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Hyperosmia after COVID-19: hedonic perception or hypersensitivity?

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Abstract. – OBJECTIVE: COVID-19 has been associated with a wide range of quantitative and qualitative disorders of smell, including hyposmia/anosmia, parosmia, and phantosmia; however, no reports to date have reported hyperosmia as a sequela of SARS-CoV-2 infection.

PATIENTS AND METHODS: We present two cases of subjective hyperosmia in a South Tyrolean Alps family, occurring within days after recovery from SARS-CoV-2 infection with transient anosmia.

RESULTS: The subjects, a mother and son, exhibited subjective hyperosmia despite normal objective olfactory testing. During independent assessments, the severity of hyperosmia and specific odors affected were highly correlated, consistent with shared genetic and environmental factors. In contrast, two other family members with COVID-19 had no perceptual distortion and normal recovery of smell.

CONCLUSIONS: Subjective hyperosmia after COVID-19 infection exhibited striking similarity in two affected family members, suggesting interaction of environment, genetics, and perception.

Key Words:
COVID-19, Anosmia, Recovery of smell, Hyperosmia, Genetic, Coronavirus, SARS-CoV-2, Olfaction, Hyposmia, Phantosmia, Perception.

Introduction

COVID-19 is associated with olfactory disturbances that include anosmia, hyposmia, parosmia, and phantosmia[1]. To date, hyperosmia following SARS-CoV-2 infection has not been described. In this observation, we report two cases of altered olfactory perception that involved enhanced reactivity to odors following COVID-19. The two patients, a mother and her son, resided in South Tyrol, as did all of their relatives. In this population, genetic variability is reduced due to isolation in the valley[2]. The etiology of hyperosmia has been ascribed to diverse causes including toxic exposures, endocrine abnormalities, neurological disorders, or infection[3-5]. This report considers the presentation, pathogenesis, and prognosis for hyperosmia after SARS-CoV-2 infection.

Patients and Methods

Cases Description

The mother and son were both diagnosed with SARS-CoV-2 infection by polymerase chain reaction (PCR) nasopharyngeal swab on November 16, 2020. Their PCR results were negative on December 16, 2020. All family members (mother, father, son, and daughter) were COVID-19 positive and suffered from fatigue, malaise, and arthralgias. All family members reported transient anosmia, which started three days after onset of the flu-like symptoms. None experienced cough, headache, or fever. The father and daughter recovered normal olfactory perception within 20 days after the negative PCR result, consistent with the typical course of COVID-19 anosmia[6]. The mother and son initially had normal recovery of olfaction, as well. But at the end of February 2021, they started to perceive several odors as exaggerated and often bothersome (Figure 1). The altered sense of smell was not associated with altered taste perception.

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Mother				Son			
Orange	Blackberry	Strawberry	Pineapple	Orange	Blackberry	Strawberry	Pineapple
Smoke	Glue	Leather	Grass	Smoke	Glue	Leather	Grass
Honey	Vanilla	Chocolate	Cinneammon	Honey	Vanilla	Chocolate	Cinneammon
Chive	Mint	Fir	Onion	Chive	Mint	Fir	Onion
Coconut	Banana	Walnuts	Cherry	Coconut	Banana	Walnuts	Cherry
Peach	Apple	Lemon	Grapefruit	Peach	Apple	Lemon	Grapefruit
Licorice	Pepper	Mustard	Biscuit	Licorice	Pepper	Mustard	Biscuit
	Chewingum	Menthol	White Spirit		Chewingum	Menthol	White Spirit
Sigarette	Sauerkraut	Garlic	Carrot	Sigarette	Sauerkraut	Garlic	Carrot
Cantaloupe	Coffee	Wine	Fish	Cantalupe	Coffee	Wine	Fish
Cloves	Plum	Orange	Meat	Cloves	Plum	Orange	Meat
Pear	Raspberry	Rose	Bread	Pear	Raspberry	Rose	Bread
Chamomile	Rum	Anise	Cheese	Chamomile	Rum	Anise	Cheese

Figure 1. High concordance of hyperosmia in a Tyrolean Alps Valley family. Green denotes odors normally perceived; purple denotes odors perceived in excess but not distasteful; and black denotes intolerable or highly distasteful odors. Notably, mother and son have nearly identical odors perception and alterations, except perception of cantaloupe and cheese (underlined), which were normal for son and intolerable and highly distasteful for the mother. Independent responses were strongly correlated (Chi Square, $p<.00001$).

To better understand the altered sense of smell, we evaluated all family members for evidence of qualitative and quantitative olfactory dysfunction. A questionnaire was administered by a physician with expertise in olfactory disorders. For each odor, the patient specified (1) normal perception of the odor; (2) increased odor perception but not repellant (hyperosmia); (3) excessive odor perception that was distasteful or intolerable (distasteful hyperosmia); (4) no perception of the odor.

The Sniffin' Sticks diagnostic battery (Sniffin' Sticks, Burghardt®, Wedel, Germany) was used as a semi-objective method to assess odor detection threshold, discrimination, and identification scores (TDI scores). The same odors were used for both portions of the evaluation (questionnaire and Sniffin' Sticks assessment). TDI scores were determined as previously described[7]. Briefly, odorants were presented to the blind-folded participants with pen-like odor dispensing devices. The olfactory detection threshold was assessed with n-butanol, which was presented in 16 dilutions in a standard staircase, three-alternative, forced-choice procedure. Odor discrimination ability was assessed by presenting 16 triplets of odorant pens (two pens containing the same odorant; the third pen containing a different odorant), with participant asked to detect the different odor. Odor identification was assessed using 16 common odors (e.g., coffee, cinnamon). Subjects identified the odors by selecting the best label from a list of four descriptors. The scores were summed to yield a composite TDI score.

The father and daughter reported normal perception of the 51 odors. In contrast, the mother and son reported several instances of abnormal perception. The pattern of olfactory dysfunction formed a highly correlated mosaic of outcomes (Figure 1).

Results

Despite normal TDI scores (32.5 for mother, 33 for son)[8], both had altered smell perception. The son had distasteful hyperosmia for 11 odors, hyperosmia for 15 odors, and normosmia for 23 odors; his mother had distasteful hyperosmia for 13 odors, hyperosmia for 17 odors, and normosmia for 21 odors. Cantaloupe and cheese were distasteful for the mother but normal for the son (black underlined in Figure 1). There was 100% concordance for hyperosmia and 91.3% concordance for normosmia, p <0.0001 (Chi-Square).

Discussion

Hyperosmia is defined as increased olfactory acuity (heightened sense of smell)[9], arising from either a lower threshold for odor detection[9] or a hedonic hyper-perception of the smell[10]. Whereas there is little evidence of objectively enhanced

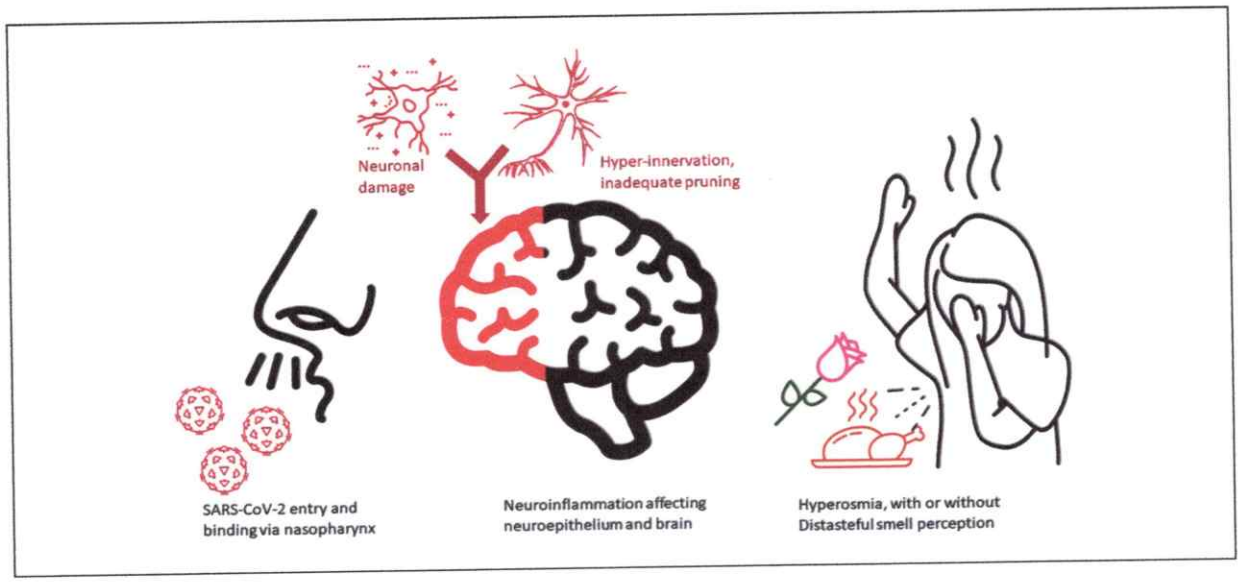

Figure 2. Proposed pathogenesis of COVID-19 hyperosmia. SARS-CoV-2 enters via the nasal passage and causes inflammation of the mucosa and neuroepithelium of the nasopharynx. This inflammation spreads to the olfactory bulbs and contiguous frontal lobes. Sprouting and hyperinnervation associated with regeneration of neuroepithelium and inadequate neuronal pruning contribute to hyperosmia after SARS-CoV-2 infection. The resulting hyperstimulation induces heightened and often distasteful perception of the odors, analogous to the hyperstimulation of olfactory pathways occurring during focal frontal lobe seizure with olfactory hallucination.

function (hypersensitivity), several etiologies of hyper-perception have been identified, from toxic exposure to post-viral sequelae[11]. Variation in perception can differ between genders[12], possibly reflecting differential activation of the frontal lobe[13]. Moreover, olfactory perception is also influenced by genetic factors[9]. Genetics can influence regenerative capacity and recovery after neuronal damage[14].

Our two cases involved subjective/hedonic hyperosmia with normal TDI scores; the latter distinguishes them from 'Super smellers' who have heightened sense of smell[8]. We hypothesize that this altered perception arises from persistent inflammation of the olfactory bulbs and frontal lobe (Figure 2). The highly concordant pattern of hyperosmia observed in the mother and son suggests genetic contributions. There could be x-linked or mitochondrial heritability of susceptibility, as shared environment did not give rise to hyperosmia in the father or daughter.

Some insights relating to parosmia may inform understanding of the present cases. Parosmia after COVID-19 is thought to arise from the aberrant regeneration of the peripheral and central smell pathways[15]. Hyperosmia might result from excessive neuronal sprouting after injury. Inadequate pruning of this prolific sprouting might interfere with recovery to baseline. Genetic inheritance, shared environment, and their interaction may explain highly concordant clinical features[9,14]. Increased gray matter volume in the anterior insula and hippocampus –both regions crucial for odor learning and olfactory integration– has also been associated with hyperosmia[8,16].

Genetic factors might thus interact with environment to influence susceptibility to hyperosmia, as in other neuroinflammatory disorders[9,14]. For example, Alzheimer and Parkinson Diseases are neurodegenerative conditions that are strongly associated with olfactory dysfunction. A recent study[17] identified a genetic link between severe COVID-19 and risk of Alzheimer's disease, related to mutation of the OAS-1 gene. Although specific genetic contributions to hyperosmia are not yet known, any persistent olfactory dysfunction after COVID-19 suggests ongoing neuroinflammation[14,18], and recovery of olfaction after COVID-19 suggests resolving neuroinflammation[19].

Conclusions

Hyperosmia is a rare form of olfactory dysfunction, and it has not previously been described after COVID-19. The two cases presented demonstrate strong familial concordance in perceptions

of smell alteration. Further work is needed to better characterize the natural history of the persistent olfactory dysfunction, the underlying genetic susceptibilities, and therapeutic options. Prospective studies that incorporate clinicogenetic, neuroimaging, and histopathological data can yield critical insights into the pathogenesis of COVID-19 olfactory disorders and their management.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Ethics Approval
The study was approved by the hospital IRB.

Consent
Patients signed a written consent to participate.

Consent for Publication
Parents authorized publication of anonymized data.

Availability of Data and Materials
Data and material are available on demand by asking the corresponding author.

Authors' Contribution
ADS: study design, analysis of data, definition of conclusions, writing article; ILM: critical review; ADS, LDA, PDL collection of clinical data; MB critical review and supporting writing.

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