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INFLUENCE OF THE SEROTONERGIC SYSTEM POLYMORPHISM ON THE EXPRESSION OF DENTAL ANXIETY

Tanja Franćeski[1], Dalibor Karlović[1,3], Vjekoslav Peitl[1], Rudolf Ljubičić[2], Ante Silić[1] and Željko Verzak[3]

[1]Department of Psychiatry, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia; [2]Department of Psychiatry, Rijeka University Hospital Centre, Rijeka, Croatia; [3]School of Dental Medicine, University of Zagreb, Zagreb, Croatia

SUMMARY – The aim of the study was to test the correlation between 5-HTTLPR polymorphism and dental anxiety. Research hypothesis was that positive relation between the expression of dental anxiety and the S allele exists in the population of healthy Caucasians. We conducted a prospective study on 159 subjects, volunteers made up of medical and non-medical staff of the Sestre milosrdnice University Hospital Centre. Both genders were included, age range 19 to 59, mentally and physically healthy (according to DSM-5 classification of mental disorders). For the purpose of this research, we used a sociodemographic questionnaire containing the following information: age, gender, education level, work status, marital status and residence. Corah's Dental Anxiety Scale-Revised (DAS-R) was used to measure dental anxiety. Data distribution was tested by Kolmogorov-Smirnov test, difference between the groups by χ^2-test and one-way analysis of variance, and correlation of variables by logistic regression. In the study population, we found positive correlation between S-allele and total result in DAS-R questionnaire. The presence of S allele suggests that the person will have a higher result in DAS-R questionnaire, i.e. higher expression of dental anxiety.

Key words: *Anxiety; Dental anxiety; Polymorphism, genetic; Serotonin plasma membrane transport proteins; Neuroticism; Croatia*

Introduction

The terms 'dental anxiety' and 'dental phobia' have different definitions in the literature. According to modern classifications, dental phobia belongs to phobic anxiety disorders, or to put it precisely, it is part of the group of specific (isolated) phobias, saying it is limited to a very specific situation, which involves going to the dentist[1]. In this study, under the term dental anxiety we consider a specific anxiety reaction which occurs as a response to a perceived threat in dental surrounding and it is measured by Corah's Dental Anxiety Scale, Revised (DAS-R), classifying it as moderate, high or severe[2,3]. According to DAS-R, severe dental anxiety is at the end of the continuum and suggests the possible presence of dental phobia, which is in accordance with the continuum concept of dental anxiety, and which supports differences in the anxiety intensity, as well as differences in the etiologic factors in the background of dental anxiety[4,5].

In the literature, dental anxiety is related to different factors including personality traits[5-7], fear of pain[8-10], previous traumatic experience connected to dental treatment[11], members of the family influenced by expressed dental anxiety[8], fear of blood and injury[12-15], genetic factors[16,17], socioeconomic factors[18], and alexithymia[19,20]. Most authors found positive correla-

Correspondence to: *Prof. Dalibor Karlović, MD, PhD*, Department of Psychiatry, Sestre milosrdnice University Hospital Centre, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: dalibor.karlovic@gmail.com
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tion between dental anxiety and anxious personality dimensions[6-8]. The prevalence of dental anxiety is high[21-23] and persons with expressed dental anxiety have significantly worse oral health in relation to general population[24,25].

The pathophysiological processes involved in anxiety are not completely defined, although it is considered that systems of noradrenaline, serotonin, dopamine and γ-aminobutyric acid (GABA) play a significant role in the interaction of other neurotransmitters and peptides such as corticotrophin-releasing hormone. Taking into consideration that with the use of available psychopharmacologicals, it is possible to influence each of the mentioned systems, it is not surprising that the achieved level of anxiety reduction opened the path to further research of relations of changed concentrations, receptor functions and different neurotransmitter carriers regarding anxiety. It is known that serotonin plays an important role in neural development, as well as in general cerebral functioning. In addition to anxiety connection, serotonin is involved in the regulation of a whole array of functions and behavior like emotions, mood, sleep, appetite, motor activity and neuroendocrine functioning. The effects of serotonin are numerous and widespread through the entire body *via* plasma, platelets, suprarenal (adrenal) gland, neuroendocrine and gastrointestinal systems, and other peripheral systems[26]. Serotonin is also one of the neurotransmitters involved in the regulation of neurotransmission in amygdala and in the processing of negative emotions, and it is considered that its disturbed function (in terms of reduced availability) may result in the development of various anxious but also depressive symptoms[27]. Serotonin availability within synapses, together with its connection to serotonin receptors of postsynaptic neurons, is defined by the size and speed of serotonin removal from the synaptic gap into the presynaptic neuron by a specific process, so called serotonin reuptake[28]. The key role in serotonin reuptake is played by serotonin transporter (SERT or 5-HTT) on presynaptic membranes. The activity of serotonin transporter is regulated by the SLC6A4 gene located at the second arm of chromosome 17, in the q11.2 (17q11.1-q12) region, and it consists of around 37800 nucleotides (monomer units of nucleic acids which consist of a nitrogenous base, phosphate and glucose) or 37.8 kilobases. It contains 15 exons (chromosome code parts, i.e. DNA regions in charge of protein code) that consist of 3756 nucleotides. The most important polymorphisms of the SLC6A4 gene in human population include the promoter gene and are situated about 1400 bp upwards from the start of the coding region. That region is called polymorphic region linked to the serotonin transporter gene, 5-HTTLPR, named after 5-HT transporter gene-linked polymorphic region. Variations in this region emerge among a variable number of recurring nucleotide sequences (length 20-23 bp), that is their insertion or deletion, which can result in two frequent alleles, i.e. long (insertion) or L variant with 16 recurring sequences and short (deletion) or S variant with 14 recurring sequences[29,30]. Although at the beginning, two original variants (S and L) of 5-HTTLPR polymorphism were intensely researched, in 2006 it was discovered that 5-HTTLPR polymorphism is functionally a three-allele one. It was discovered that the substitution of one base in L allele (A→G) was equivalent to S allele[31].

Functional polymorphism in the promoter region of the 5-HTT gene is connected with changes in serotonin activity, in a way that the short variant (S allele), and particularly its homozygote, i.e. S/S genotype, is linked to reduced transcription efficiency of 5-HTT promoter; therefore, it reduces SERT expression and neuron serotonin reuptake, which has been proven in many studies[32-34].

In patients suffering from anxiety disorders, we detected a higher frequency of S allele[35], as in patients with expressed personality traits of anxiety[36-39]. In the literature, there is no information on the relation between dental anxiety and gene polymorphism of serotonergic system, although recent studies confirm heritability of dental anxiety[10,16,17]. The aim of this study was to identify relation of 5-HTTLPR polymorphism and dental anxiety. Our hypothesis presumed positive relation of the expression of dental anxiety with S allele in the population of healthy Caucasians.

Subjects and Methods

Subjects

We conducted a prospective study on 159 subjects, volunteers recruited from medical and non-medical personnel of the Sestre milosrdnice University Hospital Centre. Both genders, age range from 19 to 59,

Table 1. Sociodemographic characteristics of study participants

			N=159	%
Gender:	Male		80	50.3
	Female		79	49.7
Marital status	Married		124	78.0
	Single		35	22.0
Education	College/ university degree		72	45.3
	Secondary		83	52.2
	Primary		4	2.5
Residence	Rural		60	37.7
	Urban		99	62.3
Work status	Personal income		123	77.4
	Income support		36	22.6
Age (years) Mean ± SD		31.9 ±9		

physically and mentally healthy (without diagnosed disorders according to DSM-5 classification) were included in the research. The subjects received a written notification about participation in the research and gave their informed consent. The study protocol was approved by the Ethics Committee of the Sestre milosrdnice University Hospital Centre, Zagreb, Croatia, and the research was carried out in compliance with the Declaration of Helsinki. The mean (± SD) age of study subjects was 31.9±9 years. The sample consisted of 79 women and 80 men. According to marital status, 124 subjects were married and 35 single. According to the level of education, 72 subjects had college or university degree, 83 had secondary school and four had primary school. Ninety-nine subjects lived in urban and 60 in rural area. Regarding their income, 127 subjects had their own income, and 32 subjects were on support income. Subject sociodemographic characteristics are shown in Table 1.

Methods

For the purpose of this study, we used a sociodemographic questionnaire containing the following information: age, gender, education level, work status, marital status, and residence. For measuring dental anxiety, we used Corah's Dental Anxiety Scale-Revised (DAS-R). DAS-R is a self-evaluating scale consisting of 4 questions and 5 answers offered to questions. The questionnaire is valid and reliable, and depending on the total score, it classifies dental anxiety as moderate, high or severe.

In order to isolate subject DNA and determine gene polymorphism for serotonin transporter, we used 5 mL of fresh blood using anticoagulant EDTA. Isolating DNA from the blood is done by the macro method of salting out. The quality of isolated DNA is assessed by 0.3% agarose gel electrophoresis with ethidium bromide. For gene analysis (genotype) of serotonin transporter, we used the method of polymerase chain reaction (PCR). Using PCR, we identified homozygote and heterozygote transporters of long arm 'L allele' (528 pb) and transporters of short arm 'S allele' (484 bp).

We employed descriptive statistics methods along with parametric and nonparametric statistical methods, depending on the distribution of data of certain variables. Data distribution was tested by Kolmogorov-Smirnov test. For testing group difference, we used χ^2-test and one-way analysis of variance. For determining variable correlations, we used logistic regression. Statistics was performed by the commercial statistical program SPSS version 20.

Results

Table 2 shows means and SD with 95% confidence interval and lower and upper value for the results in Corah's DAS-R. Regarding the prevalence of certain alleles, i.e. genotypes in study sample, 26 subjects had S/S genotype, 42 subjects had L/L genotype, and 91 subjects had L/S genotype. For 5-HTTLPR polymorphism, we calculated the expected frequency for a certain genotype (Hardy-Weinberg principle); using χ^2-test, we assessed the existence of statistically significant difference between the expected (calculated) frequencies and frequencies recorded in the study. From the value obtained (χ^2=3.9; p>0.05), we concluded that there was no difference between the expected and recorded frequencies and that the distribution of

Table 2. Sample results in Corah's Dental Anxiety Scale-Revised (DAS-R)

	Mean± SD	Confidence bounds Lower value	95% Upper value
Dental anxiety	8.8±3.5	8.3	9.4

Table 3. Prevalence of 5-HTTLPR genotype in study population

Genotype	Frequency n	%	Expectancy	Allele frequency	
				L n (%)	S n (%)
LL	42	26.4	48.2		
LS	91	57.2	78.7	175 (55%)	143 (45%)
SS	26	16.4	32.2		

Table 4. Means and standard deviation of dental anxiety in study participants with S/S, L/L and L/S genotypes (ANOVA)

	Genotype	Mean±SD	Confidence bounds Low value	95% High value	F	p
Dental anxiety	SS	10.6±4	9.3	12		
	LL	9.1±4.6	7.5	10.8	8.1	0.001
	LS	8±2.4	7.5	8.5		

Table 5. Logistic regression coefficient, predictor variable – presence of S allele, dependent result variable in Corah's Dental Anxiety Scale-Revised (DAS-R)

	B	SE	Wald	df	p	Exp(B)
DAS-R	0.2	0.1	11.0	1	0.001	0.8

5-HTTLPR polymorphism did not differ from the Hardy-Weinberg principle. In the study population, there was 55% of L allele and 45% of S allele. These results are shown in Table 3.

In order to confirm the effect of 5-HTTLPR polymorphism on the expression of dental anxiety, we conducted one-way ANOVA, which yielded a considerable statistical difference in the results obtained on DAS-R scale depending on genotype ($F=8.1$; $p=0.001$). These results are shown in Table 4.

Furthermore, we assessed difference in the results on DAS-R scale according to particular genotypes. Post hoc Bonferroni correction confirmed a statistically significant difference between the S/S and L/S genotypes in relation to dental anxiety ($p<0.001$). We found no statistically significant difference between S/S and L/L genotypes ($p=0.2$), or between L/L and L/S genotypes ($p=0.3$).

In addition, it was necessary to establish the relation between 5-HTTLPR allele polymorphism and expression of dental anxiety as assessed by DAS-R scale. To confirm the relation, we applied logistic regression where the predictor variables indicated the presence or absence of S allele. In other words, the entire sample was divided into subjects having at least S allele (S/L) or both S alleles (S/S), and compared them to those that had L/L genotype. According to previous research in Caucasian populations, the S allele has mutated resulting in weaker functioning of serotonin transporter.

In the situation observed, the model in which the presence of S allele was a dependent variable, and predictor variable was the result on DAS-R scale, showed statistical significance ($\chi^2=11.5$, $df=1$; $p<0.01$), which indicated difference in subjects regarding the presence of S allele. The model in whole explains 7%-10.6% of variants (Cox and Snell $r^2=0.1$; Nagelkerke $r^2=0.1$) and accurately classifies 78.6% of cases.

Table 5 shows logistic regression coefficient in which the predictor variable reflects the presence of S allele and the dependent variable reflects the results on DAS-R scale. Looking at the logistic regression coefficient, we can see positive relation between the S allele and total result on DAS-R. The presence of S allele suggests that a person will have a higher result on DAS-R scale, or in other words, a higher expression of dental anxiety.

Discussion

The aim of this study was to assess the correlation between 5-HTTLPR polymorphism and dental anxiety with the supposed work hypothesis on the positive

relation of the expression of dental anxiety and S allele 5-HTTLPR polymorphism in healthy Caucasian population. In the population observed, we confirmed the following allele frequencies: 55% of L allele and 45% of S allele, i.e. 26.4% of LL genotype, 57.2% of LS genotype, and 16.4% of SS genotype, which is in accordance with previous research in the European population[40]. Gonda *et al*. in 169 healthy subjects found very similar frequencies, 61.3% of L allele and 38.7% of S allele[36]. Culej *et al*. in a Croatian population of 307 healthy subjects of both genders found the following genotype frequencies: LL 37%, LS 44% and SS 19%, i.e. 59% of L allele and 41% of S allele[41]. Considering that the distribution of 5-HTTLPR polymorphism in the study sample did not differ from Hardy-Weinberg principle, we conclude that the sample was representative.

In the study population, we established positive relation of S allele and total score on DAS-R scale. In other words, the presence of S allele is suggestible to higher score on DAS-R scale, i.e. higher expression of dental anxiety, which supports the previously noticed relations between S allele 5-HTTLPR polymorphism and anxiety, anxious people and neuroticism[5-7].

Post hoc Bonferroni correction confirmed a statistically significant difference between the S/S and L/S genotypes in relation to dental anxiety ($p<0.001$), which reinforces the already mentioned role of S allele in the pathogenesis of dental anxiety, and especially concerning S/S genotype, which is out of all genotypes linked to the weakest activity of 5-HTTLPR[32-34]. Contrary to our expectations, we did not find a statistically significant difference between S/S and L/L genotypes ($p=0.2$) or between L/L and L/S genotypes ($p=0.3$). Therefore, it is difficult to conclude unanimously to what degree the presence of S allele influences the development and expression of dental anxiety, i.e. to what degree the presence of L allele would be protective in the same context. However, the results obtained point to a specific role of 5-HTTLPR polymorphism regarding dental anxiety, together with other aspects of anxiety[35], although this study, just like many others, resulted in obviously contradictory findings regarding anxiety[42,43]. Considering that our sample excluded all individuals with any type of anxiety disorder in diagnostic criteria, one of the possible explanations would be that healthy subjects are by far more genetically heterogeneous population for anxiety assessment, especially when we previously noticed frequent presence of S allele in anxious and depressive subjects[26,35].

Considering that dental anxiety is a multidimensional construct with numerous etiologic theories, one of these theories would be genetic. Results from several studies done on twins point to genetic factors in developing dental anxiety although relevant genes have not yet been identified. Ray *et al*. on a sample of 2000 twins confirmed heritability of dental anxiety and pointed to the possible gender differences[16]. Randall *et al*. confirmed heritability of dental anxiety (dental anxiety is 30% heritable, $p<0.001$) and indicated genetic correlation between dental anxiety and fear of pain[17]. Vassend *et al*. on a relatively small sample of adult twins (N=188) confirmed moderate heritability of dental anxiety and indicated it to be triggered by the presence of neuroticism to a larger extent[10].

Numerous researchers point to the relation between 5-HTTLPR polymorphism and personality traits linked to neuroticism defined by anxiety, depression, helplessness, guilt, aggressiveness and somatization. It is considered that neuroticism is hereditary in 40%-50% and very prevalent in people with anxious and depressive disorders accompanied by frequently present S allele frequencies[36]. To date, five meta-analyses on the relation between 5-HTTLPR polymorphism and dimensions of anxiety have been conducted; Sen *et al*.[37] and Schinka *et al*.[38] indicate significant relation, whereas Munafo *et al*. report contradictory results; they did not find significant relation between 5-HTTLPR polymorphism and neuroticism as assessed by the Eysenck Personality Questionnaire, but they did find a relation with neuroticism as assessed by the NEO-Personality Inventory[44]. Minelli *et al*. in a meta-analysis of 44 studies found correlation between SLC6A4 gene polymorphism and personality dimensions of anxiety, although in subsequent research conducted on mentally healthy subjects no such correlation was found[39]. On the other hand, numerous studies suggest the relation between neuroticism and dental anxiety[5-7], as well as a higher frequency of S allele in subjects suffering from depression and anxiety disorders[35]. Halonen *et al.* in their research found a significant and positive correlation between dental anxiety and neuroticism and a significant although negative correlation with extraversion[5]. If we look at dental anxiety in a broader context as one of

the manifestations of anxiety, then the results from this research support earlier correlation of SLC6A4 gene polymorphism and anxiety, although due to relatively contradictory results that correlation does not seem unambiguous[39], and it is definitely premature to make any conclusions. Nevertheless, the correlation supports the influence of the serotonergic system on the pathophysiology of dental anxiety and by further research it is necessary to discover the causal factors in the background of dental anxiety and phobia as its extreme, both within the serotonergic system, as well as in other systems in accordance with the suggested multifactorial etiology of dental anxiety. Considering that 5-HTTLPR polymorphism as an endophenotype of dental anxiety was not a research topic in previous studies, the results of this study could bring us closer to the explanation of genotype influence on the possible dental anxiety development. Following this, it would be interesting to investigate in a larger sample whether there is a relation between dental anxiety and 5-HTTLPR polymorphism, as in other functional polymorphisms of serotonergic system. At the same time, we should assess more thoroughly the relation between 5-HTTLPR polymorphism and personality traits of anxiety in healthy population, which will become a possible endophenotype related to psychiatric disorders such as specific phobias, in this case dental phobia. All the above could in the near future bring psychiatric genetics closer to the goal of discovering risky profiles for developing dental anxiety, thus allowing the possibility of prevention by using psychological and biological therapeutic measures[45].

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Sažetak

UTJECAJ POLIMORFIZAMA GENA SEROTONINSKOG SUSTAVA NA IZRAŽENOST DENTALNE ANKSIOZNOSTI

T. Franćeski, D. Karlović, V. Peitl, R. Ljubičić, A. Silić i *Ž. Verzak*

Cilj studije bio je ispitati povezanost polimorfizma 5-HTTLPR i dentalne anksioznosti. Naša hipoteza pretpostavlja pozitivnu povezanost izraženosti dentalne anksioznosti s S alelom u populaciji zdravih bijelaca. Provedena je prospektivna studija na 159 ispitanika, dobrovoljaca koje je sačinjavalo medicinsko i nemedicinsko osoblje KBC-a "Sestre milosrdnice". U istraživanje su uključeni ispitanici obaju spolova, dobnog raspona od 19 do 59 godina, tjelesno i psihički zdravi (bez poremećaja prema klasifikaciji DSM-5). U istraživanju smo rabili sociodemografski upitnik sa sljedećim podacima: dob, spol, stupanj naobrazbe, radni status, bračno stanje, mjesto stanovanja. U svrhu mjerenja dentalne anksioznosti primijenjen je Corahov upitnik o dentalnoj anksioznosti (*Corah Dental Anxiety Scale-Revised*, DAS-R). Raspodjela podataka testirana je Kolmogorov-Smirnovljevim testom. Za testiranje razlike među skupinama primijenjen je χ^2-test i jednosmjerna analiza varijance. Za utvrđivanje povezanosti među varijablama primijenjena je logistička regresija. U ispitivanoj populaciji našli smo pozitivnu povezanost S alela i ukupnog rezultata na upitniku DAS-R. Prisutnost S alela ukazuje na to da će osoba imati veći rezultat na upitniku DAS-R, odnosno veću izraženost dentalne anksioznosti.

Ključne riječi: *Anksioznost; Dentalna anksioznost; Polimorfizam, genetski; Serotoninski prijenosni proteini na plazmatskoj membrani; Neuroticizam; Hrvatska*