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Short Communication

Third of patients have gustatory dysfunction 9 months after SARS-CoV-2 infection: the ANOSVID study

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Olfactory and/or gustatory dysfunctions (OGD) are specific symptoms of COVID-19 (Salmon Ceron et al., 2020). Olfactory (OD) dysfunction have drawn considerable attention in the beginning of the pandemic, more than gustatory dysfunction (GD) (Klopfenstein et al., 2020; Parma et al., 2020). However, OGD's impact on quality of life seems to be majority due to GD (Coelho et al., 2021) which is defined as partial (hypogeusia) or complete (ageusia) loss of taste. Questions about COVID-19 GD remain, especially GD duration and the proportion of patients with persistent GD (Hopkins et al., 2021). In this work we describe persisting GD in patients with confirmed SARS-CoV-2 infection.

ANOSVID (Zayet et al., 2021b), an observational retrospective study in Nord Franche-Comté Hospital, France; was designed in accordance with the declaration of Helsinki and was conducted in accordance with French legislation. We included all adult inpatients and outpatients (\geq 18 years old) with a diagnosis of COVID-

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19 confirmed by RT-PCR on respiratory samples from March 1st, 2020, to May 31st, 2020. Patients' consent was collected by phone calls and then filled in an online questionnaire. The persistence of GD was defined by the presence (at the date of questionnaire responses) of any GD related to SARS-CoV-2 infection, and which was not present before SARS-CoV-2 infection. Patients who related a final date for GD due to SARS-CoV-2 infection before relapse were considered to have a "recurrence of symptoms" after an asymptomatic period. Patients who had a persistence of symptoms since the beginning of SARS-CoV-2 infection (without an asymptomatic period) were considered to have "continuous symptoms". Data was collected during the first quarter of 2021.

During the study period (Zayet et al., 2021b), 214 patients of 354 patients presented GD and were included (65.9% had ageusia, n=141 and 34.1% had hypogeusia, n=73). The mean age of patients was 48.8 years \pm 18.7 [18-98], with female predominance (n=140, 65.4%) and 74 (34.6%) were hospitalized. One hundred ninety-two of patients with GD (89.7%) had olfactory dysfunction associated.

At day 90, 186 patients (86.9%) had recovery from their GD (Figure. 1). GD was resolved in 32.8 \pm 47.0 days. However, after a mean of 9.5 months after symptoms onset (283.9 days \pm 26.1

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Figure 1. Gustatory recovery over time in the ageusia (n=141) or hypogeusia (n=73) groups or total patients (n=214) after SARS-CoV-2 infection.

[211-366]), GD were persisting in 64 patients (p-GD group, 29.9%) versus were resolved in 150 patients (r-GD group, 70.1%). Among the p-GD group, 55 patients (85.9%) reported a recurrence of GD after recovery, and only 9 patients (14.1%) patients reported continuous GD (persistence of GD since the beginning of SARS-CoV-2 infection); 62 of the 64 patients (96.9%) had hypogeusia and only 2 patients (3.1%) had ageusia. At symptoms onset, about the 62 patients with hypogeusia persistence, 40 (64.5%) have had ageusia and 22 (35.5%) have had hypogeusia; concerning the 2 patients with ageusia persistence, both have had ageusia initially.

GD duration during acute COVID-19 was longer in p-GD group than r-GD group (respectively 51.2 ±70.4 days [median duration of 24 days] versus 26.4 ±32.8 days [median duration of 14 days], p=0.01); However, GD intensity (ageusia or hypogeusia) and modalities (salty, sweet, bitter and sour) did not differ (p=1 and p=0.70 respectively). Concerning others symptoms present at the onset of the disease, cacosmia was clearly more described in p-GD group than r-GD group (respectively 19[29.7%] versus 20[13.3%], p=0.008). Only asthenia was less described in p-GD group than r-GD group (respectively 57[89.1%] versus 146[97.3%], p=0.018). Two others symptoms were more described in p-GD group than r-GD group: sneezing (28[43.7%] versus 41[27.3%] respectively, p=0.03) and arthralgia (37[57.8%] versus 62[41.3%] respectively, p=0.04). Concerning biological findings at the onset of the disease, creatinine (63.5 \pm 12.3 μ mol/L versus 88.3 \pm 34.7 μ mol/L respectively, p=0.001), total bilirubin (9.6 \pm 3.0 µmol/L versus 13.5 \pm 8.3 µmol/L respectively, p=0.02) and haemoglobin (13.1 \pm 1.5 g/dL versus 14.0 ± 1.5 g/dL respectively, p=0.04) were lower in p-GD group than r-GD group. No other significant differences were found about clinical and biological findings and no significant differences were found about sex, age, comorbidities, imaging findings and outcome.

Nine months after COVID-19 GD, hypogeusia is present in 29% of cases (62/214) while ageusia is scarce, 0.01% of cases (2/214), this kind of heterogeneous and (sometimes) long recovery timeline has been described (Bussière et al., 2021; Riestra-Ayora et al., 2021). The more likely explanation is that the damage to the olfactory/ gustatory epithelium varies between cases, and extensive damage will take a longer time to regenerate than focal lesions (Butowt et al., 2021; Thakur et al., 2021). Gustative disorders were self-reported which are the main limitation of ANOSVID as most of studies on this topic (2-8). Furthermore, patients with persistence GD presented rather "symptoms recurrences" than "continuous symptoms" and confounding factors responsible of GD could explain a part of these results; for example, other viral infection with nasal obstruction or COVID-19 re-infection (but it seem to be scarce at this period (Zayet et al., 2021a)); however, on another hand these episodes of GD recurrences could be linked to the persistence of the virus in a reservoir (sanctuary site) with viral rebound (Zayet et al., 2021a), as suggested for other viral infections (Zayet et al., 2021a).

Nasal obstruction and dyspnea have been notified as risk factors for the persistence of OGD (Riestra-Ayora et al., 2021). A long duration of GD (> 50 days) and the presence of cacosmia at the onset of the disease could be also predictive factors of GD recurrence/persistence after SARS-CoV-2 infection.

Author contributions

TK, CT and SZ were the major contributors in writing the manuscript and performing the literature review. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability Statement

Data available on request due to privacy restrictions. The data presented in this case study are available on request from the corresponding author.

Ethical Approval statement

The ANOSVID study was sponsored by Nord Franche-Comté Hospital in France and was designed in accordance with the declaration of Helsinki and conducted in accordance with French legislation with approval obtained from the local ethics committee and the CPP (Comité de Protection des Personnes) SUD-EST IV, n° 20.10.08.63102.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- Bussière N., Mei J., Lévesque-Boissonneault C., Blais M., Carazo S., Gros-Louis F., De Serres G., Dupré N., Frasnelli J.. Chemosensory Dysfunctions Induced by COVID-19 Can Persist up to 7 Months: A Study of Over 700 Healthcare Workers. Chem. Senses 2021;46 bjab038. doi:10.1093/chemse/bjab038.
- Butowt R., Meunier N., Bryche B., von Bartheld C.S.. The olfactory nerve is not a likely route to brain infection in COVID-19: a critical review of data from humans and animal models. Acta Neuropathol. (Berl.) 2021;141:809–22. doi:10.1007/s00401-021-02314-2.
- Coelho D.H., Reiter E.R., Budd S.G., Shin Y., Kons Z.A., Costanzo R.M.. Quality of life and safety impact of COVID-19 associated smell and taste disturbances. Am. J. Otolaryngol. 2021;42. doi:10.1016/j.amjoto.2021.103001.
- Hopkins C., Surda P., Vaira L.A., Lechien J.R., Safarian M., Saussez S., Kumar N.. Six month follow-up of self-reported loss of smell during the COVID-19 pandemic. Rhinology 2021;59:26–31. doi:10.4193/Rhin20.544.
- Klopfenstein T., Kadiane-Oussou N.J., Toko L., Royer P.-Y., Lepiller Q., Gendrin V., Zayet S., Features of anosmia in COVID-19. Médecine Mal. Infect. 2020;50:436–9. doi:10.1016/j.medmal.2020.04.006.
- Parma V., Ohla K., Veldhuizen M.G., Niv M.Y., Kelly C.E., Bakke A.J., Cooper K.W., Bouysset C., Pirastu N., Dibattista M., Kaur R., Liuzza M.T., Pepino M.Y., Schöpf V.,

Pereda-Loth V., Olsson S.B., Gerkin R.C., Rohlfs Domínguez P., Albayay J., Farruggia M.C., Bhutani S., Fjaeldstad A.W., Kumar R., Menini A., Bensafi M., Sandell M., Konstantinidis I., Di Pizio A., Genovese F., Öztürk L., Thomas-Danguin T., Frasnelli J., Boesveldt S., Saatci Ö., Saraiva L.R., Lin C., Golebiowski J., Hwang L.-D., Ozdener M.H., Guàrdia M.D., Laudamiel C., Ritchie M., Havlícek J., Pierron D., Roura E., Navarro M., Nolden A.A., Lim J., Whitcroft K.L., Colquitt L.R., Ferdenzi C., Brindha E.V., Altundag A., Macchi A., Nunez-Parra A., Patel Z.M., Fiorucci S., Philpott C.M., Smith B.C., Lundström J.N., Mucignat C., Parker J.K., van den Brink M., Schmuker M., Fischmeister F.P.S., Heinbockel T., Shields V.D.C., Faraji F., Santamaría E., Fredborg W.E.A., Morini G., Olofson J.K., Jalessi M., Karni N., D'Errico A., Alizadeh R., Pellegrino R., Meyer P., Huart C., Chen B., Soler G.M., Alwashahi M.K., Welge-Lüssen A., Freiherr J., de Groot J.H.B., Klein H., Okamoto M., Singh P.B., Hsieh J.W., GCCR Group Author, Reed D.R., Hummel T., Munger S.D., Hayes J.E.. More Than Smell-COVID-19 Is Associated With Severe Impairment of Smell, Taste, and Chemesthesis. Chem. Senses 2020;45:609–22. doi:10.1093/chemse/bjaa041.

- Riestra-Ayora J., Yanes-Diaz J., Esteban-Sanchez J., Vaduva C., Molina-Quiros C., Larran-Jimenez A., Martin-Sanz E., Long-term follow-up of olfactory and gustatory dysfunction in COVID-19: 6 months case-control study of health workers. Eur. Arch. Oto-Rhino-Laryngol. Off. J. Eur. Fed. Oto-Rhino-Laryngol. Soc. EU-FOS Affil. Ger. Soc. Oto-Rhino-Laryngol. - Head Neck Surg. 2021;278:4831–7. doi:10.1007/s00405-021-06764-y.
- Salmon Ceron D, Bartier S, Hautefort C, Nguyen Y, Nevoux J, Hamel A-L, et al. Self-reported loss of smell without nasal obstruction to identify COVID-19. The multicenter Coranosmia cohort study. J Infect 2020;81(4):614–20.
- Thakur K.T., Miller E.H., Glendinning M.D., Al-Dalahmah O., Banu M.A., Boehme A.K., Boubour A.L., Bruce S.S., Chong A.M., Claassen J., Faust P.L., Hargus G., Hickman R.A., Jambawalikar S., Khandji A.G., Kim C.Y., Klein R.S., Lignelli-Dipple A., Lin C.-C., Liu Y., Miller M.L., Moonis G., Nordvig A.S., Overdevest J.B., Prust M.L., Przedborski S., Roth W.H., Soung A., Tanji K., Teich A.F., Agalliu D., Uhlemann A.-C., Goldman J.E., Canoll P. COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. Brain J. Neurol. 2021;144:2696–708. doi:10.1093/brain/awab148.
- Zayet S., Royer P.-Y., Toko L., Pierron A., Gendrin V., Klopfenstein T., Recurrence of COVID-19 after recovery ? A case series in health care workers. France. Microbes Infect. 2021a;23. doi:10.1016/j.micinf.2021.104803.
- Zayet S., Zahra H., Royer P.-Y., Tipirdamaz C., Mercier J., Gendrin V., Lepiller Q., Marty-Quinternet S., Osman M., Belfeki N., Toko L., Garnier P., Pierron A., Plantin J., Messin L., Villemain M., Bouiller K., Klopfenstein T.. Post-COVID-19 Syndrome: Nine Months after SARS-CoV-2 Infection in a Cohort of 354 Patients: Data from the First Wave of COVID-19 in Nord Franche-Comté Hospital. France. Microorganisms 2021b;9:1719. doi:10.3390/microorganisms9081719.