

CASE REPORT

Severe autonomic dysfunction associated with autoimmune thyroiditis in post-COVID-19 patient

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Summary

Introduction: We present a case of Hashimoto's thyroiditis and severe autonomic dysfunction three months after the resolution of the acute phase of COVID-19 infection in a patient with no prior thyroid disease and autonomic dysfunction.

Patient Review: We discuss our patient's clinical presentation, diagnostic evaluation, and subsequent management and follow-up. The patient had previously tested positive for COVID-19. A 53-year-old female developed Hashimoto's thyroiditis with normal thyroid function and severe autonomic dysfunction. Her heart rate variability (HRV) is depressed, and her High-Frequency power (HF) is high.

Conclusion: Our findings suggest that COVID-19 could have long-term negative effects on antithyroid antibodies. Therefore, testing antithyroid antibodies should be included in the follow-up algorithm for COVID-19 survivors. Autonomic nervous system dysfunction related to COVID-19 may be reversible and early aggressive therapy is necessary. The new technique is important for the early detection of post-acute sequelae of SARS-CoV-2 infection (PASC) in the autonomic nervous system.

Keywords: COVID-19, Hashimoto's thyroiditis, autonomic dysfunction

INTRODUCTION

World Health Organization (WHO) defines post-acute sequelae of SARS-CoV-2 infection (PASC) as the development of new, continuing, or recurring symptoms 3 months after the initial SARS-CoV-2 infection, lasting at least 2 months (1,2). One of the most common long COVID entities is referred to dysautonomia which is manifested as fatigue, dizziness, syncope, dyspnea, orthostatic intolerance, nausea, vomiting, and heart palpitations (3). It has been observed that within the complex pathogenesis of SARS-CoV-2 infection, especially if there is an aberrant immune response, some autoimmune diseases could be triggered during an active infection, but also during recovery. As for the endocrine system, it has been shown that one of the most prevalent COVID-related autoimmune diseases is Hashimoto's thyroiditis (4). We present a case of severe dysautonomia and autoimmune thyroid disease following SARS-Cov-2 infection.

CASE REPORT

A 53-year-old female patient was hospitalized in February 2021 for bilateral COVID-19 pneumonia. Among the symptoms on admission, the patient reported high fever, severe weakness, headache, and shortness of breath. At the emergency room, a chest X-ray revealed bilateral pneumonia, a nasopharyngeal swab was positive for SARS-CoV-2 and her blood test revealed an inflammatory state with a marked increase in CRP (C-reactive protein) - 21 mg/L and a D-dimer within the range. She was on oxygen therapy, corticosteroids, and other symptomatic therapy. In her personal history, she reported asthma in childhood which was treated until 2016 with a Symbicort inhaler. Family history is positive for diabetes mellitus type 2, cardiovascular diseases, and colorectal carcinoma.

Three months later, due to severe fatigue accompanied by palpitations, dizziness or lightheadedness (especially when standing up), fatigue, weakness, chest pain, shortness of breath, lack of concentration, frequent headaches, trouble swallowing, and constipation, she visited a cardiologist. The cardiologist's objective finding was that the patient was conscious, oriented, compensated, and normally nourished (BMI (body mass index) 25 kg/m²). The cardiac function was described as rhythmic, with clear tones, and without murmurs. Over the lungs, there was a normal respiratory sound without accompanying findings. The liver and spleen were not palpable as enlarged, kidneys were insensitive to percussion and the lower extremities were without edema and varicose veins. The ECG (electrocardiogram) finding was normal with sinus rhythm, frequency 78/min, without changes in the T wave and ST segment.

As part of additional diagnostics, the function of the thyroid gland was evaluated because the patient had fatigue, trouble swallowing, and constipation. The level of thyroid hormones was within the physiological range (FT4 14 pmol/l FT3 5.14 pmol TSH 1.2 uIU/ml). Thyroid antibodies were elevated (Anti-TPO 114.48 IU/ml and Anti-Tg antibodies 4.14 IU/ml) which indicated autoimmune thyroid diseases. Ultrasonographically, the thyroid gland was described as hypoechogenic, with regular position and size, and with a nonhomogeneous pseudo-nodulated structure. The patient did not respond adequately to conventional hormone replacement therapy with levothyroxine. She was treated with Prednisone therapy one month after COVID-19 pneumonia. Throughout this period, she consistently took supplements including selenium, zink, magnesium, and vitamin D to support thyroid hormone metabolism. The patient had no other viral infections such as Herpes (HSV), Epstein-Barr (EBV), or influenza after COVID-19 pneumonia.

Furthermore, the patient was tested according to the protocols in the Neurocardiology Laboratory for

Table 1. Short-term heart rate variability analyses

Parameter	First value*	Second value**	Normal range
IBI (INTERBEAT INTERVAL)	791	855	785 -1160
SDNN	55	75	102 - 180
PNN 50%	6-29	15-32	>3%
RMSSD	46	39	19 - 107
TOTAL POWER	2514.1	2198.5	750 - 12000
VLF	600	1358.1	400 - 1750
LF	1344	664.1	300 - 1750
HF	557.6	163	50 - 120
LF/HF ratio	2.4	4.1	1.5 -2

*First value on the beginning **Value after 3 years IBI interbeat interval SDNN Standard deviation of NN intervals
PNN% Percentage of successive RR intervals that differ by more than 50 ms RMSSD Root mean square of successive RR interval differences VLF -very low- frequency power LF- low- frequency power HF -high- frequency power
LF/HF ratio <1,5 Parasympathetic dominance
LH/HF ratio>2 Sympathetic dominance

Table 2. Ewing battery test scoring system

	Normal Result (0)	Borderline Result (1)	Pathological Result (2)
Handgrip Test	> 16 mmHg	11-15 mmHg	< 30 mmHg
Orthostatic Hypotension	< 10 mmHg	11-29 mmHg	> 30 mmHg
Valsalva Maneuver Test	> 1.21 mmHg	1.11-1.20 mmHg	< 1.10 mmHg
Deep Breathing Test	> 15 mmHg	11-14 mmHg	< 10 mmHg
Stand Up Test	> 1.04 mmHg	1.01-1.03 mmHg	< 1.0 mmHg

accessing ANS function. The protocol included complete testing of the ANS Ewing battery tests (Ewing DJ, Clarke BF 1982.), 24-hour Holter ECG, and ambulatory blood pressure monitoring. Complete testing first included cardiovascular reflex tests, followed by short-term heart rate variability (HRV) mathematical analysis in frequency-domain and time domain (Table 1).

Ewing battery of autonomic tests consists of various analyses of heart rate variations during deep breathing (DB), lying to standing (LS), standardized Valsalva maneuver (VM), analysis of blood pressure variations on standing (PH) and sustained handgrip (SHG). The existence of autonomic dysfunction is determined by the scoring system for the group of tests that the Ewing battery consists of and 24-hour Holter ECG (Tables 2,3,4).

Table 3. Results of Ewing's cardiovascular reflex tests

Tests for accessing autonomic function	
Hand grip test	2
Median (min-max)	(0-2)
Orthostatic hypotension	0
Median (min-max)	(0-2)
Sympathetic dysfunction	1
Median (min-max)	(0-1)
Valsalva maneuver	2
Median (min-max)	(0-2)
Deep breathing test	1
Median (min-max)	(0-2)
Stand up test	2
Median (min-max)	(0-2)
Parasympathetic dysfunction	2
Median (min-max)	(0-2)
Total	7 (severe autonomic dysfunction)

A 24-hour blood pressure Holter showed that the systolic blood pressure was within the reference values in 67% of the measurements, while the diastolic pressure was in the reference values in 74%, the maximum blood pressure measured was 145/104 mmHg - detailed report

Table 4. Level of ANS dysfunction scoring system

Score	0-1	2-3	4-6	7-10
Level of ANS dysfunction	Normal Result	Mild dysfunction	Moderate dysfunction	Severe dysfunction

in the attachment. The results of ANS testing showed that the patient had severe complete autonomic dysfunction (Table 4). Short-term frequency-domain spectral analysis showed higher HF, associated with modification in parasympathetic activity. Tilt-Table Test (5,6) was positive (orthostatic hypotension). The patient had reduced HRV during a deep breathing maneuver. The LF/HF (Low Frequency/High Frequency power) ratio was high (Table 1).

Follow-up after three years indicated that the treatment provided by endocrinologists and cardiologists was effective. The function of the thyroid gland is good, function of the autonomic nervous system has improved. The level of thyroid hormones is within the physiological range (FT4 15.4 pmol/l, FT3 4.88 pmol/l, TSH 2.35 mIU/l). Thyroid antibodies are a little higher than 3 years ago (Anti-TPO antibodies 148.0 IU/ml and Anti-Tg antibodies 77.0 IU/ml) (Table 5).

Table 5. Hormonal and immunological analyses

Parameter	First value*	Second value**	Normal range
FT4	14	15.4	9.0-19.1 pmol/l
FT3	5.14	4.88	2.63-5.70 pmol/l
TSH	1.2	2.35	0.35-44.94 mIU/l
Anti-TPO	114.48	148	0.00-5.61 IU/ml
Anti-Tg	4.14	77	0.00-4.11 IU/ml

*First value on the beginning **Value after 3 years

FT4-free thyroxine

FT3-free triiodothyronine

TSH-thyroid-stimulating hormone

Anti-TPO-Thyroid peroxidase antibodies

Anti-Tg-Thyroglobulin antibodies

DISCUSSION

Globally, 6,957,216 people have died from COVID-19, with an estimated mortality rate of approximately 1% in Serbia (7, 8). However, PASC is a much greater burden for the health system. One study found that PASC led to more than 80 disability-adjusted life years, or DALYs, for every 1,000 people who weren't hospitalized for their initial infection (9). Most patients tested positive for

COVID-19 and recovered, but the latest data indicate that every fifth patient experiences a variety of mid- and long-term effects after convalescence (10). For the new treatment for PASC, it is important to consider viral persistence or reactivation of viruses. The persistence of SARS-CoV-2 RNA or antigens has been reported in some organs, but the pathogenic immune response remains unclear (11). The most common symptoms of PASC are chronic fatigue, cognitive symptoms, orthostatic hypotension, chronic pain, etc. (12). Many of these symptoms could be found in patients with autonomic dysfunction and hypothyroidism, such as our reported case.

Minnotti et al. (2024) retrieved 35 studies with data on 42,934 children, adolescents, and adults under 20, who had post-viral infection symptoms (13). These studies reported both physical and physiological symptoms, with similar symptom duration for PASC and post-EBV (gastrointestinal virus syndromes, ranging between 10 days to 18 months).

As expected, fatigue was a dominant persistent symptom of the post-EBV and PASC conditions in older children and adolescents, which likely hindered their everyday tasks and activities. However, neurocognitive symptoms such as the lack of concentration and loss of taste and smell were specific to post-COVID conditions, and even their underlying mechanics were unestablished (13). Some of the previous studies described similar cases to the one we are presenting. Some people with Hashimoto's thyroiditis have normal thyroid-stimulating hormone (TSH). The treatment for Hashimoto's disease with normal TSH usually does not involve medication. Instead, there are lifestyle changes a person can make, like getting optimal nutrition that can help them manage the diseases. The patient in our reported case consumed selenium, zinc, magnesium, and vitamin D supplements to improve thyroid hormone metabolism. Three years later thyroid function is normal but thyroid antibody is high. The patient in our reported case had severe autonomic dysfunction. She was treated with diet without gluten, lactose, and refined sugar, beta-blockers (Concor) and natural antioxidants (glutathione, coenzyme Q10), antioxidant vitamins (Vitamin C, Vit.B12, Vit D). She used NADH which plays a role in generating energy in organisms and peptan collagen which is helpful for joint, bone, and muscle health.

Agnihotri et al. presented a case of autonomic neuropathy as a PASC in a 47-year-old woman. The patient reported palpitations, hyperhidrosis, and tremulousness but in comparison to our patient, without syncopal events. Autonomic testing results indicated sympathetic vasomotor impairment but without a significant drop in blood pressure in a 10-minute head-up tilt test. During autonomic testing, tachycardia response in the second half of the tilt period could explain symptoms such as palpitations, agitation, and vertigo (14). Test results of our patient did not indicate a drop in pressure in the Tilt-up test, but other tests showed that there is a pathological response of ANS.

In a Mayo Clinic study of patients with symptoms related to postinfectious autonomic dysfunction after COVID-19, 63% were found to have abnormal findings on standardized tests of autonomic function, such as cardiovagal function, which analyzes heart rate responses to deep breathing and the Valsalva maneuver (15).

Our findings suggest that our patient had depressed HRV during the deep breathing test, indicating parasympathetic dysfunction.

Jammoul et al. investigated the possible pathophysiological mechanism of autonomic dysfunction as PASC (16). They suggested persistent inflammation, hypoxia, sympathetic overactivation due to higher release of pro-inflammatory cytokine, and tissue damage as one of the key factors involved in the pathogenesis of the disease. Imbalance of the renin-angiotensin aldosterone system, due to the binding of the SARS-Cov-2 virus to ACE-2 receptors with consequent effects on blood pressure and volume, and viral invasion of autonomic centers could also be the possible mechanisms (17).

It has been shown that virus infection in predisposed individuals could lead to the activation of some autoimmune diseases (18). Since the SARS-Cov-2 infection outbreak, many cases of endocrine autoimmune diseases have been reported during the active infection or recovery period. Feghali et al. noted several cases of autoimmune thyroid gland disease related to COVID-19. One of the patients was a 38-year-old health worker who tested positive for COVID-19 and a month later noted thyroid enlargement along with fatigue, dry skin, and depression. Laboratory tests pointed to elevated TSH, anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies, and decreased levels of thyroid gland hormones. Results from fine needle aspiration biopsy verified the diagnosis of chronic lymphocytic thyroiditis – Hashimoto's disease (4). The results of our patient are the same with the exception that the thyroid hormones are in the physiological range. However, it is not excluded that later autoimmune thyroiditis will become manifest and lead to hypothyroidism. Some people with Hashimoto's disease have normal TSH levels. In such cases, treatment usually does not involve medication. Instead, lifestyle changes, such as obtaining optimal nutrition, can help manage the disease. The patient in our case report consumed selenium, zinc, magnesium, and vitamin D supplements to improve thyroid hormone metabolism. Three years later, thyroid function is normal, but thyroid antibody levels remain high. The patient also had severe autonomic dysfunction. The patient was treated with a diet free of gluten, lactose, refined sugar, beta-blockers (Concor), natural antioxidants (glutathione, coenzyme Q10), and antioxidant vitamins (vitamin C, vitamin B12, vitamin D). She also used NADH, which plays a role in generating energy in the body, and peptan collagen, which is beneficial for joint, bone, and muscle health.

Hypothyroidism is a commonly seen endocrine disorder with a well-known pathophysiological background and a thoroughly established association with other medical disorders (19). The underlying mechanism of most of the cardiovascular and neurological manifestations of hypothyroidism could be due to autonomic dysfunction. Antony et al. investigated the connection between the hypofunction of the thyroid gland and dysautonomia. Results showed that severe autonomic dysfunction is far more common in hypothyroid individuals in comparison to euthyroid patients. About $\frac{3}{4}$ of the patients were diagnosed with sympathetic dysfunction and of $\frac{2}{3}$ individuals had parasympathetic dysfunction. No significant association between autonomic dysfunction and the duration of hypothyroidism was found (20). Since sympathovagal imbalance is associated with an increased risk of development of arrhythmias and sudden cardiac death one of the required tests is heart rate variability (HRV). Brusseau et al. (2022) investigated in their meta-analysis how hyperthyroidism influences HRV parameters (21). Their study concluded that heart rate variability is decreased in hyperthyroid patients, with increased sympathetic and decreased parasympathetic activity (21). These results could be explained by the various effects thyroxine has on the cardiovascular and autonomic systems (22). Although short-term spectral analysis showed higher, it cannot be claimed with certainty that the cause of heart rate variability is autoimmune thyroiditis, because the patient was euthyroid all the while. A worsening of symptoms can certainly be expected if thyroiditis progresses to hypothyroidism.

Ashrafi et al. (2024) found in meta-analysis a 26% prevalence of NTIS (non-thyroidal illness syndrome) and a 10% prevalence of thyrotoxicosis (23). Therefore, it can be inferred that SARS-CoV-2 can affect the thyroid either directly (via direct viral effects) or indirectly (through immune system dysregulation). It is noteworthy that some patients experiencing thyroiditis after COVID-19 experience a subclinical hypothyroidism phase about three months later (24). Furthermore, Graves' disease and Hashimoto's thyroiditis can occur several months after subacute thyroiditis, raising the possibility that viral infection may cause autoimmune thyroid disease (24).

The connection between Hashimoto's thyroiditis and dysfunction of the autonomic nervous system remains unclear.

The cerebellum plays a vital role in the regulation of the hypothalamus which is most important in the regulation of ANS. Initial brain MRI of Hashimoto's thyroiditis was normal but follow-up MRI showed diffuse cerebellar atrophy. Similar outcomes have been reported in Anti-TPO antibodies that have been shown to bind to cerebellar glial cells (25).

CONCLUSION

Our findings suggest that COVID-19 could have long-term negative effects on antithyroid antibodies. Therefore, testing antithyroid antibodies should be included in the follow-up algorithm of COVID-19 survivors. The COVID-19 dysfunction of the autonomic nervous system may be reversible, and early aggressive therapy is necessary. The new technique is important for the early detection of PASC in the autonomic nervous system.

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Authors' contribution: Conception or design of the study GM, MM; Acquisition of the data LJD, BS; Analysis or interpretation of data GM, MR, NM, TJP; Drafting of the manuscript GM, LJD, NM, BS, TJP; Critical revision of the manuscript for important intellectual content MM, MR; Final approval of the version to be submitted GM, MM, MR, LJD, NM, BS, TJP; Agreement to be accountable for all aspects of the work GM, MM, MR, LJD, NM, BS, TJP

Ethical approval: Ethical approval to report this case was obtained from the Ethics Committee of the Faculty of Medicine University of Belgrade, No. 25/V-21 (date 22.05.2024). Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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TEŠKA AUTONOMNA DISFUNKCIJA POVEZANA SA AUTOIMUNIM TIREOIDITISOM KOD POST-KOVID 19 PACIJENTA

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Sažetak

Uvod: Cilj našeg rada je prikazati slučaj Hašimoto tiroiditisa i teške autonomne disfunkcije koji su se razvili tri meseca nakon oporavka od akutne faze infekcije izazvane kovidom 19 kod 53-godišnje pacijentkinje bez prethodne istorije bolesti štitaste žlezde i autonomne disfunkcije.

Prikaz slučaja: Klinička evaluacija pokazala je očuvanu funkciju štitaste žlezde uprkos dijagnozi Hašimoto tiroiditisa, uz izraženu autonomnu disfunkciju — smanjenu varijabilnost srčane frekvencije (HRV) i povišenu komponentu visoke frekvencije (HF) u spektru snage. Diskuto-

vani su klinički tok, dijagnostički pristup i strategije lečenja, kao i praćenje pacijentkinje.

Zaključak: Naša istraživanja ukazuju na to da infekcija virusom kovid 19 može imati dugoročne negativne efekte na antitireoidna antitela. Stoga, testiranje antitireoidnih antitela treba da bude uključeno u algoritam praćenja kod osoba koje su preležale kovid 19. Disfunkcija autonomnog nervnog sistema uzrokovana kovidom 19 može biti reverzibilna, te je neophodna rana i agresivna terapija. Stoga je važno rano otkrivanje disfunkcije autonomnog nervnog sistema u PKS (post-kovid sindromu).

Ključne reči: kovid 19, Hašimoto tiroiditis, disfunkcija autonomnog nervnog sistema

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