Six month follow-up of self-reported loss of smell during the COVID-19 pandemic*

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Abstract

Introduction: Loss of smell and taste is now recognised as amongst the most common symptoms of COVID-19 and the best predictor of COVID-19 positivity. Long term outcomes are unknown. This study aims to investigate recovery of loss of smell and the prevalence of parosmia.

Methodology: 6-month follow-up of respondents to an online surgery who self-reported loss of smell at the onset of the COVID-19 pandemic in the UK. Information of additional symptoms, recovery of loss of smell and the development of parosmia was collected.

Results: 44% of respondents reported at least one other ongoing symptom at 6 months, of which fatigue (n=106) was the most prevalent. There was a significant improvement in self-rating of severity of olfactory loss where 177 patients stated they had a normal smell of smell while 12 patients reported complete loss of smell. The prevalence of parosmia is 43.1% with median interval of 2.5 months (range 0-6) from the onset of loss of smell.

Conclusions: While many patients recover quickly, some experience long-term deficits with no self-reported improvement at 6 months. Furthermore, there is a high prevalence of parosmia even in those who report at least some recovery of olfactory function. Longer term evaluation of recovery is required.

Key words: COVID, olfactory disorders, health status

Introduction

There is now abundant evidence that loss of sense of smell is one of the most common symptoms of COVID-19 infection and in some cases the only symptom[1]. Since the onset of the pandemic, there has also been a steady increase in the number of studies and peer-reviewed literature that investigate the relationship between COVID-19 and anosmia[2, 3], addressing the prevalence and severity of olfactory dysfunction[4], the value of olfactory loss as a prognostic marker[5, 6], possible meachanims[7, 8] and more recently recovery rates[9-12]. Studies evaluating recovery rates have included both self-reported outcomes and psychophysical testing but to date have almost exclusively focused on quantitative olfactory loss.

Following the initial press-release[13] which highlighted the potential link between COVID-19 and loss of smell, the first author received a deluge of emails from colleagues and patients reporting recent onset loss of smell seeking advice and volunteering help. These patients were asked to complete a survey regarding their symptoms. The outcome of this survey and a follow-up survey 1 week later have previously been reported[14, 15]. The work reported in this paper builds upon these previous 2 reports and surveys the initial cohort 6 months after they first responded. The aim of the present study is to investigate the longer-term effect of COVID-19 infection on self-reported olfactory and gus-

tatory functions, including the ongoing severity of dysfunction, development of parosmia, associated symptoms and changes in patient's appetite and weight.

Materials and Methods

An initial survey to audit the onset of anosmia and associated symptoms was designed and sent to patients making contact with the first author by email for advice regarding recent onset smell loss, along with an advice sheet[16]. The survey was initially conducted anonymously, and no reward was offered for completion. At 7 days, 2,428 responses had been received, after sending a link to the survey in approximately 600 emails in response to patient queries, suggesting wider dissemination. After confirmation that ethical approval was not required to allow patients wishing to participate in future studies to leave contact details, an optional box was added, 613 patients with known email contact details were contacted to complete a second survey 1 week after the completion of the first. 382 patients completed the survey at 1 week. All 613 patients were contacted again 6 months after their first response. The survey was modified to include additional questions on parosmia (with an accompanying description in the invitation email; "We have also found that some people develop a distorted sense of smell, called parosmia - which is when certain smells such as coffee, onions or even toothpaste trigger a really odd and often unpleasant smell. This has been described in different ways from a rotting smell, burnt or smoky smell, or sometimes a sickly-sweet smell"), weight change and appetite. No identifying information was collected.

Descriptive data is presented for the whole cohort. Tests for significance were performed using a Chi-Squared test and Mann-Whitney U Tests. The cohort was dichotomised into those with proven COVID-19 on PCR and/or serology and those where it was unproven to identify any differences between the two groups.

Results

Demographics

Four hundred and thirty-four completed a 6-month follow-up survey (giving a response rate of 70.6%). Similarly, as in the first and second survey, 74.9% of respondents were female and median age was 40 (range 19-77) years.

COVID-19 diagnostic testing

76 (17.3%) patients reported that they had undergone reverse transcription polymerase chain reaction (RT-PCR) testing for COVID-19 out of which 19 (25%) tested positive. Only 15 out of the 76 patients who underwent RT-PCR swabs received these within 2 weeks of onset of symptoms, of whom 12 tested positive.

Out of 138 patients who had received serological assays for IgM and/or IgG COVID-19 antibodies, 108 (78%) respondents tested positive. The mean time interval between loss of smell and serology testing was 3.36 months (SD=1.39) in those with detectable antibodies and 4.25 (SD=2.1) in those who tested negative for COVID-19 antibodies (p=0.08).

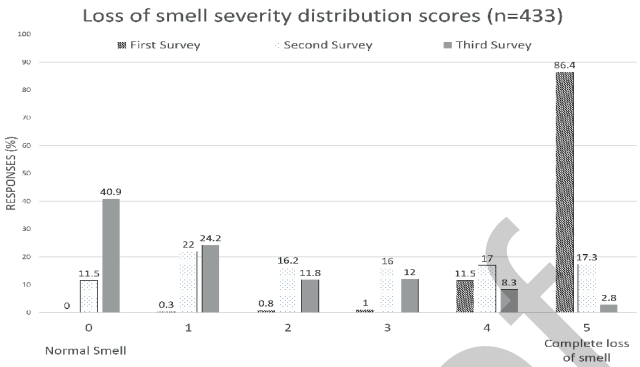

Figure 1. Prevalence of associated ongoing symptoms in the 193 patients who report ongoing symptoms.

19 patients who had confirmed COVID-19 on RT-PCR, also underwent serological assays for COVID-19 antibodies of whom 13 (68%) had detectable antibodies at the time of testing. Overall, 114 respondents tested positive for COVID-19 on either RT-PCR or serological assays.

There were no significant differences between the proven COVID-19 group (positive PCR or antibodies) and the unproven COVID-19 group with respect to age, gender or reported recovery rates (p=0.009).

Other ongoing symptoms

In this cohort, 193 (44.5%) of respondents reported at least one other ongoing symptom at 6 months, of which fatigue (n=106) was the most prevalent followed by headaches/sinus pain (n=67), shortness of breath (n=50), cough (n=33), dizziness (n=29), gastro-intestinal upset (n=25), nasal blockage (n=23), high temperature (n=22) and runny nose (n=21) (Figure 1).

Loss of smell and parosmia

Of cohort, 40.7% reported having regained their sense of smell fully, 31.7% almost fully, 18.5% partially, 6.9% very little and 2.1% reported no improvement at all. At the time of completion of the third survey, there was a significant improvement in self-rating of severity of olfactory loss (p<0.001) where 177 patients (40.9%) stated they had a normal smell of smell while 12 patients (2.8%) reported complete loss of smell (Figure 2).

In our cohort, the prevalence of parosmia is 43.1% (n=187) with median interval of 2.5 months (range 0-6) from the onset of loss of smell. Of those with parosmia, 20.3% reported full

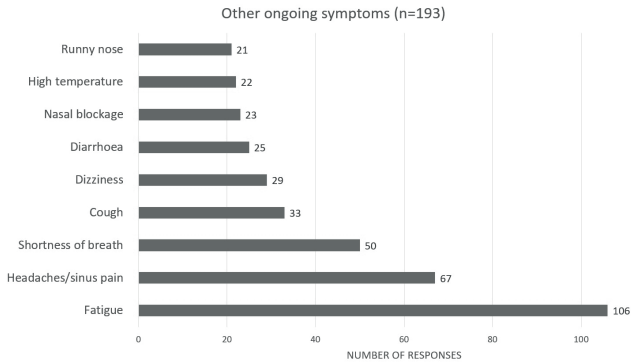

Figure 2. Severity rating of loss of sense of smell at first, second and third survey.

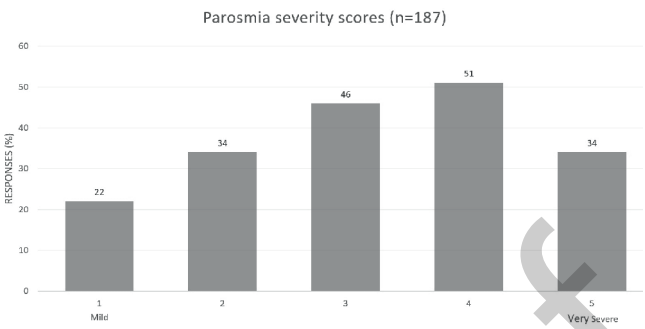

Figure 3. Parosmia severity scores at 6-months in 187 patients who report this symptom at 6 months.

improvement of smell when parosmia started, 62% respondents observed partial and 17.6% reported no improvement at all.

Parosmia was judged as severe by 34 patients (18.2%) and 22 patients (11.8%) reported mild parosmia (Figure 3). At the time of completion of the third survey, only 8.5% of patients reported full improvement of parosmia, 50.8% partial and 40.6% no improvement at all.

Loss of taste

At the time first survey, 94.8% responded that their sense of taste was reduced, which had fallen to 75% at the second and 35.3% at the third survey ($p<0.001$). Ability to differentiate between sweet, salty, sour and bitter tastes improved from 60% (first survey) to 88.9% (second survey) and finally to 97.2% (third survey) ($p<0.001$).

Furthermore, we asked patients whether their weight had changed in the last 6 months due to altered smell and taste after COVID-19. Of the cohort, 8.3% of patients stated that their weight increased and 10.8% reported weight loss that they attributed to their altered smell or taste after COVID-19. The remainder felt that their weight stayed the same (53.9%) or changed but was unrelated to their smell and taste deficit (27%). 17.1% reported that they have experienced moderate problems with appetite, and 6% severe problems with appetite due to their altered smell or taste.

Self-reported COVID-19 management

41 patients accessed support groups for loss of sense of smell and 55 reported using olfactory training (OT). At the time of the third survey, patients who used OT reported significantly worse smell (median 3 (range 0-5)) judged by severity grading when compared to those that did not perform OT (median 1 (range 0-5)) ($p<0.001$).

With regards to other treatments, 26 patients used nasal steroids, 22 patients reported using omega 3 supplements and 3 used Vitamin A drops. 6 patients had been given oral steroids. We also asked whether patients had seen general pratictioner (GP) or ENT specialist regarding loss of smell. Majority of respondents felt they did not need to see GP (77.2%) or ENT specialist (82%), while 12.9% and 15.6% stated that they had been unable to.

Discussion

We present 6-month follow-up date in a cohort of patients who presented with sudden loss of smell in March 2020. Studies have found high rates of COVID-19 detected in more than 90% patients reporting sudden loss at this time[17, 18], however RT-PCR testing was unavailable to patients with suspected COVID-19 UK in March unless they required hospitalisation. Only 15 patients had undergone formal testing within 2 weeks of developing symptoms, of whom 80% were positive. At 6 months, an additional 61 patients report having been tested later than 2 weeks after onset, of whom only 4 received a positive RT-PCR swab. This likely reflects the delay between onset of symptoms and testing and we do not believe this excludes COVID-19 as the cause of olfactory dysfunction. it is not clear why patients were tested at a later stage, but some patients actively seek RT-PCR swab results weeks after the onset of symptoms to confirm that they are 'clear' of the virus after infection, and some may have received swabs for persistent olfactory loss once this was adopted as a qualifying symptom for testing in May 2020.

Antibody tests are not freely available in the UK and patients usually have to self-pay for these tests. In the 138 patients who had undergone serological assays for COVID-19 antibodies, 78% tested positive for antibodies. The mean time interval between loss of smell and serology testing was shorter in those testing positive when compared with those testing negative. Studies have shown progressive decline in antibody levels, such that 8 weeks after discharge 12.9% of symptomatic cases who seroconvert no longer have detectable antibodies[19]. Rapid decay of anti-SARS-CoV-2 antibodies has been shown to continue up to

at least 90 days[20]. It is quite likely therefore that at least some of those tested at over 4 months after onset had previously seroconverted but had lost detectable antibodies. Finally, we found no significant differences in age, gender or recovery rates between the proven COVID-19 and suspected COVID-19 groups, further supporting the same aetiology in both groups. Taking all of this into account, we are confident that the majority of our cohort have developed olfactory loss as a consequence of COVID-19, although a limitation of this study is that we cannot be certain.

At the time of the first survey, 86.4% reported complete anosmia and a further 11.5% a very severe loss of smell. At the follow up survey one week later 80.1% reported lower severity scores, 17.6% were unchanged and 1.9% were worse; 17.3% reported persistent complete loss of smell, while 11.5% reported having fully regained their sense of smell. At 6 months, 40.7% reported having regained their sense of smell fully, 31.7% almost fully, while only 2.1% reported no improvement at all. This high rate of self-reported recovery is very encouraging, although patients may over-estimate the extent of their recovery – studies have shown that patients who self-rate as fully recovered may still have persistent deficits on psychophysical testing[21]; in one study evaluating resolution of post-COVID-19 OD at 7 weeks after onset, 61.7% participants self-reported complete recovery, while only 46% were normosmic on psychophysical testing. There is only a moderate correlation between self-reported loss of smell and olfactory testing[22], therefore it further studies should include formal testing of long-term recovery. Nonetheless, psychophysical testing is not widely available outside of a research setting, and therefore it is still important to evaluate self-report olfactory function, and this may better reflect the impact of smell loss on quality of life, as if a patient feels fully recovered that implies that they are not suffering any ongoing negative impact even if olfactory testing identifies a persistent deficit.

Other studies looking at recovery rates also show progressive reduction in those reporting no improvement – at 4 weeks Boscolo-Rizzo et al. reported that 48.7% had recovered completely, 40,7% partially while 10.6% had noticed no improvement[9]. In a different study, at 60 days 7.2% were found to have severe deficits on psychophysical testing[11]. While the high recovery rate is encouraging, given the very high prevalence of COVID-19 worldwide, if nearly 3% of those with OD are left anosmic, this represents a significant burden of disease.

As for taste, the prevalence of self-reported reduction in sense of taste reduced from 94.8% in the first survey to 35.3% in the last. It is difficult to interpret self-reported taste dysfunction as patients may instead report loss of flavour perception, mediated by retrognathic olfaction, as loss of taste. This is consistent with the finding that at six months, only 2.8% of the subjects reported that they were still unable to discriminate between primary tastes or sweet, sour, salty, bitter and umami. Data regarding true taste recovery are very limited as most studies focus on smell or report overall data on chemosensory disturbances. The recovery of gustatory function seems to be faster than olfaction, occurring, on average, within the first ten days[23]. Other prospective cross-sectional studies investigating taste have found self-reported complete recovery in 60.3% at 20 days[24] and 82% at 30 days[25]. Obviously, the possible biases introduced by an evaluation based solely on what patients' self-report are also valid for taste[21]. In a recent prospective psychophysical study[11], persistence of gustatory disturbance was detected in 37% of patients at 30 days and in 8.2% of cases at 60 days. In this last 2-month follow-up, 4.3% of patients were unable to discriminate the four primary tastes, suggesting our finding of 2.8% persisting taste disturbance is in keeping with the observed ongoing recovery, but highlights that a small number of patients do have ongoing taste loss.

Although all patients were initially sent an advice sheet signposting patient support groups, only 41 respondents had accessed them – perhaps reflecting lack of need for support. Other than olfactory training, undertaken by 14.3% of respondents, use of other treatments including oral and systemic steroids, and over the counter treatments was relatively uncommon. With the exception of smell training[26], there is only weak evidence to support the use of any specific therapeutic strategies[27], although several trials are ongoing. We have recently shown that patients randomised to receive a combination of oral and intranasal corticosteroids, decongestant and mucolytic achieved better recovery rates thon those not receiving treatment, but further work if required to identify which components contributed to the observed benefit[28]. In our cohort, greater improvement in smell was reported by those that did not use any treatment but this most likely reflects selection bias due to the observational nature of the study; controlled studies in confirmed COVID-19 patients are required.

Parosmia has previously been reported to affect a high proportion of patients with post-infectious loss, with 56% cases reporting parosmia in one study[29]. The prevalence of parosmia has largely been overlooked in studies to date. Parma et al. reported that parosmia was a rare finding in a survey study, being reported by only 7% of patients with confirmed COVID-19[30]; however, patients were asked to respond to the survey within 2 weeks of onset of symptoms. This is the first study to look at the prevalence of parosmia in a longitudinal cohort and found that nearly half of our cohort reported parosmia, with a median interval of 2.5 months from the onset of loss of smell. Interestingly 20.3% reported that their loss of smell had fully recovered prior to the onset of parosmia. The parosmia was reported to have a range of severity, but was still present at 6 months in 93% of

those affected. There is a growing body of literature focusing on 'Long COVID', or post-acute covid-19, which is thought to affect up to 10% patients[31], but to date there has been no mention of qualitative olfactory dysfunction, with studies only reporting persistent loss of smell, which will underestimate the full extent of olfactory dysfunction[32].

More than 1 in 10 respondents reported that they had lost weight due to their altered smell and taste, and 1 in 3 reported at problems with their appetite to some extent. There are few therapeutic options available to treat parosmia, but patients will need support and advice, and this is an area where further research is urgently required.

Nearly half of the cohort reported other ongoing symptoms at 6 months, with 106 respondents (24.4% of the total) reporting ongoing fatigue over 6 months after the onset of their loss of smell. This is also the most commonly reported persistent symptom in other studies[33, 34]. Sudre et al. found that more than 1 in 10 patients report long-term, with fatigue, headache and loss of smell the most commonly reported, Female patients were more likely to develop Long-COVID. The rate of associated symptoms reported by our cohort is higher than expected, and some, such as high temperature and diarrhoea may not be reliable and due to the nature of the study these cannot be verified. However, other studies have also reporting long-lasting gastrointestinal disturbance as part of Long-COVID[33, 34].

Headache/sinus pain was also a common symptom in our cohort, reported by 67 patients (15.4%), and along with ongoing disturbances of smell and taste, may drive patients to seek help from primary care or ENT specialists. While 77% and 82% felt that they did not need to see a primary care doctor or ear, nose, and throat (ENT) specialist, 12.9% and 15.6% reported that they had been unable to. While online tools and guidelines have been development to support both patients and primary care doctors, in order to reduce the need for ENT referrals, as many as 1 in 6 patients seem to feel that they have not been able to access the care that they need. We are encouraged by reports of dedicated clinics for Long COVID, and hope that ENT will be involved in delivering such services to optimise care. The authors have seen many patients who have received repeated courses of antibiotic for presumed sinusitis prior to referral, but endoscopic and radiological assessment have revealed no evidence of infection.

There are a number of limitations to this study. We have already discussed the risk that our cohort may include patients' alternative aetiologies. We do not know what RT-PCR or antibody tests were used or their sensitivity or specificity. We had a 70.9% response rate from the original cohort of 612 patients who provided email addresses. Responses were made anonymously and therefore we cannot analyse if there is a difference at baseline between those that completed the 6-month survey and those that did not respond. It is possible that those that replied were more likely to do so if they had ongoing symptoms and therefore were more motivated to raise awareness of this. One large study of patients reporting olfactory loss who were confirmed to be PCR reported a predominance of females (69%)[2]. In our initial cohort, 73% respondents were female, while 74.9% of those responding at 6 months are female, suggesting slight gender bias both in the initial response and the tendency to complete the follow-up survey. Finally, as discussed, self-reported recovery may under or over-estimate recovery rates and long-term follow-up studies with psychophysical testing are required.

Conclusion

This study highlights that while the majority of patients report at least partial recovery in loss of smell and taste following COVID-19 infection, some have persistent deficits 6 months after onset. With over 50 million known cases world-wide to date and smell and taste loss being one of the most prevalent symptoms, if our estimate of persistent anosmia is correct there may be more than 1 million cases with at significant deficits at 6 months. In addition, a significant proportion of patients report parosmia, which has been largely overlooked by studies to date. It is clear that longer-term follow-up is essential to capture the full extent and burden of olfactory and gustatory dysfunction after COVID-19 infection.

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None.

Authorship contribution

CH developed concept for study, designed survey, analysed data and prepared manuscript; PS developed concept for study, designed survey, collected and analysed data and provided critical review of manuscript; MS assisted with manuscript preparation; LV, JL, SS and NK developed concept for study, interpreted data and provided critical review of manuscript.

Conflict of interest

There are no relevant conflicts to declare.

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