REVIEW ARTICLE

Otorhinolaryngological manifestations of COVID-19 infection

Otorynolaryngologiczne manifestacje infekcji COVID-19

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Article history: Received: 05.03.2021 Accepted: 22.04.2021 Published: 30.04.2021

ABSTRACT: COVID-19 manifests itself in a wide spectrum of clinical symptoms, both in terms of their variety and severity. It can be asymptomatic or abortive, mild, moderate, severe and fulminant, i.e. having a septic course with multiple organ failure and shock. Typical leading symptoms of COVID-19 include: high fever poorly responding to drugs, severe loss of strength, chest pain, dyspnoea, headaches, bone and joint pain and muscle pain, and finally the onset of acute respiratory distress syndrome (ARDS). However, other symptoms not related to the lower respiratory tract involvement are also mentioned as possible in numerous publications. These include gastrointestinal disorders, damage to the central and peripheral nervous system, catarrh of the upper respiratory tract, and dysfunctions of the sensory organs. The aim of this literature review was to determine the frequency of various head and neck dysfunctions that are part of COVID-19. Symptoms of conjunctivitis, nasal mucostis, pharyngits and laryngitis are reported by about ¾ of patients, albeit they do not always occur at the same time, as in infections caused, for example, by rhinoviruses. Anosmia/hyposmia or ageusia/hypogeusia occur with a similar frequency. Symptoms of damage to the equilibrium system, such as dizziness, are reported by approx. ⅓ of patients, vertigo and hearing loss by approx. 5–6%, of patients, tinnitus by approx. 10% of patients. To date, reports of peripheral paresis of the facial nerve coexisting with COVID-19 are relatively scarce and the symptom is often included in the category of neurological symptoms, the frequency of which also corresponds to about ⅓ of COVID-19 cases. Importantly, both catarrhal and other symptoms listed herein may precede, co-occur or follow the onset of the leading symptoms of COVID-19. They can also be the only symptoms of this disease. This should prompt otorhinolaryngologists to be particularly vigilant in this regard.

KEYWORDS: COVID-19, otorhinolaryngology, symptoms

STRESZCZENIE: COVID-19 manifestuje się szerokim spektrum objawów klinicznych, zarówno pod względem ich różnorodności, jak i natężenia. Może przebiegać bezobjawowo lub poronnie, lekko, średnio, ciężko oraz piorunująco, jako stan septyczny z niewydolnością wielonarządową i wstrząsem. Typowymi wiodącymi objawami COVID-19 są: wysoka gorączka słabo reagująca na leki, mocno odczuwalna utrata sił, ból w klatce piersiowej, duszność, ból głowy, bóle kostno-stawowe i mięśniowe, aż do wystąpienia zespołu ostrej niewydolności oddechowej (ang. *acute respiratory distress syndrome*; ARDS). Jednakże wiele publikacji wymienia wśród możliwych objawów także inne, niezwiązane z zajęciem dolnych dróg oddechowych. Są to: zaburzenia żołądkowo-jelitowe, uszkodzenia ośrodkowego i obwodowego układu nerwowego, nieżyt górnych dróg oddechowych i dysfunkcje narządów zmysłów. Celem niniejszego przeglądu piśmiennictwa było określenie częstotliwości różnych dysfunkcji w obrębie głowy i szyi, będących elementami COVID-19. Objawy nieżytu spojówek, błony śluzowej nosa, gardła i krtani podaje ok. ¾ chorych, jednak nie zawsze występują one wszystkie i jednoczasowo, jak w infekcjach wywoływanych np. przez rhinowirusy. Z podobną częstotliwością występują *Anosmi/hyposmia* lub *ageusia/hypogeusia*. Objawy uszkodzeń układu równowagi w postaci *dizziness* zgłasza ok. ⅓, *vertigo* i niedosłuch ok. 5–6%, szum uszny ok. 10%, pacjentów. Doniesienia o współwystępowaniu z COVID-19 obwodowego niedowładu nerwu twarzowego są na razie stosunkowo nieliczne i często zaliczane do zaburzeń neurologicznych, których częstotliwość wynosi również ok. ⅓ przypadków COVID-19. Co ważne, zarówno objawy nieżytowe, jak i pozostałe tu wymienione mogą poprzedzać, współwystępować lub następować po wystąpieniu wiodących objawów COVID-19. Mogą być także jedynymi objawami tej choroby. Powinno to skłaniać otorynolaryngologów do szczególnej czujności w tym zakresie.

SŁOWA KLUCZOWE: COVID-19, objawy, otorynolaryngologia

 DOI: 10.5604/01.3001.0014.8514

ABBREVIATIONS

AC2 – angiotensin converting enzyme 2
ARDS – acute respiratory distress syndrome
COVID-19 – Coronavirus Disease 2019
CT – computed tomography
MERS – Middle East Respiratory Syndrome
MRI – magnetic resonance imaging
SARS – severe acute respiratory syndrome
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
TEOAE – otoacoustic emission

INTRODUCTION

COVID-19 (Coronavirus Disease 2019) is an acute infectious disease first diagnosed in Wuhan, China in December 2019 [1, 2]. The etiological factor responsible the disease is the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, the disease has caused more than 2.39 million deaths, including more than 40 000 deaths in Poland [3]. SARS-CoV 2 belongs to the family of coronaviruses previously described as etiological factors responsible for the epidemics of upper and lower respiratory tract infections in China in years 2002–2003 [4] and the Middle East Respiratory Syndrome (MERS) in the Middle East, mainly Saudi Arabia, in years 2012–2013 [5].

Natural history of COVID-19 involves high fever poorly responding to pharmacotherapy, severe loss of strength, chest pain, dyspnoea, headaches, bone and joint pain and muscle pain, and finally the onset of acute respiratory distress syndrome (ARDS) [6]. These symptoms were included in the first reports on the disease from Asia where the pandemic started [7, 8]. Less frequently, but also reported are catarrh of the upper respiratory tract, and disturbed sense of smell and taste [9]. All these symptoms, although quite common in viral infections [10, 11], are of particular interest in COVID-19 due to the fact that they are not always accompanied by rhinitis and may constitute the only symptoms of the disease. Moreover, if these are the only signs of disease (not accompanied even by fever), they may not raise any suspicion of COVID-19 and be ignored [12, 13].

In the available literature, a number of reports con be found on different clinical courses of COVID-19, in which problems within the head and neck region are the important, or even the only symptoms of the disease. The aim of this study was to review the available data and provide a synthetic summary for educational purposes.

COMMONLY REPORTED SYMPTOMS OF COVID-19

COVID-19 manifests itself in a wide spectrum of clinical symptoms, both in terms of their variety and severity. It can be asymptomatic or abortive, mild, moderate, severe and fulminant, i.e. having a septic course with multiple organ failure and shock [14]. Despite the pandemic spread and the large numbers of patients, the clinical presentation and pathomorphological mechanisms remain unclear due to the short-term nature of observations [15].

According to various authors, the leading symptoms of the disease include high fever (70–77%), dry tiring cough (53–61%), dyspnoea (38–40%), chest pain (23–30%), headache (30–33%), general fatigue/weakness, loss of strength (25–30%), and muscle and joint pain (10–15%). Nausea/vomiting (3–4%), diarrhoea (4–5%), or constipation (less than 1%) ale also observed [1, 2, 8, 9, 15–24].

According to some authors, productive cough is not uncommon (27%) [25]. According to others, fever may not the most common symptom [20, 26]. Individual patients present with variable combinations of several of the above symptoms; in some cases, the symptoms may occur in an isolated form.

Symptomatic patients are expected to be several times outnumbered by asymptomatic patients. Among the symptomatic patients, mild or moderate course (with no pneumonia or mild pneumonia) is predominant (81%). Less frequently (14%) inflammation spreads onto more than 50% of pulmonary parenchyma causing dyspnoea and hypoxia while being critically severe in the lowest percentage of cases (5%) [27].

RHINITIS AND PHARYNGITIS IN COVID-19

In general, symptoms of upper respiratory tract inflammation are common in COVID-19. They are reported by approximately 3/4 of subjects [12, 13], albeit they do not always occur at the same time, as in infections caused, for example, by rhinoviruses. For this reason, COVID-19 is significantly different from typical viral infections of the upper respiratory tract [28]. Korkmaz et al. [21] observed nasal congestion, runny nose, and sneezing in only 27.5%, 13.7%, and 12.9% of patients, respectively. Throat pain, pain-related dysphagia, hoarseness, and the sensation of throat obstruction were reported by 32.7%, 20.6%, 19.8%, and 13.7% of subjects, respectively.

A survey of 155 patients diagnosed with and treated for mild COVID-19 in an outpatient setting revealed that 57.4% of patients presented with ENT symptoms. These were significantly more common in women and in the younger age group (18–30 years) [29].

The most complete data were presented by El-Anwar et al. [30] who had conducted a meta-analysis of 11 publications on the ENT symptoms observed in the course of COVID-19 as published by the end of April 2020 [1, 2, 16–18, 20, 22–25, 31, 32]. In this manner, they had established a database of 1773 patients. Of the 1773 laboratory-confirmed COVID-19 infections, the most common symptoms within the head and neck region included throat pain (11.3%) and headache (10.7%). Throat redness (5.3%), nasal obstruction (4.1%), runny nose (2.1%), general URT infection (1.9%), and tonsillar enlargement (1.3%).

A more detailed breakdown of these symptoms, with their intensity being indicated using a scale of 0 to 4, is presented in Tab. I., which was prepared on the basis of the paper presenting the results of a multi-center survey conducted in 417 patients with mild or moderate disease [12].

Tab. I. The percentage of patients reporting ENT symptoms associated with COVID-19 in a sample of 131 patients. Symptom severity scale: 0 – none, 4 – very severe.

SYMPTOM/INTENSITY	0	1	2	3	4
Obstruction of nasal cavities	31.49	(21.88)	77 (18.51)	67 (16.11)	50 (12.02)
Runny nose	37.11	(29.40)	81 (19.52)	40 (9.64)	18 (4.34)
Dryness, itching within the nasopharynx	48.80	(23.32)	61 (14.66)	26 (6.25)	29 (6.97)
Sore throat	46.15	(23.08)	57 (13.70)	38 (9.13)	33 (7.93)
Pain, feeling of facial compression	47.60	15.87	59 (14.18)	39 (9.38)	54 (12.98)
Ear pain	74.52	45 (10.82)	32 (7.69)	16 (3.85)	13 (3.13)
Dysphagia	22.64	40 (37.74)	24 (22.64)	11 (10.38)	7 (6.60)

DISTURBANCES OF SMELL AND TASTE IN THE COURSE OF COVID-19

Anosmia/hyposmia or ageusia/hypogeusia are typical symptoms accompanying viral infections of the upper respiratory tract. They are also observed coronaviral infections. In the infections caused by the so-called old coronaviruses, these symptoms were recorded in 10-15% of cases [33]. However, already the earliest reports pointed out that in the case of COVID-19, these disorders often occurred without rhinitis [15, 34].

Different authors report different data on the prevalence of smell and taste disturbances in the course of COVID-19 [35, 38, 39], with prevalence rates differing between regions. Values reported by Asian authors are significantly smaller, ranging between 5 and 6% [2, 7, 8, 16–18, 36], while the values reported for European populations are much higher, on the order of several dozen per cent. For example, in a survey study of 116 patients asked to describe their smell and taste disturbances using a visual analogue scale, hyposmia/anosmia was confirmed by 37.9% of subjects and hypogeusia/ageusia by 41.37% of subjects [21]. According to Menni et al. [35], the prevalence of smell and taste disturbances in their group of patients amounted to 59%. The same authors calculated that the presentation of smell and taste disturbances as being concomitant with fever, cough, fatigue, and gastrointestinal disorders was a positive predictor of COVID-19 characterized by specificity and sensitivity rates of 86% and 54%, respectively.

The problem of smell and taste disorders in COVID-19 was systematically investigated by a team of ENT specialists from four countries (Belgium, France, Spain, Italy) in a multi-center prospective clinical trial including 417 patients (263 females and 154 males) [12]. Included in the survey were questions regarding the time and nature of the onset of taste and smell disorders as well as on the impact of these dysfunctions on the quality of patients' lives. It turned out that as many as 85.6% of patients reported olfactory problems associated with COVID-19 infection. What is important and typical of COVID-19, nearly 80% of patients negating the symptoms of rhinitis (runny nose, congestion), confirmed the presence of hyposmia or anosmia. In this group, 79.6% (68.1% of all subjects) experienced anosmia whereas 20.4% (17.5% of all subjects) experienced hyposmia. In the hyposmia group, cacosmia and/or parosmia were reported by 32.4% of subjects whereas fantosmia was reported by 12.6% of subjects. Olfactory disturbances developed before (11.8%), after (65.4%), or together (22.8%) with the first symptoms of the disease while only 9.4% of the subjects were unable to determine the time of their onset.

For 11.2% of patients, it was impossible to provide answers to questions related to taste disorders. The remaining 88.8% of patients (82% of the total population) were able to provide their answers to questions on ageusia/dysgeusia. Of the 43 patients negating taste disorders, 19 patients denied experiencing any olfactory disturbances while accompanying anosmia and hyposmia were reported by 16 and 4 subjects, respectively. In 73.8% of patients reporting taste disturbances, the symptoms were of stable intensity as compared to presenting in a fluctuating manner in 23.4% of subjects.

In more than ¼ of the patients, the senses of smell and taste are recovered within 2 weeks after the resolution of the main symptoms but as many as 56% continue to report taste and/or smell disturbances afterwards [12].

US data on smell and taste disturbances are similar to those reported for the European countries. In one of the studies, carried out in a sample of 237 patients, anosmia was diagnosed in 73% of subjects, including 26.6% of subjects who experienced it as the first symptom of the disease. In fact, the authors recommend that COVID-19 should be the first diagnostic suspicion in cases of isolated anosmia /ageusia without any comorbidities [37].

Smell/taste disorders in the natural history of COVID-19 are in fact more common than it is commonly believed. In a study conducted in Italy in a group of 384 COVID-19 patients, taste or smell disturbances were reported in 34% of cases while simultaneous taste and smell disturbances were reported in 19% of cases [9]. However, another study carried out by the same authors, this time in a prospective and multi-center manner in a group of 138 subjects, revealed that as many as 84.8% of patients presented with abnormal results of electrogustometric and olfactometric examinations carried out in the first 4 days of the study, suggesting the presence of discrete, subclinical

taste/smell disturbances. These dysfunctions resolved gradually, with fastest resolution times being within the first 10 days of the disease in the case of smell disturbances, and within the first 10–20 days in the case of taste disturbances. However, in 60.7% of patients, taste disturbances resolved only within the next 10 days; in 80.9% of patients, resolution was complete within 20 days. Analogous results for smell disturbances were 13.8% and 54%, respectively. After 60 days of follow-up, significant disturbances were reported by only 7.2% of subjects.

The literature reports emphasize that isolated olfactory disturbances not accompanied by rhinitis must always give rise to the suspicion of coronaviral infection and that each patient presenting with such symptoms should be considered potentially infected. This should be sufficient to refer the patient to the test via online consultation [41]. ENT specialists and dentists are at particular risk of infection. Services provided by these specialists should be limited to only health- or life-saving procedures [41, 42].

As early as in 2007, the presence of SARS-CoV-1 coronavirus had been demonstrated in the nasal cavity secretion collected from a patient with unexplained anosmia without accompanying symptoms of rhinitis or laryngitis [10]. Although the etiopathogenesis of smell disturbances has not been fully elucidated, viral penetration of the olfactory bulb is being taken into account as the possible explanation as the virus has the biomolecular properties required for penetration of the central nervous system via peripheral sensory endings [43]. The presence of the virus within the olfactory bulb was demonstrated in transgenic mice, with the virus being detected in this locus as early as 60–66 hours after experimental inoculation. The virus was also present in all smell and taste-related areas of the limbic lobe as well as in the basal nuclei [44]. Autopsies carried out in the deceased SARS patients also revealed the presence of the virus in their brains [45]. Benvenuto et al. [46] compared the genomes of 15 viruses from different regions of China, taking note in the mutations within the spike (S) and nucleocapsid (N) proteins. These proteins play the key role in viral penetration of cells as well as in the transcription of its genome. Earlier, Chang et al. [18] described 5 mutations of the Wuhan virus with genetic similarity indices being not higher than 68%; the authors believed that these mutations were characterized by higher affinity to the ACE2 receptor version present in the European population. In addition, some variants of this receptors were found to hinder the binding of the S protein and different levels of ACE2 expression within different tissues may be additionally responsible for the differences in their susceptibility to infection [47]. The polymorphism of the ACE2 gene is significant, particularly in terms of differences between European and Asian populations [48].

DISTURBANCES OF HEARING AND EQUILIBRIUM IN THE COURSE OF COVID-19

Hearing loss and dizziness/vertigo were also reported in the course of COVID-19. Turkish researchers reported that in a sample of 116 hospitalized patients, dizziness was experienced by 31.8% of patients, vertigo was experienced by 6% of patients, tinnitus was experienced by 11% of patients, and hearing loss was experienced by 5.1% of patients [21].

Interesting observations were made in examination of 20 volunteers with positive results of RT PCR screening for SARS-CoV-2 infection but presenting with no COVID-19 symptoms and no history of audiological disorders along with an equally numbered and age-adjusted control group of subjects in whom the presence of SARS-CoV-2 was excluded. Tone audiometry TEOAE measurements revealed that the hearing threshold within the 4000–8000 Hz frequency range was significantly increased in the group of infected subjects ($P < 0.05$), indicating a sensory hearing loss within this range. No significant differences were observed in the range up to 3000 Hz. On the other hand, the otoacoustic emission amplitudes were significantly lower in the group of infected subjects ($P < 0.001$), suggesting a damage to the external cilliary cells within the organ of Corti in the basal turn of the cochlea [49].

Ciliary cell damage is a known complication of viral infections. Direct infection of these cells was taken into account along with damage to stria vascularis, cochlear spiral ganglion, and the auditory pathway within the brain stem. All these changes may result from an excessive reaction of the immune system against viral antigens, resulting in cochlear vascularization disorders as reported for cytomegaloviral infections [50]. Central damage may also be taken into account as being responsible for dizziness or vertigo. Reports of possible viral penetration into the central nervous system were published for an experimentally-induced coronavirus infection in rat as early as in 1984 [51].

Dizziness is considered to be the most common neurological symptom accompanying COVID-19 [36]. This is due to the neuroinvasive potential of the virus. As proposed by Baig et al. [52], the virus may enter the neurons via the ACE2 receptors. Thrombosis-related disturbances in microcirculation are also taken into account [53].

Dizziness as one of the symptoms of COVID-19 was reported in 11 publications. In nearly all cases (over 87%), it was not accompanied by typical respiratory symptoms [54]. Dizziness is reported in 7–20% of in COVID-19 cases (20, 36, 55–59). About 2% of patients reported it to be the first symptom of COVID-19 [58–60], including cases where it was the isolated symptom of the disease [60]. Only 2 studies paid more attention to this symptom, providing detailed description of the cases [61, 62].

Malaya et al. [62] described a case of a 29-year-old female patient with COVID-19 hospitalized in an emergency department with a typical vestibular syndrome she had experienced for the previous 2 days to be completely resolved as the result of subsequent treatment. The symptoms were accompanied only by severe fatigue/weakness with no other symptoms suggestive of COVID-19 as well as no olfactory or taste disturbances. Vestibular neuritis was diagnosed from the natural course of the disease, although the researchers admit that the patient had not been evaluated for nystagmus at the ED. The episode of vertigo's episode was the first in patient's life.

Kong et al. [61] also reported a case of a female patient with SARS-CoV-2 who, in addition to dizziness, experienced only throat dryness with no other symptoms, including severe symptoms. In addition to a positive SARS-CoV-2 test, discrete lesions typical of COVID-19 were revealed by a pulmonary CT scan.

PERIPHERAL FACIAL NERVE PARESIS IN THE COURSE OF COVID-19

Peripheral facial nerve paresis is another symptom classified at the borderline of otolaryngology and neurology and being reported in COVID-19 patients Literature contains case reports, summaries of observations or relatively small patient groups, and statistical studies which compare the incidence of paresis in years before the pandemic to that in the pandemic period. The latter provide indirect evidence potentially supporting the causal relationship of at least some of the observed cases with COVID-19. In the population of patients presenting at an emergency department in Liverpool between January and June 2020, the percentage of patients presenting with facial nerve paresis was 3.5% as compared to only 1.3% a year before [63]. A retrospective analysis of patients presenting at the emergency departments within the Reggio Emilia region in Italy in the early period of the epidemic (27 February–3 May 2020) revealed a total of 38 patients being admitted with peripheral facial nerve paresis as compared to only 22 patients being admitted in the corresponding period of 2019, translating to an increase factor of 1.73. Eight of the 38 patients admitted for treatment in 2020 presented with symptoms of typical of COVID-19 as compared to only 2 out of the 22 patients in the year before, suggesting a possible relationship with the coronavirus infection [64].

Among the case reports, there was also described a case of a patient in whom bilateral facial nerve paresis was preceded by a typical course of COVID-19, with predominant symptoms being observed within the lower airways, and with comorbid Epstein-Barr infection [65]. Lima et al. described a total of 8 cases (7 females, 1 male) of peripheral facial nerve paresis in the course of COVID-19 as observed in just 3 months of 2020. In 3 patients, paresis was the first symptom of the disease; in the remaining patients, the onset of the symptom occurred between days 2 and 10. All patients presented with mild respiratory symptoms and none of them required hospitalization. Neural dysfunction grade was mild in 5 patients and moderate in 3 patients. Neurological examinations of all patients revealed no deviations from normal. Seven patients presented with unremarkable CT or MRI scans whereas features of facial nerve oedema within the tympanic and mastoidal segments of the Fallopian canal. No presence of SARS-CoV-2 was confirmed within the CSF [66].

In other available publications, the facial nerve paresis as observed in the course of COVID-19 was a part of more general neurological disorders, namely the Guillain-Barré syndrome [65, 66]. The damage to the central nervous system in COVID-19 may also develop in the form of encephalitis, encephalopathy, or spinal cord inflammation as observed in more than ⅓ of the patients [36, 69, 70].

Damaged vascularization of the facial nerve or the demyelinating lesions due to inflammation are considered as the potential causes. Another possible cause consists in disseminated microthrombi, including those within both central and peripheral nervous tissues. These are common in viral infections, including the SARS-CoV-2 infection [72, 73]. Just as in the case of smell and taste disturbances, a hypothesis has been raised concerning the neuronal cell membrane being penetrated by the virus via the ACE2 receptor pathway [52, 59].

CONCLUSIONS

1. COVID-19 is characterized by a clinical course that is very diverse in terms of both severity and symptomatology, with ENT manifestations belonging to the common symptoms of the disease;

2. Most of the publications related to COVID-19 symptoms within the hearing and equilibrium organs, upper respiratory tract, or facial nerve, are based on observation of patients with mild to moderate disease since, for obvious reasons, patients with severe disease and the deceased cannot be included in survey-type studies. As a result, the reported statistical data on the prevalence of these symptoms is incomplete;

3. Pathophysiological mechanisms leading to damage within the sensory organs and peripheral nerves are diverse and not fully explained.

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Word count: 3760 Tables: 1 Figures: – References: 72

Access the article online: DOI: 10.5604/01.3001.0014.8514

Table of content: https://otorhinolaryngologypl.com/issue/13832

Competing interests: The authors declare that they have no competing interests.

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Cite this article as: Wysocki J.: Otorhinolaryngological manifestations of COVID-19 infection; Pol Otorhino Rev 2021; 10 (2): 18-24