

Diagnostic and clinical significance of “atypical” symptoms in coronavirus disease 2019

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by Sierpiński et al,
see p. 501

It seems now virtually indubitable that coronavirus disease 2019 (COVID-19) will be remembered for a long time as the worst infectious disease that has affected humanity after the notorious “Spanish” flu pandemic, which occurred almost a century ago, in 1918 to 1919.¹ This ongoing outbreak, caused by a new member of the Coronaviridae family called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged from the city of Wuhan (China) at the end of 2019, and has then spread all over the world, affecting several millions of people and causing over 450 000 deaths so far.¹ Albeit formally classified as a respiratory disease, whereby bilateral interstitial pneumonia is commonplace in patients with COVID-19, the gradually increasing understanding of the physiopathology of SARS-CoV-2 infection has now enabled us to conclude that in 5% to 15% of predisposed patients (especially older, male, and bearing additional comorbidities), the pathology may evolve into a severe systemic illness, characterized by an exaggerated inflammatory response and a hypercoagulable state, which may then foster the development of multiple-organ dysfunction, focal or disseminated thrombosis, and ultimately lead to death.¹

As for most human pathologies, early diagnosis is essential for influencing, and especially reversing, an otherwise unfavorable disease progression. This concept is even more straightforwardly transferable to COVID-19, whereby accurate and timely identification of SARS-CoV-2 infection not only enables an earlier and more appropriate patient management but will also permit rapid isolation of infected individuals, especially during the early symptomatic phase when viral spread through respiratory droplets seems to be the highest, thus avoiding the risk of virus transmission to other people, especially to close contacts such as relatives, friends and colleagues.²

Reliable information on presenting symptoms of COVID-19 can be found in a large retrospective

United States study, recently published by Argenziano et al,³ and involving as many as 1000 patients with SARS-CoV-2 infection. As summarized in [FIGURE 1](#), lower respiratory tract symptoms were found to be largely prevailing (eg, fever, cough, dyspnea were present in over 60% of all patients), whilst the most common upper respiratory tract symptoms (eg, sore throat, rhinorrhea and conjunctival congestion, among others) appeared relatively uncommon in patients with this new coronavirus disease, typically present in less than 20% of cases. Notably, a considerable prevalence of “atypical” symptoms for infectious respiratory disorders, such as diarrhea and headache, has also been reported (ie, about 24% and 10%, respectively), which confirms evidence provided in some prior or subsequent clinical investigations ([FIGURE 1](#)).

Sierpiński et al,⁴ in their study published in this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), describe some additional aspects of the “atypical” clinical presentation of COVID-19. Briefly, the authors carried out a large cross-sectional survey, involving nearly 2 thousands nonhospitalized patients with COVID-19 in Poland, aimed at addressing the self-reported prevalence of symptoms of SARS-CoV-2 infection. Beside describing a prevalence of diarrhea of around 24%, which is almost identical to that reported in the previous United States survey,³ the authors emphasize that additional unusual symptoms for an infectious respiratory disease could be recorded with a relatively high frequency in COVID-19. These basically encompass olfactory disorders (eg, anosmia, present in 49% of all patients), taste disorders (eg, dysgeusia, present in 48% of all patients), and lack of appetite (present in 47% of all patients). Interestingly, both olfactory or taste disorders were found to be more prevalent (approximately 1.3-fold higher) in the female than in the male sex, thus re-emphasizing the existence of some paradigmatic

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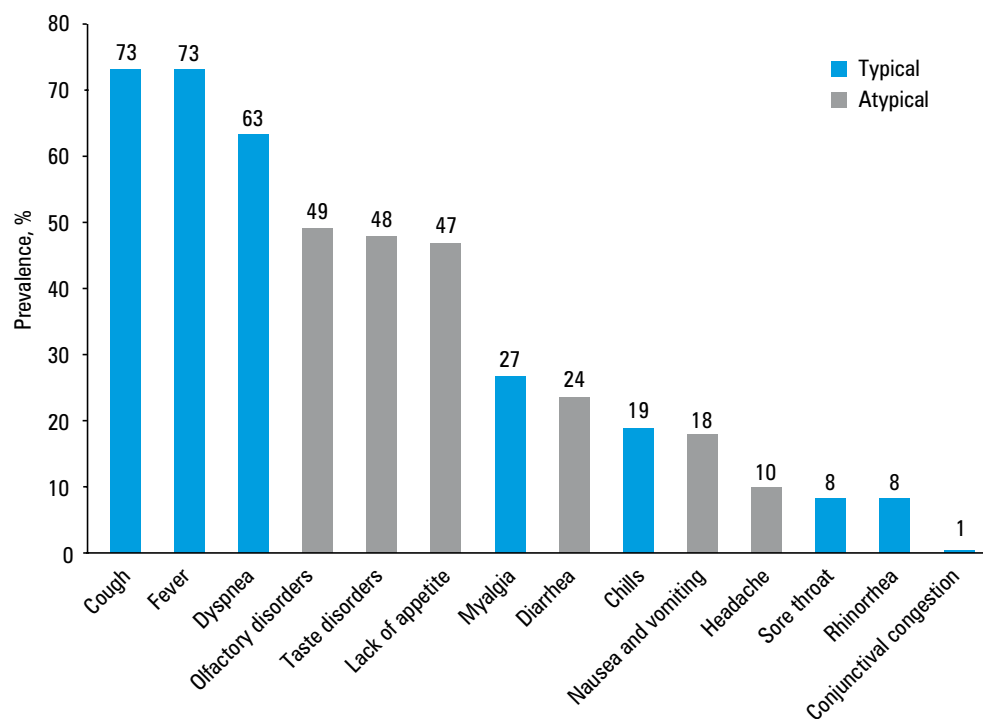
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FIGURE 1 Most prevalent typical and atypical (for infectious respiratory diseases) presenting symptoms observed in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection



immunobiological differences in the way SARS-CoV-2 seems to interplay with sex biology.⁵

The 2 important neurological symptoms, that is, anosmia and dysgeusia, appear very specific for COVID-19, since they have not been clearly described in other coronaviruses infections, neither during the 2 earlier outbreaks of severe acute respiratory syndrome (SARS) in 2002 and 2003 and Middle-East respiratory syndrome (MERS) in 2012,⁶ and shall hence raise a high degree of clinical alertness and suspicion. A systematic review of scientific literature, carried out by Tong et al,⁷ recently reported quite similar Figures as those found by Sierpiński et al,⁴ whereby the mean prevalence of olfactory dysfunctions (10 studies, 1627 patients) and gustatory dysfunctions (9 studies, 1390 patients) was found to be 52.7% (95% CI, 29.6–75.2) and 43.9% (95% CI, 20.5–68.9), respectively. Notably, these disturbances have been found to develop relatively early in the course of COVID-19, approximately 4 days after SARS-CoV-2 infection, thus even before the onset of other and more paradigmatic symptoms such as fever, cough or dyspnea.⁸ The positive predictive value of both conditions altogether was found to be so high (ie, 83%)⁸ that they could be considered important drivers of molecular biology testing, especially in low-resource geographies, where test availability is limited or even inaccessible.

With regards to the possible origin of these olfactory and taste disorders, both indirect (hyperinflammatory response, swelling) and direct (neuropathic, demyelinating, cytotoxic) injuries triggered by SARS-CoV-2 have been advocated.⁹ Overall, the presence of both anosmia and dysgeusia in COVID-19 seems to be limited in time (ie, between 1–3 weeks) and self-resolving in the vast majority of patients,⁷ thus being

currently classified as transitory neurotoxic or cytopathic injuries.

Some important take-home messages can hence be gleaned from the work of Sierpiński et al.⁴ The onset of olfactory and taste disorders, alone or in association with other unusual symptoms such as lack of appetite and even unusual headache,¹⁰ seems to be much more frequent than the appearance of upper respiratory tract symptoms in patients with SARS-CoV-2 infection (especially in the female sex), develops early in the course of the disease (whilst anosmia and dysgeusia are usually reported postinfection in patients with common cold or influenza), and shall not be overlooked or underestimated. The onset of these disturbances should always persuade patients to seek clinical advice and, especially, should be followed-up by molecular biology testing aimed at carrying out an accurate and timely diagnosis of SARS-CoV-2 infection, which will enable early isolation of infected subjects and their more appropriate clinical management. Finally, consideration shall be given to including anosmia, dysgeusia, and lack of appetite within the current validated protocols for case definition and quarantine.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

CONFLICT OF INTEREST None declared.

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