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Ageusia and anosmia, a common sign of COVID-19? A case series from four countries

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Abstract

Over the course of the pandemic due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), multiple new clinical manifestations, as the consequence of the tropism of the virus, have been recognized. That includes now the neurological manifestations and conditions, such as headache, encephalitis, as well as olfactory and taste disorders. We present a series of ten cases of RT-PCR confirmed SARS-CoV-2 infected patients diagnosed with viral-associated olfactory and taste loss from four different countries.

Keywords: anosmia; ageusia; clinical manifestations; neurological; SARS-CoV-2; COVID-19

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Introduction

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to evolve, novel signs and symptoms continue to emerge and expand the clinical manifestations of Coronavirus Disease 2019 (COVID-19) (Rodriguez-Morales *et al*, 2020a). This includes an ever-increasing number of reports linking the virus to a number of presumed neurological disorders (Paniz-Mondolfi *et al*, 2020).

The spectrum of neurological manifestations includes headache (Rodriguez-Morales *et al*, 2020b), encephalitis, Guillain-Barre syndrome (Zhao *et al*, 2020), as well as olfactory and taste dysfunction (Ollarves-Carrero *et al*, 2020). Despite recognition of these symptoms, there is still a lack of reports, delving deeply into the clinical and pathophysiological aspects of SARS-CoV-2 related anosmia and ageusia. Herein, we present a series of ten cases of RT-PCR confirmed SARS-CoV-2 infected patients diagnosed with viral-associated olfactory and taste loss from four different countries. Of these, nine patients presented with ageusia and eight with anosmia, with seven of them presenting overlapping anosmia/ageusia persisting for a range of 4 to 25 days.

Cases

The median age of these COVID-19 patients was 48 years old, seven females and three males (Table 1). Patients 1 and 3 were related, as well as patients 5 and 6. Four patients were from Germany, three from the USA, two from Venezuela, and one from Bolivia. Eight referred cough as the most common presenting symptom, with only five presenting fever. Other symptoms included dyspnea, generalized weakness, headache, diarrhea, dehydration, polyarthralgia, nausea, and vomiting (Table 1). The patients 1, 4, and 7 required hospitalization for 17, 15, and 10 days, respectively. Notably, ageusia and anosmia were among the most common signs found in all patients with a median time of presentation at two days after onset of symptoms for ageusia and three days for anosmia.

Anosmia was the debuting clinical sign in three patients, of whom two presented with olfactory loss at day 1, and one (patient 7), two days previous to the onset of symptoms. Ageusia was also

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an early sign, presenting between days 1-2 in five patients and between days 4-5 in three. Late-onset anosmia (day 7) and ageusia (day 10) was observed in patient 10. Ageusia persisted for a median of 8 days (ranging 4 to 25) and anosmia for a mean of 11 days (5 to 25). In two patients, co-infection with the Influenza virus was assessed, resulting in negative by RT-PCR, patients 1 and 4 (Table 1). Patient 1 had repeated positive RT-PCR testing for SARS-CoV-2 at days 6, 10, 11, and 17 of disease.

Discussion

Our results, from four very different countries in Europe, North and South America, are consistent with those found by other groups were postviral olfactory loss presents more commonly in women, with a female-to-male ratio of 2:1 and typically over 50 years of age (Seiden, 2004). Concurrent affectation of the sense of taste suggests that most probably ageusia in these patients is secondary to a diminished taste perception as a consequence of anosmia. However, sensorineural impairment due to direct viral injury cannot be entirely excluded (Elterman *et al*, 2014; Rahban *et al*, 2015).

Recent data suggest that smell and taste disorders may be significantly more frequent among COVID-19 patients than influenza patients. As we observed in our patients, deficits in olfactory and taste function were usually of acute onset and at early stages of the disease, presenting for most cases as the initial clinical manifestation throughout the first days (Beltran-Corbellini *et al*, 2020). In a recent case-control study with 17 patients with smell and taste disorders, the mean duration of symptoms was 7.5 days (Beltran-Corbellini *et al*, 2020). To date, despite the massive ongoing pandemic affecting over 3.1 million people worldwide, as of April 28, 2020, there is scarce information regarding the real prevalence of ageusia, anosmia, and other sensorineural related disorders associated to SARS-CoV-2 infection. Olfactory and taste dysfunction has been reported as a clinical manifestation of a wide range of viral infections, particularly those causing upper respiratory tract infections (Seiden, 2004).

However, these symptoms are usually attributed as conductive or obstructive signs due to mucosal edema and not as direct sensorineural noxa by the virus, leading to substantial under-reporting in a high proportion of patients (Seiden, 2004). Multiple viruses are known to use the olfactory nerve

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as a shortcut into the central nervous systems, including the influenza virus, which can also lead to long-term olfactory disorders in some cases (Ollarves-Carrero *et al*, 2020; van Riel *et al*, 2015). Rhinovirus, respiratory syncytial virus, paramyxovirus, adenovirus, echovirus, and enterovirus have also been linked to cytopathic damage of the olfactory epithelium (Seiden, 2004). Hypogeusia, dysgeusia, hyposmia, and dysosmia associated with COVID-19 require more detailed studies to understand their pathophysiology, but especially their clinical course and potential long-term implications (Ollarves-Carrero *et al*, 2020).

As the pandemic continues to expand, early detection and screening for suspicious cases, based on broader clinical findings, would be a useful aid to diagnosis, besides rRT-PCR confirmation; particularly in resource depleted settings such as Latin America were numerous regions are already reaching concerning epidemic proportions (Cimerman *et al*, 2020). Despite some reports, anosmia is not frequent in the context of common cold and flu. An increase in this common finding, in the context of the ongoing COVID-19 pandemic, make this case series of relevance.

We endorse the assessment of smell and taste disorders, such as ageusia and anosmia, as a critical component of the anamnesis and as a helpful diagnostic clue for COVID-19. Early recognition of these signs, along with flu-like symptoms, may aid in supporting individuals' self-isolation in the current epidemic context (Beltran-Corbellini *et al*, 2020). Finally, as a consequence of this, multiple national guidelines are considering both of these cardinal clinical signs as part of the constellation of findings defining COVID-19, as has already been even included in Chile and Colombia (Gutiérrez *et al*, 2020), where no cases of ageusia and anosmia have been reported to date.

Ethics approval and consent to participate. Written consent from all the patients was obtained.

Consent for publication. Written consent from the patient was obtained for publication.

Availability of data and material. Copy of the clinical data of the patients is available.

Competing interests. We declare that we have no competing interests, except JM and MPTT, they are the patients 5 and 10 of this case series.

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Authors' contributions. JAVG, AJRM, APM conceived the report. JAVG, AJRM, APM, DW, RS, JPEA, collected data, analyzed, and interpreted clinical data. AJRM wrote the first draft. AGRM, DKBA, performed a review of the literature. All authors approved the subsequent draft versions. All authors approved the final submitted version.

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Table 1. Summary of clinical features of the patients infected with SARS-CoV-2.

	Patient									
	P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**
Country	Germany	Germany	Germany	Germany	USA	USA	Venezuela	Venezuela	Bolivia	USA
Age (years)	86	51	50	66	38	45	44	61	32	39
Sex	F	M	F	M	F	M	F	F	F	F
Relationship	Mother-in-Law of P3	-	Daughter-in-Law of P1	-	Wife of P6	Husband of P5	-	-	-	-
Occupation	Housewife	Carpenter	Housewife	Retired	Unemployed veterinarian	Dialysis Hospital cleaning and disinfection company manager	Housewife	Engineer	Government employee	Physician
Chronic medical illness	Coronary bypass 13 years ago, breast cancer 24 years ago	None	None	None	None	None	Systemic lupus erythematosus (SLE)	Type 2 diabetes mellitus	None	Adult Still's disease
Symptoms started, date	18-Mar-20	14-Mar-20	23-Mar-20	23-Mar-20	18-Mar-20	10-Mar-20	11-Apr-20	09-Mar-20	21-Mar-20	7-Apr-20
Interval between symptom onset and consultation (days)	1	2	1	4	2	2	1	2	12	0
Consultation date	19-Mar-20	16-Mar-20	24-Mar-20	27-Mar-20	20-Mar-20	12-Mar-20	12-Apr-20	11-Mar-20	2-Apr-20	7-Apr-20
Presenting symptoms and signs										
Fever	-	-	-	D1	-	D1	D2	D2	-	D3
Cough	D1	D1	D1	D1	D1	D2	D1	D1	-	-
Malaise	D1	-	-	-	D3	D1	D1	D1	D1	-
Dyspnea	-	D1	D1	-	D2	-	-	D1	-	-
Generalized weakness	-	-	-	-	-	D1	D1	D2	-	D3
Headache	-	-	-	-	D3	-	D1	D1	-	-
Diarrhea	-	-	-	-	D3	D1	-	-	-	D21
Polyarthralgia	-	-	D5	-	-	-	D2	-	-	-
Dehydrated	D3	-	-	-	-	-	-	-	-	-
Ageusia	**D2-D7, 5 days**	**D1-D5, 5 days**	**D5-D7, 22 days**	**D1-D11, 11 days**	**D5-D16, 11 days**	**D4-D29, 25 days**	**D2-D8, 7 days**	**D2-D5, 4 days**	-	**D10-D18, 8 days**
Anosmia	-	-	**D5-D7, 22 days**	**D1-D11, 11 days**	**D5-D16, 11 days**	**D4-D29, 25 days**	**2D(POS)-D4 then D7-D14, 13 days**	**D1-D5, 5 days**	**D1-D7, 7 days**	**D7-D15, 8 days**
Hospitalized	Yes	No	No	Yes	No	No	Yes	No	No	No
Discharged at day	17	-	-	15	-	-	10	-	-	-
Body temperature (°C)	36.9	37.0	37.0	39.0	37.0	37.9	37.3	37.0	37.0	38.6
Systolic blood pressure (mmHg) at income	125	105	110	120	N/A	N/A	120	110	N/A	N/A
Dyastolic blood pressure (mmHg) at income	80	70	70	80	N/A	N/A	85	70	N/A	N/A
Cardiac frequency (bpm)	91	72	70	60	N/A	N/A	81	75	N/A	N/A
Oximetry saturation (%)	98	N/A	N/A	92	N/A	N/A	97	98	N/A	93-94
White blood cell count (× 109 cells per L); (normal range 3·9–9·9)	5.08	N/A	N/A	6.75	N/A	N/A	5.05	6.70	N/A	N/A
Lymphocyte count (× 109 cells per L); (normal range 1·1–3·6)	508	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Platelet count (× 109 cells per L); (normal range 162–341)	140	N/A	N/A	259	N/A	N/A	130	140	N/A	N/A
D-dimer (µg/mL); (normal range 0·0–0·5)	1.48	N/A	N/A	0.88	N/A	N/A	N/A	N/A	N/A	0.64
Ferritin (ng/mL); (normal range 12-150)	312	N/A	N/A	1,288	N/A	N/A	240	190	N/A	N/A
Fibrinogen (g/dL); (normal range 2·0–4·0)	370	N/A	N/A	1,000	N/A	N/A	N/A	N/A	N/A	N/A
C-reactive protein (mg/L); (normal range 0·0–5·0)	33	N/A	N/A	71.2	N/A	N/A	43	35	N/A	55
Aspartate aminotransferase (U/L); (normal range 0·0–32·0)	53	N/A	N/A	230	N/A	N/A	N/A	N/A	N/A	N/A
Potassium (mmol/L); (normal range 3·5–5·1)	2.8	N/A	N/A	4.5	N/A	N/A	N/A	N/A	N/A	N/A
Serum chloride (mmol/L) (normal 98–107)	95	N/A	N/A	96	N/A	N/A	N/A	N/A	N/A	N/A
Lactate dehydrogenase (U/L); (normal range 135–214)	376	N/A	N/A	414	N/A	N/A	N/A	N/A	N/A	N/A
IL-6 (pg/ml); (normal <7)	7.3	N/A	N/A	29.7 (D5), 49.4 (D6), 14.4 (D10)	N/A	N/A	N/A	N/A	N/A	N/A
RT-PCR for Influenza viruses	Negative	N/A	N/A	Negative	N/A	N/A	N/A	N/A	N/A	N/A
RT-PCR for SARS-CoV-2	Positive, D6, D10, D11, D17	Positive	Positive	Positive	Positive	Positive	Positive, D3	Positive, D2	Positive	Positive
Antibodies, Anti-SARS-CoV-2 (OD ratio); (normal <8)										
IgG	13.93 (D11), 14.54 (D17)	8.04 (D23)	N/A	14.74 (D10), 12.17 (D18)	N/A	N/A	N/A	N/A	N/A	N/A
IgA	8.0 (D11), 12.3 (D17)	8.19 (D23)	N/A	40.21 (D10), 38.58 (D18)	N/A	N/A	N/A	N/A	N/A	N/A

F, female. M, male. P1, patient 1. P2, patient 2. P3, patient 3. P4, patient 4. P5, patient 5. P6, patient 6. D, day of the disease. -, negative. N/A, not assessed. IL-6, interleukin 6. RT-PCR, reverse-transcriptase polymerase chain reaction. SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2. Written consent was obtained from all the patients. 2D(POS): 2 days before the onset of symptoms.