopamine and reduces its accumulation, thus preventing DNA oxidative damage and cell carcinogenesis (Sun et al. 2016). The COMT gene is located on chromosome 22, and studies have shown that the 158th codon G and A polymorphisms of this gene are closely related to COMT activity (Wongpratate et al. 2019). Sak found that the mutation of COMTval158met allele G to A can lead to a significant decrease in COMT activity, accumulation of endogenous catechol estrogen, and its active intermediates, increase the risk of tumor disease (Sak 2016). The HAMA scale is mainly used for the evaluation of the severity of anxiety symptoms in nerves and other patients and is widely used in clinical practice (Wang et al. 2019). The SCL-90 scale contains comprehensive psychopatholog-

ical symptoms and can comprehensively assess mental health in terms of 10 aspects. It is one of the most widely accepted and widely used mental scales (Wang et al. 2019). The pain threshold is the minimum amount of stimulation that causes the body to consciously be aware of the pain and is used to evaluate pain sensitivity. The pain tolerance threshold refers to the amount of maximum stimulation that the human body can tolerate, and is often used to evaluate pain tolerance (Gaab et al. 2017; Kandemir et al. 2019). Besides, some studies have shown that the COMT gene polymorphism can affect human perception of pain by altering the activity of COMT and by regulating psychological and stress factors and, therefore, may become one of the genetic determinants of individual differences in tolerance and response to pain or other stressors. The results of this study showed that the distribution frequency of COMTval158met alleles accorded with the law of genetic balance, and there was no significant difference in maternal age, body weight, and gestational age of each genotype, indicating that the study included reasonable samples and could be representative. The study also showed that the maternal HMS and terror sentiment score in the A/A group and the A/G group were significantly greater than those in the G/G group, and the maternal anxiety score in the A/A group was significantly greater than those in the G/G group, and the maternal pain threshold and pain-resistance threshold in the A/A group was significantly greater than that of the A/G group and the G/G group, and the number of maternal drugs use and the frequency of help-seeking in the A/A group were significantly greater than those in the A/G group and the G/G group.

CONCLUSION

In summary, the COMTval158met gene polymorphism can affect maternal pain sensitivity and tolerance and is associated with antenatal anxiety and labor analgesia, suggesting that the COMTval158met gene polymorphism and maternal antenatal anxiety are related. Therefore, the COMT gene polymorphism was found to be associated with labor anxiety and analgesia in pregnant women, and a mutated COMT allele could lead to worse labor anxiety and less-effective labor analgesia in pregnant women.

RECOMMENDATIONS

Anxiety causes increased sympathetic excitability resulting in increased nociceptor activity, and thus lowering the pain tolerance threshold. Naturally, preoperative anxiety will increase the degree of postoperative pain and, therefore, postoperative pain should be checked and controlled for the mother to get out of anxiety. However, these factors remain unrelated to genotypes.

ABBREVIATIONS

CATECHOL-O-METHYLTRANSFERASE (COMT)
HAMILTON ANXIETY RATING SCALE (HAMA)
SELF-RATING SCALE OR THE SYMPTOM CHECKLIST-90 (SCL-90)

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