

## Hypothyroidism is associated with prolonged COVID-19-induced anosmia: a case-control study

Since the onset of COVID-19 pandemic, an exponentially increasing body of data suggests that infection with SARS-CoV-2 affects multiple organs with short-term and long-term outcomes that remain still unknown.<sup>1</sup> Viral effects on thyroid function can, inevitably, lead to multisystem involvement, as thyroid hormones affect the development and function of virtually all human cells, including neural maturation of olfactory receptor neurons.<sup>2</sup> A recent prospective observational study by Lui *et al* found abnormal thyroid function tests, defined as deranged thyroid-stimulating hormone (TSH) and/or free thyroxine (fT4) and/or free triiodothyronine (fT3) in 25 patients (13.1%), suggesting that SARS-CoV-2 might directly induce viral thyroiditis.<sup>3</sup> Moreover, low fT3 values were independently associated with an increased likelihood for clinical deterioration; the researchers concluded that 'there may be a direct effect of SARS-CoV-2 on thyroid function, potentially leading to exacerbation of pre-existing autoimmune thyroid disease'.<sup>3</sup> However, it was not clear whether thyroid dysfunction was more frequent among patients with particular clinical features, that is, anosmia, or not.

Our multidisciplinary collaborative team has previously investigated the prevalence and neuroimaging findings in patients with COVID-19 presenting with olfactory disorders.<sup>4 5</sup> We have used validated smell test (containing microencapsulated odorant strips) to quantitatively assess olfactory dysfunction in patients with COVID-19 and controls.<sup>4 5</sup> The prevalence of normosmia

was significantly lower in cases than controls (23% vs 64%).<sup>4</sup> In addition, high-resolution brain MRI revealed that COVID-19-induced persistent (>40 days) anosmia/hyposmia was associated with olfactory bulb (OB) atrophy.<sup>5</sup> However, to the best of our knowledge, there are no data regarding potential risk factors that may be associated with protracted olfactory dysfunction and development of OB atrophy in patients with COVID-19.

In view of the former considerations, we conducted a prospective case-control study comparing the prevalence of hypothyroidism in patients with prolonged COVID-19-induced hyposmia/anosmia (>40 days) versus age-matched and sex-matched patients with COVID-19 without subjective and objective olfactory disorders, at a referral centre in Athens, Greece between 22 May 2020 and 15 January 2021. Written informed consent was obtained by all participants and patients' data were handled under strict anonymity in agreement with the Helsinki Declaration. All subjects had a laboratory-confirmed COVID-19 infection, using real-time reverse transcriptase PCR on respiratory samples. Olfactory function was objectively assessed using the three-odorant test Quick Smell Identification Test (Q-SIT; Sensonics, Haddon Heights, New Jersey, USA), that consists of individual 5×5.5-inch tear-out cards, each of which contains three microencapsulated odorant strips.<sup>4</sup> Q-SIT was selected on the basis of cost, convenience, format, standardisation and validation.<sup>6</sup> Q-SIT score is computed by summing the correct responses, with scores of 0, 1, 2 and 3 corresponding to anosmia, moderate/severe microsmia, mild microsmia and normosmia, respectively. We excluded patients (1) who reported olfactory disorder prior to the onset of COVID-19 respiratory symptoms, (2) who reported a history of movement disorders and (3) patients who declined olfactory function testing.<sup>5</sup> All control patients had a Q-SIT score of 3 and reported no subjective symptoms of smell disorders.

We evaluated a total of 12 cases (25% men, median age 45 years; IQR: 26–53) with prolonged anosmia/hyposmia (as the only lingering symptom of COVID-19, along with taste disorders in seven patients) and 24 controls (38% men, median age 48 years; IQR: 36–59). Cases were all PCR negative at the time of inclusion, while the control subjects consisted of a mixture of post-COVID-19 (PCR negative at the time of recruitment, n=8) and PCR-positive patients (n=16) with mild disease. The median Q-SIT score of cases was 1 (IQR: 0–2). The two groups did not differ (p>0.2) in demographics, baseline characteristics, COVID-19 severity, vascular and COVID-19 risk factors. Notably, a

medical history of hypothyroidism had a higher prevalence (50% vs 8%;  $p=0.009$  by Fisher's exact test) among cases than in controls. All subjects with hypothyroidism ( $n=8$ , six cases and two controls), had a medical history of autoimmune thyroiditis, treated with oral levothyroxine supplementation. History of normal thyroid function in cases and controls was confirmed by measuring thyroid hormone levels (TSH, fT3, fT4) during admission. After adjusting for potential confounders (age and sex), hypothyroidism was independently ( $p=0.021$ ) associated with higher likelihood of persistent olfactory dysfunction among patients with COVID-19 (OR: 21.1; 95% CI: 2.0 to 219.4).

Certain limitations of the present report should be highlighted including the small sample size and the fact that the controls were tested with Q-SIT 14–20 days post-symptom onset. Regarding the latter limitation, 14–20 days were considered as a sufficient time interval for objective smell testing, based on the fact that olfactory dysfunction generally develops within a median of 4–5 days post-COVID-19 symptom onset.<sup>4,7,8</sup> Furthermore, in our pilot study, we used as screening test the Q-SIT that is composed of only three items. We are planning to use a more robust test, the SIT (32014), a comprehensive and accurate 40-item test in future larger multicentre studies.

The present preliminary findings are by no means confirmatory but support an intriguing hypothesis. SARS-CoV-2-induced smell dysfunction could be triggered by a direct viral insult of both the olfactory nerve and the thyroid gland. The absence or the slow recovery of olfaction may be impelled by the viral-induced downregulation of thyroid function that may blunt the effects of thyroid hormones into the maturation and regeneration of olfactory neuronal cells especially in patients with a history of thyroid dysfunction. This preliminary observation and

hypothesis require confirmation in larger case–control studies that may control for other confounders including but not limited to those related to thyroid dysfunction (eg, family history, thyroiditis), and/or history of autoimmunity.

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