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COVID-19

The importance of early detection of ENT symptoms in mild-to-moderate COVID-19

Importanza del rilevamento precoce dei sintomi ORL nella COVID-19 lieve-moderata

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SUMMARY

Objectives. Patients with coronavirus disease-19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may present with a wide range of symptoms. In this paper, a detailed characterisation of mild-to-moderate ear, nose nd throat (ENT) symptoms is presented with the aim of recognising the disease early to help reduce further spread and progression.

Methods. A total of 230 cases testing positive for SARS-CoV-2 and 134 negative controls were recruited for a case-control analysis. Symptoms were analysed using the Acute Respiratory Tract Infections Questionnaire, while other symptoms were investigated by *ad hoc* questions.

Results. Among the study samples (n = 364), 149 were males and 215 were females with age ranging from 20 to 89 years (mean 52.3). Four main groups of symptoms were obtained: influenza-like symptoms, ENT-symptoms, breathing issues and asthenia-related symptoms, representing 72%, 69%, 64% and 53% of overall referred clinical manifestations, respectively. ENT symptoms, breathing issues and influenza-like symptoms were associated with positivity to SARS-CoV-2, whereas asthenia-related symptoms did not show a significant association with SARS-CoV-2 infection after controlling for other symptoms, comorbidities and demographic characteristics.

Conclusions. ENT symptoms are equally represented with influenza-like ones as presenting symptoms of COVID-19. Patients with ENT symptoms should be investigated for early identification and prevention of SARS-CoV-2 spread.

KEY WORDS: COVID-19, SARS-CoV-2, early diagnosis, ENT symptoms

RIASSUNTO

Obiettivo. *I pazienti con malattia da Coronavirus-19 (COVID-19) causata dal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) possono presentare una vasta gamma di sintomi. In questo articolo, è mostrata una caratterizzazione dettagliata dei sintomi nei pazienti con malattia lieve-moderata, al fine di riconoscere precocemente la malattia e ridurne l'ulteriore diffusione.*

Metodi. *Un totale di 230 pazienti risultati positivi per infezione da SARS-CoV-2 e 134 soggetti risultati invece negativi sono stati reclutati per questa analisi caso-controllo. I sintomi sono stati analizzati utilizzando l'Acute Respiratory Tract Infections Questionnaire, mentre altri, sono stati indagati mediante domande ad hoc.*

Risultati. *La popolazione oggetto dello studio era composta da 364 soggetti; 149 erano maschi e 215 femmine con età compresa tra 20 e 89 anni (media 52,3). Sono stati identificati quattro gruppi di sintomi: sintomi simil-influenzali, sintomi ORL, problemi respiratori e sintomi astenia-correlati che rappresentavano rispettivamente il 72%, 69%, 64% e 53% delle manifestazioni cliniche. Sintomi ORL, problemi respiratori e sintomi simil-influenzali erano associati a positività a SARS-CoV-2, mentre i sintomi correlati all'astenia non mostravano un'associazione significativa con l'infezione da SARS-CoV-2 dopo il controllo di altri sintomi, co-morbidità, e caratteristiche demografiche.*

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Conclusioni. I sintomi ORL sono ugualmente rappresentati rispetto a quelli simil-influenzali nell'esordio della COVID-19. I pazienti con sintomi ORL devono essere studiati per l'identificazione precoce e la prevenzione della diffusione del SARS-CoV-2.

PAROLE CHIAVE: *COVID-19, SARS-CoV-2, diagnosi precoce, sintomi ORL*

Introduction

In December 2019, a world pandemic was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which originated in China [1]. The virus belongs to the beta coronavirus genus which has resulted in prior epidemics, notably the severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) [2]. The virus has been noted to infect target cells by binding to the angiotensin-converting enzyme 2 (ACE2), which is overexpressed in patients affected by hypertension and diabetes who are treated with ACE inhibitors and angiotensin II receptor blockers [3,4].

The resultant syndrome has been called coronavirus disease-19 (COVID-19) and has an incubation period ranging from 2 to 14 days with a variety of potentially exhibited symptoms [5]. This can include asymptomatic patients as well as those with mild to moderate cases of influenza-like illnesses, without the need for hospitalisation [6-8].

In this paper, we present a case-control series focusing on mild to moderate symptoms to formulate a general overview of COVID-19. Our study has two main goals: to characterise the symptom structure of COVID-19, focusing on those that may be encountered by an otolaryngologist and to identify symptoms that could be used for early diagnosis of SARS-CoV-2 infection.

Materials and methods

Participants and procedure

Participants were recruited from those who were tested positive for SARS-CoV-2 RNA by polymerase chain reaction (PCR) on nasopharyngeal and oropharyngeal swabs. Patients underwent nasal swabs at Treviso General Hospital (Italy) and were living in the same geographical area. These patients had undergone swab tests as they were either symptomatic, or had been in close contact with SARS-CoV-2 positive patients, or were healthcare professionals, and were all performed in-line with the local healthcare system COVID-19 guidelines. Only adults (≥ 18 years old) and non-hospitalised subjects were included to represent a mild-moderate spectrum of affected COVID-19 individuals, amounting to 230 patients who were self-isolating at home. We also recruited age- and sex-matched 134 controls that had negative SARS-CoV-2 PCR swabs as part of our case-control study design. Stratification of this group was not considered, in order to obtain the most general results as possible.

The study was approved by the ethics committee of Treviso and Belluno provinces, and informed consent was obtained verbally for telephone interviews.

Questionnaire

The Acute Respiratory Tract Infections Questionnaire (ARTIQ) [9], a questionnaire commonly used to investigate symptoms of respiratory infections, was employed as well as *ad hoc* questions. Questionnaires were administered by the authors G.S., C.F., A.M., F.M., and P.G. by telephone interview. The ARTIQ questionnaire contains symptoms belonging to five subscales: Physical-upper respiratory tract symptoms (13 items; e.g., "Dry Cough"), Physical-lower respiratory tract symptoms (8 items; e.g., "Sweating"), symptoms connected to sleep quality (4 items; e.g., "Poor quality of sleeping"), psychological symptoms (5 items; e.g., "Difficulty in thinking clearly"), and medication usage (8 items; e.g., "Taken eye drops"). It also has 8 items that were not part of any specific subscale: 5 of them investigated other physical or psychological symptoms (e.g., "Joint pains", "Felt dizzy"), whereas three investigated other experiences that did not directly assess symptoms (e.g., "Cancelled leisure activities", "Taken painkillers"). Participants indicated the experience of each symptom on a three-point scale (0 = No, 1 = Yes – some, and 2 = Yes – a lot). We investigated five additional symptoms (diarrhoea, nausea, vomiting, abdominal pain, and dizziness) by *ad hoc* questions using the same response scale, for a total of 51 items. However, the analyses focused on a subset of 40 items to better examine the configuration of the physical and psychological symptoms of SARS-CoV-2 infection, excluding those related to use of medicines and other experiences.

Participants also indicated their smoking status (current, former, never), and isolated or associated comorbidities [hypertension, cardiovascular disease, diabetes, chronic obstructive pulmonary disease (COPD), renal disease, liver disease, cancer, cerebrovascular disease].

All analyses were performed using package psych [10] in the software R 4.0.0. [11].

Characterisation of symptoms

The first goal of this study was to characterise the symptoms of infection with SARS-CoV-2. We used principal component analysis as implemented in the psych R package [10] to examine the structure of the 40 symptoms in the overall

sample. Since symptoms were rated on an ordinal response scale, we analysed the polychoric correlation matrix. The scree-plot and parallel analysis [12] converged in indicating that four components provided an adequate description of the symptom structure (the first six eigenvalues were 18.34, 2.86, 2.08, 2.00, 1.65 and 1.47; the first six eigenvalues extracted from randomly resampled data were 2.94, 2.23, 2.06, 1.94, 1.84 and 1.76). Through an inspection of component loadings, we identified the first component as asthenia-related symptoms, combining both psychological symptoms and sleeping issues of the ARTIQ. The second component, i.e. Ear, Nose, Throat (ENT) symptoms, mainly reflected physical-upper respiratory tract symptoms. The third component (influenza-like) included mostly influenza-like symptoms, also including gastrointestinal symptoms, whereas the last component (breathing-issues) received the highest loadings by symptoms connected with breathing issues. The four components all correlated with each other (RS ranging between 0.31 and 0.46). We saved component scores to use in subsequent analyses.

For each symptom component, we defined a set of marker symptoms, symptoms that showed a primary loading > 0.40 on that component and whose remaining loadings were at most half of their primary one. These symptoms were thus those more clearly connected with a certain component, and not being as strongly connected to other components.

We further investigated whether marker symptoms would allow the identification of SARS-CoV-2 infection. We performed logistic regression analysis in which we regressed the diagnosis (1 = positive *vs* 0 = negative) on age, gender, smoking status, the three most frequent health conditions (hypertension, cardiovascular diseases and diabetes), and the principal component scores for each symptom component.

Results

Baseline characteristics

A total of 364 individuals (149 males and 215 females) were recruited for the study with ages ranging from 20 to 89 years (mean 52.3, SD = 15.8). 217 cases (94.3%) and 110 controls (82.1%) were never/former smokers, while 11 patients (4.8%) and 24 controls (17.9%) were ever smokers, respectively ($P < 0.001$). Comorbidities were observed in 146 cases (63.3%) and 39 controls (29.0%) (Tab. I). Even if hypertension, cardiovascular diseases and diabetes were significantly more prevalent in cases (Tab. I), a chi-square test for independence showed that the pattern of comorbidities was not significantly different between cases and controls, $\chi^2(7) = 9.58$, $P = 0.222$.

Table I. Comorbidities.

	Cases	Controls	p-value
Hypertension	67 (29.1%)	12 (9.0%)	< .001
Cardiovascular diseases	26 (11.3%)	8 (6.0%)	.003
Diabetes	21 (9.1%)	3 (2.2%)	< .001
COPD	10 (4.3%)	7 (5.2%)	.629
Tumours	9 (3.9%)	5 (3.7%)	.424
Renal diseases	7 (3.0%)	3 (2.2%)	.344
Cerebrovascular diseases	5 (2.2%)	1 (0.7%)	.219
Hepatic diseases	1 (0.4%)	0 (0%)	-

COPD: chronic obstructive pulmonary disease. A series of exact binomial tests revealed that, when examined individually, hypertension, cardiovascular diseases, and diabetes were significantly associated to SARS-CoV-2.

Symptoms in SARS-CoV-2 positive subjects

Component loadings are reported in Table II. First we focused on the mere presence of any of the marker symptoms for each cluster and overall. Table III shows the proportion of cases and controls who reported none of the marker symptoms (column "Absent"), the proportion of those who reported at least one marker symptom, independent of whether it was reported as mildly present (Yes – some) or severely present (Yes – a lot; column "At least one"), and the proportion of those who reported at least one marker symptom as severely present (column "At least one severe"). Most patients reported at least one of the marker symptoms as at least mildly present (92%), whereas most controls (80%) did not report any marker symptom.

Second, we inspected the number of reported symptoms. For each symptom component, we computed the average number of marker symptoms, independent of whether a symptom was reported as mild or severe, and also computed the average number of severely present symptoms (Tab. IV). On average, cases reported more than one symptom for each cluster as mild or severe, whereas controls reported on average less than one symptom. A series of Welch independent samples t-tests indicated that differences among cases and controls were higher when examining reporting symptoms independent of their severity, then when focusing on symptoms reported as severe.

Indicators of SARS-CoV-2 infection

Since data were not randomly sampled from the population but were obtained using a case-control strategy, aimed at balancing the number of positive and negative subjects, positive patients were overrepresented compared to the general population. We controlled for potential biases by applying the corrections for rare-event logistic regression suggested by King and Zeng [13,14], as implemented in the relogit module of the R package Zelig [15]. Using public-

Table II. Principal component analysis (PCA) of 51 symptoms.

Variable	Asthenia-related symptoms	ENT-symptoms	Influenza-like symptoms	Breathing issues
Been awake most of the night	**0.91**			
Difficulty falling asleep	**0.91**			
Waking up several times at night	**0.79**			
Poor quality of sleeping	**0.78**			
Been irritable	**0.68**		0.21	
Been in a bad mood	**0.64**		0.26	
Not feeling yourself	0.45		0.32	0.33
Vertigo	0.34	0.21	0.24	
Swollen glands	0.28	0.26		0.24
Blocked nose		**0.86**		
Runny nose		**0.84**		
Sneezing		**0.73**		
Muscle pain		**0.67**	0.32	
Joint pain		0.59	0.30	0.21
Painful sinuses	0.38	0.58		-0.25
Painful pressure in ears	0.27	**0.58**		
Sore throat	0.25	**0.56**		
Tickles in the throat	0.21	**0.51**		
Watery eyes		0.42		0.27
Hoarseness		0.38		
Vomiting			**0.86**	-0.20
Nausea			**0.78**	
Chills		0.28	**0.64**	
Feeling feverish			**0.63**	0.24
Diarrhoea			**0.59**	0.20
Abdominal pain	0.24		**0.58**	
Headache		0.44	0.51	
Sweating			0.48	0.28
Loss of appetite	0.30		0.48	
Felt tired	0.33		0.38	0.38
Difficulty in thinking clearly	0.26		0.38	0.30
Felt dizzy	0.32		0.34	0.27
Shortness of breath				**0.92**
Problems breathing				**0.91**
Wheezing				**0.90**
Being so unwell you had to stay in bed	0.37		0.32	0.48
Dry cough				**0.46**
Difficulty in going about your daily business	0.35		0.38	0.41
Coughing up mucus	-0.30	0.23	0.33	0.40
Chest pain	0.25	0.20		0.27
Correlation among rotated components				
Asthenia-related symptoms	1.00			
ENT symptoms	0.46	1.00		
Influenza-like symptoms	0.45	0.36	1.00	
Breathing issues	0.42	0.31	0.39	1.00

The first panel reports oblimin-rotated component loadings, the second panel reports correlations among components. PCA was performed on the smoothed polychoric correlation matrix among symptoms. A continuity correction of 0.50 was applied to empty cells when computing polychoric correlations (9). Loadings smaller than 0.20 in absolute value are not shown. Primary loadings larger than 0.40 are shown in bold when no other loading was larger than half the primary loading.

Table III. Presenting symptoms in cases and controls.

Symptom	Cases			Controls		
	Absent	At least one	At least one severe	Absent	At least one	At least one severe
Asthenia-related symptoms (6 marker symptoms)	109 (47%)	121 (53%)	38 (17%)	120 (90%)	14 (10%)	8 (6%)
ENT symptoms (7 marker symptoms)	72 (31%)	158 (69%)	56 (24%)	110 (82%)	24 (18%)	12 (9%)
Influenza-like symptoms (6 marker symptoms)	64 (28%)	166 (72%)	72 (31%)	114 (85%)	20 (15%)	8 (6%)
Breathing issues (4 marker symptoms)	83 (36%)	147 (64%)	44 (19%)	117 (87%)	17 (13%)	5 (4%)
Total (23 marker symptoms)	19 (8%)	211 (92%)	122 (53%)	107 (80%)	27 (20%)	13 (10%)

For each symptom component, column "Absent" reports the proportion of participants without any of the marker symptoms. Column "At least one" reports the proportion of participants with at least one marker symptom (independent of whether the symptom was indicated as mildly or severely present). Column "At least one severe" reports the proportion of participants who reported at least one marker symptom as severe.

Table IV. Prevalence of symptoms by component.

Symptom	Mild or severe					Severe				
	M (SD) controls	M (SD) patients	*t*	*df*	*p*	M (SD) controls	M (SD) patients	*t*	*df*	*p*
Asthenia-related symptoms (6 marker symptoms)	0.38 (1.26)	1.47 (1.85)	6.69	353.91	< .001	0.15 (0.71)	0.39 (1.04)	2.63	353.26	.009
ENT-symptoms (7 marker symptoms)	0.51 (1.37)	1.86 (1.77)	8.10	333.82	< .001	0.24 (0.94)	0.38 (0.77)	1.46	237.50	.145
Influenza-like symptoms (6 marker symptoms)	0.43 (1.18)	1.69 (1.51)	8.86	332.31	< .001	0.12 (0.54)	0.53 (0.93)	5.40	361.94	< .001
Breathing issues (4 marker symptoms)	0.23 (0.70)	1.37 (1.41)	10.19	354.74	< .001	0.05 (0.31)	0.34 (0.84)	4.74	317.73	< .001
Total (23 marker symptoms)	1.55 (3.82)	6.39 (4.38)	11.03	309.81	< .001	0.56 (2.08)	1.65 (2.37)	4.57	308.79	< .001

For each symptom component, the table reports the average number of marker symptoms indicated as mild / severe (left panel) or severe (right panel) for patients and control. The table reports also the standard deviations (SD) and a Welch t-test for independent samples comparing the prevalence of symptoms in patients and controls. df = degrees of freedom.

domain data from the Italian Civil Protection in the Veneto region on 497,045 swabs (updated to May 16th 2020) [16], we estimated that the proportion of positive cases over swabs was 3.8%. About 17% of positive subjects were hospitalised with symptoms, whereas 83% were not hospitalised. Therefore, we estimated that the probability of testing positive by a swab without being hospitalised, was about 3.1%. We used this as the estimate of the tau parameter for the rare-event logistic regression [13]. The results are reported in Table V and show that males and non-smokers were more

Table V. Rare-event logistic regression predicting SARS-CoV-2.

Predictor	*b*	Exp(*b*)	*S.E.*	*Z*	*p*
(Intercept)	-4.463	0.012	0.556	10.56	< 0.001
Age	0.017	1.017	0.011	1.49	0.105
Gender[a]	1.009	2.744	0.295	2.93	< 0.001
Smoking status[b]	-1.598	0.202	0.491	2.94	0.001
Hypertension[c]	0.748	2.112	0.426	2.03	0.079
Cardiovascular diseases[c]	-0.035	0.965	0.532	0.14	0.947
Diabetes[c]	-0.056	0.946	0.708	0.06	0.937
Asthenia-related symptoms	0.196	1.216	0.222	0.82	0.377
ENT-symptoms	0.696	2.007	0.212	3.29	0.001
Influenza-like symptoms	0.647	1.91	0.228	1.98	0.004
Breathing issues	0.824	2.28	0.259	2.98	0.001

[a] Gender was coded as 0 for females and 1 for males. [b] Smoking status was coded as 0 for never or former, and 1 for current smokers. [c] Hypertension, cardiovascular diseases and diabetes were coded as 0 for absent and 1 for present. S.E.: Standard Error.

likely to be diagnosed as positive. Crucially, of the four symptom components, ENT-symptoms, breathing issues and influenza-like symptoms were associated with positivity for SARS-CoV-2, whereas asthenia-related symptoms did not show a significant association with SARS-CoV-2 infection after controlling for other symptoms, comorbidities and demographic characteristics.

Discussion

According to CDC guidelines [17], COVID-19 must be suspected in case of fever or chills, cough, shortness of breath, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhoea. Among the 364 patients recruited in this study, 230 tested positive for SARS-COV-2 via nasopharynx and oropharynx swabs. Statistical analysis of data underlined that, in mild-to-moderate COVID-19, four main symptom groups may be identified using principal component analysis. These components are influenza-like symptoms, general ENT-symptoms, breathing and asthenia-related issues. Interestingly, the two latter components did not clearly mirror components identified by Aabenhus et al. [9].

In contrast to 80% of negative-swab subjects who did not exhibit any symptom, 92% of positive-swab patients presented with at least one symptom. Specifically, 72% of patients showed influenza-like symptoms, 69% showed ENT symptoms, 64% showed breathing issues and 53% asthenia-related symptoms.

When examined individually, hypertension, cardiovascular diseases and diabetes were significantly associated with SARS-CoV-2 infection. These few correlations may derive from the number of the cases analysed, which had mild-to-moderate symptoms. On the other hand, other comorbidities may have a greater impact in patients showing severe clinical manifestations [18].

Moreover, our results show a significant lower prevalence of COVID-19 in females and current smokers. This significantly reduced risk of SARS-CoV-2 infection among smokers is quite intriguing considering that smokers are usually more prone to respiratory infections. According to the authors' personal experience, even if not validated, there is a paradoxical protective role of current smoking on COVID-19.

Viruses of the SARS-CoV-2 family have been known to cause prior pandemics; the SARS coronavirus in 2002-2003 and Middle East respiratory syndrome (MERS) coronavirus in 2012. These two viruses mainly resulted in respiratory symptoms, as the infection tended to be localised in the lower airway tract [19]. Literature published on SARS showed that the most frequent symptoms were persistent fever (99%), nasal symptoms (15-73%), dyspnoea (71%), headache (46.4%), cough (44.9%) and dizziness (43.5%), with diarrhoea present in only a few cases (4.3%) [20,21]. An analysis of the commonest MERS symptoms by Assiri et al. [22] found that fever was present in 98% of cases, nasal symptoms in 87%, dyspnoea in 72%, cough in 47%, diarrhoea in 26% and headache in 13%.

A comparison between components of the three SARS-CoV-2 subtypes revealed that ENT symptoms are present in less than 50% of SARS and MERS patients (mean rates 44.7% and 49%, respectively), whereas they account for almost 70% in COVID-19. Conversely, influenza-like components are present in 51% of SARS, 62% of MERS and 72% of COVID-19 patients. On the other hand, breathing issues are slightly higher, with 70% of presentations in SARS and MERS (mean rates 71% and 72%, respectively), and only 64% in mild-to-moderate COVID-19. There was a high rate of discrepancy in asthenic-symptom components with rates of 78% in SARS and 53% in COVID-19.

ENT symptoms accounted for 69% of overall mild-to-moderate symptoms in our case series of positive cases. These comprised of nasal obstruction, rhinorrhoea, sneezing, ear fullness, sore throat, tearing, neck swelling, hoarseness and dizziness. In particular, among these clinical manifestations, it is worth noting that some of these symptoms (i.e. nasal obstruction, rhinorrhoea, sneezing, ear fullness, sore throat, throat discomfort) were significantly more prevalent compared to other comparable ENT ones (e.g., vertigo, chills, headache, swollen glands).

Alterations of smell and taste were previously widely evaluated by our research group. We analysed 202 patients with positive COVID-19 swabs and showed that 65% reported smell and taste alterations in addition to the other ENT symptoms reported above [23]. These patients were reviewed 4 weeks after onset of their sensory changes: 50% m recovered completely, 40% had improvement and 10% had unchanged or worsened symptoms [24-26]. Reports from a different study on household members with positive COVID-19 swabs found that 38% showed typical COVID-19 symptoms and 22% had these symptoms in association with altered sense of smell and taste, while 4% only had alteration of smell and taste as an isolated symptom [27]. These data sets are consistent with a recent systematic review and meta-analysis on 3563 patients who had positive swab for SARS-CoV-2. The authors found that 67% of mild to moderate cases had smell or taste loss, whereas the rates among hospitalised patients was 31% [28].

Conclusions

ENT symptoms during the COVID-19 pandemic should be treated with caution and not underestimated. Patients

with new onset nasal obstruction, sore throat and ear fullness should lead to a suspicion of COVID-19, with cases of sudden loss of smell and taste raising further alarm bells. These aspects must be taken into account together with known symptoms from World Health Organization guidance, as they can play a major role in early detection of mild to moderate SARS-CoV-2 infection. Further high-powered studies are needed to provide more concrete links to help us identify if these ENT symptoms should form part of the screening pathway for COVID-19 to be adopted by nations faced with the pandemic.

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