

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.¹ 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.² 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.³ 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'.³ 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.^{4,5} We have used validated smell test (containing microencapsulated odorant strips) to quantitatively assess olfactory dysfunction in patients with COVID-19 and controls.^{4,5} The prevalence of normosmia was significantly lower in cases than controls (23% vs 64%).⁴ In addition, high-resolution brain MRI revealed that COVID-19-induced persistent (>40 days) anosmia/hyposmia was associated with olfactory bulb (OB) atrophy.⁵ 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.⁴ Q-SIT was selected on the basis of cost, convenience, format, standardisation and validation.⁶ 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.⁵ 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.^{4,7,8} 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.

Georgios Tsigoulis ¹, Paraskevi C. Fragkou,² Emmanouil Karofylakis,² Maria Paneta,² Konstantinos Papathanasiou,³ Lina Palaiodimou,¹ Constantin Psarros,⁴ Matilda Papathanasiou,⁵ Stefanos Lachanis,⁶ Petros P. Sfrikakis,⁷ Sotirios Tsiordas²

¹Second Department of Neurology, National and Kapodistrian University of Athens School of Medicine, Athens, Attica, Greece

²Fourth Department of Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece

³Second Department of Propedeutic Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece

⁴Eginition Hospital, First Department of Psychiatry, National and Kapodistrian University of Athens, Athens, Attica, Greece

⁵Second Department of Radiology, National and Kapodistrian University of Athens, Athens, Attica, Greece

⁶Iatropolis Magnetic Resonance Diagnostic Centre, Athens, Greece

⁷First Department of Propedeutic Internal Medicine, National and Kapodistrian University of Athens School of Medicine, Athens, Attica, Greece

Correspondence to Dr Georgios Tsigoulis, Second Department of Neurology, National and Kapodistrian University of Athens School of Medicine, Athens 15344, Attica, Greece; tsioulisgiorg@yahoo.gr

Contributors Study conception and design were performed by GT, PCF and ST. Data collection, analysis and interpretation were performed by PCF,

EK, MPaneta, KP and LP. Drafting and revising the manuscript were performed by GT, PCF and LP. Critical comments during manuscript revision were provided by EK, MPaneta, KP, CP, MPapathanasiou, SL, PPS and ST. All authors read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study has been approved by the Local Institutional Review Board (Attikon University Hospital, Athens, Greece)—protocol number 259/18-05-2020.

Provenance and peer review Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download

and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

© Author(s) (or their employer(s)) 2021. No commercial re-use. See rights and permissions. Published by BMJ.

GT and PCF contributed equally.



To cite Tsigoulis G, Fragkou PC, Karofylakis E, *et al.* *J Neurol Neurosurg Psychiatry* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jnnp-2021-326587

Received 9 March 2021
Revised 25 March 2021
Accepted 31 March 2021

J Neurol Neurosurg Psychiatry 2021;0:1–2.
doi:10.1136/jnnp-2021-326587

ORCID iD

Georgios Tsigoulis <http://orcid.org/0000-0002-0640-3797>

REFERENCES

- 1 Puelles VG, Lütgehetmann M, Lindenmeyer MT, *et al.* Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med* 2020;383:590–2.
- 2 Świdziński T, Linkowska-Świdzińska K, Czerniejewska-Wolska H, *et al.* Hypothyroidism affects olfactory evoked potentials. *Biomed Res Int* 2016;2016:1–7.
- 3 Lui DTW, Lee CH, Chow WS, *et al.* Thyroid dysfunction in relation to immune profile, disease status, and outcome in 191 patients with COVID-19. *J Clin Endocrinol Metab* 2021;106:e926–35.
- 4 Tsigoulis G, Fragkou PC, Delides A, *et al.* Quantitative evaluation of olfactory dysfunction in hospitalized patients with Coronavirus [2] (COVID-19). *J Neurol* 2020;267:2193–5.
- 5 Tsigoulis G, Fragkou PC, Lachanis S, *et al.* Olfactory bulb and mucosa abnormalities in persistent COVID-19-induced anosmia: a magnetic resonance imaging study. *Eur J Neurol* 2021;28:e6–8.
- 6 Jackman AH, Doty RL. Utility of a three-item smell identification test in detecting olfactory dysfunction. *Laryngoscope* 2005;115:2209–12.
- 7 Klopfenstein T, Kadiane-Oussou NJ, Toko L, *et al.* Features of anosmia in COVID-19. *Med Mal Infect* 2020;50:436–9.
- 8 Meng X, Deng Y, Dai Z, *et al.* COVID-19 and anosmia: a review based on up-to-date knowledge. *Am J Otolaryngol* 2020;41:102581.