SPECIFIC CHARACTERISTICS OF MENTAL STATUS IN PATIENTS WITH RHEUMATIC ARTHRITIS DEPENDING ON SEX

Liudmyla Protsiuk
Ph.D., MD, Associate Professor, National Pirogov Memorial Medical University, Vinnytsia, Ukraine
e-mail: rossata@ukr.net, orcid.org/0000-0001-9650-2504

Liudmyla Kotsur
Ph.D., MD, Associated Professor, National Pirogov Memorial Medical University, Vinnytsia, Ukraine
e-mail: santas2767@gmail.com, orcid.org/0000-0001-6191-5798

Summary

The work is devoted to the study the specific characteristics of mental status in patients with different variants of polymorphic regions of the A1438-G gene of the serotonin receptor 2A (HTR2A), ill with rheumatoid arthritis, depending on gender, and to study the relationship between anxiety-depressive disorders and pain intensity and clinical signs of the disease. Materials and methods used in the study. The distribution of genotype rate of serotonin receptor 5-HT2A A1438-G gene was studied in 100 patients with RA. Anxiety level was assessed by Spielberger State-Trait Anxiety Scale. Depressive status and depression severity was evaluated by Hamilton Depression Rating Scale. Females with GG genotype were found to have higher level of pain feelings and the presence of anxiety signs associated with depression symptoms, while in males with GG genotype had the prevalence of inflammatory component and the depression symptoms.In females with AA genotype pain syndrome indices were associated with high anxiety indices, and in females with AG genotype they were dependent on the presence or absence of anxiety and depression, while in males with AG genotype pain syndrome was associated with SA indices.

Key words: rheumatic arthritis, polymorphism, serotonin receptor 5-HT2A A1438-G gene, depression.

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1. Introduction

Study of anxiety and depression severity in patients with rheumatic arthritis (RA) is rather urgent problem nowadays, as this pathology affects mainly individuals of young and middle age, leading to psychosocial maladjustment caused by pain syndrome, restricted activity followed by disability and loss of social relations. Patients with RA, according to many experts, have complicated dynamics of mental disorders, adversely influencing the course and prognosis of underlying disease *(Chassin-Troubert et al. 2019; Peterson et al. 2019; Machin et al. 2020*). Such psychological factors as stress and individual clinical features of stress reactivity as anxiety, depression and aggression can modulate immune functions and influence the clinical pattern of many chronic diseases, including RA *(Smesam et al. 2022).* Depression and anxiety are the main manifestations of mental disorders (*Amaowei 2022;Lwin et al. 2020*).

Chronic inflammation impairs the physiological responses to stress including effective coping behaviours, resulting in depression, which leads to a worse long-term outcome in RA. In RA patients, the pain score is not always solely related to inflammatory arthritis and immunological disease activity. Non-inflammatory pain secondary to anxiety, depression, sleep disturbance and the psychosocial situation needs to be considered (*Lwin et al. 2020*).

The most common conception of anxiety and depressive disorders is serotonin theory *(Nomura et al. 2015).* For today the degree of influence of serotonin metabolism disorder on RA clinical manifestations is underinvestigated. Besides, according to recent literature data, there is controversy as to the existence of impact of polymorphic sites on psycho-emotional sphere in patients with RA, disease course in particular, which is important for early diagnosis and development of adequate programs of social support of that category of patients.

Objectives. To study the specific characteristics of mental status in patients with different variants of polymorphic regions of the A1438-G gene of the serotonin receptor 2A (HTR2A), ill with rheumatoid arthritis, depending on gender, and to study the relationship between anxiety-depressive disorders and pain intensity and clinical signs of the disease.

Materials and methods. 100 RA patients, 73 females (73.0%) and 27 males (27.0%) were studied. Their age ranged from 18 to 75 years, the mean age being 51.5 ± 3.04 years. The distribution of genotype frequency of 2A serotonin receptor HTR2A A1438-G gene was determined in 100 patients taking a course of treatment at Vinnytsia Regional Clinical Hospital named after M.I.Pirogov. Clinical characteristics of patients depending on genotype and sex are given in Table 1.

Clinical diagnostics was made on the basis of ACR/EULAR criteria of 2010 *(Aletaha et al. 2010).* The study was carried out in compliance with the provisions of World Medical association Declaration of Helsinki (1989), and was approved by Ethics Committee at Vinnytsia National Pirogov Memorial Medical University.

All patients gave an informed consent to participate in the study.

Polymorphic sites of A1438-G gene were amplified with polymerase chain reaction. Anxiety level was assessed by Spielberger State-Trait Anxiety Scale (STAI) (*Spielberger 1966*). Depressive status and depression severity were evaluated by Hamilton Depression Rating Scale (HDRS*) (Hamilton 1960).*

Statistical data processing was done with Statistical package for Windows v. 8.0 (№ AXXR910A374605FA) using parametric and nonparametric methods. Digital information

Table 1

Clinical characteristics of RA patients, included in the study, depending on genotype and sex

Sign	RA patients (n = 100)	AG (n = 47)	AA (n=17)	GG (n=36)
Females, n (%)	73 (73.0)	31 (42.5)	13 (17.8)	29 (39.7)
Average age, females, years (M ± SD)	51.6 ± 12.0	49.5 ± 10.8	55.6 ± 13,0	51.7 ± 12.2
Males, n (%)	27 (27.0)	16 (59.2)	4 (14.8)	7 (25.9)
Average age, males, years (M ± SD)	49.2 ± 11,8	51.7 ± 14.9	50.0 ± 5.0	45.6 ± 11.5
Duration of the disease, years Me [LQ;UQ],	6,0 [2,0;12,0]	7,0 [2,0;14,0]	6,0 [2,0;20,0]	8,0 [2,5;14,0]

of all clinical investigations was processed by variance statistical method calculating the mean value (M) and its error (m). Modified Pearson's Chi-Squared criterion (p) was used to check the correspondence of empiric distribution of genotype frequency to theoretically expected Hardy-Weinberg equilibrium (steady distribution). Yates' continuity-corrected Shi-Squared test for small samples as well as two-tailed Fisher's exact test (F) were used in pair-wise comparison of allele and genotype frequencies in studied groups. For all specific data, the median (Me), lower and upper quartiles [LQ25-UQ75] were established.

Comparison of quantitative values in some clinical groups was done using non-parametric – Kruskal-Wallis H-test, $p < 0.05$ was considered significant difference. In case of significant differences between the groups, their pair-wise comparison was performed using Mann-Whitney U-test with regard to Bonferroni correction for multiple testing. The difference between the groups according to Bonferroni adjustment was considered statistically significant in $p < 0.017$.

Correlation analysis with calculation of Spearman rank correlation (r) was used to establish the relationship between the studied indices. Differences were considered significant if significance value was 95% ($p < 0.05$).

2. Result

The study found no deviation of genotype frequency from Hardy-Weinberg equilibrium. Determination of allele frequency in patients with RA in locus of A-1438-G gene revealed the prevalence of G allele in both male and female patients with RA when compared to A allele. It is noteworthy that G allele occurred 1.5 times more frequently than A allele among females with RA ($p = 0.0087$), (See Table 2).

Detailed study of clinical signs of RA, irrespective of variants of polymorphic sites of promotor region of 5-HTR2A A-1438-G gene, revealed the signs of asthenic syndrome (AS) in 64 patients (53.3%) which was manifested by poor attention, mood swings, dizziness, irritability, tearfulness, increased sweating, tachycardia, nausea, decreased appetite, etc.

Debilitating chronic joint pain, functional disability, social tension of patients with RA contributes to the development of anxiety and depressive disorders (ADD), affecting greatly the disease course.

AS was found to occur significantly more often in female RA patients with GG genotype (90.1%) by contrast to those with AG genotype (38.1%; Fisher's (et) $p = 0.0042$), while no significant difference was found between female patients with AA and GG genotypes (85.7%; Fisher's (et) $p = 1.000$), respectively. With high probability of correlation between AS frequency in female patients with RA and CC genotype, strong degree of this correlation ($\varphi = 0.61$,

Table 2

Genotype frequency of polymorphic loci A1438-G of 5-HTR2A gene in RA patients depending on sex (%)

Locus	Sex	n	Genotypes			Alleles	
			AG	AA	GG	A	G
A-1438-G	M	27	59.3%	14.8%	25.9%	44.4%	55.6%
	χ^2 =1.08; p = 0.299; Fisher's exact test: p = 0.344 | F(ST) = 0.475						
	F	73	42.5%	17.8%	39.7%	57.5%	42.5%
	χ^2 = 0.85; p= 0.357; Fisher's exact test: p = 0.277 | F(ST) = 0.165						

$p < 0.01$) was found as well. It should be noted that among male patients with AG genotype, only the tendency to increased AS frequency as compared to those with GG genotype (57.1% versus 33.0%; Fisher's (et) $p = 0.060$, $p > 0.05$). Comparison of that parameter between groups of RA patients – females and males with different variants of polymorphic sites, significant increase of AS frequency was found exclusively in female patients with GG genotype by contrast to males with the same genotype (90.1 versus 33.0%; Fisher's (et) $p = 0.0198$), (Fig. 1).

Among the major signs of AS, weakness was the most frequent, irrespective of genotype, with no significant difference between the groups of female or male patients, and between the groups of RA patients – females and males ($p > 0.05$).

Dizziness was found to occur significantly more often in male patients with AG genotype when compared to those with GG genotype (63.6% versus 11.1%; Fisher's (et) $p = 0.0281$, respectively).

With high probability of correlation between dizziness frequency in male patients with AG genotype, strong degree of this association was found as well ($\varphi = 0.53$, $p < 0.001$), while no statistically significant difference in that parameter was established between the groups of patients with RA – females and/or males with various polymorphic sites ($p = 0.08$).

Mood swings occurred significantly more frequently in RA male patients with AG and AA genotypes (63.6% and 85.7% versus 11.1%; Fisher's (et) $p = 0.0281$, and Fisher's (et) $p = 0.0087$, respectively) by contrast to those with GG genotype. With high probability of correlation between the prevalence rate of that symptom in male patients with AG genotype, relatively strong degree of this association was found as well ($\varphi = 0.53–0.75$, $p < 0.001$, respectively).

Analysis of the results obtained demonstrated relatively strong degree of this association ($\varphi = 0.453$, $p < 0.01$) and significantly higher prevalence rate of emotional instability in RA female patients with AA genotype (90.5% versus 50.0%; Fisher's (et) $p = 0.0219$), as compared to those with GG genotype (See Fig. 1).

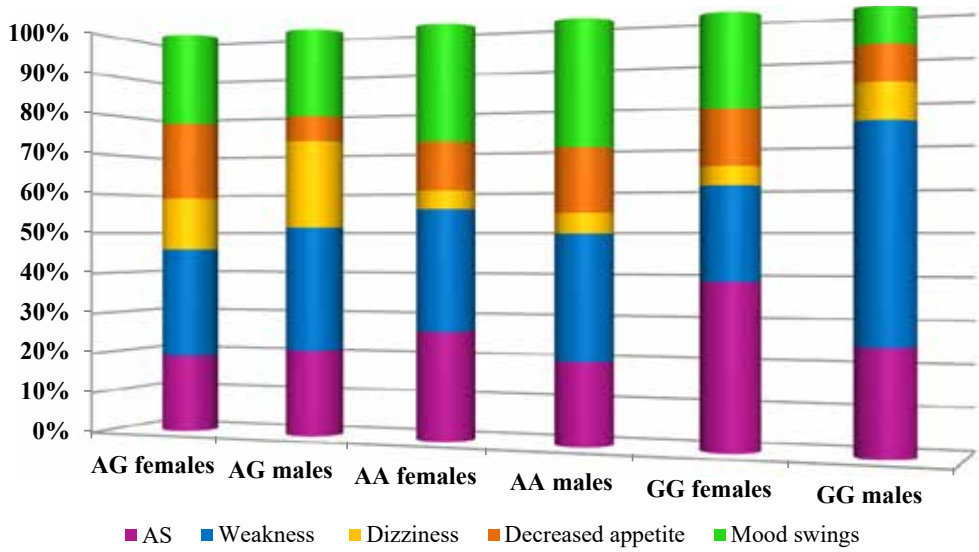

Fig. 1. Sex-dependent prevalence rate of clinical symptoms of asthenic syndrome in RA patients with different variants of polymorphic sites of promotor region of 5-HTR2A A-1438-G gene

Detailed analysis of clinical data found the following signs of anxiety and depressive disorder (ADD) in 71 year old male patient with RA: chronic fatigue, feeling of anxiety, hopelessness, melancholy, depression, memory impairment, dry mouth, loss of weight, etc.

It was found that 90.3% of females and 93.8% of males with AG genotype, 92.3% of females and 50.0% of males with AA genotype, and 86.2% of females and 71.4% of males with GG genotype, patients with RA, suffered from chronic fatigue with no significant difference between the groups ($p > 0.05$, respectively).

The probability of such symptom as hopelessness proved to be significantly higher in females with AA and AG genotypes ($\chi^{2Y} = 19.51$; $p = 0.0000$ and $\chi^{2Y} = 4.02$; $p = 0.0451$, respectively) compared to those with GG genotype. Along with high probability of correlation between the frequency of those symptoms in RA female patients with AA and AG genotypes, strong and moderate degree of this association was found as well ($\varphi = 0.69$; $p < 0.001$, $\varphi = 0.35$; $p < 0.01$, respectively).

Anxiety was reported by 77.4% of RA female patients with AG genotype, by 76.9% - with AA genotype, and by 72.4% – with GG genotype. Comparison of that parameter between the groups of female patients with various genotypes found no significant difference ($p > 0.05$, respectively), while males with AG genotype complained of anxiety significantly more often compared to those with AA and GG genotypes (50.0% versus 25.0% and 28.6 % ($p < 0.05$, respectively).

Determining state and trait anxiety (SA and TA, respectively) in patients with different variants of polymorphic sites of A1438-G gene by Spielberger scale, average values of both SA and TA were found to correspond to high level of anxiety in RA female patients, while anxiety indices in males appeared to be moderate (Table 3).

Table 3

Indices of state and trait anxiety in RA patients with different variants of polymorphic sites of A-1438-G gene by Spielberger scale, depending on sex Me [LQ; UQ]

Sign	State anxiety (scores)		Trait anxiety (scores)	
	Females	Males	Females	Males
AG	45,0 [37,0;49,0]	39,5 [33,0;45,0]	44,0 [35,0;49,0]	40,0 [36,0;44,0]
AA	47,0 [44,0;52,0]	38,5 [34,0;42,5]	48 [42,0;53,0]	40,0 [36,0;43,0]
GG	47,0 [42,0;54,0]	38,0 [32,0;45,0]	41,0 [36,0;47,0]	34,0 [30,0;36,0]

Study of SA and TA levels in RA patients with different variants of polymorphic sites of A1438-G gene by Spielberger scale demonstrated significantly higher levels of both SA (M-W: U = 138.5, Z=-2.45, p=0.001) and TA (M –W: U=90.0, Z= -3.54, p=0.0003) in females with AG and GG genotypes (SA (M-W: U=47.5, Z=2.15, p=0.003) and TA (M –W: U=33.0, Z= 2.73, p=0.005), by contrast to males with AG and GG genotypes, respectively, while no significant difference was found in both SA (M-W: U=16.0 Z=-1.51, p=0.15) and TA (M-W: U=23.5, Z= -0.80, p=0.44), between RA female and male patients with AA genotype (Table 3).

No significant difference in those parameters was found between both female patients with AG and AA, AG and GG and AA and GG genotypes, and male patients with various genotypes of A-1438-G locus (p>0.017) (Table 3).

The analysis of depressive disorder (DD) values in females with different variants of polymorphic sites of A-1438-G gene by HDRS scale showed significant difference between the groups (K-W test: H (2) = 7.05, p=0.02, p<0.05).

Significantly lower level of DD was registered in females with AA genotype compared to those with GG genotype (M-W: U=90.0, Z= -2.67, p=0.007).

Significantly lower DD values were found in males with AG genotype in comparison with females with AG genotype (M-W: U = 105.0, Z = -3.21, p = 0.0013), while no significant difference was revealed between the groups of females and males with AA and GG genotypes (p > 0.017).

There were no significant differences in the level of depressive disorders by HDRS scale between groups of females and males with different variants of polymorphic sites of A-1438-G gene, (p > 0.017, respectively) (Table 4).

Table 4

Indices of depressive disorders, by HDRS scale, in RA patients with different variants of polymorphic sites of A-1438-G gene, depending on sex

Variants of polymorphic sites of A-1438-G of 5-HTR2A gene							
Sign		n	AG	n	AA	n	GG
Females	Me[LQ;UQ]	31	14,0 [11,0;17,0]	13	12,0 [10,0;18,0]#	29	14,0 [12,0;17,0]
	M ± SD		13,74 ± 4,23		12,46 ± 4,87		14,24 ± 4,0
Males	Me[LQ;UQ]	16	8,5 [7,0;12,5]	4	10,0 [8,5;14,5]	7	8,0 [6,0;9,0]
	M ± SD		10,31 ± 4,17		11,5 ± 4,50		7,85 ± 3,18

3. Conclusions

Correlation analysis found direct association between pain intensity by VAS scale and indices of HDRS (r_s = 0.44; p < 0.01), SA and TA (r_s = 0.45; r_s = 0.39; p < 0.01, respectively) in females with AG genotype of polymorphic sites of A-1438-G gene. But in males with AG genotype only direct correlation between pain intensity and SA indices was detected (r_s = 0.53; p < 0.05).

Direct correlation between pain intensity by VAS scale was detected in females with AA genotype (r_s = 0.57; r_s = 0.63; r_s = 0.62; p < 0.05, respectively), while in males with AA genotype no probable correlation with those indices was found.

Females with GG genotype had direct positive correlation between pain intensity by VAS scale and indices of HDRS (r_s = 0.58; p < 0.01) and TA (r_s = 0.42; r_s = 0.05; p < 0.05), while in males with GG genotype there was direct correlation between indices of HDRS and inflammatory process activity by DAS28 (r_s = 0.84; p < 0.01).

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