ORIGINAL ARTICLE

PREVALENCE OF SENSORY DYSFUNCTIONS IN ADULT UKRAINIAN POPULATION WITH LABORATORY CONFIRMED COVID-19

DOI: 10.36740/WLek202203119

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ABSTRACT

The aim: To analyse the structure of sensory impairments, associated with COVID-19. To identify terms of recovery periods depending on severity of disease, age and gender of the patients.

Materials and methods: Within two weeks, 2225 patients with confirmed COVID-19 completed a questionnaire, created by Google Forms. General complaints, peculiarities of sensory impairments and recovery time were specified. After exclusion criteria application, data of 2108 patients were analyzed by R Statistics Package, Student's t-test, Wilcoxon rank-sum test, Fisher's exact test, Spearman's rank test.

Results: Among patients enrolled (973 males and 1135 females, mean age 28.6±0.18) the most frequent were olfactory (91.32%) and gustatory (66.03%) dysfunctions. Olfactory manifestations were usually accompanied by gustatory disorders (73.72%). Average duration of olfactory dysfunction was 15.46±0.45 days, gustatory - 11.3±0.33, hearing - 4.3±0.16, and visual - 6.53±0.23 days. It was found a correlation between duration of olfactory and gustatory impairments ($r=0.65$; $p < 0.001$), hearing and visual disorders ($r=0.49$; $p < 0.05$).

Conclusions: Olfactory and gustatory disorders are prevalent symptoms in Ukrainian population. 7.87% of respondents who had impairment of all four sensory functions had the longest recovery time. Duration of sensory impairments did not depend on age, type of treatment and severity of disease, which rises the question about the neurogenic pathway of virus.

KEY WORDS: early detection of disease, COVID-19, sensory disorders

Wiad Lek. 2022;75(3):670-677

INTRODUCTION

Pandemic infection of COVID-19 or SARS-Cov-2, recently announced by WHO, causes mild and moderate symptoms in majority of cases. As of February 24, 2021, a total of 97,464,094 confirmed cases were registered worldwide, including 2,112,689 deaths [1]. First case of this disease was confirmed in Ukraine on 3 March 2020. Since then 1,191,812 laboratory cases of COVID-19 have been confirmed, including 21,861 deaths of people infected with this disease. SARS-Cov-2 put enormous pressure on every country and now it requires implementation of preventive measures. Early diagnosis of coronavirus-19 disease is the most important factor of improving its outcomes and therefore, an important public health strategy. Being transmitted mainly through aerosols and droplets, COVID-19 primarily affects respiratory system and accompanied by such symptoms as tiredness, fever, dry cough, anorexia. Rhinorrhea, conjunctivitis, sore throat, headache, a rash on a skin are less common symptoms. It has been reported [2] that early stages of this disease are usually accompanied by various olfactory dysfunctions, such as anosmia (loss of smell) and ageusia (loss of taste). Besides, patients reported having temporary hearing loss after they had been hospitalized with COVID-19 [3]. Cases of ocular manifestations are not so common but attract an attention of scientists. It was shown that COVID-19 positive patients had ocular abnormalities [4]. Variety of sensory disorders in patients with COVID-19 requires deep studying. However, since the outbreak of pandemic, an attention has been paid to loss of smell and in many cases leaves out other sensory impairments, which determine the quality of people's life. Recognizing all kinds of sensory impairments in patients infected by SARS-Cov-2 is highly important for understanding of underlying mechanisms playing role in the spread of infection and for the developing preventive strategies.

The majority of studies concerning sensory impairments, based on self-reported symptoms or retrospective questionnaires [5-6], related to separate sensory disturbances.

Until now, a comprehensive epidemiological study concerning different types of sensory disorders among patients with confirmed COVID-19 has not been conducted.

Table I. Demographic and epidemiological characteristics of the respondents

Variable	Gender		Total n (%)
	female n (%)	male n (%)	
Average age, years	27.7±0.26 (53.84)	29.7±0.26 (46.16)	28.6±0.18 (100)
Self-reported health status			
excellent	153 (7.26)	136 (6.45)	289 (13.71)
good	879 (41.70)	779 (36.95)	1658 (78.65)
bad	98 (4.65)	68 (2.75)	156 (7.40)
very bad	5 (0.24)	-	5 (0.24)
Severity of COVID-19			
mild	629 (29.84)	529 (25.09)	1158 (54.93)
moderate	458 (21.73)	404 (19.17)	862 (40.89)
severe	44 (2.09)	34 (1.61)	78 (3.70)
critical	4 (0.19)	6 (0.28)	10 (0.47)
Type of treatment			
outpatient	1095 (51.94)	917 (43.50)	2012 (95.45)
inpatient	40 (1.90)	56 (2.66)	96 (4.55)

Table II. Number of self-reported olfactory manifestations in groups of patients with different severity of disease

Severity of COVID-19	Duration of GD, days				
	none*	1-4	5-8	9-14	>15
mild	87	148	367	248	308
moderate	88	89	249	196	240
severe	18	8	19	19	14
critical	4	1	1	1	3
Grand total, n (%)	197 (9.35)	246 (11.67)	636 (30.17)	464 (22.01)	565 (26.80)

* 4 patients reported slight OD during several hours were added in this group

THE AIM

The present article aimed to conduct an epidemiological study, characterizing the prevalence of sensory impairments (gustatory, olfactory, hearing, visual) in patients with laboratory-confirmed COVID-19 infection, analyse their prevalence, features and interactions.

MATERIALS AND METHODS

Within two weeks, 2225 patients completed a questionnaire created by Google Forms. Patients answered 25 questions including six general questions (age, gender, self-reported general health state, severity of COVID-19, presence/absence of laboratory-confirmed case of disease, outpatient/inpatient treatment), 18 questions about peculiarities of sensory dysfunctions (duration, features of impairments, associated symptoms, recovery time, presence of sensory disfunctions in anamneses), and one general clinical question about symptoms associated with SARS-Cov-2. Severity of COVID-19 was classified following the WHO recommendations [7] and included four phases (mild, moderate, severe, critical). The mean recovery time of all sensory dysfunctions was assessed according to four periods: 1-4 days, 5-8 days, 9-14 days, and more than 15 days. This gradation is widely used in the modern literature [8] and based on the fact that viral load significantly reduced after the beginning of disease [9].

Exclusion criteria were: patients under 18 years old, those who did not have confirmed COVID-19 infection by laboratory test, incomplete responses.

R Statistics Package was used to perform statistical analyses. Normally distributed data were reported as mean (deviation). Difference between means was calculated using Student's t-test. Non-normally distributed data were reported as median (interquartile range) and compared using Wilcoxon rank-sum test. Categorical data were presented as n (percentage) and compared using Fisher's exact test. Correlation analysis was performed using Spearman's rank test. A level of $p < 0.05$ was used to determine statistical significances.

RESULTS

A total of 2225 patients completed the questionnaire. After applying of exclusion criteria, 2108 participations remained. Average age of the patients was 28.6±0.18 years old (range 18-77). There were 1135 females and 973 males. The majority of the group reported having mild (n=1158;54.93%) or moderate (n=862 (40.89%) COVID-19

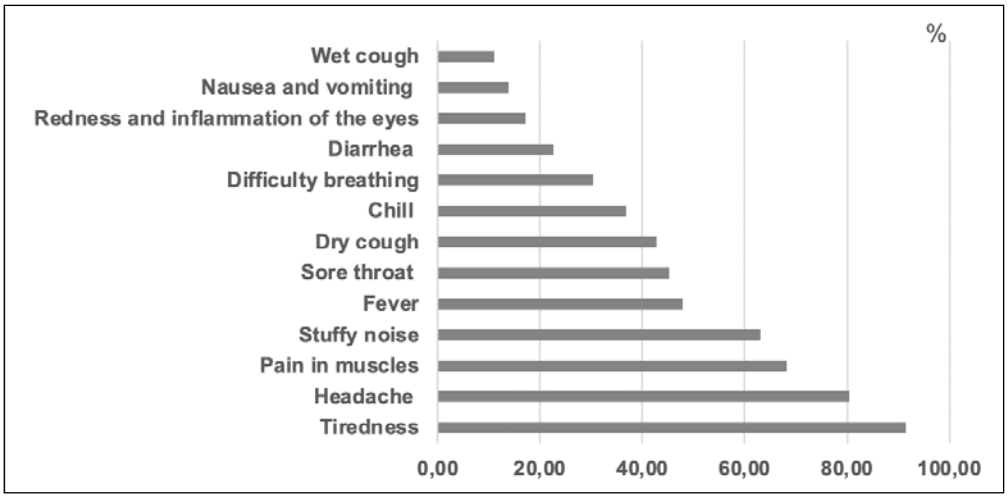

Fig. 1. General symptoms associated with COVID-19

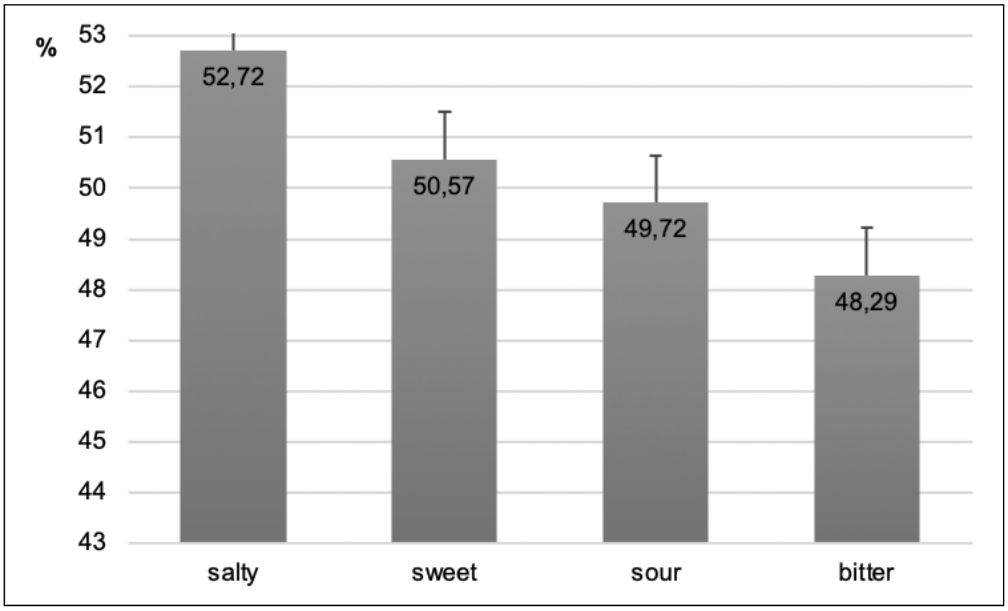

Fig. 2. Taste-quality specific changes

progression, while 78 patients (3.70%) had severe form of disease and 10 (0.47%) – critical one. Self-reported assessment of health status revealed that 289 or 13.71% of respondents had excellent health status before the disease, 1658 (78.65%) – good, 156 (7.40%) – bad and 5 (0.24%) – very bad. 96 people (4.55%) were hospitalized, 2012 (95.45%) had outpatient treatment at home. Demographic characteristics, self-reported health status and severity of disease of the respondents are shown in the Table I.

CLINICAL OUTCOMES

The distribution of self-reported symptoms reported by the patients as associated with COVID-19 is shown in the Fig.1. The most common ones were tiredness, headache, pain in muscles, stuffy noise, fever etc. There were no statistically significant differences in symptoms reported by males and females.

Less common self-reported outcomes (6.9%) included hemoptysis, dizziness, painful lymph in the neck, apathy, tachycardia, stomatitis, runny nose, constipation, low-grade fever (10 days – one month), skin rashes, faintness, pain in kidneys, mental depression, irritable bowel syndrome, pain in joints, dry nose, insomnia, hypertension within 14 days of COVID-19.

PREVALENCE AND FEATURES OF OLFACTORY DYSFUNCTIONS (OD)

A total of 1819 (86.29%) patients reported OD related to COVID-19, 96 people (4.55%) reported partial OD without anosmia and 193 (9.16%) patients did not have olfactory manifestations. Most of the patients with olfactory manifestations had mild or moderate mode of the disease (Table II).

One patient reported hyperosmia (heightened sense of smell). The majority of the respondents had OD within 15.46±0.45 days (median value was 10) and a long recovery time which lasted from two weeks to 240 days. Another reported OD were functional anosmia such as permanent feeling of smell of vinegar, festerment or other unpleasant odours, reduced sense of strong or unpleasant odours (chlorine). Among the participants was a woman who had

Table III. Duration of gustatory dysfunctions in patients with different severity of COVID-19

Severity of COVID-19	Duration of GD, days				
	none*	1-4	5-8	9-14	>15
mild	299	196	302	205	156
moderate	214	126	234	145	143
severe	28	5	19	14	12
critical	3	1	2	2	2
Grand total, n (%)	544 (25.81)	328 (15.56)	557 (26.42)	366 (17.36)	313 (14.85)

* 66 patients reported short-time GD during several hours were added in this group

Table IV. Frequency and duration of self-reported sensory impairments

Type of sensory impairment	Frequency of self-reported dysfunctions, n (%)			Average duration, days	Maximal duration, days
	significant	partial	total		
OD	1819 (46.87)	96 (4.55)	1915 (91.32)	15.46±0.45	240
GD	293 (15.6)	1099 (58.77)	1392 (66.03)	11.3±0.33	180
HD	280 (13.28)	302 (14.33)	582 (27.61)	4.3±0.16	60
VD	285 (13.52)	233 (11.05)	518 (24.57)	6.53±0.23	150

COVID-19 twice. She reported having had hyposmia after she had been infected in February. Her olfaction had not recovered yet when she was infected second time in November.

At the moment of completing questionnaire, only 100 (4.74%) patients reported anosmia while the majority of the group had partial (n=693; 32.87%) or full recovery (n=1131; 53.65%) of the ability to feel and distinguish odours. Most of the study population did not have any complaints on olfactory function before the infection (n=1982; 94.02%), 95 people (4.51%) reported nonsignificant dysfunctions and 31 (1.47%) went to doctor before being infected.

The was no correlation between duration of OD and age. Difference in average duration of OD was not statistically significant between groups of in- and outpatients and between groups with different severity of COVID-19 (p>0.05).

PECULIARITIES OF GUSTATORY DYSFUNCTIONS (GD)

There were 478 patients without gustatory dysfunctions (25.56%), whereas the majority of the participants had partial (n=1099; 58.77%) or complete (n=293; 15.67%) loss of ability to recognize taste stimuli (Table III). Average duration of GD in the study population was 11.3±0.33 days (ranged from several hours to 180 days), median value was 7 days.

Besides, participants were asked to report changes in specific taste-qualities (salty, sweet, sour, bitter). 519 (24.62%) patients reported impairments of all four taste qualities. Bitter and sour taste loss reported less frequently comparing to salty. Results are shown the Fig. 2.

Partial GD were accompanied by taste distortion. For instance, several patients reported that "all the food was bitter", other ones complained on absence of shades of taste: "when tasting a lemon, I felt only a little acid, and there was no taste of citrus" or "there was no difference between cookies and chocolate - they were just sweet". Inability to feel pleasure in eating manifested itself as following: "At the moment I cannot stand the taste of fresh cucumbers. They acquired for me a metallic-caustic-rotten taste, from which vomiting sensations arise. After eating cucumbers for several hours, nothing else interrupts this taste (and it continues to stand in the mouth). At the same time the taste of other products fades, and in some places completely disappears" or "The onion seemed to be rotting, the taste of coffee changed, the meat smelled unpleasantly". Patients also described the taste of food as "spoiled", "like a grass", "toilet paper", "plastic", "rubber".

97.11% of patients did not have any taste dysfunctions before infection, 45 people (2.13%) reported partial GD and 0.76% had to consult with doctor due to significant gustatory disorders before COVID-19.

By the end of follow-up, the majority of the patients reported partial (n=297;14.09%) or full recovery (n=1315; 62.38%) of gustatory function, whereas it had not returned to normal in 48 patients (2.28%). Duration and prevalence of GD depended neither age nor gender.

FEATURES OF HEARING DISORDERS

Hearing disorders were not so as common as OD and GD. 1526 patients (72.39%) did not have hearing disturbances associated with COVID-19, 302 people (14.33%) reported partial dysfunctions and 280 (13.28%) confirmed significant problems with auditory analyzer, affecting life quality. It is necessary to underline that the majority of the participants (n=1982; 94.02%) did not experienced HD before COVID-19. 69 people (3.27%) had nonsignificant complaints and 57 (2.70%) went to otolaryngologist before infection. Presence of auditory disorders in the anamneses (57 patients) can be a reason of hearing impairment during infection. We found that the difference between those who

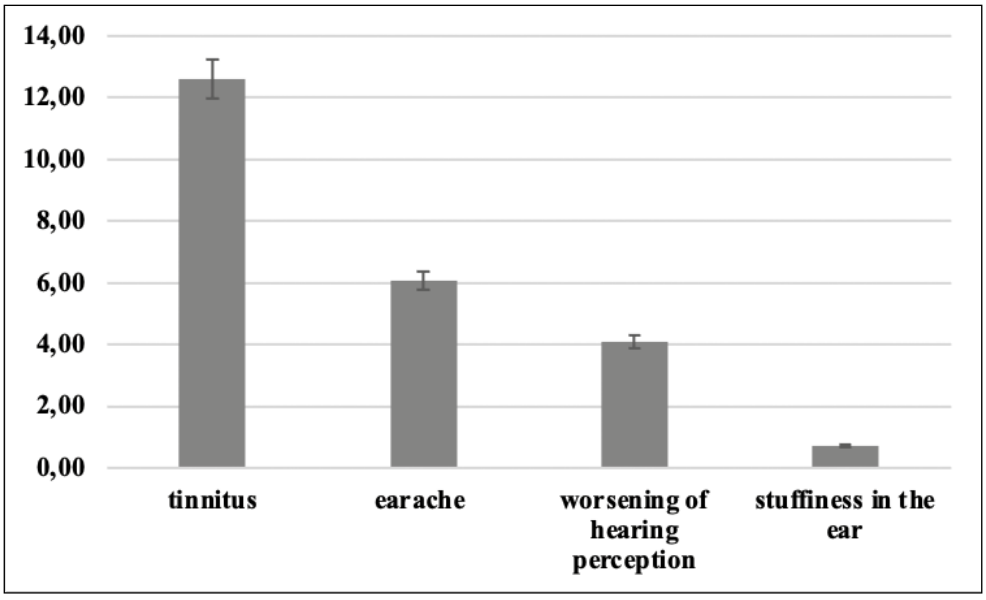

Fig. 3. The most common types of otologic dysfunctions reported by the patients with confirmed COVID-19

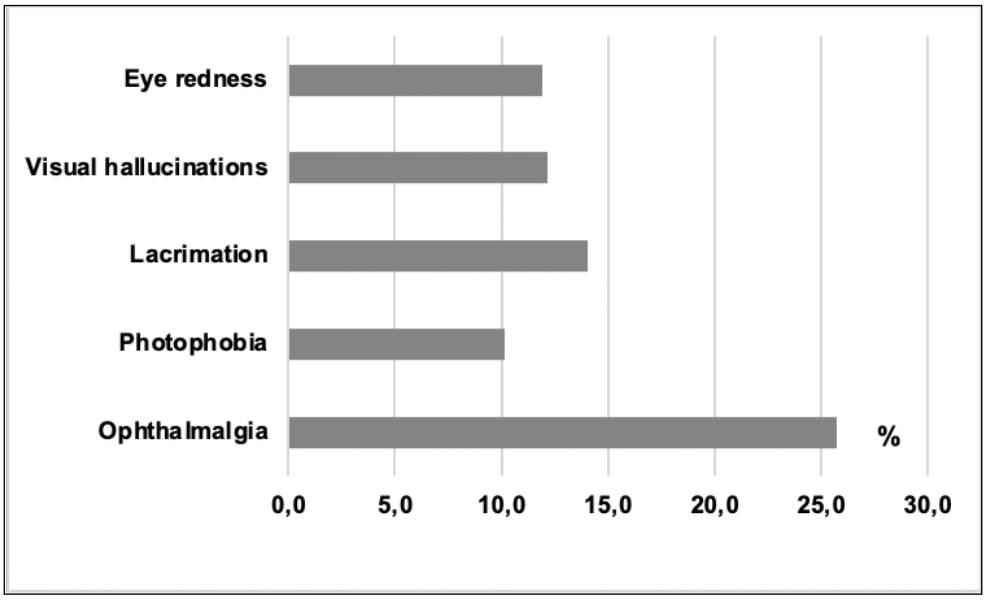

Fig. 4. Ocular manifestations reported by the patients

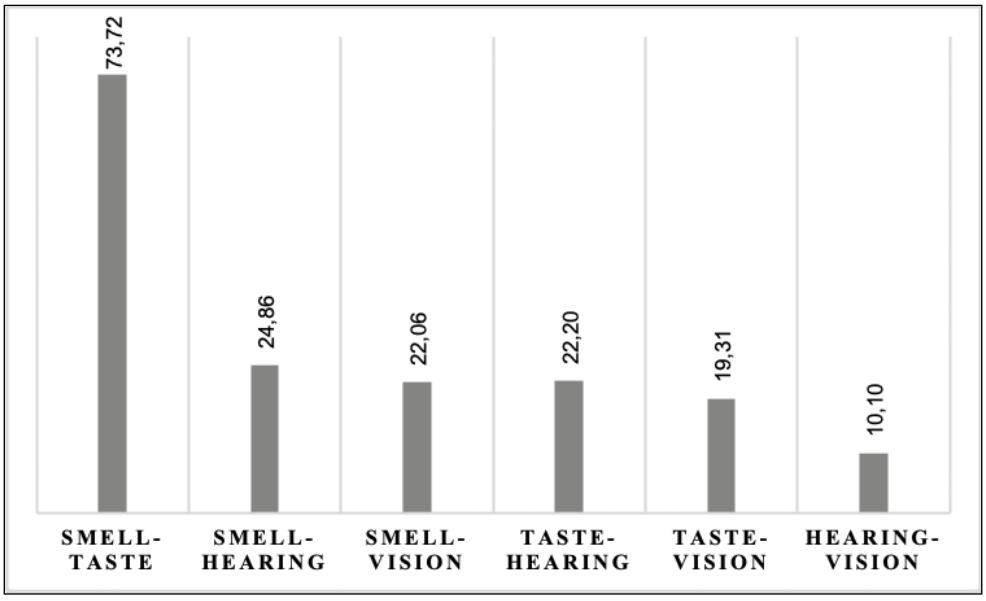

Fig. 5. Frequency of pair combination of sensory impairments regardless to other dysfunctions

reported otologic dysfunctions, associated with COVID-19 (n=27; 47.4%) and those who denied having them (n=30; 52.6%) was statistically nonsignificant. Average duration of hearing impairment associated with SARS-Cov-2 was 4.3±0.16 (ranged from 1 to 60 days). The most common dysfunctions reported by the patients (Fig. 3) were tinnitus (n=266; 12.62%) and earache (n=128; 6.07%), whereas worsening of hearing perception was reported by 86 participants (4.08%) and stuffiness in the ear – by 15 people (0.71%).

Stuffiness in an ear was compared to feelings, occurred in the mountains due to the changes of atmospheric pressure. Another patient described it as "being in an aquarium". Less common complaints reported by the participants were clack sounds in the ear, appearance of permanent irritative noise, temporary decreasing of hearing, accompanied by headache. One patient reported increasing of hearing sensitivity. HD remained in 38 patients (1.80%), 44 people (2.09%) reported partial recovery of hearing function.

CHARACTERISTICS OF OCULAR COMPLICATIONS IN STUDY POPULATION

A total of 518 of 2108 patients had ocular manifestations. Among them were partial (n=233; 11.05%) and significant (n=285; 13.52%) complications, associated with COVID-19. 1590 participants (75.43%) did not have any problems with visual analyzer. Presence of ocular complications did not depend on severity of disease and gender of the patients. Average duration of visual dysfunctions was 6.53±0.23 days (ranged from 1 to 150 days). The most common complaints reported by the patients are shown in the Fig. 4.

The main ophthalmic complaints included (in decreased order): ophthalmalgia (n=542; 25.71%), lacrimation (n=296; 14.04%), visual hallucinations, such as flickers, dots, flashes in the field of vision (n=257; 12.19%), eye redness (n=251; 11.91%), photophobia (n=214; 10.15%). Conjunctivitis was reported by 74 people (3.51%). Apart from this, patients complained on periodical reduction of visual clarity, blurred vision (for 4 weeks maximum), hypersensitivity of eyes, rapid visual deterioration.

Before having COVID-19 449 people (21.3%) had complaints on vision and went to ophthalmologist (the highest number of sensory dysfunctions before infection reported by the respondents). It is necessary to underline, that majority of patients who had in anamneses ophthalmological problems (n=293; 65.3%) did not have any ocular manifestations during COVID-19.

ASSOCIATIONS BETWEEN DIFFERENT SENSORY DISORDERS AND OTHER CLINICAL OUTCOMES

Sensory impairments reported by the respondents were different in frequency and duration (Table IV). Difference in average duration of sensory impairments was significant between all types of sensory impairments ($p<0.05$).

Besides, it was found a correlation between duration of OD and GD ($r=0.65$; $p<0.001$) and HD-VD ($r=0.49$; $p<0.05$). Probably, it can be explained by the presence of combined sensory dysfunctions (Fig. 5). In the majority of the respondents OD were accompanied by GD (n=1554; 73.72%).

Combination smell-taste-hearing dysfunction was reported by 455 people (21.58%), smell-taste-vision – by 396 respondents (18.79%), smell-hearing-vision – by 189 patients (8.97%), taste-hearing-vision – by 170 (8.06%).

Only 166 people (7.87%) had partial or significant impairment of all four sensory functions. This unique group included 95 females and 71 males who experienced different modes of COVID-19, reported all possible health states before the disease (from excellent to very bad). Most of them denied having sensory dysfunctions before infection (90.96% had no previous history of OD, 95.78% - GD, 87.34% - HD and 52.41% - VD). Interesting, that this group included people with the maximal recovery time of sensory functions (see table IV) except hearing (maximal recovery time in this group was 30 days).

DISCUSSION

Our results confirm and substantially extends previous studies concerning sensory impairments associated with COVID-19. The exact pathophysiological mechanisms of sensory impairments caused by SARS-CoV-2 remain unclear. However, according to the most popular hypothesis, coronavirus uses an olfactory pathway as a gate to the central nervous system.

Generally, OD can be either quantitative, when strength alteration takes place or qualitative involving the changing of odors. First group is classified into hyposmia (reduced sense of smell), functional anosmia (when a person can detect only occasional odors), and anosmia (total loss of the ability to detect one or more smells) [10].

The prevalence of self-reported OD and GD obtained in our study stay within data published earlier. The prevalence of OD and GD were analyzed among 8438 patients in a systematic review conducted by Agyeman A et al. [11]. They concluded that the reported prevalence of OD ranged from 3.2 to 98.3%, and the pooled prevalence was 41.0%, whereas gustatory dysfunctions were reported or objectively confirmed in the range from 5.6% to 62.7% of patients with COVID-19 and the pooled prevalence was 38.2%. Our findings about average duration of sensory impairments partially confirm results of other scientists. For example, Klopfenstein et al. [12] studied 114 patients with confirmed COVID-19 and found that the mean duration of anosmia was 8.9 days.

Our results support an idea [13] that this viral infection and inflammatory response may lead to disruption of saliva composition, normal taste transduction or the continuous renewal of taste buds. For instance, SARS-CoV-2 may occupy the binding sites of sialic acid on the taste buds. Reduction of sialic acid lead to increasing of gustatory threshold [14].

As it was mentioned above, we did not find any correlations between OD/GD and age or gender of the patients.

It corresponds to the latest research in adult population, which shows that sex is not associated with smell and taste disturbances [15]. At the same time, Giacomelli A. and Pezzati L. conducted as a verbal interview with 69 patients, hospitalized patients with COVID-19, and showed that olfactory dysfunctions were more prevalent in younger people and women [16]. Approximately the same conclusion was made another group of scientists studying prevalence of chemosensory dysfunctions in infected patients. Von Bartheld CS et al. conducted a systematic review and meta-analysis. The authors found that smell or taste dysfunction or both decreased with older age, male gender, and disease severity [17]. Their study also revealed significant ethnic difference: Caucasians had a three times higher prevalence of chemosensory dysfunctions (54.8%) than Asians (17.7%). Probably, uncontrolled factors (genetic, individual immune resistance etc.) play the main role in chemosensory dysfunctions. Testing of this hypothesis requires additional studies and usage of factorial analysis. While the underlying mechanisms of chemosensory dysfunction is still under discussion, an international research team of Harvard Medical School made a progress in their explaining [18]. It was suggested that such mechanisms are determined not by the direct infecting the neurons, but by the affection the vascular cells in the nervous system. Losing of taste and smell differs from those, caused by flu or cold. For instance, COVID-19 patients don't have a stuffy or runny nose and can breathe freely. Ageusia is usually accompanied by the significant reducing of sensitivity and inability to distinguish bitter or sweet. Combination of taste and smell impairments in 73.72% of respondents (Fig. 5), confirms that these senses are closely linked to each other, having many overlapping brain areas. Inflammatory damage of frontobasal region may alter both senses.

We did not find any comprehensive epidemiological studies devoted to self-reported hearing dysfunctions among patients infected by SARS-Cov-2 in scientific literature. Data concerning hearing dysfunctions associated with COVID-19 are scarce and usually are limited by case studies [19]. In a systematic review, published by Maharaj S. et al in 2020 [20] 62 articles were analyzed. The authors found only 5 case reports and 2 case series describing 28 patients with hearing loss, associated with COVID-19. According to results, obtained by Munro K et al., 13.2% of patients admitted to Manchester University Hospital reported changes in hearing and/or tinnitus, associated with coronavirus [21], which is comparable with our results. It is well known that sudden sensorineural hearing loss (SSNHL) is associated with viral infections (measles, mumps, meningitis). Auditory pathway, including cochlear nerve, cochlea, perilymphatic tissue can be affected due to ascending infection from the nasopharynx or damaged due to restricted oxygen and blood supply. Taking medication, emotional strain caused by pandemic, fatigue are also possible explanations of hearing dysfunctions during COVID-19. Even though none of our respondents reported having deafness or SSNHL, we obtained valuable data concerning the prevalence and features of HD among patients with confirmed COVID-19.

Since viral RNA have been found in the tears of infected people [22], ocular manifestations in confirmed COVID-19 patients attract an attention of scientists. In a systematic review [23] which included 16 studies reporting 2347 confirmed cases of COVID-19, the authors found that 11.64% of COVID-19 patients had ocular dysfunctions. The most common ocular abnormalities were ocular pain (31.2%), increased secretions (19.2%), redness (10.8%), conjunctivitis (7.7%). According to recent studies, the incidence of conjunctivitis among COVID-19 patients is ranged between 8 and 31.6% [24-25]. Probably, it happens because the ocular surface could be a portal of entry and a reservoir for viral transmission. Studies of ocular manifestation associated with COVID-19 are highly criticized. In the mentioned above systematic review, Aggarwal K et al. were skeptical about results, published earlier for "it is not clear whether these ocular features were pre-existing or occurred as a result of COVID-19 infection". According to our results, the majority of patients who had previously experienced ophthalmopathy did not have any complaints on eye disorders during infection. So that ocular manifestations reported by the patients can be considered as nonspecific evidence of SARS-Cov-2 along with other sensory impairments.

CONCLUSIONS

1. The axiomatic statement concerning the necessity of early recognition of SARS-Cov2 and strict adherence to the patient's roadmap requires the visualization of markers that herald the disease onset. Which, according to the obtained results, can be the appearance of signs of sensory dysfunctions.
2. Analysis the frequency and mechanism of sensory impairments in COVID-19, highlights one of the potential cornerstones of understanding the infectious process. Obtained results can be used to develop guidelines for personal protective equipment during a pandemic.
3. Significant prevalence of quantitative and qualitative manifestations of chemosensory dysfunctions requires further study of the virus penetration. An activation of a large number of neurovegetative impairments confirms the possibility of neurogenic pathway of virus.
4. Patients with all four sensory dysfunctions demonstrate significantly slower recovery time and need extended rehabilitation and psychological support. An inclusion of ophthalmologists and otolaryngologists in the early treatment stages is necessary for early recognition and better therapy of sensory dysfunctions.

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Conflict of interest:

The Authors declare no conflict of interest.

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Received: 10.02.2021
Accepted: 30.11.2021

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article