Case Series

Hyperthyroidism and Covid-19, Early or Late: A Case Series from South-West Nigeria

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Abstract:

The Coronavirus disease 2019 (COVID-19) pandemic has put the world on its toes for more than 2 years. It is caused by a novel virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Initial symptoms associated with the virus were mainly respiratory in nature but over time, varied presentations have been noted in persons infected with the disease. Research has shown that COVID-19 can cause both pulmonary and systemic inflammation, which may result in multi-organ dysfunction. The effects of COVID-19 on metabolism including glucose regulation and diabetes mellitus have been highlighted in literature and it is now known that persons with poorly controlled diabetes will most likely have a poor clinical outcome when infected with SARS-CoV-2. Biochemical abnormalities of the thyroid hormones during and post-COVID infection have been noted by some authors, however, there is scanty information available in sub-Saharan Africa. The essence of this case series is to document the experience of an endocrine facility as regards thyroid abnormalities observed in persons who presented with confirmed COVID-19 infection and COVID-19 related symptoms without confirmation by PCR.

Introduction

SARS-CoV-2 was first discovered in Wuhan, China in December 2019.[1],[2] It is an enveloped single stranded ribonucleic acid (RNA) virus that belongs to the family β coronaviruses, similar to SARS-COV and MERS (Middle East Respiratory Virus), which are also pathogenic respiratory viruses that previously infected parts of the world.[1],[3] As at October, 2022, over 620 million cases of COVID-19 have been confirmed since the outbreak of the disease, which has also accounted for more than 6 million deaths worldwide.[4] The impact of COVID-19 on the world generally has been enormous, affecting different aspects of national wellbeing, including social, economic and health framework. The disease is principally transmitted via respiratory secretions in form of droplets and also through direct contact.[1],[2] The respiratory tract appears to be the most affected system for COVID-19 with patients presenting with cough and at times shortness of breath.[1],[2],[5] However, being a novel virus, continuous studies on the disease over time have widened understanding to the extent that it could be said that the effects of COVID-19 span beyond that of the respiratory system, with hematologic, gastroenterological, renal, dermatologic, neuropsychiatric and endocrine manifestations being elucidated.[5]-[7] SARS-COV-2 gains cellular entry through the angiotensin-converting enzyme 2 (ACE2) receptor in a process that also requires the transmembrane serine protease 2 (TMPRSS2) protein.[1],[6],[8] Both ACE2 and TMPRSS2 are widely expressed in many endocrine glands, including the thyroid[6],[9],[10] and there is an interesting postulation that they are expressed in the thyroid gland at an increased level more than the lungs.[10] The prevalence of thyroid dysfunction (abnormal thyroid function tests) among patients with COVID-19 varies between 13-75%.[10],[11] New onset thyroid dysfunction in previously thyroid healthy patients diagnosed with COVID-19 (from subclinical thyroid hormone derangement to overt thyrotoxicosis due to subacute thyroiditis) and the possible negative impact of COVID-19 on patients with pre-existing thyroid diseases have been reported.[11] Some of the thyroid abnormalities may be noticed after the acute COVID-19 illness might have resolved. We hereby highlight 3 cases of patients with symptoms and diagnosis of COVID-19 who presented with thyroid abnormalities.

Case Series

Case 1 was a 54-year-old lady, 11 years post near total thyroidectomy, on Levothyroxine replacement and longstanding hypertension. She presented on account of palpitations and tiredness. She had history of a non-specific febrile illness treated as malaria and also had dry cough which was persistent, in addition to loss of taste, loss of smell and generalized body weakness.

Physical examination revealed only tachycardia; there was no goitre. COVID-19 test done was negative (febrile illness and cough had resolved prior to the test). Patient continued to feel unwell with persistent palpitations and lethargy, necessitating endocrinology review after review by other physicians. There

was no recent weight gain or weight loss and no recent change in her dose of levothyroxine.

Initial Thyroid function test (TFT): TSH- < 0.005mIU/L, Free T3- 4.1pmol/l, Free T4- 19.7pmol/L. Repeat TFT after 3 weeks showed TSH- <0.05 (0.27-4.2) mIU/L, normal Free T3 and Free T4, as shown in Table 1. Results of Electrolyte/Urea/Creatinine and Complete blood counts were normal.

TABLE 1: Results of Laboratory Investigations with their Normal Reference ranges

BLOOD	Reference range	At Presentation	Three weeks after presentation	3 months after presentation
TSH (mIU/L)	0.27-4.2	<0.005	<0.05	0.064
FT4 (pmol/L)	10.16-22	19.7	16.3	19.2
FT3 (pmol/L)	2.8-7.1	4.1	5.4	8.1
CRP (mg/l)	0-5	7.2		

TSH= Thyroid Stimulating hormone   FT4= Free thyroxine   FT3= Free triiodothyronine
CRP= C-reactive protein

Diagnostic consideration was likely Post COVID thyroiditis, as against Thyrotoxicosis factitia where both elevated Free T4 and Free T3 are seen with a suppressed TSH. Levothyroxine was initially stopped but later reduced to 50mcg daily.

Follow up TFT in 3 months revealed TSH- 0.064 mIU/L (0.270-4.20), Free T3- 8.1 pmol/L (3.9-6.7), Free T4- 19.2 pmol/L (12-22).

Patient was no longer symptomatic and was to be followed up in 6 months.

Case 2 was a 53-year-old lady, who had a febrile illness and was managed for malaria with no resolution of symptoms. She also had palpitations and screened positive for COVID-19 following poor response to antimalarials. She had recurrent episodes of tachycardia (Pulse rate 90-130 bpm) and mild elevations of blood pressure. TFT done showed elevated FT3 only: TSH- 1.505mIU/L (0.380-5.33), FT4- 15.91pmol/L (7.2-16.4), FT3- 6.08pmol/L (3.6-6.0). Patient was yet to do a repeat TFT, though her symptoms are completely resolved.

Case 3 was a 35-year-old lady, who presented with a 4-day history of high grade, intermittent fever and dry cough. There was associated palpitation, pleuritic chest pain and generalized throbbing headache. She had exertional dyspnoea and easy fatiguability but no orthopnoea or paroxysmal nocturnal dyspnoea. There was history of heat intolerance, excessive sweating, weight loss, increased thirst, hair loss, recent anterior neck swelling but no menstrual disorder. No history of seizures, altered sensorium or loss of consciousness. There was no known family history of goitre and patient was not previously diagnosed with diabetes mellitus or hypertension. She had just visited a secondary health facility prior to presentation where she was placed on oral Propranolol 20mg daily and Carbimazole 5mg daily on account of biochemical results suggesting hyperthyroidism. She had been noted to have episodes of loose stool and sore throat at presentation. Examination findings revealed a young lady with fever (T- 37.9^{0}C) and tremors, anicteric, diaphoretic. Neck examination showed a diffuse, firm, non-tender anterior neck swelling which measured 6cmx 4cm, moved with swallowing but not with tongue protrusion. There was bilateral proptosis of the eyes, periorbital edema with conjunctival injection, lid retraction but no lid lag and no ophthalmoparesis. The pulse rate was 108 b/min, blood pressure was 140/90mmHg.

Respiratory rate was 32cpm, SPO2 was 94% in room air and she had fine crepitations in the midlung zone bilaterally. The Burch-Wartofsky score was 35. The TFT done revealed TSH- 0.2 mIU/L (0.3-4.5), FT4- 42.37 pmol/L (11.46-22.14), FT3- 15.08 pmol/L (3.07-6.46). She had mild hypokalemia but the liver function and blood glucose tests were essentially normal. An assessment of severe thyrotoxicosis with community acquired pneumonia was made, to rule out COVID-19 pneumonia. The dose of Propranolol was increased to 40mg tds and Carbimazole was increased to 20mg tds. Tab Slow K was added for hypokalemia and patient also had oral azithromycin 500mg daily for 3 days. A rapid diagnostic testing for COVID-19 was positive and the COVID-19 polymerase chain reaction (PCR) also turned out positive. She felt better after commencement and intensification of antithyroid medications; cough, fever, palpitations and tachycardia subsided and patient was discharged to continue further isolation at home after spending 6 days on admission. She is to be reviewed in the outpatient clinic after 6 weeks of commencement of antithyroid medications with a repeat TFT.

Discussion

Thyroid dysfunction has been reported in up to three-quarters of patients infected with SARS-CoV-2,[10],[11] and low TSH, seen in 2 of the cases presented, appears to be the most common abnormality as reported by Chen et al in China and Khoo et al in London.[11]-[13] Also, studies have shown that the prevalence of thyroid dysfunction in COVID-19 patients is significantly higher compared to control groups (healthy controls and non-COVID-19 pneumonia patients as well). [12],[13] Correlation between thyroid dysfunction and clinical severity of COVID-19, more specifically positive correlation between the degree of the decrease in TSH levels and FT3 levels with the severity of the disease has been reported.[11],[12],[14] In contrast, a retrospective study done in Pakistan reported higher TSH values in critically-ill COVID-19 patients who required mechanical ventilation and/or intensive care than those classified as severe COVID-19, but it is notable that the study had higher percentage of critically ill patients than severe ones.[10]

The relationship between COVID-19 and the thyroid gland likely stems from the finding that both ACE2 and TMPRSS2

are widely expressed in many endocrine glands, including the thyroid,[6],[9],[10] with suggestion that they are expressed in the thyroid gland at an increased level more than the lungs.[10],[15] It may therefore imply that increased ACE2 is able to facilitate SARS-CoV-2 entry and this could portend higher harmful outcomes of COVID-19 resulting from higher infectivity.[16] SARS-CoV-2 effects on the thyroid may occur via different mechanisms, such as direct virus damage to the gland or an indirect effect on the hypothalamus–pituitary gland axis, systemic inflammation due to the secretion of cytokines and chemokines, vascular derangement and autoimmune reactions.[11],[13],[15] L-thyroxine (T4) and triiodothyronine (T3) stimulate the production of cytokines, contributing to cytokine storm, which could also result in thyroid gland inflammation.[15]

Spectrum of COVID-19 related thyroid disorders have been mentioned in some studies and this include thyrotoxicosis, hypothyroidism and non-thyroidal illness.[11],[15] These manifestations could occur through direct viral effects on the hypothalamus-pituitary-thyroid axis or indirectly via immune-inflammatory response to the virus.[11],[15] COVID-19 related thyrotoxicosis could manifest as subacute (De Quervain) thyroiditis, silent (painless) thyroiditis, atypical thyroiditis or overt thyrotoxicosis.[11],[15],[17],[18] Subacute thyroiditis is a self-limited thyroid disease caused by viral or post viral inflammatory process, that can span 3 consecutive phases: thyrotoxicosis (first few months), followed by hypothyroidism (about 3 months) and then euthyroidism.[15],[18] Though neck pain is a cardinal feature of subacute thyroiditis, this may be absent in the setting of COVID-19 due to lymphopenia with reduced formation of giant cells preventing stretching of the thyroid capsule.[15] Subacute thyroiditis could present along with manifestation of SARS-COV-2, during few days on admission, or after remission of COVID-19 and patients typically have negative TSH-Receptor antibody (TRAb) and antibody to thyroxine peroxidase (anti-TPO),[15],[18] though these were not done by any of the patients presented. However, persistent tachycardia (like 2 of the patients presented- cases 1 and 2) similar to a case reported by Mattar et al in Singapore[18] and presence of neck pain (may be mistaken for sore throat) despite clinical improvement of COVID-19 and the absence of other common cardiac causes suggest COVID-19 related subacute thyroiditis.[15],[18] Atypical thyroiditis is a form of subacute thyroiditis without neck pain and is also a possibility in case 1 presented, considering the low TSH, and it has been reported to occur in up to 15% of COVID-19 patients admitted in the intensive care unit, though more common in males than females unlike COVID-19 subacute thyroiditis.[15],[19] Contrary to subacute thyroiditis, silent thyroiditis is painless and associated with positive antibody to thyroxine peroxidase.[15] While it is not typical that a patient with near total thyroidectomy will have thyroid abnormality tending towards a thyrotoxic state as described in case 1, rare cases of thyrotoxicosis have been documented following near total thyroidectomy according to reports by Paul Gaschen et al in the USA.[20] COVID-19 could be a trigger for overt thyrotoxicosis or cause a recurrence of

Graves' disease in patients that might have previously gone into remission.[17] It seems the patient described in case 3 has an underlying Graves' disease which was not treated until she was infected with SARS-CoV-2 and became frankly symptomatic for hyperthyroidism. This is similar to cases presented by Jimenez-Blanco et al in Spain.[17] Furthermore, Muller et al in Italy reported overt thyrotoxicosis in 15% of patients admitted to the intensive care unit.[19]

COVID-19 related primary, secondary, subclinical hypothyroidism have been reported in some studies at a lesser frequency than thyrotoxicosis and there is suggestion that hypothyroidism could have negative impact on outcome of COVID-19, though at a lesser extent than thyrotoxicosis.[15] Notable is the fact that reversal of the observed hormonal changes occurred after recovery from COVID-19, thus highlighting plausible transient effects of COVID-19 on HPT axis.[15],[19]

In different acute/chronic systemic disorders, nonthyroidal Illness (NTI), also known as low T3 syndrome, which is evidenced by decreased free triiodothyronine (T3), increased reverse T3, with low-normal or decreased free thyroxine (T4) and low-normal thyrotropin (thyroid-stimulating hormone; TSH) could occur and increased risk of NTI has been reported in critical COVID-19 cases.[7],[15] None of the cases presented here has biochemical profile in keeping with NTI. NTI is assumed to be an adaptive mechanism but could turn out to be associated with poor clinical outcomes in some cases.[7],[15]

Conclusion

Viral infections could be responsible for thyroid diseases by various means, including liberation of antigens (via necrosis or apoptosis), formation of altered antigens or molecular mimicry, release of proinflammatory cytokine and chemokine secretion, induction of aberrant HLA-DR expression and Toll-Like Receptor (TLR) activation.[15],[21] The clinical resolution of symptoms and normalization of thyroid abnormality later after being infected with COVID-19 likely suggest subacute thyroiditis in some cases and this should be considered as a differential diagnosis when infected patients present with tachycardia without evidence of progression of COVID-19 illness. While routine thyroid function is not advocated in all patients with COVID-19, monitoring of thyroid function is recommended in patients with previous autoimmune thyroid disorders and in persons with persistent tachycardia after treatment and resolution of COVID-19.

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