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Case report

Case report of familial COVID-19 cluster associated with High prevalence of anosmia, ageusia, and gastrointestinal symptoms

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ABSTRACT

Background: Patients with COVID-19 most commonly report respiratory symptoms, with a minority reporting gastrointestinal (GI) symptoms in currently available reports. Additionally, little is known about the symptoms of anosmia/hyposmia, ageusia, and dysgeusia anecdotally seen in COVID-19 patients, which may potentially be considered both GI and sensory/neurological manifestations of infection. We hope to clarify the prevalence of these symptoms and patterns of transmission within a family cluster.

Case presentation: We interviewed 7 patients via oral inquiries and a questionnaire, collecting data on subject symptoms and their durations. Reverse transcriptase-polymerase chain reaction (RT-PCR) was used to confirm 2 of these cases. We report a familial cluster of 5 presumed and 2 confirmed COVID-19 cases, all of whom reported one or more GI symptoms and 5 of whom reported sensory symptoms of anosmia/hyposmia, ageusia/hypogeusia, and/or dysgeusia.

Conclusions: This frequency of GI symptoms is high relative to currently available epidemiological reports, which also infrequently report on sensory symptoms. COVID-19 exhibits wide variation in duration, severity, and progression of symptoms, even within a familial cluster.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus identified as the causative agent of the pandemic coronavirus disease of 2019 (COVID-19). As a member of the beta-coronavirus genera, it is closely associated with the pandemic viruses SARS-CoV and MERS-CoV, and all 3 viruses are known to predominantly cause upper respiratory infections. As of April 12, 2020, 1,777,666 confirmed cases of COVID-19 have been reported internationally [1]. Of these, 529,951 cases (29.8 %) have been confirmed in the US following the first case, reported on January 20, 2020 [2]. Investigational reporting of cases in the literature has varied from retrospective epidemiological reports to studies of transmission within small family clusters [3,4].

It is well-established that SARS-CoV-2 infection most commonly presents with fever, myalgias, fatigue, and respiratory symptoms including cough and dyspnea [5]. Less commonly reported symptoms include gastrointestinal (GI) manifestations such as nausea, vomiting, and diarrhea [5]. In a literary review of 12 cohort studies addressing COVID-19 GI manifestations, wide variation was observed in the prevalence of GI symptoms [6]. Diarrhea was observed in 2.0–35.6 % of patients, nausea in 1–17.3 %, vomiting in 1–6.4 %, and abdominal pain in 2.2–5.8 %. These studies varied by location, cohort type (hospital vs. outpatient settings), and cohort size. The presumed mechanism for GI symptoms is thought to be due to the propensity of the virus to not only enter and infect type II alveolar cells and stratified esophageal epithelial cells via the ACE2 receptor, but also cholangiocytes and enterocytes of the colon and ileum, in which ACE2 expression is also observed [7]. It is thought that the cytopathic effects of viral infection of enterocytes and/or cholangiocytes may contribute to symptoms such as nausea, vomiting, diarrhea, anorexia, and abdominal pain. Multiple studies have noted the persistence of viral RNA in stool samples of patients infected with SARS-CoV-2, supporting the theory that the virus may replicate in the GI tract. Moreover, related viruses including SARS-CoV, which also enters and infects cells via the ACE2 receptor, are documented to also be associated

Abbreviations: GI, gastrointestinal; RT-PCR, reverse transcriptase polymerase chain reaction; COVID-19, coronavirus disease of 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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with GI symptoms. SARS-CoV has even been histologically observed replicating within enterocytes [8]. Thus, while the prevalence of GI symptoms in patients presenting with COVID-19 is often overshadowed by respiratory symptoms, the capacity for SARS-CoV-2 to replicate and persist in the GI tract must be considered, as this raises concerns for fecal-oral transmission in addition to respiratory droplet and fomite transmission.

On the other hand, while GI symptoms with COVID-19 are recognized in the literature, sensory symptoms including anosmia/hyposmia, ageusia, and dysgeusia have been anecdotally reported, with few investigations addressing their prevalence and mechanisms at present. Both the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) and ENT UK at the Royal College of Surgeons have issued public statements recognizing anosmia, hyposmia, and dysgeusia as symptoms possibly associated with SARS-CoV-2 infection [9,10]. The few cohort studies available include a report of a spike in online survey reporting of anosmia in Iran coinciding with simultaneous outbreak of COVID-19 in the same geographic region [11]. Another retrospective cohort study in Italy found that 34 % of hospitalized COVID-19 patients reported taste and/or olfactory disorders, with 19 % reporting both taste and olfactory disorders [12]. Numerous hypotheses exist regarding the mechanism of these sensory manifestations. Some postulate that SARS-CoV-2 may cause a demyelinating reaction in olfactory neurons, directly infects neurons by hematogenous or retrograde neuronal routes [13], and/or causes an inflammatory or autoimmune process that mediates neural injury [14,15], causing these sensory symptoms. A neuroinvasive process has been supported by evidence of viral encephalitis and other neurological complications, with identification of SARS-CoV-2 in cerebrospinal fluid [15]. Furthermore, other coronaviruses including SARS-CoV and MERS-CoV have been identified as possibly neuroinvasive, contributing to a variety of neurological symptoms and syndromes [15]. Some hypothesize that COVID-19-associated sensory symptoms may be related to ACE inhibition or ACE2-mediated viral entry into cells of the olfactory epithelium [16,17]. Though many hypothetical explanations exist, little to nothing has been well established regarding the significance and mechanism of SARS-CoV-2-associated anosmia/hyposmia, ageusia/hypogeusia, and dysgeusia.

We report here on a family COVID-19 case cluster of 7 individuals with high prevalence of both GI symptoms and sensory manifestations of anosmia, ageusia, and dysgeusia. We hope the characterization of this cluster contributes to better understanding of the transmission and highly variable presentation of COVID-19.

Case presentations

We retrospectively interviewed and reviewed 7 patients with presumed COVID-19 in Denver, Colorado ranging in age from 17 to 54 yo. We collected epidemiological and symptomatic data by questionnaire. Some symptoms were provided additional descriptions to eliminate potential ambiguity, listed as follows. Shortness of breath was described as “having to catch one’s breath” or “feeling winded, e.g. while climbing stairs,” chest pain as “pain while inhaling/breathing,” and chest tightness as “chest feeling tight or restricted when inhaling.” Ageusia/hypogeusia was described as “loss of taste” or “dulled sense of taste.” Dysgeusia was described as “altered taste” or “odd or different taste from usual.” Anosmia/hyposmia was described as “loss or dulling of smell.” Anosmia and hyposmia were considered synonymous and interchangeable, with hyposmia representing decrease of smell and anosmia representing loss of smell. Patients were asked to estimate the duration of each symptom.

Of 7 presumed cases, 2 were confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) of nasopharyngeal swabs. Both cases were confirmed by Roche cobas 6800 EUA RT-PCR at a certified tertiary care hospital. The other 5 were presumed based on case proximity, temporal progression, and comparable symptomatic presentation. All subjects were cohabitants in a single-family home and were exposed to the same surfaces without precautionary measures (e.g. surface disinfectants, individual room quarantine, etc.) for the first 11 days following the index case’s first symptoms, until the first test was identified as positive. None of the patients required hospital admission, and none had recent domestic nor international travel prior to symptom onset.

GI symptoms

All 7 cases reported GI involvement with 1+ symptoms of: nausea (5/7), diarrhea (4/7), abdominal pain (3/7), anorexia (3/7), and emesis (2/7). Duration of GI symptoms ranged from 2 to 15 days, with a mean of 10 days. In 4 of 7 patients, GI symptoms came later in the disease/symptomatic course and were not presenting symptoms. The delay between initial symptoms and GI symptoms in these patients ranged from 1 to 8 days, with a mean of 4 days.

Sensory symptoms

5 subjects reported sensory symptoms including anosmia/hyposmia (5/7), ageusia (5/7), and dysgeusia (3/7). Subjects with anosmia and ageusia reported that these symptoms always occurred together; neither anosmia nor ageusia were seen independently. Of the 5 that reported sensory manifestations, 3 reported only anosmia and ageusia, while 2 reported anosmia, ageusia, and dysgeusia. Length of anosmia and ageusia ranged from 5 to 29 days (29 days thus far; one patient still experiences persistent anosmia/ageusia at present). The mean length of anosmia and ageusia was 12 days, and the mean length of dysgeusia was 6 days. Sensory symptoms preceded respiratory and constitutional symptoms in 1 patient, presented together with respiratory and constitutional symptoms in 2 patients, and occurred later in symptomatic course in 2 patients.

Subject profiles

The dates and durations of each subject’s constitutional (fever, chills, myalgias), respiratory (cough, dyspnea, chest pain/tightness), GI, and sensory symptoms are illustrated in Fig. 1. The clinical profiles of each case are reported below:

- The index case was a 54 yo male who presented with nonproductive cough one day after presumed exposure, then nausea on day 3 of symptoms. He reports volunteering at a homeless clinic with acutely ill patients on March 14, 2020. His symptoms lasted ~10 days. Relevant comorbidities include coronary artery disease and hypertension.
- Case 1 was a 24 yo female who presented with fevers up to 39°C, fatigue, chills, myalgias, and nonproductive cough, followed by dyspnea, chest pain/tightness, nausea, diarrhea, abdominal pain, anorexia, ageusia, and dysgeusia on day 6 of symptoms. Her symptoms lasted ~20 days. Relevant comorbidities include history of immunodeficiency with recurrent respiratory and mucosal infections.
- Case 2 was a 17 yo female who presented with fatigue, nonproductive cough, emesis, nausea, anosmia, and ageusia. On day 7, she developed additional symptoms of fevers up to 38°C, chills, myalgias, and exertional dyspnea. She reported diarrhea, anosmia, and ageusia as her final symptoms, with her sensory symptoms persisting to present (April 13). Apart from sensory loss, the majority of her symptoms lasted ~14 days. She has no relevant comorbidities to report.

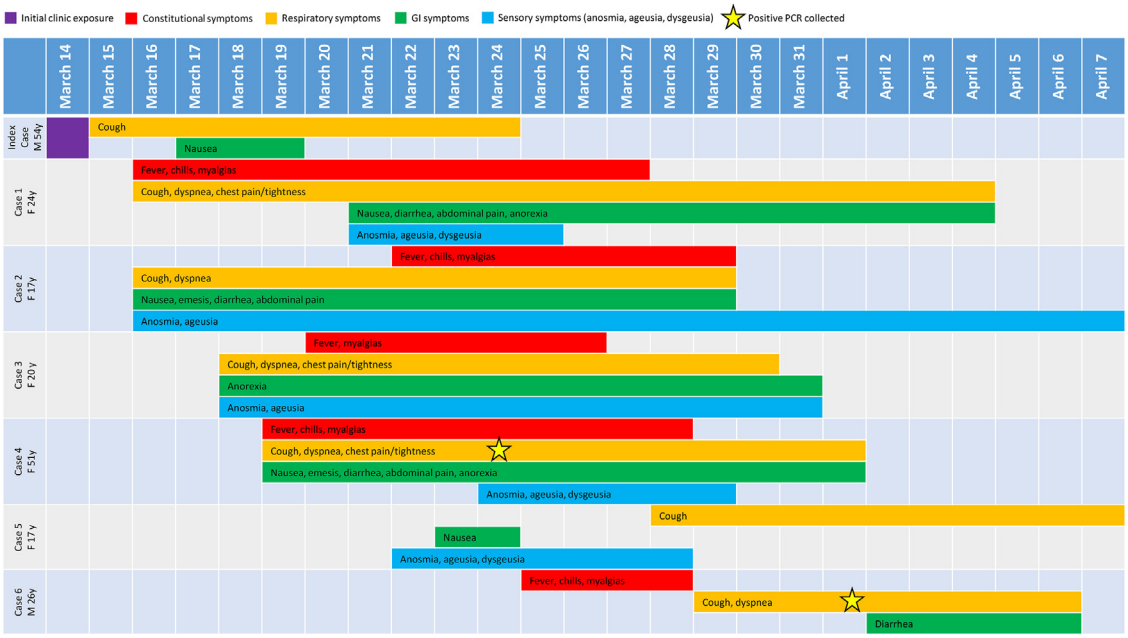

Fig. 1. Timeline of Symptoms and Exposure to Index Case in Familial COVID-19 Cluster.

- Case 3 was a 20 yo female who presented with fatigue, nonproductive cough, anorexia, anosmia, and ageusia. On day 3, she reported subjective fevers, and on day 7, she developed myalgias, dyspnea, and chest pain/tightness. Her symptoms lasted ~14 days. She has no relevant comorbidities to report.
- Case 4 was a 51 yo female who presented with fevers up to 39.5°C, chills, myalgias, fatigue, nonproductive cough, and headache, followed by nausea and vomiting on day 3, diarrhea, abdominal pain, anosmia, ageusia, and dysgeusia on day 6, and dyspnea, chest pain/tightness, and retroorbital pain on day 10. Her symptoms lasted ~14 days and were dominated by symptoms of fever, nausea, diarrhea, and ageusia/dysgeusia. She was tested on day 6 of symptoms. Relevant GI comorbidities include Crohn's disease, ulcerative colitis, and ankylosing spondylitis.
- Case 5 was a 17 yo female who presented with fatigue, anosmia, ageusia, and dysgeusia, followed by nausea and headache on day 2 and nonproductive cough on day 7. Apart from a residual cough, her symptoms lasted ~7 days. She has no relevant comorbidities to report.
- Case 6 was a 26 yo male who presented with subjective fevers, chills, fatigue, and myalgias, followed by a nonproductive cough and dyspnea on day 5 and diarrhea on day 9. His symptoms lasted ~13 days. He has no relevant comorbidities to report. He was tested on day 8 of symptoms.

Overall findings

The duration of illness ranged from 7 to 20 days, and the mean duration was 13 days. The most commonly reported symptoms among this cluster were dry cough (7/7), fatigue (6/7), fever (5/7), myalgias (5/7), nausea (5/7), dyspnea (5/7), ageusia (5/7), and anosmia (5/7).

Other symptoms not reported above included chills (4/7), headache (4/7), chest pain (3/7), chest tightness (3/7), and retroorbital pain (3/7).

Discussion

This family case cluster of 7 patients demonstrates the highly variable presentation of COVID-19 with regards to symptomatic presentation as well as duration, severity, and progression of symptoms (Fig. 1). While one 17 yo female patient experienced a mild, 7-day disease course with predominantly sensory symptoms and dry cough (case 5), a related 24 yo female patient reported a 20-day disease course with significant respiratory, constitutional, and GI symptoms in addition to sensory symptoms. Consistent with other reports, nonproductive cough, fatigue, myalgias, and fever were the most common symptoms [18–20], but in this cluster, these were accompanied by other GI and sensory symptoms that are reported at far lower frequency, inconsistently, or sparsely in the existing literature.

GI symptoms

Among our 7 cases, the prevalence of GI symptoms was far higher than reported in recent studies. While nausea was reported in 71 % of our patients, it was reported in 10 % [21], 10.1 % [18], and 17.3 % of patients in recent cohort studies [19]. Diarrhea was reported in 57 % of our patients, compared with 2.6 % [20], 10.1 % [18], 12 % [21], and 12.9 % [19]. Abdominal pain was reported in 43 % of our patients, compared with 2.2 % [18], 5.8 % [19], and 9 % [21]. Anorexia was reported in 43 % of our patients, compared with 12.2 % [19], 27 % [21], and 40 % [18]. Emesis was reported in 29 % of our patients, compared with 3.6 % [18], 5 % [19], and 10 % [21].

While our case number was small, the considerably higher rate of GI symptoms among this cluster is likely largely attributable to significant disparities between our patient population and other study cohorts. First, none of our cases ultimately required hospitalization, while the majority of epidemiological reports thus far have used data from hospitalized patients [18–20]. This likely contributes to disparities in case severity between our study and other investigations, as well as the information extracted from subjects. Our study subjects had ample opportunities to document and reflect on symptoms very early in disease course and post-infectious symptoms that persisted (e.g. diarrhea) after acute illness had subsided. Additionally, our patients were not dealing with a life-threatening illness, and thus were likely more alert and able to accurately report symptoms. Other investigations' subjects were presumably unable to report more mild, post-viral symptoms that persisted after hospital discharge due to lack of follow-up.

Second, our case cluster involved a younger population than most other studies. The mean age of our subjects was 30 yo, while the median ages of other studies were 49 [20], 56 [18], and 57 [19]. We can infer that our cluster was overall younger and likely healthier, experienced milder disease courses, and had fewer comorbidities than other studies. It is possible that GI symptoms may be seen more commonly in younger patient cases, or that they may be overlooked in older patients with severe respiratory and constitutional symptoms. Another family cluster study of 6 patients hospitalized with confirmed COVID-19 found that the 2 patients that reported GI symptoms of diarrhea were 2 of the younger study subjects (36 and 37 yo), while older members of the family (63, 65, 66 yo) reported no such symptoms [3]. Third, 6 of our 7 subjects were first-degree relatives, including 2 parents and 4 of their children. One of the parents had a history of severe inflammatory bowel disease (IBD) and other autoimmune comorbidities that may have contributed to her persistent GI symptoms. Though none of her children reported any autoimmune history, this might contribute to higher frequency of GI symptoms within the cluster via an unclarified genetic predisposition. While this is a confounding variable in ours and other case cluster studies [3,4], in recent cohort studies, familial relations are unlikely to limit study generalizability given far larger sample sizes.

Presuming that the aforementioned were not interfering variables in the vast differences observed in prevalence of GI symptoms, it is possible that patterns of transmission and symptomatology may differ between family clusters and larger cohort studies with predominantly community-acquired disease. Jin et al. found that COVID-19 patients with GI symptoms were more likely than patients without GI symptoms to report family clustering as opposed to community transmission of COVID-19 (31.08 % vs. 20.45 %) [22]. Perhaps this difference is related to types of exposure; family clustering may involve higher rates of fecal-oral and fomite transmission from communally shared surfaces, while community transmission may involve higher rates of transmission from respiratory droplets. This raises questions related to the tissue involvement of SARS-CoV-2; are patients that initially acquire infection via particle ingestion (fomite, fecal-oral transmission) more likely to experience GI symptoms than patients that initially acquire infection by replication in pulmonary epithelium? If so, is this related to replication within GI epithelium? Is spread of infection from the GI tract to other organ systems attributed to hematogenous spread of viral particles?

Sensory symptoms

In addition to unusually high frequency of GI symptoms, our case cluster also documented a remarkably high prevalence of sensory disturbances in the form of olfactory and taste disorders, which include anosmia/hyposmia, ageusia/hypogeusia, and dysgeusia. We observed wide variation in duration of these sensory disorders, which range from 5 to 29 days thus far, with one subject still reporting persistent anosmia and ageusia at present. Among our 7 patients, 71 % reported sensory symptoms (5/7), and all reported coinciding anosmia and ageusia. Few studies have examined the epidemiologic features of olfactory and taste disorders, which have largely been reported anecdotally. A recent study of 59 hospitalized COVID-19 patients by Giacomelli et al. found that 34 % of patients reported an olfactory or taste disorder, while 19 % reported both [12]. In contrast with our study, this study also found that taste disorders more commonly occurred early in disease course, prior to hospitalization.

With regards to differences between our case cluster and recent epidemiological cohort studies, they include those mentioned above; our patients were unhospitalized and presumably less severe cases than the hospitalized patients interviewed in Giacomelli et al.'s study. Furthermore, while this study reported symptoms at time of hospitalization, our data was acquired by interview post-infection. These factors may account for why our study reported such high frequency of sensory symptoms.

Conclusions

Our study is one of few documenting rates of sensory symptoms and GI manifestations within a family cluster. We found an unusually high rate of both among our 7 cases, but the lack of understanding surrounding the mechanisms, pathophysiology, and overall epidemiology of these symptoms ultimately beckons the critical need for further investigation.

Direct evidence of replication within enterocytes and cholangiocytes, i.e. histology, electron microscopy, or viral particle detection (as was found in SARS-CoV by Leung et al.) [8], has yet to be released. The existing preliminary evidence that SARS-CoV-2 may replicate in the GI tract includes confirmed ACE2 expression in gastrointestinal epithelium and persistence of viral nucleic acid in stool [2,7,23,24]. Confirmation of viral GI replication may warrant supplemental precautionary measures to reduce fecal-oral transmission. These might include additional mandatory personal protective equipment (PPE) for employees at high risk of GI exposure, including otolaryngologists and healthcare workers involved in GI procedures such as endoscopies [25,26]. Additionally, direct contacts of COVID-19 patients that experience GI symptoms, even in the absence of other symptoms, may need to be quarantined, as these symptoms can precede respiratory or constitutional symptoms or even present without them [6]. These less acutely severe cases may be overlooked, leading to widespread viral shedding [27]. Transmission control also relates to the mechanism of sensory symptoms. Olfactory and taste dysfunction may indicate that SARS-CoV-2 has the potential to be neuroinvasive and/or cause damage to olfactory epithelium, especially given that other β-coronaviruses have been found to be neuroinvasive [15]. The implications of this relate to disease control as well; patients presenting with sensory disorders, even in the absence of other COVID-19 symptoms, may need to be quarantined to reduce transmission. The mechanistic underpinnings of GI and sensory symptoms in COVID-19 warrant close consideration and analysis, especially as it relates to reducing disease transmission.

Ethics approval and consent to participate

Informed consent was obtained from all study participants, with the explicit intent of publishing results. Approval by an ethics committee was waived.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare that they have no competing interests

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Authors' contributions

BEH and APH conceived the idea, BEH drafted the paper, and all authors collected data and reviewed the paper. All authors contributed to, read, and approved the final manuscript, which has not been previously published and is not being considered for publication elsewhere. If accepted, it will not be published elsewhere in the same form.

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