Comparison of prevalence and evolution of COVID-19 olfactory disorders in patients infected by D614 (wild) and B.1.1.7. Alpha variant: a brief report

Jérôme René Lechien, Shannon Wajsblat, Mihaela Horoi, Paolo Boscolo-Rizzo, Serge Daniel Le Bon, Luigi Angelo Vaira, Sven Saussez

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SHORT COMMUNICATION

Comparison of prevalence and evolution of COVID-19 olfactory disorders in patients infected by D614 (wild) and B.1.1.7. Alpha variant: a brief report

Jerome R. Lechien[1,2,3,4,9] · Shannon Wajsblat[4] · Mihaela Horoi[4] · Paolo Boscolo-Rizzo[5] · Serge D. Le Bon[6] · Luigi A. Vaira[7,8] · Sven Saussez[2,4]

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Abstract

Objectives To investigate the prevalence and the evolution of olfactory disorders (OD) related to coronavirus disease 2019 (COVID-19) in patients infected during the first and the second European waves.

Methods From March 2020 to October 2020, COVID-19 patients with OD were recruited and followed over the 12-month post-infection. The following data were collected: demographic, treatments, vaccination status, and olfactory function. Olfaction was assessed with the Olfactory Disorder Questionnaire (ODQ), and threshold, discrimination, and identification (TDI) test. Outcomes were compared between patients of the first wave (group 1: wild/D614G virus) and the second wave (group 2: B.1.1.7. Alpha variant) at 1-, 3- and 12-month post-infection.

Results Sixty patients completed the evaluations accounting for 33 and 27 patients in group 1 and 2, respectively. The 1-month TDI score (23.7 ± 5.3) was significantly lower in group 2 compared to group 1 (29.8 ± 8.7; $p = 0.017$). Proportion of normosmic patients at 1-month post-infection was significantly higher in group 1 compared to group 2 ($p = 0.009$). TDI scores only significantly increased from 1- to 3-month post-infection in anosmic and hyposmic patients. Focusing on There was a negative association between the 1-month ODQ and the 1-month TDI ($r_s = -0.493$; $p = 0.012$). ODQ was a significant predictor of TDI scores at 3- and 12-month post-infection. The 12-month prevalence of parosmia was 60.6% in group 1 and 42.4% in group 2, respectively. There was no significant influence of oral corticosteroid treatment, adherence to an olfactory training and vaccination status on the olfactory outcomes.

Conclusions Patients of the second wave (Alpha B.1.1.7. variant) reported significant higher proportion of psychophysical test abnormalities at 1-month post-infection than patients infected during the first wave (D614G virus).

Keywords COVID-19 · Otolaryngology · Rhinology · SARS-CoV-2 · Anosmia · Parosmia · Olfactory · Smell · Recovery · Variant

Introduction

Since the beginning of the coronavirus disease COVID-19 (COVID-19) pandemic, olfactory dysfunctions (OD) were a common symptom in Western country population [1], affecting 30–86% of patients [2–4]. In most cases, patients completely recovered smell in the four post-infection weeks [3]. However, a significant number of individuals report mid- to long-term OD, including persistent anosmia, hyposmia, phantosmia or parosmia [5]. Depending on the method used for the olfactory assessment, the 12-month prevalence of persistent OD ranged from 15 to 70% [6–8]. The prevalence and the types of OD appeared to change over the successive severe acute respiratory syndrome coronavirus type-2

Luigi A. Vaira and Sven Saussez have equally contributed to the paper and are joined as co-senior authors.

Jerome R. Lechien and Shannon Wajsblat have equally contributed to the paper write and are joinder as co-first authors.

✉ Jerome R. Lechien
Jerome.Lechien@umons.ac.be

Extended author information available on the last page of the article

(SARS-CoV-2) variant waves but few reports are currently available and most of them focusing on clinical findings during the infection and not on long-term outcomes [9, 10].

In the present study, we investigated the prevalence of long-term OD in patients infected by SARS-CoV-2 in the first and the second European waves.

Methods

Setting and patients

Patients with OD related to COVID-19 were consecutively recruited and followed from March 2020 to October 2022 at the University Hospital of Brussels (CHU Saint-Pierre, Brussels, Belgium). Patients were infected during the first (March 2020) and the second (October 2020) European waves by the European wild (D614G) and the B.1.1.7. Alpha variant SARS-CoV-2, respectively. Because the wild virus concerned the Chinese population and the first European cases was related to one of the first variant, named D614G, we decided to use European 'wild' virus/D614G variant in the present paper. The COVID-19 diagnosis was performed through high-sensitive next-generation sequencing that may differentiate the D614G and the B.1.1.7 'Alpha variant' SARS-CoV-2. At the time of the diagnosis, the patient recruitment was based on the patient-perception of partial or total loss of smell sense. Patients self-reporting partial or total loss of smell were included. All of them completed the validated French version of the Olfactory Disorder Questionnaire (ODQ) [11], and psychophysical evaluations were performed.

Patients did not report sinus or olfactory region abnormalities, including chronic rhinosinusitis with or without polyposis, olfactory or nasal tumor at the tomodensitometry or magnetic resonance imaging. Patients with the following conditions were excluded: post-traumatic, neurological, post-viral (other than COVID-19), idiopathic OD prior to the pandemic; pregnancy; chronic rhinitis; history of nasal chemo/radiation or functional endoscopic sinus surgery.

The study protocol was approved by the local ethics committees (CHU Saint-Pierre, CE/21-12-03). The informed consent was obtained for all patients.

Demographic, clinical and olfactory outcomes

The following data were collected at the first evaluation (throughout the 4-week post-diagnosis): age; gender; history of olfactory training protocol and medication. Patient-reported olfactory dysfunction and psychophysical tests were assessed 1-, 3-, and 12-month post-infection.

The patient-reported olfactory symptoms were evaluated through the validated French version of the Olfactory Disorder Questionnaire (ODQ) [11]. Parosmia was defined for patients as a qualitative distortion of smell perception [12]. The psychophysical tests were made with the threshold, discrimination, and identification (TDI) testing (Medisense, Groningen, Netherlands) [13]. Anosmia consisted of a TDI score < 17, while hyposmia was established as a TDI score of less than 30.75. TDI > 30.75 was considered as normosmia. [13]

The medication and olfactory training findings were collected. The oral corticosteroid therapy consisted of 7-day solumedrol (0.5 MG/kg). The oral corticosteroids were only administrated in patients with $a < 1$-month OD history without significant comorbidities (e.g., diabetes, hypertension). The olfactory training was systematically advised to patients. Patients exposed themselves to various odors at least twice daily for 12 weeks. To the 4 traditional odors proposed by Hummel et al. [14] (rose, eucalyptus, lemon and cloves), patients were invited to smell the daily odors including fragrance, food and beverage odors, etc. They had to name the sniffed odor and reported the olfactory training protocol adherence to the physician in each consultation time with, at best, a notepad.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, v23,0; IBM Corp, Armonk, NY, USA). The evolution of olfactory evaluations was studied through the Wilcoxon Rank test. The epidemiological, clinical and olfactory outcomes were compared between groups with the Mann–Whitney U test and chi-square according to data features. The association between epidemiological, clinical, and olfactory outcomes was analyzed with Spearman coefficient. A p value < 0.05 was considered as significant.

Results

Sixty patients completed the evaluations, including 33 and 27 patients from the first and the second waves, respectively. The epidemiological and clinical outcomes of both groups are described in Table 1. There were no significant differences between groups regarding age, gender and vaccine findings. Patients of the first wave were less frequently treated with oral corticosteroids than those of the second wave. The adherence to an olfactory training protocol was significantly higher in patients of group 1 compared to those of group 2 (Table 1).

The 1-, 3- and 12-month proportion of anosmic, hyposmic and normosmic patients are described in Table 2 and Fig. 1. At the first evaluation time, 11.5% and 9.1% of patients of groups 1 and 2 were anosmic, respectively

Table 1 Demographic and Clinical Features of Patient groups

Outcomes	Group 1	Group 2	*p* value
Age (mean, SD)	42.0 ± 16.2	41.0 ± 4.9	NS
Gender			
Female (*N*, %)	28 (85)	21 (78)	NS
Male (*N*, %)	5 (15)	6 (22)	
Initial treatments			
Oral corticosteroids	6 (18)	12 (44)	0.042
Olfactory training	19 (58)	7 (26)	0.007
None	8 (24)	8 (30)	NS
Vaccination (*N*, %)	28 (85)	17 (63)	NS

N number; *NS* non-significant; *SD* standard deviation

(Table 2). The proportion of 1-month psychophysical test abnormalities was significantly higher in group 2 compared to group 1, respectively ($p = 0.009$; Table 2). There were no significant differences in proportion of anosmic, hyposmic and normosmic patients between groups at 3- and 12-month post-infection.

In group 1, the 1-, 3- and 12-month TDI scores were 29.8 ± 8.7, 30.8 ± 7.0, 28.9 ± 6.2, respectively. The 1-, 3- and 12-month TDI scores of the second wave group were 23.7 ± 5.3, 28.2 ± 6.5, 32.0 ± 2.8, respectively. The TDI scores did not significantly change from 1- to 12-month post-infection in both groups. The mean 1-month TDI score of patients of group 2 was significantly lower than the TDI score of patients of group 1 ($p = 0.017$). There were no significant differences between TDI scores of both groups at 3- and 12-month post-infection.

The mean ODQ was 44.8 ± 21.6 in group 1 and 51.4 ± 23.6 in group 2, respectively. The 1-month ODQ was comparable between groups.

Focusing on data of only hyposmic and anosmic patients of group 1, the mean TDI scores at 1, 3 and 12 months were 22 ± 6.1, 26.9 ± 5.4 and 26.7 ± 5.7, respectively. There were a significant increase of TDI score from 1 to 3 months ($p = 0.013$) but not from 3 to 12 months of follow-up ($p = 0.343$). In group 2, the mean TDI scores were 23.7 ± 5.3, 28.2 ± 6.5, 32.0 ± 2.8, respectively (all patients were hyposmic or anosmic at baseline (Table 2)). The increase of TDI was significant from 1- to 3-month post-infection

Table 2 Anosmic, hyposmic and normosmic proportions of patients according to groups

	Group 1			Group 2			*p* value
	Anosmic	Hyposmic	Normosmic	Anosmic	Hyposmic	Normosmic	
1 mo	11.5	38.5	50.0	9.1	90.1	0.0	0.009
3 mo	0.0	38.5	61.5	0.0	58.3	41.7	NS
12 mo	0.0	44.4	55.6	0.0	16.7	83.7	NS

The results consisted of percentage of patients

NS non-significant

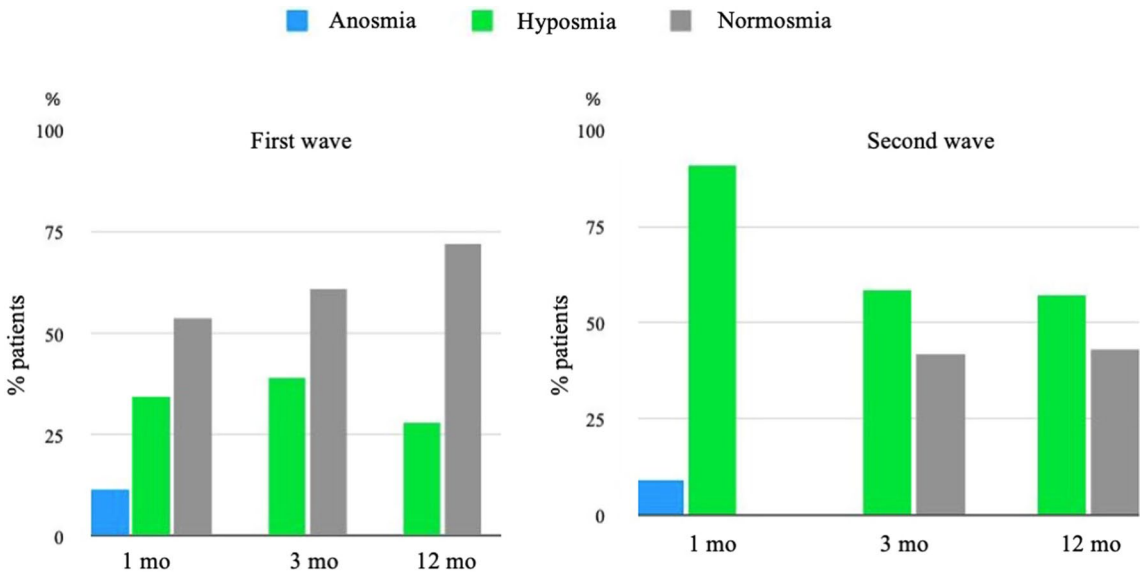

Fig. 1 Evolution of psychophysical evaluations and olfactory disorder questionnaire. *mo* month

($p = 0.047$). There was no significant increase from 3- to 12-month post-infection ($p = 0.109$).

The 12-month prevalence of parosmia was 60.6% in group 1 and 42.4% in group 2, respectively. Phantosmia occurred in 37.0% and 22.2% of patients of group 1 and 2, respectively. The prevalence of parosmia and phantosmia did not differ between groups. The occurrence of parosmia was significantly associated with the occurrence of phantosmia ($r_s = 0.441$; $p = 0.010$).

The 1-month ODQ was negatively correlated with the 1-month TDI ($r_s = -0.493$; $p = 0.012$), the 3-month TDI ($r_s = -0.472$; $p = 0.023$), and the 12-month TDI ($r_s = -0.658$; $p = 0.004$). There were no significant influences of the oral corticosteroid treatment, the adherence to an olfactory training and the vaccination status on the 1-, 3-, and 12-month olfactory outcomes.

Discussion

The primary finding of the present study was the lack of significant improvements of 1–12-month psychophysical tests in patients with persistent OD 1 month after the infection. Moreover, our analysis suggested that the 1-month psychophysical tests were predictive on the 12-month TDI scores. One year after the infection, 44.4% and 16.7% of patients infected with D614G and B.1.1.7. Alpha variant SARS-CoV-2 had persistent psychophysical test abnormalities, while the TDI scores significantly improved from 1- to 3-month post-infection. Note that the increase of hyposmic proportion in group 1 was related to the development of parosmia in some patients who were consequently unable to detect some odors at the TDI. The long-term persistence of OD in patients without early smell recovery corroborated the results of several studies [15–17]. Boscolo-Rizzo et al. observed 46% of abnormal psychophysical tests (TDI) after a median of 401-day post-COVID-19 [16]. Similar results were found in the study of Fortunato et al. with 70% of patients without smell recovery at 1-year post-COVID-19 [17].

Depending on the SARS-CoV-2 type, the prevalence of parosmia at 1 year ranged from 42.4 to 60.6%. Ferreli et al. reported 23.1% of parosmia at 18-month post-COVID-19 [15], while we reported that parosmia occurred in 23.4% of patients infected by the D614G SARS-CoV-2 at 2-year post-infection [18].

The originality of the present study was the comparison of the evolution of OD between patients infected with the D614G SARS-CoV-2 and the B.1.1.7. Alpha variant. Our preliminary data suggested that the B.1.1.7. Alpha variant infection was associated with a higher significant prevalence of hyposmic and anosmic patients compared to D614G virus infection 1 month after the infection. This finding may reflect potential differences in olfactory mucosa injuries according to variants.

The follow-up period did not, however, reveal significant differences in the recovery process between groups at 3- and 12-month post-infection. The comparison of OD prevalence and evolution between variants was poorly investigated. In a recent study, Hintschich et al. investigated the patient-reported OD prevalence at the time of the infection diagnosis according to variants. Authors reported that patients infected with the D614G SARS-CoV-2 reported significant higher OD (73%) compared to those infected with B.1.1.7. Alpha (41%) or the B.1617.2. Delta (48%) variant [19]. The patients included in the study of Hintschich et al. self-assessed the olfaction with a 8-item blinded smell identification test at home and authors considered normosmia when the responses were correct in ≥ 75% of cases. In another recent paper, Vaira et al. did not report significant differences between D614GG, Alpha and Delta periods according to the Connecticut Chemosensory Clinical Research Center olfactory test [20]. The comparison of our results with those of the literature remains difficult, because the time and the tools of OD evaluations differ from one study to another. Most COVID-19 patients with OD recovered in the first weeks of the infection course [3], and may have normal psychophysical test at 1 month. Moreover, the prevalence of OD may vary according to the definition of hyposmia and anosmia and, therefore, the type of smell tool assessment [21]. However, to the best of our knowledge, this study is the first study comparing the evolution of OD according to variants. Thus, any comparison is limited to data reported by other authors about the prevalence of OD during infection, because there are no other prospective studies on long-term recovery differences between variants.

In this study, groups differed regarding the initial treatment/olfactory training. D614G patients more likely adhered to an olfactory training protocol compared to Alpha variant group, because the use of corticosteroids at the start of the pandemic was controversial. The proportion of oral corticosteroids was significantly higher in Alpha variant compared with D614G patients. We believe that these differences did not influence the statistical comparison of groups, because the usefulness of oral or nasal corticosteroids in the smell recovery was not formally demonstrated [22, 23]. Saussez et al. reported in a controlled study that nasal or oral corticosteroids may accelerate the smell recovery in the first weeks of the infection but at 2 months, the smell of corticosteroid *versus* olfactory training groups was similar [22]. Moreover, in the present study, the Alpha variant patients who more likely received corticosteroids did not report better olfaction at 1 month than D614G patients, suggesting a lack of influence of corticosteroids in the baseline smell outcomes. The lack of evidence about the usefulness of corticosteroids in COVID-19 smell loss was supported in a

recent Cochrane Database paper [23]. Similar observation may be made for olfactory training with a suspected mid-to-long term benefit on smell sense but not after few weeks of training [24].

The primary limitation of this preliminary report is the low number of patients in both groups. However, it was difficult to perform psychophysical tests in the first pandemic year regarding the lockdown of the European population. Moreover, the advanced sequencing of the viral genome that allowed to distinguish between the variants was not routinely used and we preferred to include only patients with certain determination of the VOC. Another limitation was the lack of ODQ evaluation throughout follow-up period, because olfactory assessment ideally includes both patient-reported outcome questionnaire and psychophysical tests, which may be not correlated. The use of ODQ throughout the follow-up was also important to determine the time of occurrence of phantosmia or parosmia, and their respective evolution.

Future studies could compare olfactory findings between D614G, B.1.1.7.Apha variant and omicron virus, which appears to be associated less frequently with persistent OD.

Conclusion

Patients infecting during the B.1.1.7.Apha variant wave reported significant higher proportion of OD at 1 month post-infection compared to patients of the first wave (D614G virus). The prevalence of psychophysical test abnormalities, parosmia or phantosmia did not differ between groups at 1-year post-infection.

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Author contributions JRL: design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SW: design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SLB: design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MH: design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Luigi Vaira: data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. PB-R: data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. SS: design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials Data are available on request.

Declarations

Conflict of interest The authors have no conflicts of interest.

Research involving human participants and/or animals IRB was obtained from CHU Saint-Pierre (CE/21–12-03).

Informed consent Patients consented to the study.

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Authors and Affiliations

Jerome R. Lechien[1,2,3,4,9] · Shannon Wajsblat[4] · Mihaela Horoi[4] · Paolo Boscolo-Rizzo[5] · Serge D. Le Bon[6] · Luigi A. Vaira[7,8] · Sven Saussez[2,4]

1 Department of Otolaryngology, Polyclinic of Poitiers, Elsan, Poitiers, France

2 Division of Laryngology and, Bronchoesophagology, EpiCURA Hospital, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium

3 Department of Human Anatomy and Experimental Oncology, Faculty of Medicine, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium

4 Department of Otorhinolaryngology and Head and Neck Surgery, CHU Saint-Pierre, Brussels, Belgium

5 Department of Medical, Surgical and Health Sciences, Section of Otolaryngology, University of Trieste, Trieste, Italy

6 Department of Otorhinolaryngology and Head and Neck Surgery, CHU de Genève, Geneva, Suisse

7 Maxillofacial Surgery Operative Unit, Department of Medicine, Surgery and Pharmacy, University of Sassari, 07100 Sassari, Italy

[8] Biomedical Science Department, PhD School of Biomedical Science, University of Sassari, 07100 Sassari, Italy

[9] Department of Otorhinolaryngology and Head and Neck Surgery, School of Medicine, Foch Hospital, UFR Simone Veil, Université Versailles Saint-Quentin-en-Yvelines (Paris Saclay University), Paris, France