Psychiatria Danubina, 2021; Vol. 33, Suppl. 9, pp 130-136 *Conference paper*

CLINICAL FEATURES IN RUSSIAN PATIENTS WITH COVID-ASSOCIATED PAROSMIA/PHANTHOSMIA

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SUMMARY

Background: *Olfactory dysfunction is a typical symptom of COVID-19 infection. While COVID-associated anosmia is well-described, knowledge of parosmia (olfactory distortions) and phanthosmia (olfactory hallucinations) is relatively lacking. We undertook a clinical study of the parosmia/phanthosmia phenotype, aiming to support improved prediction and management of these symptoms.*

Subjects and methods: *In a cross-sectional study between September 2020 and May 2021, we recruited 187 COVID-19 patients with parosmia/phanthosmia via social media and a matched healthy control group from neurologists. The patients received an online video-consultation with a neurologist trained in olfactory research and completed a questionnaire to assess the nature of their subjective olfactory disorder.*

Results: *In the acute period of COVID-19 parosmia/phanthosmia, patients often experienced comorbid manifestations such as fatigue, fever, headache, myalgia, and "brain fog". Isolated phanthosmia was observed in 13.9% of acute COVID-19 patients, as compared to 34.2% in the long term. Parosmia was described in 89.8% of patients in the long-term course of the disease. COVID-associated parosmia/phanthosmia was more common in women (81.3%) than men (18.7%). Almost all parosmia/phanthosmia patients had an acute history of anosmia, which often progressed to hyposmia. A third of the patients had a history of taste disturbance The long-term COVID-19 sequelae such as fatigue, brain fog, and dizziness are significantly more common among patients with parosmia/phanthosmia, as were autonomic symptoms such as awareness of heartbeat and rapid pulse. The incidence of migraine with aura was significantly higher in the parosmia/phanthosmia group than in the control group (8% versus 0.9%). The allergy was reported significantly more frequent in the study group compared to the control group.*

Conclusions: *Qualitative olfactory disorders occur frequently in COVID-19 patients. Those with the parosmia/phanthosmia phenotype have a higher risk for other symptoms, notably headache (including migraine with aura), fatigue, brain fog, dizziness, and cardiovascular/autonomic manifestations, as well as allergy. We suppose that further investigation of this phenomenon will reveal phenotypic variants depending on particular symptoms cluster; improved nosology of qualitative olfactory disorders in COIVD-19 is a prerequisite for establishing appropriate treatments.*

Key words: *COVID-associated olfactory dysfunction - parosmia - phanthosmia - migraine - brain fog*

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INTRODUCTION

COVID-19-related olfactory dysfunction occurring as a single symptom or in combination with other respiratory symptoms is gaining increasing recognition (Cooper et al. 2020, Moein et al. 2020, Strauss et al. 2020, Kandemirli et al. 2021). The olfactory epithelium is targeted by the SARS-CoV-2 virus due to the presence of angiotensin converting enzyme-2 protein in sustentacular and olfactory stem cells (Brann et al. 2020). Olfactory disorders can be classified either as quantitative when affected odor sensitivity (f.e. hyposmia/ anosmia), or qualitative olfactory disorders (parosmia, phanthosmia orolfactory hallucinations) (Hummel et al. 2017). The most common variants of olfactory disorders in COVID-19 are hyposmia or sudden onset of anosmia (Parma et al. 2020; Gerkin et al. 2021). However, there are increasing literature reports of cases of parosmia and phanthosmia associated with COVID-19 infection, which implies an involvement of central olfactory pathways in addition to the primary olfactory epithelium (Duyanb 2021, İşlek 2021).

Parosmia is described as a distorted perception of a real odor and phanthosmia refers to the odor sensation without an odor source (Leopold 2002, Hummel et al. 2017, Liu et al. 2021). These olfactory disorders can negatively affect the quality of life (Ciurleo et al. 2020). Moreover, some studies have shown that olfactory distortion illicits in patients greater discomfort than anosmia, the isolated loss of the sense of smell (Leopold 2002, Saltagi et al. 2018). Although parosmia is more often described in the literature as occurring during recovery in patients with post-infectious olfactory dysfunction (Cavazzana et al. 2018, Liu et al. 2021, Raad 2021), sometimes parosmia is the earliest and leading symptom of COVID-19 (Brelie et al. 2020).

Henkin et al. have classified phanthosmia into three main types: (1) cacosmic (rotten, decayed or fecal, (2) torquosmic (burnt, metallic, chemical) or (3) mixed, a combination of cacosmia and torquosmia (Henkin et al. 2013). There is also a classification of phanthosmia into primary and secondary varieties; in this schema, primary phanthosmia is an odor occurring in the absence of any apparent stimulus and without any apparent underlying clinical or disease process, whereas secondary phanthosmia is the perception of an odor in the absence of any apparent stimulus, which is associated with a known clinical disease process (Henkin et al. 2013).

The pathogenesis of the parosmia/phanthosmia phenomenon is currently unclear. One hypothesis would attribute the development of qualitative olfactory disorders to partial loss of olfactory receptors, resulting in the inadequate formation of a typical odor-specific pattern in the olfactory bulb (Leopold 2002). Another theory argues that parosmia results from aberrant processing of odors in the central nervous system, for example, by the olfactory bulb (Mueller et al. 2005, Rombaux et al. 2010), and/or in integrative brain structures that are part of the olfactory system (Frasnelli et al. 2004). Decreased volume of the olfactory bulb in patients with parosmia may indicate a decreased number of bulb interneurons, resulting in decreased lateral inhibition (Mori et al. 1999), which will cause an irregular pattern of olfactory activation that alters olfactory perception (Hong et al. 2012). Previous reports have suggested that phanthosmia arises either in the peripheral olfactory nervous system and/or in central brain regions (Stevenson et al. 2012). However, a patient study reported successful resolution of phanthosmies in 7 of 8 patients by excision of the olfactory epithelium, which certainly emphasis the importance of aberrant primary sensory responses (Leopold et al. 2002). Thus, phanthosmias likely occur due to disturbances in the functional interactions of the peripheral and central olfactory pathway (Sjölund 2017).

While quantitative variants of olfactory disorder are readily assessed using tests of olfactory function, for example using «Sniffin 'Sticks» or Smell Identification Test (UPSIT), there are no objective assessments of qualitative olfactory dysfunction (Iannilli et al. 2019, Ciurleo et al. 2020). Structural magnetic resonance imaging (MRI) of the olfactory bulbs and nerves is an important technique for measuring degeneration of the primary olfactory pathway, as may occur in association with previous trauma, viral infection, and neurodegenerative diseases (Eliezer et al. 2020, Strauss et al. 2020, Tsivgoulis et al. 2021). However, structural changes do not readily map to the subjective phenomena of parosmia/phanthosmia.

Many research groups have assessed olfactory disorders in post-COVID-19 patients, but there remains considerable uncertainty about the true prevalence of olfactory disorders, the expected time of onset after infection, the outcome of olfactory function, and associated risk factors. We designed the present study to assess prospectively newly diagnosed olfactory dysfunction in patients with mild to moderate COVID-19 using a special questionnaire. Our objective is to obtain new information about the manifestation of olfactory dysfunction in COVID-19.

SUBJECTS AND METHODS

This study was conducted in a cross-sectional study design between September 2020 and May 2021 according to a protocol approved by the institutional human research ethics committee and confiming with the 1964 Helsinki declaration and its later amendments or comparable ethical standards at the Kirov Medical University. We recruited patients with parosmia/phanthosmia through Telegram, who were gathered in the number one chat room. Those who signed the informed consent form were transferred to chat room number two, and then underwent an online video consultation neurologist trained in olfactory research. The first 15 patients were examined by a panel of expert doctors; findings of the panel informed the creation on the questionnaire, which was subsequently used as a standard instrument in the consultations.

Inclusion criteria:

- men and non-pregnant women over 18 years of age with self-reported new-onset parosmia/phanthosmia;
- signed written informed consent;
- positive nasal/pharyngeal swab for SARS-CoV-2 (RT-PCR).

Exclusion criteria:

- patients under 18 years of age;
- legal incapacity or limited legal capacity;
- patients with a history of endoscopic sinus surgery;
- patients with mental or developmental disorders that may impair the ability to give informed consent;
- patients with pre-existing self-reported olfactory dysfunction such as chronic sinusitis, etc.

The response rate (relative to all patients) was 25%. The control group consisted of individual who had neither COVID-19 nor present olfactory disorders, with recruitment aiming to obtain gender and age matching using the PSPP random number generator.

Descriptive statistics for qualitative features are presented in the form n/N (P ± %SD), where n is the absolute number of patients with a certain quality, N is the total number of patients, P is the relative indicator (percentage, in %), and %SD is the relative standard error. In the case of zero values or 100% values, a 95% confidence interval was calculated using the Clopper-Pearson method. Normality of data was checked using the Kolmogorov-Smirnov test with the Liliefors and

Shapiro-Wilk corrections. To represent quantitative features with an asymmetric distribution, the median (Me) and quartiles (quartiles) were used.

To compare groups by qualitative characteristics, we used Fisher's exact test (with two grades of a feature) and Pearson's Chi-square test with a likelihood correction (more than two grades of a feature), for quantitative features with an asymmetric distribution, the Mann-Whitney test. Statistically significant differences were determined at $p<0.05$. Statistical processing was performed using the PSPP program and R.

RESULTS

187 patients with positive SARS-CoV-2 infection confirmed by polymerase chain reaction agreed to participate and were enrolled in this study. Of these 187 participants, 35 were male and 152 female, with an overall mean age of 35 years (range, 21-87 years; Figure 2). The control group consisted of 111 individuals. Comparison by gender and age showed no significant differences in parosmia/phanthosmia and control groups (Figure 1, Figure 2).

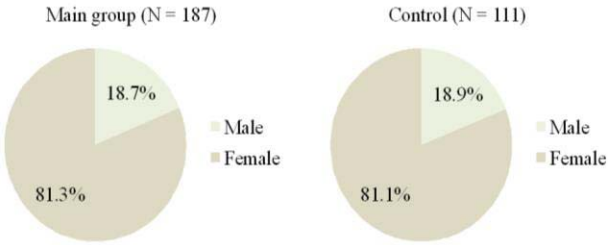

Figure 1. Comparison of groups by gender (p=1,000)

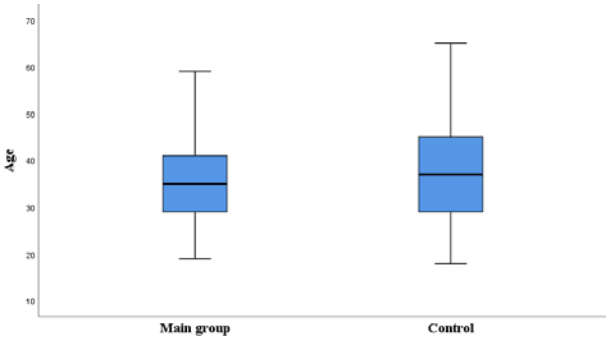

Figure 2. Comparison of groups by age, Me (quartiles), age in years, Main group – 35 (29; 41), Control – 37 (29; 45) (p=0.170)

Table 1. Distribution of anamnestic parameters of the main group and the control group at the time of examination, n/N (P±m, %)

№	Signs	Main group (N=187)	Control (N=111)	p
1	Fatigue	46/187 (24.6±3.1)	15/111 (13.5±3.2)	0.026*
2	Brain fog	40/187 (21.4±3.0)	5/111 (4.5±2)	<0.001*
3	Sleep disorder	32/187 (17.1±2.8)	20/111 (18±3.6)	0.875
4	Feeling of heart beating	62/187 (33.2±3.4)	17/111 (15.3±3.4)	0.001*
5	Rapid pulse	47/187 (25.1±3.2)	12/111 (10.8±2.9)	0.003*
6	Dizziness	28/187 (15±2.6)	4/111 (3.6±1.8)	0.002*
7	Lipothymia	5/187 (2.7±1.2)	1/111 (0.9±0.9)	0.417
8	Traumatic brain injury in anamnesis	25/187 (13.4±2.5)	14/111 (12.6±3.1)	1.000
9	Migraine without aura	31/187 (16.6±2.7)	16/111 (14.4±3.3)	0.743
10	Migraine with aura	15/187 (8±2)	1/111 (0.9±0.9)	0.007*
11	Tension headache	36/187 (19.3±2.9)	20/111 (18±3.6)	0.878
12	Another headache	58/187 (31±3.4)	21/111 (18.9±3.7)	0.029*
13	Epilepsy	2/187 (1.1±0.8)	0/111 (0; 3.3)	0.531
14	Thyroid pathology	21/187 (11.2±2.3)	14/111 (12.6±3.1)	0.714
15	Allergy	74/187 (39.6±3.6)	21/111 (18.9±3.7)	<0.001*
16	Allergic rhinitis	18/187 (9.6±2.2)	7/111 (6.3±2.3)	0.391
17	Chronic rhinosinusitis	13/187 (7±1.9)	8/111 (7.2±2.5)	1.000
18	Smoking			0.464
18.1	1. Yes	28/187 (15.0±2.6)	18/111 (16.2±3.5)	
18.2	2. No	121/187 (64.7±3.5)	79/111 (71.2±4.3)	
18.3	3. E-cigarettes	12/187 (6.4±1.8)	6/111 (5.4±2.1)	
18.4	4. In anamnesis	22/187 (11.8±2.4)	7/111 (6.3±2.3)	
18.5	5. Cigarettes and e-cigarettes	4/187 (2.1±1.0)	1/111 (0.9±0.9)	

Note: * - significant difference (p<0.05)

The absence of significant differences in the main demographic characteristics made it appropriate to compare the groups in terms of individual anamnestic and clinical characteristics (Table 1).

Description of the main group in terms of individual anamnestic and clinical characteristics in acute COVID-19 period (Figure 3, Figure 4, Figure 5).

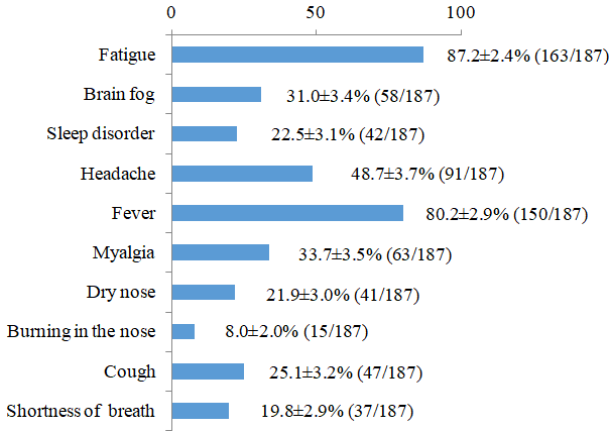

Figure 3. Distribution of anamnestic parameters of the main group in acute COVID-19 period, P±m, % (n/N)

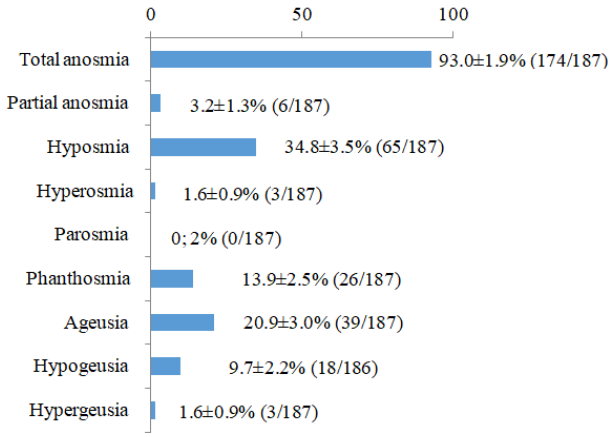

Figure 4. Chemosensory dysfunctions in main group subjects during acute COVID-19 illness phase, P±m, % (n/N)

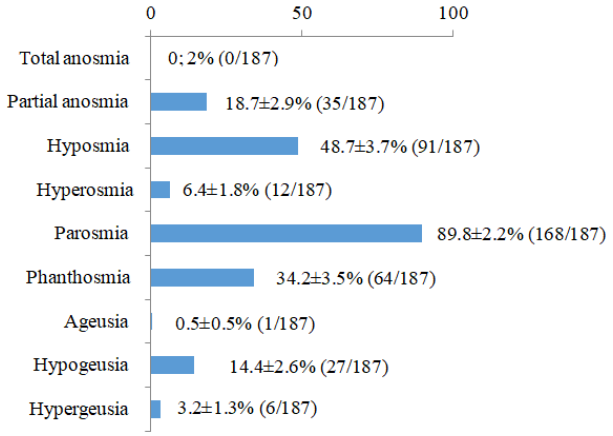

Figure 5. Chemosensory dysfunctions in main group subjects at the time of video examination (> 2 months from the onset), P±m, % (n/N)

DISCUSSION

Olfactory disorders appear to be a key symptom cluster in European and American patients with mild to moderate COVID-19 (Lechien et al. 2020), which is certainly supported by the results of our study. Our survey indicated self-reporting of phanthosmia in the acute phase of COVID-19 in 13.9% of patients in the absence of parosmia symptoms. In the same group of informants, parosmia was self-reported in 89.8% and phanthosmia in 34.2% of patients during the long-term period of the disease. Prevalence of qualitative changes in olfaction (parosmia/phanthosmia) depends on the time from the onset of the disease (Hopkins et al. 2021): it happens quite rare in short term follow up studies (Parma et al. 2020) and raises significantly higher in long follow up studies (Hopkins et al. 2021, Vaira et al. 2021). To date, leading theories for pathophysiology of parosmia suggest a peripheral origin of the disorder. The axons of newly born sensory neurons in olfactory epithelium must define the proper targets in the olfactory bulb. Mistargeting may be a reason of wrong signaling (Schwob et al. 2017). After injury, it takes approximately 1-3 months for axons to reach the bulb. This time frame matches the timing of parosmia in our study (2 months+) favoring the peripheral origin of the disorder and supporting the notion that the presence of parosmia is associated with clinically relevant recovery in olfactory discrimination and identification function in patients with post-infectious olfactory dysfunction (Liu et al. 2021). Our results indicated that COVID-associated parosmia/phanthosmia is considerably more common in women than in men (81.3% versus 18.7%) though our sample is predominantly female which does not allow to make clear conclusions. Several studies report an association of postcovid parosmia with female gender (Hopkins et al. 2021). Follow up studies in social media group also revealed an association with female gender and poor recovery rate (Cook et al. 2021, Koyama et al. 2021), though all mentioned studies also reported female predominance among subjects. We often noted combination of quantitative and qualitative olfactory disturbances; almost all parosmia/phanthosmia patients had a history of anosmia and hyposmia, with the anosmia often spilling over into hyposmia.

About one third of the patients also reported a history of taste disturbances during the acute phase of COVID-19. Currently hundreds of survey-based studies (Saniasiaya et al. 2020, Gerkin et al. 2021) support the hypothesis that COVID-19 affects taste function, though a few studies that used objective taste testing, showed that sense of taste was well preserved (Hintschich et al. 2020) or mildly affected (Le-Bon et al. 2021). Post-viral loss of taste is quite rare (Pritbitkin et al. 2003). Rigorous psychophysical evaluation in specialized chemosensory clinics showed that most patients with "taste" complaints present a normal gustatory function

with an olfactory dysfunction (Pritbitkin et al. 2003). The senses of smell and taste interact with each other to create a flavor: very often people describe flavor as a taste of foods and beverages. Most likely that in our study subjects misinterpreted loss of retronasal smell as a loss of taste. Data from our survey are in line with our hypothesis: occurrence of ageusia (20.9±3.0%) and hypogeusia (9.7±2.2%) was coupled with prevalence of anosmia (93.0±1.9%)and hyposmia (34.8±3.5%); among long term symptoms there are no prevalence of ageusia (0.5±0.5%) or anosmia (0%).Our hypothesis also supported by the recent study performed in 101 subjects using a 7-item Candy Smell Test: retronasal olfactory function was lowered over the course of 7 weeks in laboratory proven COVID-19 patients or suspected ones (Prem et al. 2021).

In the long-term period after infection with COVID-19, such symptoms as fatigue, brain fog, dizziness were significantly more common among patients with parosmia/phanthosmia (24.6, 21.4, and 15% versus 13.5, 4, 5, and 3.6%, respectively). Also, the parosmia/phanthosmia group reported significantly more often than the controls, cardiovascular or autonomic manifestations such as preception of heartbeating and rapid pulse (33.2 and 25.1% versus 15.3 and 10.8%, respectively). An increased incidence of lipothymia or sleep disturbances was not reported in parosmia/phanthosmia patients. Based on these data, as consider it necessary to study more carefully the relationship between parosmia/phanthosmia and fatigue, brain fog, dizziness, cardiovascular manifestations, especially since their presence implies a more systemic disease with greater involvement of the central and peripheral nervous systems. These comorbid complaints should be actively identified in parosmia/phanthosmia patients and considered as important factors for patient management. Of the remarkably interesting features emerging from this study is that more than half of the parosmia/phanthosmia patients have a history of headache prior to disease. In particular, migraine with aura was significantly more common in the parosmia/phanthosmia group than in the control COVID-19 group (8% versus 0.9%). To the best of our knowledge, the association of parosmia/phanthosmia with headache, and specifically, with migraine with aura, not previously reported. These findings suggest that they may share a common mechanism, which deserves further investigation.

We did not find an increased incidence of epilepsy, thyroid pathology, traumatic brain injury, allergic rhinitis, chronic rhinosinusitis in the reported history of parosmia/phanthosmia patients, however, allergy was reported significantly more frequent in the study group compared to the control group. There was no association between cigarette or e-cigarette smoking and the development of parosmia/phanthosmia.

In the acute COVID-19 period, patients with parosmia/phanthosmia often had such comorbid manifestations as fatigue (87.2%), fever (80.2%), headache (48.7%), myalgia (33.7%), and "brain fog" (31%). Such complaints as dry nose were reported in 21.9% and burning nose in 8% are features of anamnesis in acute COVID-19 that might help to predict the development of parosmia/phanthosmia.

CONCLUSIONS

Given the high prevalence of olfactory disorders in people with previous COVID-19, we recommend the assessment of olfactory function for every patient with a new diagnosis of COVID-19 infection. In addition, present results emphasis the high prevalence of qualitative olfactory disorders in the longer term of a COVID-19 infection. The phenotype of parosmia/phanthosmia patients is likely to occur along with serious complaints such as headache (especially migraine with aura), fatigue, “brain fog”, dizziness, cardiovascular/autonomic manifestations, and allergy. To the best of our knowledge, the association of parosmia/phanthosmia with headache, and specifically, with migraine with aura, not previously reported. These findings suggest that they may share a common mechanism, which deserves further investigation. Probably, with further accumulation of data, this broad phenotype will stratify into several subtypes based on the distribution of additional complaints; the co-occurrence of central manifestations such as “brain fog” seems especially important in the context of “long COVID-19” (Moghimi et al. 2021), whereas cardiovascular manifestations may be relevant to the risk of cardiovascular morbidity (Kurz et al. 2020). Such a nosology would properly inform the selection of therapy for specific phenotypes of parosmia/phanthosmia. In addition, present research results are applicable for patient counseling to better indicate expectations and outcomes.

Acknowledgements:

The authors thank Prof. Paul Cumming, Institute of Nuclear Medicine, Inselpital, Bern University, Bern, Switzerland & School of Psychology and Counselling and IHBI, Queensland University of Technology, Brisbane, Australia, for independent expert opinion on the study design and language review of the manuscript.

Conflict of interest: None to declare.

Contribution of individual authors:

Svetlana Kopishinskaia: conceived and designed the analysis, collected the data, wrote the first draft of the manuscript and revised upon input from the other coauthors.

Daria Lapshova & Mikhail Sherman: data or analysis tools, performed the analysis.

Ivan Velichko, Nikolai Voznesensky & Vera Voznesenskaia wrote the text of the manuscript, edited the text of the manuscript.

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