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Review

Thyroid disorders and SARS-CoV-2 infection: From pathophysiological mechanism to patient management

Atteintes thyroïdiennes au cours de l'infection par le SARS-CoV-2 : du mécanisme physiopathologique à la prise en charge des patients

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ABSTRACT

The World Health Organization (WHO) declared the COVID-19 epidemic to be a global pandemic in March 2020. COVID-19 is an infection caused by SARS-CoV-2, a coronavirus that utilizes the angiotensin-2 converting enzyme to penetrate thyroid and pituitary cells, and may result in a “cytokine storm”. Based on the pathophysiological involvement of the pituitary-thyroid axis, the current review discusses the diagnosis of abnormal thyroid function test, and the management of patients presenting with thyrotoxicosis, thyroid-associated orbitopathy and hypothyroidism in the context of SARS-CoV-2 infection.

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R É S U M É

En mars 2020, l'Organisation mondiale de la santé (OMS) a déclaré l'épidémie COVID-19 une pandémie mondiale. L'infection est causée par le SARS-CoV-2, un coronavirus qui utilise l'enzyme de conversion de l'angiotensine 2 pour pénétrer dans les cellules thyroïdiennes et hypophysaires et qui peut entraîner un « orage cytokinique ». Sur les bases physiopathologiques de l'infection par le SARS-CoV-2 sur l'axe hypophyso-thyroïdien, nous abordons dans cette revue le diagnostic des perturbations fonctionnelles thyroïdiennes et la prise en charge des patients avec une thyrotoxicose, une orbitopathie basedowienne et une hypothyroïdie au cours d'une infection par le SARS-CoV-2.

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The World Health Organization (WHO) declared the COVID-19 epidemic to be a global pandemic in March 2020. The condition involves SARS-CoV-2 infection and may result in acute pneumonitis, severe forms of which determine prognosis. Recent clinical and epidemiological data report varied extra-pulmonary visceral (cutaneous, neurological, cardiovascular, ophthalmological, etc.) but also endocrine (pancreatic, pituitary, etc.) involvement, and particularly thyroid disorders associated with COVID-19.

An understanding of the pathophysiological involvement of an abnormal pituitary-thyroid axis in SARS CoV-2 infection may

enable correct interpretation of thyroid function test anomalies and accurate assessment of thyroid function, particularly in patients with severe forms requiring Emergency Room (ER) treatment, allowing appropriate management of thyroid dysfunctions, in particular thyrotoxicosis and thyroid insufficiency.

1. Pathophysiology of the pituitary-thyroid axis in SARS-CoV-2 infection

The SARS-CoV-2 coronavirus can cause immune response hyperactivity involving Th1/Th17 lymphocytes [1,2] leading to release of pro-inflammatory cytokines (interleukin 1-6, tumor necrosis factor α), and which may cause a “cytokine storm”. In

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the acute phase, increased concentrations of interleukins, and in particular of interleukin 6, lead to thyrotoxicosis, the prevalence of which correlates with interleukin 6 elevation [3], disruption of desiodases and thyroid hormone transport proteins, and impaired pituitary cell TSH secretion, resulting in abnormal thyroid functional parameters. There is a decrease in free T3 concentration, correlating with an increase in interleukin 6 [4], normal or moderately decreased free T4 and normal or decreased TSH. These anomalies are described as “low T3 syndrome” or “euthyroid sick syndrome” (anomalies of thyroid function parameters reported in non-thyroid-related conditions). These thyroid function test anomalies are generally transient and do not require specific treatment [5].

During follow-up, the “cytokine storm” may cause immune system dysregulation, leading to autoimmune disorders such as anti-phospholipid syndrome, thrombocytopenia, hemolytic anemia, Guillain-Barré syndrome, and, in terms of thyroid disorders, Graves' disease and, more rarely, chronic autoimmune thyroiditis [6].

Autopsy studies conducted in the aftermath of the SARS-CoV epidemic found destruction of thyroid follicular cells [7], also reported from histological data obtained from patients who experienced an infectious event related to SARS-CoV-2 [8]. Histological examination of the thyroid revealed absence of lymphocytic infiltrates but presence of extensive apoptosis, suggestive of destructive thyroiditis which may be the causal factor in thyrotoxicosis [9].

In addition, recent studies demonstrated the presence of SARS-CoV-2 RNA in serum and plasma from COVID-19 patients, indicating episodes of viremia [10]. The SARS-CoV-2 virus uses the angiotensin II converting enzyme, a membrane carboxypeptidase, as a “receptor” to gain entry into cells. Angiotensin II converting enzyme is expressed on thyroid follicular and pituitary cells [11], and this may explain the incidence of thyroid and pituitary disorders reported during COVID-19 episodes [12,13].

2. Abnormal thyroid function test during SARS-CoV-2 infection

Thyroid function tests from 48 patients evaluated in acute-phase SARS-CoV infection showed decreases in T3 and T4 concentrations in 94% and 46% of patients, respectively. These anomalies persisted during convalescence [4]. T3 decrease correlated with disease severity, and there was also a decrease in TSH concentration. A study of SARS-CoV survivors reported that 6.7% developed hypothyroidism; one-quarter of these patients presented peripheral autoimmune thyroiditis (presence of antithyroid autoantibodies) and three-quarters central thyroid insufficiency, associated with corticotropin insufficiency in 66% of patients, and correlated with pituitary disorders that proved to be transient on long-term follow-up [14].

A recent study of patients with SARS-CoV-2 lung infection showed a decrease in total T3 and TSH concentrations compared to controls or to patients with non-COVID-19 pneumonia [15]. These anomalies, and particularly the decrease in T3 concentration, were more pronounced in patients with the severe forms resulting in death than in SARS-CoV-2 survivors [16].

Although, on March 13, 2020, the World Health Organization (WHO) did not recommend systematic thyroid function test of hospitalized COVID-19 patients [17], it seems useful to perform thyroid function test in patients admitted to the ER or Intensive Care Unit (ICU), given the prevalence of thyroid dysfunctions, and also during follow-up to detect onset of hypothyroidism in the context of a pituitary disorder and to diagnose thyrotoxicosis linked to inflammatory or destructive thyroiditis [18].

3. Thyrotoxicosis and SARS-CoV-2 infection

During the course of SARS-CoV-2 infection, thyrotoxicosis may be complicated by thromboembolic episodes and cardiac rhythm disorders (atrial fibrillation), increasing morbidity and mortality [19–22].

Thyrotoxicosis may be secondary to various conditions:

- Graves' disease is an autoimmune thyroid disorder related to the presence of TSH receptor-stimulating antibodies. Activation of an autoimmune response, irrespective of context [23] and thus including during COVID-19 infection, may induce onset or relapse of Graves' disease [24]. The risk of SARS-CoV-2 infection is not higher in diagnosed or treated Graves' patients. Conversely, in the elderly with Graves' disease that is not well controlled by medical treatment, severe SARS-CoV-2 infection may lead to a thyrotoxic storm, increasing COVID-19-related mortality. This highlights the importance of continuing treatment of Graves' disease during a COVID-19 episode.

Antithyroid drugs are the first-line treatment in Graves' disease [25]. A “block-replace” regimen should be considered for both children and adult patients [26], to facilitate control of thyrotoxicosis, minimize hormone level check-ups and teleconsultations [27] during lockdown. Antithyroid therapy may be complicated by agranulocytosis, a rare but serious hematological complication, which can produce infectious signs and symptoms similar to those of a COVID-19 episode. Agranulocytosis requires immediate discontinuation of antithyroid drugs and complete blood count [28]. Weekly complete blood counts should be suggested at the initiation of antithyroid drug treatment, for early detection of neutropenia and prevention of agranulocytosis. In infectious episodes, and particularly pulmonary infection due to SARS-CoV-2, agranulocytosis may exacerbate COVID-19 symptoms;

- subacute inflammatory or destructive thyroiditis in COVID-19 patients can be secondary to the “cytokine storm”, with interleukin-6 elevation inducing inflammatory thyroiditis [3], or alternatively be secondary to the SARS-CoV-2 infection, which causes destructive thyroiditis [29], as observed during other viral infections that induce a thyrotoxicosis episode (cytomegalovirus, enterovirus, coxsackievirus) [30]. Following case reports of patients with thyrotoxicosis related to subacute thyroiditis [29,31–33], a retrospective study of 287 patients hospitalized for COVID-19 infection found higher incidence (20.2%) of thyrotoxicosis related to inflammatory thyroiditis (in absence of antithyroid autoantibodies) and correlating with interleukin 6 concentration [3]. Clinical characteristics of thyroiditis during COVID-19 include: higher incidence in females [22], increased frequency of heart rhythm disorders (atrial fibrillation) [22], and silent cervical forms. Lymphocytopenia is a common hematological anomaly encountered in SARS-CoV-2 infection, and may decrease lympho-plasmocytic infiltration of the thyroid gland, thereby decreasing the pain symptoms in the anterior cervical region observed in some patients [18]; at the hormonal level, “T4 thyrotoxicosis” may result from thyroid cell lysis [4,7] releasing synthesized thyroid hormones, along with a decrease in desiodase activity in the COVID-19 infectious context, responsible for a decrease in T3 concentration. At the paraclinical level, a hypoechoic, heterogeneous non-vascularized thyroid gland may be observed on cervical ultrasound scan [22,31], not fixing on scintigraphy. Treatment with β -blockers should be considered, depending on the cardiologic context, and corticosteroid therapy (at an initial dose <0.5 mg/kg/day) should be considered, depending on the COVID-19 infectious context. Follow-up may be marked by emergence of transient hypothyroidism [22].

In practice, it is advisable to perform a thyroid function test in COVID-19 patients, particularly in those admitted to ICU, because

of the relatively high incidence of SARS-CoV-2-induced thyrotoxicosis secondary to subacute thyroiditis [18].

4. Graves' orbitopathy and SARS-CoV-2 infection

Autoimmune orbital disorders are observed in Graves' disease and Hashimoto's thyroiditis. Thyroid-associated orbitopathy is clinically significant in 30–50% of patients and impairs visual acuity in 5%. Progression of thyroid-associated orbitopathy features an inflammatory phase followed by the emergence of fibrosis with sequelae of varying severity (Rundle curve).

Patients in an inflammatory stage of orbitopathy are at greater risk of COVID-19 infection, which explains why the quarantine rules for these patients must be strictly respected. Conjunctival disorders related to SARS-CoV-2 infection may delay diagnosis of Graves' orbitopathy and expose patients to a risk of exacerbation, with eye infections and decreased visual acuity.

At the inflammatory stage and depending on the severity of the orbitopathy, the following options should be considered [25]: for mild forms, cease smoking, restore and maintain euthyroidism, and initiate oral selenium supplementation; for moderate and severe forms, initiate first-line intravenous corticosteroid therapy, or oral corticosteroid therapy although this carries a risk of side-effects (type-2 diabetes, arterial hypertension) and corticotropin insufficiency; for severe forms with decreased visual acuity, surgical orbital decompression should be discussed when intravenous corticosteroid therapy has failed. Surgery for sequelae of thyroid-associated orbitopathy may be postponed until after the COVID-19 pandemic.

Medical treatment with intravenous and oral glucocorticoids or immunosuppressive therapy with mycophenolate mofetil, azathioprine, rituximab or tocilizumab are risk factors for SARS-CoV-2 infection, and patients may develop severe forms of COVID-19 [25].

It should be noted that a recent *in vitro* study of orbital fibroblasts isolated from patients with non-inflammatory or mildly inflammatory Graves' orbitopathy evaluated chloroquine and hydroxychloroquine treatment, which have recently been discussed as potential treatments for specific infectious forms of COVID-19 [34]. This study reported dose-dependent inhibition of orbital fibroblast proliferation, adipogenesis and glycoaminoglycan production, which all contribute significantly to autoimmune orbital orbitopathy [35]. Thus, according to the authors, chloroquine and hydroxychloroquine, respecting standard contraindications and monitoring criteria, may be a treatment for Graves' orbitopathy by inhibiting orbital fibroblast autophagy.

5. Hypothyroidism and SARS-CoV-2 infection

In adults, primary hypothyroidism occurs most commonly as a result of either autoimmune thyroiditis or surgical (total thyroidectomy) or radioisotope treatment. Central hypothyroidism is much more uncommon. Epidemiological studies indicate that patients with hypothyroidism are not at increased risk of COVID-19 infection [36,37]. On the other hand, autoimmune thyroiditis may develop after the "cytokine storm" induced by SARS-CoV-2 infection, and may lead to primary hypothyroidism. Conversely, pituitary disorder during COVID-19 infection may contribute to pituitary insufficiency, resulting in thyroid and corticotropin insufficiency, requiring thyroid and corticoadrenal replacement therapy with levothyroxine and hydrocortisone [14].

Diagnostic and/or therapeutic management of hypothyroidism during SARS-CoV-2 infection does not require any other particular consideration. Treatment of pre-existing hypothyroidism should be continued during COVID-19 infection. The patient should be provided with the necessary supplies of thyroid hormones in order

to pursue treatment throughout lockdown. Levothyroxine dose should be increased by 30–50% in case of pregnancy, and should be monitored according to clinical data and TSH concentration, specifically to prevent the development of hypothyroidism.

Hydroxychloroquine treatment, alone or as part of a combined therapy [34] has been proposed as a treatment option for some COVID-19 patients. It may impair thyroxine metabolism and therefore requires TSH levels to be monitored to ensure euthyroidism is maintained [38,39].

In practice, thyroid function needs to be assessed both clinically and hormonally, in the acute phase of a SARS-CoV-2 infection and during follow-up, in order to initiate levothyroxine replacement therapy if thyroid insufficiency is detected and to discontinue replacement therapy once pituitary gland disorders, in particular, resolve during convalescence [40].

6. Conclusion

Based on the pathophysiology of SARS-CoV-2 infection in the pituitary-thyroid axis and a review of recent articles, we suggest routine assessment of thyroid function in the acute phase for COVID-19 patients requiring a high level of intensive care, as they frequently present thyrotoxicosis due to subacute thyroiditis related to SARS-CoV-2, and during convalescence in order to diagnose and adapt levothyroxine replacement treatment in patients with primary or central hypothyroidism.

Considering the ongoing COVID-19 pandemic, future prospective studies are needed to increase epidemiological and clinical knowledge and optimize the management of thyroid disorders in COVID-19 patients.

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Disclosure of interest

The author declare that they have no competing interest.

References

- [1] Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor Fedratinib. *J Microbiol Immunol Infect* 2020;53:368–70.
- [2] Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020;38:1–9.
- [3] Lania A, Sandri MT, Cellini M, Mirani M, Lavezzi E, Mazziotti G, et al. Thyrotoxicosis in patients with Covid-19: the THYRCOV study. *Eur J Endocrinol* 2020;183:381–7 [20-0335.R2].
- [4] Wang W, Ye YX, Yao H. Evaluation and observation of serum thyroid hormone and parathyroid hormone in patients with severe acute respiratory syndrome. *J Chin Antituberculous Assoc* 2003;25:232–4.
- [5] Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. *Lancet Diabetes Endocrinol* 2015;3:816–25.
- [6] Tee LY, Hajanto S, Rosario BH. COVID-19 complicated by Hashimoto's thyroiditis. *Singapore Med J* 2020;1–3.
- [7] Wei L, Sun S, Xu C-H, Zhang J, Xu Y, Zhu H, et al. Pathology of the thyroid in severe acute respiratory syndrome. *Hum Pathol* 2007;38:95–102.
- [8] Guan WJ, Ni YX, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.
- [9] Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. A pathological report of three COVID-19 cases by minimal invasive autopsies. *Zhonghua Bing Li Xue Za Zhi (Chinese J Pathol)* 2020;49:411–7.
- [10] Pal R, Banerjee M. COVID-19 and the endocrine system: exploring the unexplored. *J Endocrinol Invest* 2020;43:1027–31.
- [11] Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty* 2020;9:45.
- [12] Wei L, Sun S, Zhang J, Zhu H, Xu, Ma Q, et al. Endocrine cells of the adeno-hypophysis in severe acute respiratory syndrome (SARS). *Biochem Cell Biol* 2010;88:723–30.

- [13] Lazartigues E, Qadir MMF, Mauvais-Jarvis F. Endocrine significance of SARS-CoV-2's reliance on ACE2. *Endocrinology* 2020;161 [bqaa108].
- [14] Leow MK-S, Kwek DS-K, Ng AW-K, Ong K-C, Kaw GJ-L, Lee LS-U. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). *Clin Endocrinol* 2005;63:197–202.
- [15] Chen M, Zhou W, Xu W. Thyroid function analysis in 50 patients with COVID-19: a retrospective study. *Thyroid* 2020.
- [16] Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ* 2020;368:m1091.
- [17] World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance; 2020.
- [18] Muller I, Cannavaro D, Dazzi D, Covelli D, Mantovani G, Muscatello A, et al. SARS-CoV-2-related atypical thyroiditis. *Lancet Diabetes Endocrinol* 2020;8:739–41.
- [19] Bellastella G, Maiorino MI, Esposito K. Endocrine complications of COVID-19: what happens to the thyroid and adrenal glands? *J Endocrinol Invest* 2020;43:1169–70.
- [20] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020;75:1730–41.
- [21] Shekhar S, Wurth R, Kamilaris CDC, Eisenhofer G, Barrera FJ, Hajdenberg M, et al. Endocrine conditions and COVID-19. *Horm Metab Res* 2020;52:471–84.
- [22] Brancatella A, Ricci D, Cappellani D, Viola N, SgroD, Santini F, et al. Is subacute thyroiditis an underestimated manifestation of SARS-CoV-2 infection? Insights from a case series. *J Clin Endocrinol Metab* 2020;105:dga537.
- [23] Paunkovic N, Paunkovic J, Pavlovic O, Paunovic Z. The significant increase in incidence of Graves' disease in eastern Serbia during the civil war in the former Yugoslavia (1992 to 1995). *Thyroid* 1998;8:37–41.
- [24] Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. *Rev Endocr Metab Disord* 2020;9:1–13.
- [25] Bartalena L, Chiovato L, Marcocci C, Vitti P, Piantanida E, Tanda ML. Management of Graves' hyperthyroidism and orbitopathy in time of COVID-19 pandemic. *J Endocrinol Invest* 2020;43:1149–51.
- [26] Boelaert K, Visser WE, Taylor PN, Moran C, Léger J, Persani L. Endocrinology in the time of COVID-19: management of hyperthyroidism and hypothyroidism. *Eur J Endocrinol* 2020;183:G33–9.
- [27] Griffith ML, Bischoff LA, Baum HBA. Approach to the patient with thyrotoxicosis using telemedicine. *J Clin Endocrinol Metab* 2020;14:dga373.
- [28] Pal R, Bhadada SK. Managing common endocrine disorders amid COVID-19 pandemic. *Diabetes Metab Syndr* 2020;14:767–71.
- [29] Brancatella A, Ricci D, Viola N, SgroD, Santini F, Latrofa F. Subacute thyroiditis after Sars-CoV-2 infection. *J Clin Endocrinol Metab* 2020;105:1–4.
- [30] Desailoud R, Hober D. Viruses and thyroiditis: an update. *Virol J* 2009;6:5.
- [31] Asfuroglu Kalkan E, Ates I. A case of subacute thyroiditis associated with Covid-19 infection. *J Endocrinol Invest* 2020;43:1173–4.
- [32] Ippolito S, Dentali F, Tanda ML. SARS-CoV-2: a potential trigger for subacute thyroiditis? Insights from a case report. *J Endocrinol Invest* 2020;43:1171–2.
- [33] Ruggeri RM, Campenni A, Siracusa M, Frazzetto G, Gullo D. Subacute thyroiditis in a patient infected with SARS-CoV-2: an endocrine complication linked to the COVID-19 pandemic. *Hormones* 2020;1–3.
- [34] Lam S, Lombardi A, Ouanounou A. COVID-19: a review of the proposed pharmacological treatments. *Eur J Pharmacol* 2020;886:173451.
- [35] Guo Y, Li H, Chen X, Yang H, Guan H, He X, et al. Novel roles of chloroquine and hydroxychloroquine in Graves' orbitopathy therapy by targeting orbital fibroblasts. *J Clin Endocrinol Metab* 2020;105:1906–17.
- [36] Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region. *N Engl J Med* 2020;382:2012–22.
- [37] Dworakowska D, Grossman AB. Thyroid disease in the time of COVID-19. *Endocrine* 2020;68:471–4.
- [38] Al-Bari MAA, Islam MA. Clinically significant drug interaction profiles of chloroquine analogues with adverse consequences and risk management. *J Sci Res* 2015;7:177–95.
- [39] Munera Y, Hugues FC, Le Jeune C, Pays JF. Interaction of thyroxine sodium with antimalarial drugs. *BMJ* 1997;314:1593.
- [40] Agarwal S, Agarwal SK. Endocrine changes in SARS-CoV-2 patients and lessons from SARS-CoV. *Postgrad Med J* 2020;96:412–6.