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Olfactory dysfunction is more severe in wild-type SARS-CoV-2 infection than in the Delta variant (B.1.617.2)

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ABSTRACT

Olfactory dysfunction is common in COVID-19, and sudden-onset dysosmia is an early marker for wild-type SARS-CoV-2 infection. Over 10 000 mutations of SARS-CoV-2 have been registered, with *variants of concern* (VOC) under particular scrutiny. We report a telemedicine-based, multicentre, prospective cohort study with quantitative olfaction testing comparing 79 patients with a confirmed VOC-Delta (n = 21) or wild-type (WT) SARS-CoV-2 infection. Acute SARS-CoV-2 infection led to significant decrease of olfactory function in both cohorts. A majority of patients suffered from hyposmia or anosmia at inclusion with only 26 individuals performing normosmic. Sniffin'Sticks total scores were significantly higher for VOC-Delta patients at onset of illness, compared to WT patients ($p < 0.001$). At 4 weeks follow-up, olfaction scores recovered only partially for WT patients, thus odds of recovery were stronger in VOC-Delta patients. Also, subjective self-rating of chemosensory function was lower in WT, compared to VOC-Delta patients. The need for ongoing olfaction studies and their prognosis in SARS-CoV-2 background remains urgent, also in the light of increasing numbers of olfaction-related patient presentations.

DEAR EDITOR,

Olfactory dysfunction is common in COVID-19, and sudden-onset dysosmia is an early marker for SARS-CoV-2 infection.[1–3] This finding was confirmed during the early stages of the pandemic. However, over 10 000 mutations of SARS-CoV-2 have been registered with an increased chance of having an altered phenotype of illness.[4] Some mutants give the virus selective advantages and accelerate the pandemic progression. The multiple *variants of concern* (VOCs; WHO nomenclature) are particularly under observation by the World Health Organization (WHO). In the VOC-Delta (B.1.617.2), first described in India, spike protein mutations induce an increased transmission rate.[5]

The mechanisms for long-term olfactory impairment beyond acute olfactory epithelial damage are still unclear.[6] Psychophysical testing is a common standard for the reliable evaluation of olfaction in COVID-19.[1,7] Based on previous studies, despite methodologic differences, different SARS-CoV-2 variants may differ in terms of olfaction disturbance.[1,8] To the best of our knowledge, no psychophysical quantitative measures of olfaction have yet compared wild-type SARS-CoV-2 infections with any other VOCs, particularly the VOC-Delta.

We report a telemedicine-based,[7,9] multicentre, prospective cohort study with quantitative olfaction

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testing comparing 79 patients with a confirmed VOC-Delta or wild-type SARS-CoV-2 infection.

METHODS

The study respected the Declaration of Helsinki, approval was obtained from the Ethics Committee (IRB No.14943), and all participants provided written informed consent. COVID-19 was defined by a positive SARS-CoV-2 RT-PCR on nasopharyngeal and pharyngeal swab tests. The wild-type variant (WTV) and VOC-Delta were defined by high-sensitive next-generation sequencing (NGS).

Inclusion criteria were as follows: positive RT-PCR no later than 5 days after symptom onset, no other olfaction pathology, willingness to participate, age ≥18 years, intellectual and clinical ability to self-perform a full Sniffin'Sticks olfaction test, visual analogue scales (VASs, range 1–100 min-max), and temperature measurement. The use of language-based questionnaires was avoided due to the mixed primary language background of patients. All subjects were given standardised test kits and instructions for psychophysical olfactory function tests[10] (Sniffin'Sticks, Burghart, Holm, Germany). These tests were to be performed via telemedicine consultation with a re-evaluation after 4 weeks. Prior subjective or diagnosed olfaction impairment and chronic rhinitis led to exclusion in the screening process. Patients were screened for participation at a regional COVID-19 testing facility.

Statistical analysis was performed with GraphPad Prism v6 (GraphPad Software, San Diego, USA) and included t-tests and ANOVA analyses after normality testing. See Online supplement for full data table.

RESULTS

Among the 79 patients (44 males, mean age 40.4 years [range 18–79]), 21 had an NGS-confirmed VOC-Delta (B.1.617.2) infection (Suppl. Table 1). The course of the disease was mild in both cohorts, and hospital admission was not necessary. Of note, fever did not occur in the VOC-Delta cohort (Fig. 1A, $p < 0.05$).

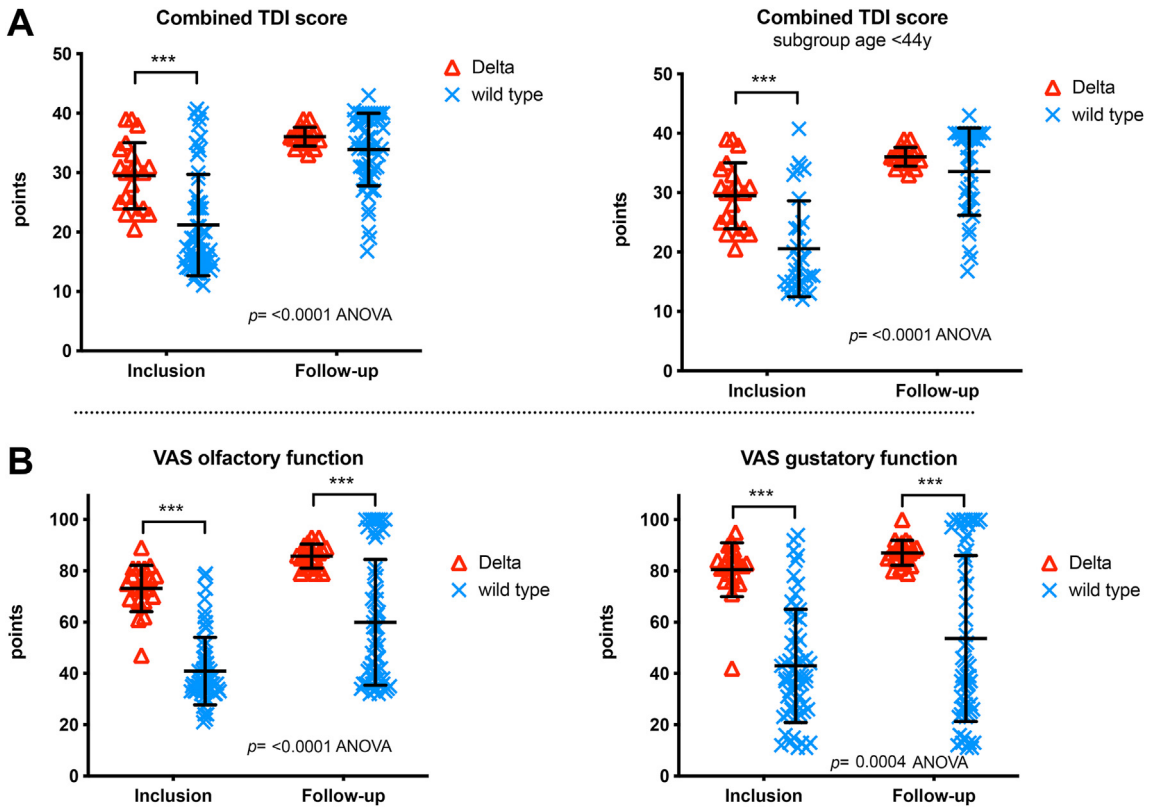

Fig. 1 A: Psychophysical olfaction testing results and body temperature of patients with Delta or wild-type COVID-19. *Left*: all patients. *Right*: matched equal-age subgroups (m = 31.4 y/o). TDI = combined score of Sniffin'Sticks subtests threshold, discrimination and identification. 2w-ANOVA and *t*-test analyses. B: self-assessment of symptoms through visual analogue scale. 2w-ANOVA and separated *t*-tests for statistical significance.

Acute SARS-CoV-2 infection led to a significant decrease of olfactory function in both cohorts. The majority of patients suffered from hyposmia or anosmia at inclusion, with only 26 normosmic cases (Suppl. Table 1). At inclusion, the Sniffin'Sticks total combined scores were significantly higher for VOC-Delta patients compared to wild-type variant (WTV) patients (29.5 vs. 21.2, $p > 0.001$, Fig. 1A). The "identification" and "discrimination" subtests were drivers of this effect: identification and discrimination scores were 3.6 or 2.8 lower for WTV patients at inclusion, compared to VOC-Delta cases (Suppl. Table 1). Threshold values were non-significantly lower for the WTV (7.2 vs. 9.0, $p = 0.15$). Since VOC-Delta patients were younger, this finding was confirmed in subgroups of equal age (44 and younger), with total combined score means of 29.5 vs. 20.6, $p < 0.001$ (Fig. 1A).

At follow-up, olfaction scores recovered only partially for WTV patients. For the entire period, a 2-way ANOVA confirmed that the VOC-Delta caused significantly less olfactory loss ($p < 0.001$). Odds of recovery within four weeks (equal-age subgroups) were stronger in the VOC-Delta patients (odds ratio 2525.0, 95CI: 11.39-449449.5), and all of the VOC-Delta patients had normosmia at follow-up.

Global nasal symptoms, obstruction and chemosensory function were all assessed with visual analogue scales (VASs). The subjective self-rating of those symptoms was diminished in both cohorts (Suppl. Table 1). Self-rating of both olfaction and gustation function showed significantly lower scores in WTV compared to VOC-Delta (Fig. 1B, $p < 0.001$).

DISCUSSION

For the first time, quantitative psychophysical analyses of olfaction have been compared in different SARS-CoV-2 variants at several time points. Our data suggest that: 1) functional anosmia in COVID-19 is more frequent in WTV patients than in those with the VOC-Delta, 2) the likelihood of long-term olfaction impairment appears to be substantially lowered in the VOC-Delta, and 3) as shown before, telemedicine consultations allow safe testing for patients and staff.

Recent observations have suggested that VOC patients are more likely to suffer from moderate and severe infections than WTV patients.[11] SARS-CoV-2-induced olfaction impairment seems to occur in a similar way to that of other upper respiratory tract viruses, despite significant differences with regards to nasal congestion and secretion.[12] The precise mechanism of action on olfaction neurons or central nervous system has not yet been determined. However, viral strain alterations may also change the destructive impact on olfaction. In our cohort, regardless of the variants, acute infection had a severe impact on all three capacities tested for by the Sniffin'Sticks psychophysical test. Correlating strongly with the patient's subjective impression of chemosensory performance, identification and discrimination of odours as well as olfactory threshold were impaired upon SARS-CoV-2 infection. Strikingly, VOC-Delta patients performed significantly better in psychophysical testing at inclusion, with significantly higher testing scores in odour identification and discrimination. To correct for age differences between cohorts, subgroups of equal age were built, and results were uniformly confirmed. Thus, the more pronounced SARS-CoV-2-dependent olfaction loss was not caused by older age, but occurred in all age groups, significantly more frequently in the WTV patients. Notably, all VOC-Delta patients recovered to normal test scores at follow-up, which may well be biased by the age difference between both groups. We can correct these results for age inequality and still see statistical significance; however there is clear need of further studies for confirmation in larger samples. Further limitations of this cohort study arise from the small cohort size and from the lack of means to characterise nasal status more thoroughly, e.g. by nasal endoscopy. Despite an increasing proportion of VOC cases relative to total infections, next-generation sequencing is not standard in all regions and test facilities, which raises problems in the recruiting of patients.

Up until now, current vaccination programmes have been effective against wild-type and VOC coronaviruses. This is vitally important for decreasing numbers of SARS-CoV-2-related olfaction disorders.[13] Further studies are urgently required to characterise this bothersome secondary symptom of COVID-19. With virtually

few options to treat the increasing number of patients presenting with long-term olfaction impairment, but also in the light of increasing numbers of occupational illness insurance claims, further knowledge about COVID-related olfactory impairment and its severity will be of great interest in the future.

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Availability of data and materials
Data and materials are not uploaded to public database, but can be provided upon request.

Author contributions
LK, JB and JH drafted the study. All authors contributed to data collection and executed the study. JH and LK analyzed the data. LK and JH drafted the manuscript. All authors interpreted results and critically revised the manuscript. All authors gave consent for publication. LK and JH contributed equally and share first authorship.

Ethics statement
The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Approval was obtained from the Ethics Committee (IRB No.14943), and all participants provided written informed consent.

Conflict of interest disclosures
The authors declare no competing interests. See ICMJE disclosure statements separately.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2022.100653.

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