

ENDOCRINE EFFECTS OF COVID 19: DIFFICULTIES IN THE MANAGEMENT OF ENDOCRINE DISORDERS FROM INDIVIDUAL TO SOCIETIES

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Abstract

Development of Covid-19 pandemic infection which started in December 2019 from Wuhan, China, impacted all medical specialities and societies. Endocrine professionals are involved in this battle, as far as many patients with endocrine co-morbidities (diabetes, metabolic syndrome, pituitary, thyroid, adrenal disorders) are most affected by the disease.

Specific recommendations for the management of endocrine disorders were released by European experts. Most rely on the same principles of epidemiological safety measures, delaying non emergency admissions and transforming the routine follow-up in telemedicine clinics.

Special attention is required to adrenal disorders, either central in the context of pituitary patients or primary. Corticosteroids are a mainstay of treatment in Covid-19 infection, therefore it is important to consider all aspects involved by high doses, including metabolic adverse reactions especially in diabetic patients. Other endocrine disorders, thyroid dysfunctions or nodules, parathyroid, adrenal, and pituitary diseases should follow specific recommendations for management. Surgery is postponed for non-emergency situations, restricting most planned surgeries, either thyroid, pituitary or adrenal. Laparoscopic surgery, if required in emergency, is including a supplementary risk, therefore all involved in the operating theater should wear PPE.

In conclusion, a coordinated response should be organized in the multidisciplinary management of endocrine patients.

Key words: Covid 19, SARS-CoV-2, pituitary, thyroid, adrenal, management.

INTRODUCTION

The pandemic infection with coronavirus strain SARS COV 2 involved every individual on the planet: the health professionals are in the first line of health care, from ER to ICU and operating theaters. Many switched their normal practice into virtual telemedicine

activities, with obvious impact upon time, performance, and abilities to follow up and control complex cases. Endocrinologists are among many others involved in this battle (1). This editorial expresses the different aspects related to management of most common endocrine conditions during this severe global effort.

Pituitary disorders, mainly pituitary adenomas, are complex cases considering aspects as abnormal, non-suppressible secretion, mass effects, and hypopituitarism. In normal circumstances, pituitary adenomas are detected sometimes incidentally using brain imaging. Abnormalities of pituitary function, excess or deficit, are another reason of diagnosis. Hypopituitarism, sometimes severe, could trigger hydroelectrolytic imbalance (2). Lack of full access to tertiary centers, fear of Covid 19 infection could delay diagnosis and proper treatment. Pituitary tumors have co-morbidities which could impact the management of COVID-19 infections (e.g. hypopituitarism, metabolic syndrome and cardiovascular diseases). Patients with central adrenal insufficiency infected with COVID-19 require appropriate steroid coverage (3). Excessive corticoid (endogenous in Cushing's disease or in adrenal insufficiency) could impact the progression of Covid 19 interstitial pneumonia.

The first line of pituitary adenoma treatment, except for prolactinomas, is transsphenoidal tumor resection (4). It is strongly recommended to test for COVID 19 not earlier than 48h before scheduled surgery. However, rarely pituitary adenoma surgery is required in emergency conditions, as pituitary apoplexy. Severe headache, cavernous sinus syndrome (palpebral ptosis, diplopia), visual loss and hypotension should be investigated by emergency computed tomography. If found, pituitary apoplexy should be solved by removal of necrotic hemorrhagic mass, with full PPE coverage for all persons involved.

First line medical treatment is reserved for

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macroprolactinomas, cabergoline being the first choice. However, care should be taken to avoid severe hypotension; 1 mg thrice weekly dose is advised, with imaging evaluation at 3 months interval. In acromegaly, if mass effects are not present, until surgery can be performed in a tertiary center for pituitary tumors, somatostatin analogues are a good choice. Octreotide LAR in increasing doses or Lanreotide PR or autogel are available options. Radiotherapy as well as periodic reevaluation pituitary imaging should be postponed with 6 months if possible, according to optic pathway status (2).

Hypopituitarism should be investigated on each individual axis, considering fT4, T3 and TSH, IGF1, testosterone. Cortisol and ACTH should be considered in relationship with corticosteroid treatment, since many emergency treatments schemes in infectious departments and ICU include dexamethasone. In addition, abnormal low values for FSH / LH single measurements in women after menopausal age could be relevant for expression of hypopituitarism. Pituitary patients should be informed about management of substitution treatment if they become Covid 19 positive. Blood samples could be considered in remote labs, close to patient's home, further results being evaluated by telemedicine by the treating physician.

Thyroid disorders are amongst the most common endocrine disturbances. Management of autoimmune thyroiditis, endemic goiter, but also thyroid nodules and cancer are subject to continuous research and development (5). Autoimmune thyroid dysfunctions, either hyper- or hypofunctional, could enter a high-risk group if comorbid conditions like atrial fibrillation, diabetes, obesity are associated. Lack of direct medical guidance could impact on this fragile equilibrium and subclinical disorders could become overt myxedema or hyperthyroidism. Autoimmune thyroid disorders could be associated with other autoimmune conditions, among diabetes or adrenal failure could be part of the syndrome. In Covid-19 cases, TSH could be unspecific low or suppressed, either due to additional corticosteroids or a central hypothyroidism, known to be significantly more frequent in these cases. Subacute thyroiditis is a self-limited inflammatory thyroid disease of viral or postviral origin, including SARS-CoV-2. The development of thyroiditis signs, neck pain, general symptoms, and thyroid dysfunction is not more different than viral subacute thyroiditis from other etiologies (6). However, access to medical facilities for close follow-up could be restricted due to this etiology.

Patients with hyperthyroidism, requiring antithyroid drugs, are prone to develop neutropenia/agranulocytosis. In this Covid 19 condition, such a patient would be considered highly suspect due to fever, sore throat, chills, and muscle/joint pain. Access to a specialized endocrine clinic is difficult, while directing such a vulnerable patient towards an infectious disease hospital (Covid 19 dedicated) could be a potentially life-threatening attitude. Patients with SARS COV2 in ICU could develop a low T3 syndrome, with a bad prognosis.

Thyroid cancer patients are also affected by pandemic (7). Routine evaluation, including ultrasound, functional imaging and periodic follow-up are not similar as before. Lack of access to medical facilities (FNAB, ultrasound), delays in previously planned surgery could facilitate progression of a potentially curable disease. Elective interventions and non-emergency operations are deferred (7). Large goiters, even with normal function, could increase the upper respiratory airways pressure from mild to severe in the event of association of a Covid 19 bronchopneumonia requiring intubation. Nuclear medicine procedures are also delayed, delivery of radioactive iodine for diagnosis and treatment was cancelled or postponed for both economic and isolation reasons. This condition inevitably affected the management of thyroid cancer patients.

Parathyroid disorders and calcium metabolism disturbances

Most patients with calcium disorders are not prone to develop supplementary disturbances. However, emergency conditions like severe hypercalcemia in the context of hyperparathyroidism of postsurgical hypoparathyroidism could impact the health status in a covid 19 positive case. Acute hypercalcemia should be managed similarly, irrespective of their covid 19 status. Rehydration, with low doses IV furosemide to avoid fluid overload, in addition to iv zoledronic acid or other iv bisphosphonates. Calcitonin and cinacalcet could be used as well. Flu-like symptoms following zoledronic acid administration should be carefully followed up and considered in the differential diagnosis with Covid 19. In addition, sc denosumab administration could give a better control of hypercalcemia. Acute hypocalcemia, either postsurgery or as routinely encountered in patients with severe illness and infections, should be promptly treated using calcium gluconate perfusion, associated with active vitamin D (calcitriol). Patients with lower serum calcium levels (especially ≤ 2.0 mmol/L) had worse clinical parameters, higher incidences of septic

shock and organ failure and higher mortality (8). The routine monitoring of patients with calcium metabolism alterations should be done in lab setting away from hot Covid 19 hospitals.

Adrenal disorders and steroid treatment during Covid 19

Patients with chronic adrenal insufficiency are at an increased risk of infection, which may be complicated by developing an adrenal crisis (9). Central hypoadrenal cases as well as primary adrenocortical failure are sensitive endocrine patients, in which any infection could trigger a crisis. Therefore, care should be taken to adapt substitution therapy as soon as an infection is diagnosed, Covid 19 included (10). Patients with adrenal insufficiency are at increased risk of developing Covid 19 infection and are at increased risk of complications. Therefore, all cases with adrenal failure should follow strict distancing and epidemiologic rules, in addition to constant supplies of substitution therapy. Patients are better protected at home, so they should be entitled to receive from their current practitioners' letters showing their fragile medical condition, to facilitate their working from home status. All adrenal failure cases should hold an Addison card, as advised by the European Society of Endocrinology, translated into native language.

In case of an infectious emergency with Covid 19, fever, chills, dry cough, fatigue, loss of sense of smell or taste, adrenal failure patients should increase their normal substitution therapy at 20 mg hydrocortisone every 6 h, while fludrocortisone should be considered at 0.1 mg/day. Care should be taken for hydro-electrolytes balance. In hospital setting, they should be switched to iv infusion of hydrocortisone (100 mg every 8 h), while pausing fludrocortisone. A regular monitoring schedule is advised in patients with adrenal insufficiency during Covid 19 crisis.

Adrenal tumours should be evaluated according to current guidelines. Patients with active Cushing's syndrome, especially when severe, are immune-compromised, so all epidemiological rules should be carefully applied. Adrenal surgery could be delayed, while medical treatment could be used until surgery is feasible. There are special measures required for laparoscopic surgery; PPE should be worn by all those in operating theatre, due to risk of aerosols generation. Patients are scheduled according to emergency degree: urgent surgery – as soon as possible for those in a life-threatening condition; semi-urgent condition in which a delay of 6-12 weeks would not change the prognosis;

high priority elective surgery for those who can wait for several months, and distant elective, for more than 6 months, that can be deferred until well after the epidemic is over (11).

The infectionist's perspective

Although Covid 19 could be seen as a mild viral disease in its general aspect, up to one quarter of symptomatic patients could develop severe forms. The risk factors for severe forms, as recognized since the beginning of the epidemic, are old age, male gender and comorbidities such as cardio-vascular diseases including hypertension, chronic lung diseases, diabetes mellitus and cancers (12). An important risk factor that was later added and overtook the others is obesity (13). Thus, the actual 'profile' of a severe Covid 19 patient is: an obese male patient, of any age (could be an old patient), with or without comorbidities such as those previously mentioned.

As a rule, the first week of Covid 19 disease is usually mild for every patient and the difference in evolution of its severity is visible during the second week, when the so-called 'cytokines storm' could occur (14). This represents the cut-off between the mild/medium and severe/critical forms, with the patients that lead to the severe forms being those with risk factors.

The cytokines storm involves a hyperactivity of the immune system. The mechanisms of immune defense involve inflammation (engaging defense cells and cytokines at the entry site – respiratory tract, in this case and subsequently systemic), fever (not just a consequence of local or systemic conflict, but a mechanism that boosts the immune activity) and coagulation (to block the spread of any aggressors from the entry site, by fibrin formation making mechanical barriers). In Covid 19 there is an enhancement of the last-mentioned defense mechanism – an impressive hypercoagulability state that is deleterious (15). This is the reason why anticoagulants are prescribed from the first week – prophylactic or curative doses, depending on the patient's profile.

Knowing the course of the disease and patient's risk factors, we could anticipate the 'cytokines storm' appearance and could mitigate it using low/medium doses of corticosteroids (at large scale), and/or IL6 monoclonal antibody (in a subset of patients), alongside anticoagulants.

Despite the overall beneficial effect of steroids in the 'cytokine storm', their use is not absolved of negative side-effects: along with the general rising of the susceptibility for superinfections, in specific

situations the steroids use could destabilize the patient – for example, a diabetic patient could need very high doses of insulin in order to cope with the important induced hyperglycemias.

In conclusion, some very frequent endocrine conditions – such as obesity and diabetes mellitus, and other rare endocrine diseases – as endocrine cancers, represent important risk factors for severe Covid 19 evolution and the general use of steroids in case of severe Covid 19 form could destabilize a sum of endocrine preexistent disorders. Besides these strict medical interferences between Covid 19 and the endocrine diseases, there are many other psycho-social and economic aspects that could impair the diagnosis and/or proper treatment of an endocrine pathology in the Covid 19 pandemic period.

Conflict of interest

The authors declare that they have no conflict of interest.

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