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LETTER

Graves' disease and Graves' orbitopathy following COVID-19

G. Lanzolla[1] · C. Marcocci[1] · M. Marinò[1]

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Dear Editor,

Upon genetic predisposition, Graves' disease (GD) is believed to be triggered by nongenetic factors, including infections [1]. The immune system plays a role in Coronavirus disease 2019 (COVID-19), being involved in its clinical course and outcome [2].

We report a case of Graves' hyperthyroidism (GH) and Graves' orbitopathy (GO) following COVID-19 in a 33-year-old woman. Symptoms of COVID-19 appeared in March 2020. Two months later, she complained with tachycardia, weight loss, heat intolerance and nervousness. Thyroid function tests showed overt hyperthyroidism with detectable anti-TSH-receptor autoantibodies. Ultrasound examination revealed a diffuse hypoechoic pattern of the thyroid. A mild, inactive GO was diagnosed by ophthalmological examination. Exophthalmometry measurements were 21 mm in both eyes, with conjunctival redness (clinical activity score 1/7 points). She had normal visual acuity and ocular motility, and no diplopia. She was given methimazole with improvement of symptoms and thyroid function tests.

As complex interplay between genetic and nongenetic factors, including infections, smoking and stress, is believed to trigger thyroid autoimmunity in GD [1]. In our patient, GH and GO appeared after COVID-19, suggesting that COVID-19 may have played a role. Infectious agents are believed to be capable of precipitating or exacerbating autoimmunity in genetically predisposed individuals, by activation of the immune response involving innate and adaptive pathways [1]. Viruses and bacteria may act through a number of mechanisms, including breakdown of central and peripheral tolerance, molecular mimicry between viral and self-antigens, stimulation of inflammasome with release of type I interferon [1]. Several agents have been postulated to be involved in thyroid autoimmunity, including *Yersinia enterocolitica*, *Enterovirus, Herpes Simplex Virus*, *Epstein–Barr Virus*, *Parvovirus-19*, and *retroviruses* [1]. Interestingly, the main target of COVID-19, the angiotensin-converting enzyme-2, is highly expressed in the thyroid, suggesting a possible involvement [1]. In addition to COVID-19, psychological stress may also have contributed the new onset of GH and GO. Thus, a number of studies have postulated a link between stress and autoimmune disorders [1].

A number of cases of autoimmune disorders in patients with COVID-19 have been reported, suggesting that the virus itself, or the response of the immune system, may act as a trigger in predisposed individuals [2]. Recently, three cases of new-onset GH occurring after COVID-19 were observed [2, 3], but all of them without a clinically overt GO, concerning which, this is to our knowledge the first report. Being GD the most frequent cause of hyperthyroidism and GO its most frequent extrathyroidal manifestation, the association might be causal. Nevertheless, given the increasing knowledge on the development of autoimmune disorders during or after COVID-19, a role of this infection cannot be ruled out.

In conclusion, the clinical manifestations of COVID-19 are still being defined. A possible link between COVID-19 and autoimmunity should be considered to define management and prognosis of patients. A speculative hypothesis for our patient is that COVID-19 could have triggered an autoimmune response against thyroid and eye antigens, through molecular mechanisms underlying the action of the virus itself as well as by inducing a long-lasting stress state.

✉ M. Marinò
michele.marino@med.unipi.it

[1] Department of Clinical and Experimental Medicine, Endocrinology Unit II, University of Pisa and University Hospital of Pisa, Via Paradisa 2, 56124 Pisa, Italy

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the individual participant included in the study.

Ethical approval All the procedures performed in the study involving human participants were in accordance with the ethical standards of the Trust and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Being a retrospective investigation, ethical approval was not required.

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