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RESEARCH NOTE

Trigeminal features in COVID-19 patients with smell impairment

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INTRODUCTION

Due to the global burden of Coronavirus Disease 2019 (COVID-19), there is a coming deluge of patients seeking care for persistent olfactory dysfunction and asking for prognostic indications.

Smell dysfunction is a frequent and early symptom of COVID-19; it is not usually associated with nasal inflammatory reaction, but rather with neuroinvasive properties of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on olfactory neuroepithelium.[1,2] Previous studies reported post-infective trigeminal nasal sensation impairment in COVID-19 patients.[3,4] The purpose of this research note is to confirm this previous anecdotical finding with both subjective and objective tests and to correlate the presence of trigeminal nasal alteration with the degree of olfactory impairment, defining its possible role as a prognostic factor for olfactory dysfunction persistency.

METHODS

Patients with COVID-19-related self-reported olfactory dysfunction were prospectively included. Those patients were part of a larger cohort of COVID-19 cases admitted to our institution from March 5 to March 23, 2020.[1] Exclusion criteria were preexisting olfactory dysfunction and chronic rhinosinusitis with/without nasal polyposis. Patients were interviewed via telephone about smell impairment at diagnosis and at 6-month follow-up with the Italian version of the Sino-Nasal Outcome Test 22 (I-SNOT-22). Trigeminal nerve nasal sensation was investigated at diagnosis and at 6-month follow-up asking patients to rate their perception of burning, cooling, or tingling sensation in the nose on a 6-point Likert scale, considering scores from 0 to 1 as severe impairment, from 2 to 4 as moderate impairment, and 5 as normal sensation. Among patients reporting persistence of smell impairment at 6-month follow-up, the 12-item Sniffin' Sticks Identification Test (worst score: 0; best score: 12) was performed to confirm olfactory dysfunction. In order to increase accuracy, each nostril was evaluated separately, and the mean score was calculated. Menthol identification during the Sniffin' Sticks Test was considered an indicator of trigeminal nasal sensation. Nasal endoscopy (2.7 mm 30° rigid endoscope) was performed just before administering the Sniffin' Sticks Test, in order to assess olfactory cleft patency and to exclude mechanical obstruction, such as nasal inflammatory secretions or the presence of nasal polyposis, as the explanatory cause for olfactory dysfunction. Trigeminal nasal sensation

TABLE 1 Pattern of smell reduction recovery after 6 months stratified on trigeminal nasal sensation at the diagnosis

		Trigeminal nasal sensation at the diagnosis (6-point Likert scale)		
		Score 0-1/5 (n = 56)	Score ≥ 2/5 (n = 42)	*p* value
Smell status at 6-month follow-up	Recovery (n = 80)	73.2% (n = 41)	92.9% (n = 39)	0.013
	Persistence (n = 18)	26.8% (n = 15)	7.1% (n = 3)	

impairment was compared to olfactory dysfunction recovery using Pearson's chi-squared test. The significance level was set at $p < 0.05$.

RESULTS

Ninety-eight out of 99 patients with COVID-19-related olfactory dysfunction were included. One patient was excluded due to nasal polyposis. A severe trigeminal nasal sensation impairment (scores 0-1) was reported by 56 patients (57.1%) at COVID-19 diagnosis. Among those, 51 (91.1%) reported a complete resolution of trigeminal symptoms at 6-month follow-up, while five (8.9%) reported persistent trigeminal nasal sensation decrease. Fifteen patients (26.8%) with severe trigeminal nasal sensation impairment at the diagnosis reported a persistent smell reduction at 6-months follow-up. Among 42 patients with a moderate impairment/normal trigeminal nasal sensation at diagnosis, three (7.1%) reported persistent smell reduction at 6-months follow-up. The difference in olfactory recovery rates between patients with 0-1 trigeminal nasal score at the diagnosis and patients with scores ≥2 was statistically significant (chi square = 6.176, $p = 0.013$) (Table 1).

After 6 months of follow-up, 18 out of 98 patients (18.4%) reported persistent smell reduction. At nasal endoscopy, all patients had free olfactory cleft and no signs of rhinosinusitis. The Sniffin' Sticks Test confirmed self-reported olfactory dysfunction, identifying 11 patients (61.1%) as hyposmic (score 8-10 points) and 7 (38.9%) patients as anosmic (score <8 points). Among the seven patients with anosmia at 6-month follow-up, six patients (85.7%) did not correctly identify menthol during the Sniffin' Sticks Test and did not experience any cooling sensation (Table 2).

DISCUSSION

To date, few papers have studied trigeminal nasal sensation in COVID-19 patients with smell reduction. Moreover,

TABLE 2 Sniffin' Sticks Test in patients with persistent smell reduction at 6-month follow-up stratified by menthol identification and cooling sensation perception

		Menthol identification and cooling sensation	
		Correct	Failed
Sniffin' Sticks Test at 6-month follow-up	Hyposmia (n = 11)	100% (n = 11)	0% (n = 0)
	Anosmia (n = 7)	14.3% (n = 1)	85.7% (n = 6)

when nasal chemesthesis was investigated, it was assessed together with olfaction in a bimodal stimulation, possibly reducing the accuracy of the results.[3] As recently demonstrated by Parma et al.,[4] our data confirmed a high rate (56.6%) of severe reduction of nasal chemesthesis in COVID-19 patients with olfactory dysfunction. Our data show that trigeminal nasal sensation resolved in a high percentage of patients after 6 months of follow-up, similarly to the recovery rate of olfactory perception.[5]

Remarkably, self-reported severe impairment of trigeminal nasal sensation at the diagnosis was associated with a lower rate of olfactory recovery at 6-month follow-up, highlighting the potential role of trigeminal nasal function as a predictor of smell recovery. These self-reported data were further investigated with menthol stick identification test, which represents a unimodal trigeminal stimulation; almost all patients with anosmia at the Sniffin' Sticks Test failed to identify menthol.

In previous studies, the menthol identification test was used as an objective screening tool for trigeminal function in subjects with persistent smell dysfunction, with low performance being correlated with self-reported impaired trigeminal function.[6]

Our findings suggest that intranasal trigeminal nerve endings may also be a potential target for SARS-CoV-2, in addition to the olfactory neuroepithelium, as shown for other respiratory neurotropic viruses.[7]

Some authors recently hypothesized central mechanisms of trigeminal damage, due to intimate central connections between the trigeminal and olfactory systems, with overlapping activations in areas such as the pyriform cortex, the ventral insula, and the middle frontal gyrus.[8] In our recent studies on SARS-CoV-2-infected patients, we observed a higher prevalence of some neurological symptoms in patients with smell and taste disorders than in those without these complaints.[2,9] This may suggest a direct action of SARS-CoV-2 on nasal epithelial cells and its possible propagation beyond the olfactory bulb. Definite conclusions can be made only after rigorous trigeminal testing, using lateralization tests, or event-related potentials, as suggested by Hummel et al.[10]

Future research should focus on the identification of characteristics and prognostic factors associated to persistent olfactory disorders, with a special attention to trigeminal nasal function.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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