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ХАРАКТЕРИСТИКИ ПСИХОНЕВРОЛОГИЧЕСКОГО ФЕНОТИПА ПОСТКОВИДНОГО СИНДРОМА

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Characteristics of The Neuropsychiatric Phenotype of Postcovid Syndrome

Резюме

Цель. Изучить характеристики психоневрологического фенотипа постковидного синдрома у реконвалесцентов COVID-19. **Материалы и методы.** Выборка 270 реконвалесцентов COVID-19 (средний возраст — 53,2±13,2; 130 (48,1 %) мужчин): 62 (23,0 %) без постковидного синдрома и 208 (77,0 %) с постковидным синдромом. В подгруппе с постковидным синдромом 134 (64,4 %) реконвалесцента имели психоневрологический фенотип. В ходе исследования учитывались данные анамнеза, проводилась оценка психоневрологического статуса по шкалам: Hospital Anxiety and Depression Scale (HADS), Multidimensional Fatigue Inventory (MFI-20), Symptom Checklist-90-Revised (SCL-90), 36-Item Short-Form Health Survey (SF-36), все пациенты были консультированы врачом неврологом, сомнологом и терапевтом. **Результаты.** Структура психоневрологического фенотипа: инсомния (n=74, 55,2 %), выраженная астения (шкала MFI-20, n=55, 41,0 %), тревога и депрессия (шкала HADS, n=37, 27,6 %, n=32, 23,9 %, соответственно), аносмия/дизосмия (n=13, 9,7 %), агевзия/дисгевзия (n=6, 4,5 %). По данным опросника SF-36 в группе лиц с психоневрологическим фенотипом было выявлено выраженное снижение показателей по всем субшкалам. По данным опросника SCL-90-R в группе с психоневрологическим фенотипом наблюдалось выраженное повышение показателей по всем субшкалам. У женщин с психоневрологическим фенотипом отмечались следующие особенности: показатели были ниже по шкалам: физическое функционирование в 1,1 раза (p=0,017), ролевое функционирование, обусловленное физическим состоянием в 1,6 раза (p=0,031) (шкала SF-36), выше показатели обсессивно-компульсивного расстройства в 1,7 раза (p=0,028), депрессии в 1,5 раза (p=0,005), тревожности в 2 раза (p=0,017) (шкала SCL-90), по результатам оценки шкалы HADS частота депрессии у женщин с психоневрологическим фенотипом постковидного синдрома выше в 3 раза (p=0,043) по сравнению с мужчинами, имеющим этот же фенотип. **Заключение.** Психоневрологический фенотип постковидного синдрома характеризуется наличием у пациентов инсомнии, выраженной астении, тревожных, депрессивных расстройств, аносмии/дизосмии и агевзии/дисгевзии. Лица с психоневрологическим фенотипом имеют сниженные показатели качества жизни и уровня психологического благополучия личности по всем субшкалам, согласно опросникам SF-36 и SCL-90-R.

Частота встречаемости психоневрологического фенотипа, а также выраженность психопатологической симптоматики статистически выше в группе женщин.

Ключевые слова: *реконвалесценты COVID-19, постковидный синдром, психоневрологический фенотип, HADS, MFI-20, SCL-90-R, SF-36*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Aim. To study the characteristics of the neuropsychiatric phenotype of postCOVID syndrome in COVID-19 convalescents. **Materials and methods.** A sample of 270 COVID-19 convalescents (mean age — 53.2±13.2, (n=130, 48.1 % men)): 62 (23.0 %) without postCOVID syndrome and 208 (77.0 %) with postCOVID syndrome. In the subgroup with postCOVID syndrome, 134 (64.4 %) convalescents had a neuropsychiatric phenotype. The study took into account medical history data, assessed the neuropsychiatric status on the following scales: Hospital Anxiety and Depression Scale (HADS), Multidimensional Fatigue Inventory (MFI-20), Symptom Checklist-90-Revised (SCL-90), 36-Item Short-Form Health Survey (SF-36), all patients were consulted by a neurologist, a somnologist and a therapist. **Results.** The structure of the neuropsychiatric phenotype: insomnia (n=74, 55.2 %), severe asthenia (MFI-20 scale, n=55, 41.0 %), anxiety and depression (HADS scale, n=37, 27.6 %, n=32, 23.9 %, respectively), anosmia/dysosmia (n=13.9.7 %), ageusia/dysgeusia (n=6, 4.5 %). According to the SF-36 questionnaire, in the group of people with a neuropsychiatric phenotype, a marked decrease in indicators was detected in all subscales. According to the SCL-90-R questionnaire, the group with the neuropsychiatric phenotype showed a marked increase in all subscales. The following features were noted in women with a neuropsychiatric phenotype: indicators were lower on the scales: physical functioning by 1.1 times (p=0.017), role-playing functioning due to physical condition by 1.6 times (p=0.031) (SF-36 scale), indicators of obsessive-compulsive disorder by 1.7 times higher (p=0.028), depression 1.5 times (p=0.005), anxiety 2 times (p=0.017) (SCL-90 scale), according to the results of the HADS scale assessment, the incidence of depression in women with the neuropsychiatric phenotype of postCOVID syndrome is 3 times higher (p=0.043) compared with men, having the same phenotype. **Conclusion.** The neuropsychiatric phenotype of postCOVID syndrome is characterized by the presence of insomnia, severe asthenia, anxiety, depressive disorders, anosmia/dysosmia, and ageusia/dysgeusia. Individuals with a neuropsychiatric phenotype have reduced indicators of quality of life and the level of psychological well-being of the individual in all subscales, according to the SF-36 and SCL-90-R questionnaires. The incidence of neuropsychiatric phenotype, as well as the severity of psychopathological symptoms, is higher in the group of women.

Key words: *COVID-19 convalescents, postcovid syndrome, neuropsychiatric phenotype, HADS, MFI-20, SCL-90-R, SF-36*

Conflict of interests

The authors declare no conflict of interests

Source of funding

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Conformity with the principles of ethics

The study was approved by the Ethics Committee of the Research Institute of Therapeutic Microbiology and Microbiology — Branch of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, Novosibirsk (Protocol No. 71 dated 11/10/2020). All participants signed a voluntary informed consent to participate in the study and process personal data.

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COVID-19 — Coronavirus Disease 2019, PCS — Post-Covid Syndrome, NIITPM — branch of ITsIG SO RAN — Scientific Research Institute of Therapy and Preventive Medicine — Branch of Federal State Budget Scientific Institution "Federal Research Center — Institute of Cytology and Genetics of the Siberian Department of the Russian Academy of Sciences", RNA — ribonucleic acid, SARS-COV-2 — Severe acute respiratory syndrome-related coronavirus 2, PCR — polymerase chain reaction, BMI — body mass index, WC — waist circumference, HR — heart rate, PA < 3 h qw — physical activity less than 3 hours weekly, SBP — systolic blood pressure, DBP — diastolic blood pressure, WHO — World Health Organization, PNP — psychoneurological phenotype, HADS — Hospital Anxiety and Depression Scale, MFI-20 — Multidimensional Fatigue Inventory, SF-36 — 36-Item Short-Form Health Survey, SCL-90-R — Symptom Checklist-90-Revised, BP — blood pressure, FPG — fasting plasma glucose, ESR — erythrocyte sedimentation rate, hsCRP — highly sensitive C-reactive protein, GAD-7 — Generalized Anxiety Disorder-7

Introduction

Coronavirus Disease 2019 (COVID-19) pandemics has significantly affected not only the somatic status of patients, but also their psychoemotional well-being [1, 2]. Currently post-COVID symptoms affecting the psychoneurological condition have become an important global issue. Based on several studies, COVID-19 reconvalescents commonly reported fatigue, insomnia, anxiety and depression [3–5]; however, the spectrum of clinical psychoneurological manifestations among COVID-19 reconvalescents is much wider [6–8], which requires further systematization and analysis for the development of a personalized approach and definition of risk groups in patients after COVID-19.

Objective: analyzing the characteristics of a psychoneurological phenotype of post-COVID syndrome (PCS) in COVID-19 reconvalescents.

Materials and Methods

A cross-sectional observational study was arranged at the Scientific Research Institute of Therapy and Preventive Medicine — Branch of Federal State Budget Scientific Institution "Federal Research Center — Institute of Cytology and Genetics of the Siberian Department of the Russian Academy of Sciences" NIITPM — branch of ITsIG SO RAN. A total of 270 COVID-19 reconvalescents (mean age 53.2±13.2 years; n = 130, 48.1 % males) were included in the study.

The study inclusion criteria were as follows: COVID-19 infection confirmed by the positive test for ribonucleic acid (RNA) of Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) using the polymerase chain reaction (PCR) method during the disease and/or detection of anti-SARS-CoV-2 IgG-antibodies; 3 months elapsed since the onse of COVID-19; signed informed consents for the examination and

Table 1. *Initial clinical characteristics of COVID-19 convalescents*

Indicator		COVID-19 Convalescents n=270
Age of years, Me [25;75]		53,0[43,0;64,0]
Men, abs (%)		130(48,1)
Severity of the course of acute COVID-19, abs (%)	Light current	127(47,0)
	Moderate current	128(47,4)
	Heavy current	15(5,6)
BMI, Me [25;75], kg/m2		28,4[24,8;32,6]
WC, Me [25;75], cm		97,0[87,0;108,0]
Smoking, abs.(%)		94(34,8)
HR, Me [25;75], beats/min		67,0 [60,0;73,0]
PA<3 hours/week, abs.(%)		197(73,0)
SBP, Me [25;75], mmHg		125,0[115,8;135,0]
DBP, Me [25;75], mmHg		80,0[74,8;87,0]
The presence of prediabetes, abs. (%)		64(23,7)
The presence of type 2 diabetes, abs. (%)		34(12,6)
The degree of arterial hypertension, abs. (%)	I degree	33 (12,2)
	II degree	55 (20,4)
	III degree	79 (29,3)
The presence of cardiovascular diseases before the debut of COVID-19, abs. (%)		161(59,6)
The presence of cardiovascular diseases after the debut of COVID-19, abs. (%)		177(65,6)
Presence of bronchopulmonary diseases before the debut of COVID-19, abs. (%)		28(10,4)
The presence of bronchopulmonary diseases after the debut of COVID-19, abs. (%)		32(12,6)

Note* BMI — body mass index, WC — waist circumference, HR — heart rate, FA<3 h/w — physical activity less than three hours per week, SBP — systolic blood pressure, DBP — diastolic blood pressure

personal data processing. Acute infections or exacerbations of chronic infections at the moment of inclusion into the study formed the non-inclusion criterion. All subjects signed the voluntary informed consent for the examination and personal data processing. The baseline clinical data of COVID-19 reconvalescents are presented in Table 1.

All subjects were divided into groups based on the presence of PCS accounting for the World Health Organization (WHO) criteria [8]: 62 (23.0 %) without PCS (n = 36, 58.1 % males) and 208 (77.0 %) with PCS (n = 94, 45.2 % males). In the PCS group, 134 (64.4 %) reconvalescents (mean age 53.79±13.28 years, n = 53, 39.6 % males) had a psychoneurological phenotype (PNP).

PNP criteria included anxiety and depression (confirmed using the Hospital Anxiety and Depression Scale (HADS)), severe asthenia (confirmed using the Multidimensional Fatigue Inventory (MFI-20)), insomnia, ageusia/dysgeusia, anosmia/dysosmia that emerged after the prior COVID-19. The PNP structure is presented in Figure 1.

PNP in combination with other post-COVID manifestations (mixed phenotype) was diagnosed in 67 (32.2 %) COVID-19 reconvalescents; isolated PNP manifestations (monophenotype) was also reported in 67 (32.2 %) COVID-19 reconvalescents among patients with PCS (Fig. 2).

Demographics (gender, age), disease history, chronic diseases were accounted for during the study. Anthropometric measurements, including height, body weight, and waist circumference (WC), were arranged. The body mass index (BMI) was calculated using the classic equation BMI = Body weight (kg) / Height $(m)^2$ [10]. Blood pressure (BP) was measured three times with two-minute intervals on the right arm in the sitting position after a 5-minute rest using an Omron automated BP measuring devices (Omron Healthcare Co., Ltd. M5-I, Japan), recording the mean value of three measurements.

All patients had their venous blood collected (once) in a fasting condition, with an overnight fasting for 8–14 hours. Complete blood count parameters (including white blood cell differential) were determined on the MicroCC-20Plus automatic hematological analyzer (HTI, USA) using Clinical Diagnostis Solution Inc and Streck Labs (USA) kits. Regardless of the automatic assesment results, the "manual" blood smear microscopy was also arranged, including the determination of total white blood cell levels and main white blood cell subpopulations (in percent). Erythrocyte sedimentation rate was determined using the indirect Panchenkov method.

Blood biochemistry parameters were determined using Thermo Fisher Scientific kits (Finland) on the Konelab Prime 30i biochemistry analyzer (Thermo Fisher Scientific, Finland).

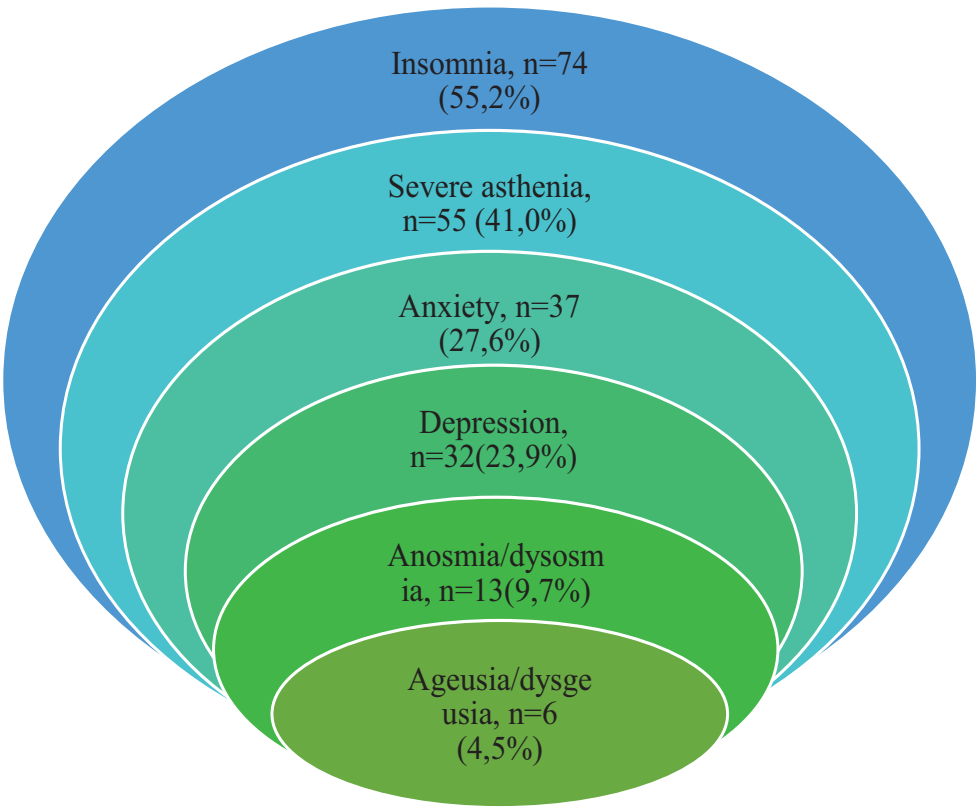

Figure 1. *The structure of the neuropsychiatric phenotype*

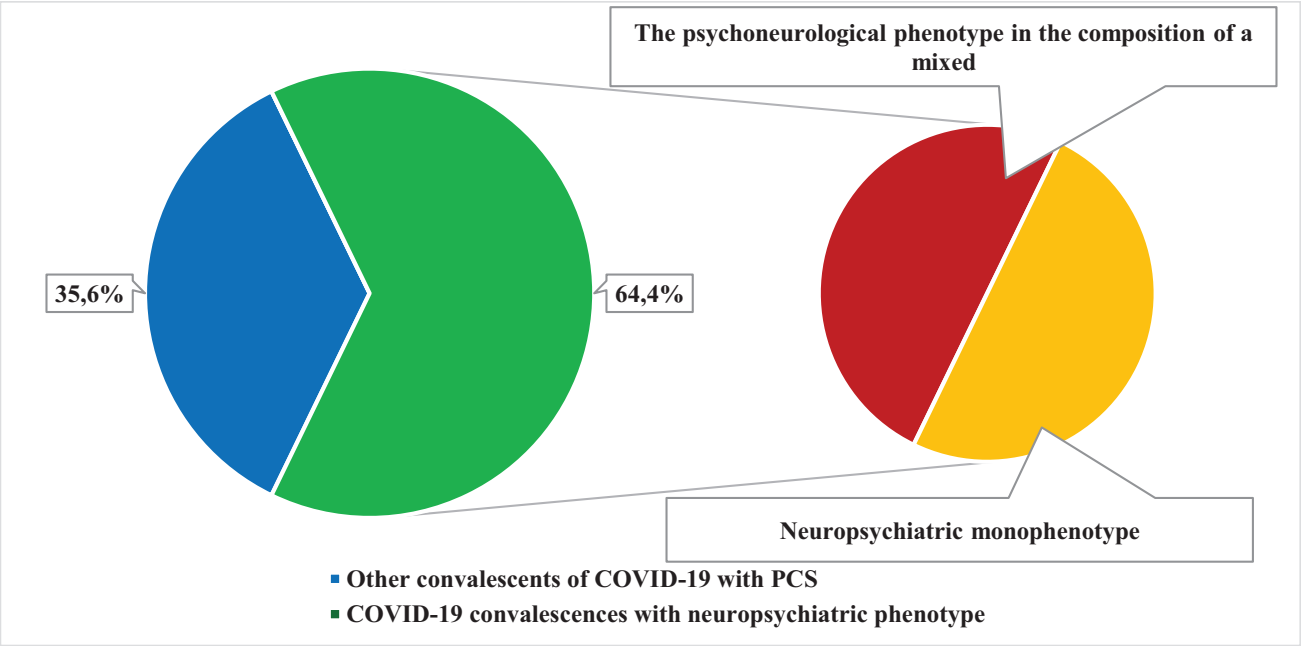

Figure 2. *Neuropsychiatric phenotype among people with postCOVID syndrome*

All examined patients underwent subjective assessment of the quality of life using the 36-Item Short-Form Health Survey (SF-36), as well as the subjective assessment of the psychic condition using the Symptom Checklist-90-Revised (SCL-90-R) questionnaire. The SF-36 survey helps to evaluate the physical, psychological, and social functioning of the patient. The SF-36 questionnaire results are presented in points by 8 scales (for a maximum of 100 points): General Health (GH); Physical Functioning (PF); Role-Physical Functioning (RP); Role-Emotional Functioning (RE); Social Functioning (SF) determined by the degree in which the physical or emotional condition limits the social activity (communication); Bodily Pain (BP); Vitality (VT); Mental Health (MH) [11]. The psychic respondent condition was subjectively assessed by the questionnaire of psychopathological symptom severity (SCL-90-R) adapted by N.V. Tarabrina [12] — it helps to determine the range and severity of psychopathological manifestations, as well as the intensity of psychological distress [13]. Anxiety and depression was diagnosed with the sum of ≥ 8 points based on the Hospital Anxiety and Depression Scale (HADS) [14]. Significant asthenic syndrome was detected based on the subjective asthenia evaluation scale (MFI-20) with the sum of ≥ 60 points for all subscales [15]. The diagnosis of insomnia was established based on the somnologist examination. Ageusia/dysgeusia and anosmia/dysosmia were diagnosed based on the general practitioner examination.

The results were statistically processed using the SPSS software package (v. 13.0). The Kolmogorov–Smirnov test was used to determine distribution. Due to the non-parametric distribution, quantitative data were presented as medians and interquartile ranges Me (Q25; Q75). The Mann–Whitney test was used to compare groups. The Pearson's chi-squared test was used to compare rates in groups. The significance level for the statistical hypothesis testing was $p < 0.05$.

Results

The following phenotypes were represented among persons with mixed PNPs as concomitant diseases: PNP + endocrine manifestations (n = 34, 50.7 %), PNP + alopecia (n = 8, 11.9 %), PNP + bronchopulmonary manifestations (n = 8, 11.9 %), PNP + cardiovascular manifestations (n = 5, 7.8 %), involvement of at least three systems, including psychoneurological manifestations (n = 12, 17.9 %).

The comparative characteristics of clinical and laboratory parameters in persons with PNP and other reconvalescents with PCS is presented in Table 2. According to the results of the analysis of laboratory parameters, fasting plasma glucose (FPG) levels was 1.1-fold lower in the group with PNP.

During the multiparametric logistic regression analysis of the odds of PNP in males and females (standardized by gender and age), a parameter with a statistical difference between groups of COVID-19 reconvalescents with PNP and other COVID-19 reconvalescents

Table 2. *Comparative characteristics of clinical and laboratory parameters of COVID-19 convalescents with neuropsychiatric phenotype and other COVID-19 convalescents with postCOVID syndrome*

Indicators	Convalescences of COVID-19 with PNF *n*=134	Other COVID-19 convalescents with PCS *n*=74	*p*
Age of years, Me [25;75]	55,00 [43,00;65,25]	56,00 [47,50;65,00]	0,467
Men, abs (%)	53 (39,6)	41 (55,4)	**0,028**
BMI, Me [25;75], kg/m^2	28,72 [24,98;32,52]	29,05 [25,61;33,69]	0,473
WC, Me [25;75], cm	109 (81,3)	62,00 (83,8)	0,839
Smoking, abs.(%)	47 (35,1)	25 (33,8)	0,851
PA<3 hours/week, abs.(%)	94 (70,1)	52 (70,3)	0,979
SBP, Me [25;75], mmHg	127,25 [115,00;135,00]	126,25 [117,50;137,50]	0,577
DBP, Me [25;75], mmHg	80,00 [74,50;87,50]	80,00 [75,00;87,50]	0,914
HR, Me [25;75], beats/min	65,50 [60,00;75,00]	67,00 [62,00;73,00]	0,680
White blood cells, Me [25;75], x10^9	5,50 [4,78;6,60]	6,10 [5,05;7,40]	**0,046**
Hemoglobin, Me [25;75], g/l	136,50 [126,00;146,00]	137,00 [126,00;149,50]	0,598
ESR, Me [25;75], mm/min	13,00 [7,00;20,00]	15,00 [10,00;20,00]	0,287
FPG, Me [25;75], mmol/l	6,10 [5,70;6,70]	6,70 [5,88;7,53]	**0,003**
hsCRP, Me [25;75], mg/l	3,78 [1,72;9,39]	3,87 [2,46;12,17]	0,231

Note. * BMI — body mass index, WC — abdominal obesity, PA<3– physical activity of less than 3 hours per week, SBP — systolic blood pressure, DBP-diastolic blood pressure, HR — heart rate, ESR — erythrocyte sedimentation rate, FPG — fasting blood plasma glucose, hsCRP — highly sensitive C-reactive protein, PCS-postcovoid syndrome, PNF-neuropsychiatric phenotype

Table 3. *Logistic multifactorial regression analysis of indicators associated with the neuropsychiatric phenotype of postcovoid syndrome (with standardization by gender and age)*

Variable	The Exp(B)1 model	*p*
Age, for 1 year	0,992 (0,968-1,017)	0,540
Sex (M/W)	1,908 (1,049-3,469)	**0,034**
BMI, per 1 kg/m^2	0,991 (0,939-1,045)	0,725
FPG, per 1 mmol/l	0,875(0,733-1,045)	0,140

Note. * BMI — body mass index, FPG-fasting blood plasma glucose

(FPG) was included into the model, as well as BMI, as based on literature obesity is one of the leading risk factors for COVID-19 [16, 17] ($\chi 2 = 9.531$, $R^2 = 0.045$, $p = 0.049$). Data are presented in Table 3.

The comparative analysis of quality of life parameters (assessed using the SF-36 survey) between two COVID-19 reconvalescent groups with PNP and other PCS phenotypes demonstrated that reconvalescents with PNP had worse parameters in all subscales (Table 4).

Table 5 presents data from the SCL-90-R questionnaire in patients with PNP. It is expected to see increased parameters of all scales in reconvalescents with PNP vs. parameters in reconvalescents with PCS, but without PNP.

Females with PNP demonstrated lower values in the SF-36 survey than in males — physical functioning (1.1-fold; $p = 0.017$) and role-physical functioning (1.6-fold; $p = 0.031$). These data are presented in Figure 3.

Based on the analysis of data from the SCL-90-R questionnaire, females had more severe symptoms in the following subscales: obsessive-compulsive disorders (1.7-fold; $p = 0.028$), depression (1.5-fold; $p = 0.005$), anxiety (2-fold; $p = 0.017$) — and in general had a more unfavorable psychopathological status (Fig. 4).

Based on the MFI-20 scale, the rate of significant asthenia in males with PNP was 37.7 %, while in females with PNP — 43.2 % (no statistically significant differences detected; $p = 0.744$).

Table 4. Data from the SF-36 questionnaire in individuals with postcovoid syndrome with neuropsychiatric phenotype and other phenotypes

Indicators	Convalescences of COVID-19 with PNF *n*=134	Other COVID-19 convalescents with PCS *n*=74	*p*
1. Physical functioning (Physical Functioning — PF)	80,00 [65,00;95,00]	90,00 [75,00;95,00]	**0,024**
2. Role-based functioning due to physical condition (Role-Physical Functioning — RP)	75,00 [25,00;100,00]	100,00 [50,00;100,00]	**0,007**
3. Pain intensity (Bodily pain — BP)	74,00 [51,00;100,00]	84,00 [69,50;100,00]	**0,012**
4. General health status (General Health — GH)	57,00 [40,00;72,00]	72,00 [60,00;82,00]	**<0,001**
5. Vital activity (Vitality — VT)	55,00 [45,00;70,00]	70,00 [58,75;80,00]	**<0,001**
6. Social functioning (Social Functioning — SF)	75,00 [62,50;100,00]	87,50 [75,00;100,00]	**0,001**
7. Role-based functioning due to emotional state (RoleEmotional — RE)	66,67 [33,33;100,00]	100,00 [66,67;100,00]	**0,001**
8. Mental health (Mental Health — MH)	64,00 [52,00;80,00]	80,00 [72,00;88,00]	**<0,001**
9. The physical component of health (Physical health — PH)	47,79 [39,16;53,27]	51,11 [46,12;55,04]	**0,022**
10. The psychological component of health (Mental Health — MH)	45,51 [35,19;52,63]	53,95 [47,60;58,24]	**<0,001**

Note. *PCS-postcovoid syndrome, PNF-neuropsychiatric phenotype

Table 5. Data from the SCL-90-R questionnaire for individuals with postcovoid syndrome with neuropsychiatric phenotype and other phenotypes

Indicators	Convalescences of COVID-19 with PNF *n*=134	Other COVID-19 convalescents with PCS *n*=74	*p*
1. Somatization (SOM)	0,75 [0,50;1,23]	0,50 [0,25;0,77]	**<0,001**
2. Obsessive-compulsive disorder (O-S)	0,70 [0,40;1,10]	0,40 [0,20;0,70]	**<0,001**
3. Interpersonal sensitivity (INT)	0,56 [0,22;0,89]	0,33 [0,11;0,56]	**0,001**
4. Depression (DEP)	0,62 [0,31;0,92]	0,23 [0,08;0,52]	**<0,001**
5. Anxiety (ANX)	0,50 [0,20;0,80]	0,20 [0,00;0,38]	**<0,001**
6. Hostility (HOS)	0,50 [0,17;0,71]	0,17 [0,04;0,50]	**<0,001**
7. Phobic anxiety (PHOB)	0,14 [0,00;0,32]	0,00 [0,00;0,14]	**0,018**
8. Paranoid symptoms (PAR)	0,25 [0,00;0,67]	0,17 [0,00;0,33]	**0,017**
9. Psychoticism (PSY)	0,15 [0,00;0,30]	0,00 [0,00;0,20]	**<0,001**
Total number of points	42,00 [28,00;75,00]	24,00 [15,00;38,00]	**<0,001**
General index of severity of symptoms (GSI)	0,47 [0,31;0,83]	0,27 [0,17;0,42]	**<0,001**
Index of personal symptomatic distress (PSDI)	1,35 [1,18;1,74]	1,15 [1,03;1,38]	**<0,001**

Note. *PCS-postcovoid syndrome, PNF-neuropsychiatric phenotype

Based on the HADS scale, depression in females with PNP was reported in 17.1 % cases, i.e. 3 times higher than in males (6.2 %, $p = 0.043$). Females demonstrated the following rates: anxiety — 27.2 %, anosmia/dysosmia — 6.2 %, insomnia — 63.0 %, ageusia/dysgeusia — 3.7 %, while in males these were 28.3 %, 15.1 %, 43.4 %, and 5.7 %, respectively, with no significant differences reported ($p = 0.872$, $p = 0.088$, $p = 0.430$, $p = 0.598$).

Discussion

Neurotropic SARS-CoV-2 potential is important in the setting of PCS. The SARS-CoV-2 spike protein is characterized by high affinity to the angiotensin-converting enzyme 2, which is expressed on the membranes of endothelial capillary cells. Viral particle efflux from endothelial cells impairs the blood-brain barrier,

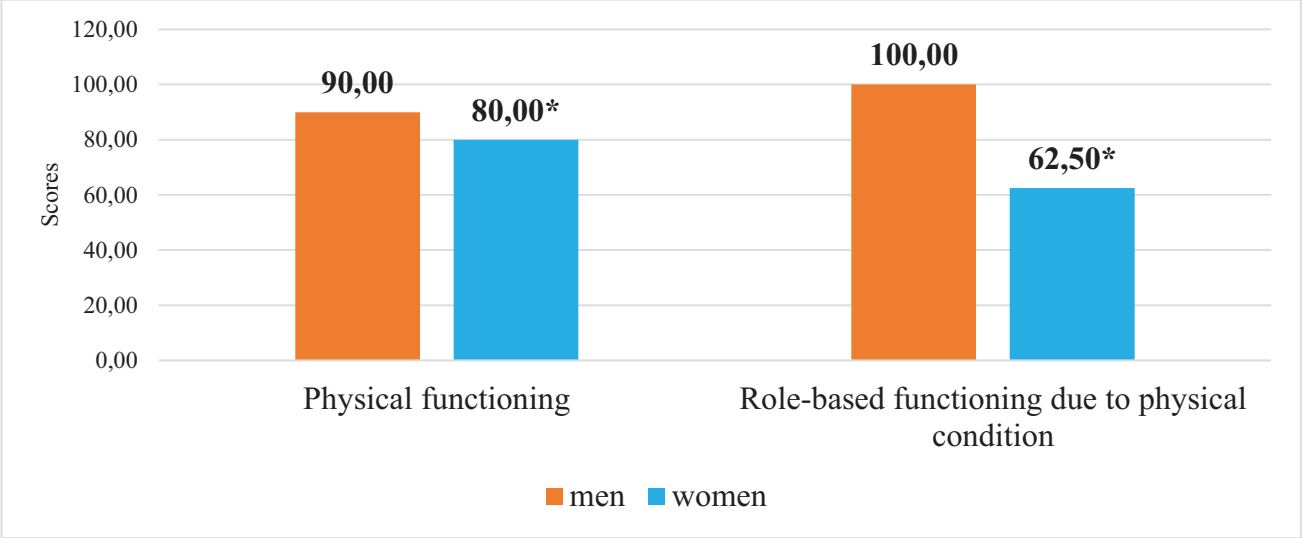

Figure 3. *Scoring of indicators of physical functioning and role functioning due to physical condition in women and men with neuropsychiatric phenotype according to the SF-36 questionnaire*

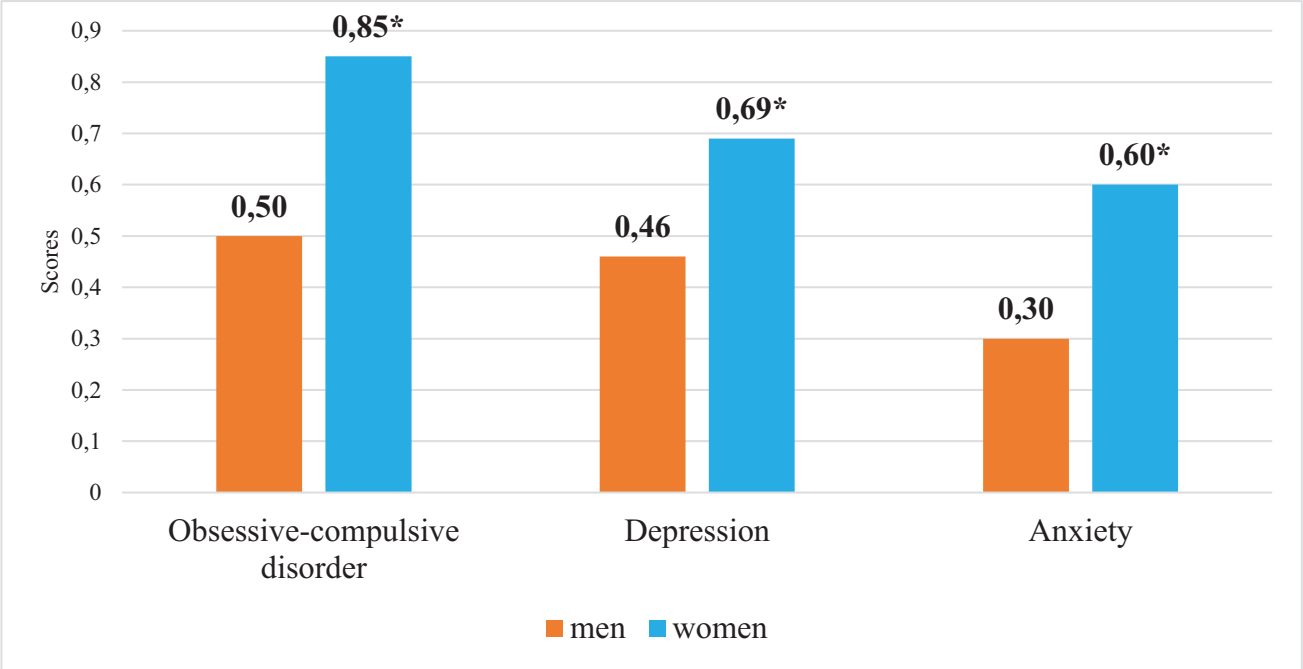

Figure 4. *Score based on the SCL-90-R psychopathological symptoms severity questionnaire for men and women with a neuropsychiatric phenotype*

leading to the virus penetration into the central nervous system [18–20]. Variable neurological signs require a detailed analysis and studies in order to organize the preventive measure and understanding of long-term COVID-19 effects.

Depressive PCS signs are one of the most common infectious complications. According to the meta-analysis (Premraj L. et al., 2022) that covered 18 studies with a total of 10,530 patients, the rate of depression in the post-COVID period was 17 % [21]. According to the study of Buttery S. et al. (2021), this rate reached 43.1 % [22]. The risk factors included the female gender, a history of psychological pathologies, and systemic inflammation in the acute period [23]. The contribution of age and severity of acute COVID-19 to the emergence of depression is doubtful [23–25]. In our study depression based on the HADS scale was more often observed in females, which corresponds to several studies [26, 27]. Age-related differences were not statistically significant in our study.

The rate of anxiety symptoms in the acute COVID-19 phase and the post-COVID period is not inferior to that of depression symptoms. Thus, a Chinese study that enrolled 7,236 subjects and was devoted to the analysis of anxiety during the COVID-19 outbreak using the GAD-7 (Generalized Anxiety Disorder-7) scale (Huang Y. et al., 2020) demonstrated that the rate of anxiety disorders reached 35.1 % regardless of gender. Age under 35 years was the risk factor in this subject category [28]. Manifestations of anxiety as remote infectious sequelae (3–6 months after the disease onset) were reviewed in several studies [29–31]. In our study the rate of anxiety symptoms in subjects was higher than that of depression symptoms, which is probably associated not only with pathogenetic characteristics and comorbidity, but also with economic and social self-isolation issues during the quarantine period of the acute infection. With that, no statistical differences were detected in gender and age categories, which characterizes anxiety disorders as an issue concerning all population strata.

Based on several studies, the prevalence of insomnia reaches 25–47 % [31, 32]. Merikanto I. et al. (2023) arranged a study to assess the prevalence of insomnia and daytime drowsiness manifestations in COVID-19 reconvalescents. Those symptoms prevailed over others and were associated with the severe disease course [32]. In our study insomnia symptoms were the predominant ones among patients with PNP; they were also not associated with the severity of acute COVID-19 course, gender, age, anxiety and depression.

It is well-known that the asthenic syndrome accompanies the majority of infectious, neurological, and somatic diseases, manifesting already during the initial stages of the pathological process [33]. This is one of the most prevalent symptom complexes observed in patients after COVID-19, especially in a long-term perspective. Based on 54 studies, prolonged COVID-19 symptoms, including asthenia, were more common among females [34]. Fernández-de-las-Peñas C. et al. (2021) described the duration of hospital stay as a risk factor for the asthenic syndrome [35]. Older age acts a risk factor for the post-COVID asthenia [36]; however, one should account for the effects of a history of concomitant diseases, decreased physical activity, slowed metabolic processes, worsened functions of the immune and hormonal systems, hypovitaminosis and drug-induced adverse effects in this patient category, as all those factors lead to clinical manifestations of asthenia. In our study we analyzed severe asthenia as one of the PNP manifestations in the post-COVID period. The analysis of factors, i.e. gender, age, severity of acute COVID-19 course, and concomitant diseases (dyslipidemia, hypertension, type 2 diabetes mellitus) did not detect statistically significant associations. However, a high rate of anxiety and depressive disorders along with insomnia was reported in the study group. These factors may both promote the primary asthenic manifestations or worsen those symptoms in combination with infectious asthenia.

Smell and taste disorders are one of the main clinical manifestations of acute COVID-19. Augustin M et al. (2021) described preserved anosmia and ageusia in 11–12 % COVID-19 reconvalescents [37]. Relative to other psychoneurological manifestations in our study, ageusia/dysgeusia and anosmia/dysosmia had relatively smaller rates, also not depending on gender and severity of acute COVID-19.

Conclusion

Psychoneurological phenotype of the post-COVID syndrome is characterized by insomnia, severe asthenia, anxiety and depression disorders, anosmia/dysosmia and ageusia/dysgeusia in patients. It was demonstrated that subjects with PNP had significantly lower parameters of quality of life (based on the SF-36 survey) and levels of psychological personality well-being (based on the SCL-90-R questionnaire) in all subscales.

Psychoneurological phenotype was associated with the female gender. Besides, females are characterized by more significant anxiety, depression, and obsessive-compulsive symptoms, as well as role-physical functioning parameters.

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