Anosmia, Ageusia and COVID-19

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Abstract
COVID-19 is certainly the greatest global health problem now and for the foreseeable future. Clinicians and scientists from all over the world have been producing evidence to understand the epidemiology, clinical profile and prognostic factors of COVID-19. In the last six months a large list of COVID-19 symptoms including loss of taste and smell have emerged which can be used for screening and risk stratification. Robust workup of this evidence will help to reach strong conclusions to advance clinical medicine, epidemiology, public health, immunology and evidence-based treatment options in the spectrum of disease that we now know as COVID-19.
Fig. 1: The human olfactory system. The odorant receptors are localized on olfactory sensory neurons, which occupy a small area in the upper part of the nasal epithelium. Every olfactory receptor cell expresses only one odorant receptor. On activation, signals from olfactory receptor cells are relayed in the glomeruli—well defined micro-regions in the olfactory bulb. Receptor cells of the same type are randomly distributed in the nasal mucosa but converge on the same glomerulus. In the glomerulus, the receptor nerve endings excite mitral cells that forward the signal to higher regions of the brain. Credit: Karolinska Institutet and Nobel Foundation, Stockholm, Sweden

the common occurrence of head injuries leading to anosmia\(^1\) and the onset of the neurodegenerative disorders with disturbance of smell sensation as we have noted in Parkinson's disease and Alzheimer's disease as early disease biomarkers.

The utilisation of University of Pennsylvania Smell Identification Test (UPSIT – 40 unit score) at the bedside and lesser versions (Q-SIT 20 unit score) of the same are expensive and cumbersome and time-consuming leading to the olfactory nerve acquiring the status of the “forgotten nerve” or unexplored nerve in clinical neurology practice. This has now proven to be a limitation to research and standardisation.

Review of ENT literature shows broad categorisation of anosmia into conductive and sensorineural types. The sensorineural anosmia implies dysfunction of the olfactory epithelium and can be permanent or have longer time course to recovery. In conductive or obstructive anosmia there is impairment of the travel of odorants to the intact olfactory epithelium resulting in temporary anosmia. Infections resulting from endemic strains of human coronavirus do cause conductive anosmia as well. Disruption of olfactory epithelium following local infection is also known to occur.

Imaging of the olfactory nerve, bulb and tract and olfactory pathways including fMRI studies and Diffusion tractography with dedicated protocols on high-resolution MRI is only recently being undertaken and has shared a lot of information on the structural alterations in the olfactory bulb and tracts\(^2\) (Figures 2 and 3). Evoked potential studies – olfactory evoked potentials are a more objective way of studying the olfactory system.

In COVID-19 the frequency of anosmia ranges between 22% to 68% dependent on case ascertainment tools.\(^3\) Olfactory dysfunction after SARS Cov infection was also reported in the past, and in other coronavirus infections: however, it represents a rare occurrence. In COVID-19 patients ageusia and anosmia are not accompanied by nasal obstruction or other rhinitis symptoms majorly. This indicates probable direct damage of the virus on the olfactory and gustatory receptors.

Retrograde propagation to higher-order neurons in the olfactory pathways has been best studied in the case of Herpesvirus.\(^4\) Retrograde spread via the olfactory and trigeminal nerve results in herpes simplex encephalitis and late viral reactivation respectively. In these post-HSE patients a more “central” pattern of olfactory impairment involving limbic areas has been noted. Since we are yet to realise the nature of CNS involvement in COVID-19 such similar patterns would come to light if there was retrograde propagation via the olfactory bulb.

In a study, patients with anosmia did not present with nasal obstruction. Anosmia during viral rhinitis with nasal obstruction usually resolves within three days. In COVID-19 amelioration of anosmia would take 9 days.\(^5\) Thus, the symptom of post viral olfactory loss in relation to different kinds of viruses including coronavirus such as HCoV-229E needs further investigation.

Disturbance of taste sensation with smell has also been reported. The definition of taste disorders varies greatly with dysgeusia in 33% and ageusia in 20%. Gustatory taste bud mediated sensations are largely limited to the basic taste qualities of sweet, sour, bitter, salt and umami. With the exception of such sensations all “tastes” are flavour sensations from olfactory receptor stimulation by volatiles entering from the nasopharynx during deglutition.\(^6\) The tendency
for many persons with smell loss to misconstrue their problems as taste loss must be considered in studies relying only on self-report. This ambiguity calls for further research to employ quantitative taste tests to definitely establish whether SARS-Cov-2 can also damage taste afferents or in rare cases more central taste related brain regions.

Research: A scarcity of advanced neuro imaging studies, difficulties obtaining histopathological tissue specimens and the absence of viral cultures of infected olfactory neural epithelium compound the difficulties in studying the phenomena of viral rhinitis.

Genetic heterogeneity of SARS-Cov and polymorphisms ACE2: Benvenuto et al\textsuperscript{17} have compared the complete genomes of 15 virus sequences from patients treated in different regions of China with other coronaviruses. The observed mutations of surface proteins (spike-S-protein and nucleocapsid-N-protein) confers stability to the viral particle. These mutations become clinically relevant as the spike protein enables viral entry and N protein in viral transcription and assembly efficiency. The biological behaviour of the virus and the choice of human receptor of entry would change which might explain potential clinical differences between patients from different world regions. ACE2, the receptor of SARS-Cov-2 entry could be specific to certain populations. Some ACE2 variants could reduce the association between human ACE2 and SARS-Cov S-protein. This would influence the susceptibility, symptoms and outcomes of COVID-19 infection. Moreover, variants of the ACE2 gene suggested that there will be a lot of ACE2 polymorphisms and expression levels between Asian and European populations.\textsuperscript{18} The mutations and polymorphisms will be determinant in studying the viral behaviour and relation to the host that would be a matter for research and understanding of the clinical spectrum of COVID-19 illness.

Not having had good validated baseline data in regards to anosmia analysis from previous coronavirus and other rhinovirus epidemic studies in regards to objective analysis of anosmia and dysageusia,\textsuperscript{19} we are having scientific challenges in being able to be certain to definitely identify these as earliest biomarkers of COVID-19 that would necessitate isolation strategies. In addition, the effect of anosmia as a drug side effect needs to be considered as well (e.g. Macrolides and others).\textsuperscript{20}

The sheer numbers of patients who will potentially exhibit sequelae to COVID-19 in the coming months and years leaves room for due concern and a vigilant clinical approach.

Take Home Message: COVID-19 is certainly the greatest global health problem now and for the foreseeable future. Clinicians and scientists from all over the world have been
producing evidence to understand the epidemiology, clinical profile and prognostic factors of COVID-19. In the last six months a large list of COVID-19 symptoms including loss of taste and smell have emerged which can be used for screening and risk stratification. Robust workup of this evidence will help to reach strong conclusions to advance clinical medicine, epidemiology, public health, immunology and evidence-based treatment options in the spectrum of disease that we now know as COVID-19.

References