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Case Report

Cardiovascular and mental symptoms of post-COVID-19 syndrome as a possible consequence of the bradykinin storm: A clinical case

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Abstract

Introduction: Although as of today, the hypothesis of bradykinin storm in COVID-19 cannot be directly confirmed, many theoretical assumptions and empirical data support its validity.

Aim: The purpose of this article is, using the example of a clinical case, to draw attention to the need for further study of the pathogenesis and clinical manifestations of COVID-19 and post-COVID-19 syndrome, considering the assessment of various theories, including bradykinin storm hypothesis.

Case study: We analysed the data from a young male patient with post-COVID-19 syndrome who referred to a consultant and expressed complaints of palpitation, blood pressure increase, muscle weakness, feeling of fear, hypochondria, sleep disturbances, and reduced working performance.

Results and discussion: We found a high degree of autonomic dysregulation (predominantly sympathetic hyperactivation), anxiety, and sleep disorder. There was no hypertension, though ambulatory blood pressure monitoring allowed to determine the status of non-dipper. Patient's blood tests after COVID-19 revealed a decrease in the plasma level of aldosterone, a significant increase in both homocysteine blood level and free cortisol in urine, and mild transient isolated increase in free triiodothyronine. All abnormal blood test parameters turned to normal in 3 months after the onset of COVID-19. We assume that the clinical symptoms and changes in a number of laboratory parameters of the presented case may be associated with the effects of bradykinin storm.

Conclusions: This clinical case suggests continuing the discussion about the potential role of bradykinin storm in the clinical course of COVID-19 and post-COVID-19 syndrome.

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1. INTRODUCTION

The COVID-19 pandemic has brought forth numerous concerns, significantly altering the healthcare systems in various countries. In addition to the immediate burden associated with the treatment of severe forms of this disease, there has been a growing concern about the reduction in physical and intellectual working capacity among those who have recovered from COVID-19 after the acute phase of the disease.[1] This has led to the emergence of new terms and recommendations for managing patients with subacute/ongoing COVID-19 and chronic/post-COVID-19 syndrome,[1,2] as well as the development of methods for predicting the course of COVID-19.[3]

The clinical manifestations of COVID-19 and post-COVID-19 syndrome are diverse.[1,4–11] Patients' symptoms with COVID-19 were initially thought to be linked to the cytokine storm, but the results of new research have introduced the bradykinin storm hypothesis, suggesting that the cytokine storm is a component of this concept.[12] The new bradykinin storm hypothesis received confirmation after an analysis conducted at the Oak Ridge National Laboratory, the largest research institution in the United States, which processed 17,000 genetic samples involving approximately 40,000 genes (about 2.5 billion correlation analyses in total) using one of the fastest supercomputers Oak Ridge Summit and Rhea.[12]

The current discussion regarding the changes in the activity of the renin-angiotensin system (RAS) in COVID-19 is fully consistent with the bradykinin storm hypothesis.[12–15] According to this hypothesis, the virus penetration into a cell is accompanied by increased expression of angiotensin-converting enzyme (ACE) 2 receptors with a decrease in ACE concentration in response to this counterregulatory axis overexpression as well as elevated levels of bradykinin and its active metabolite des-Arg973-bradykinin.[12] Excessive bradykinin accumulation due to the increased number of ACE2 receptors and, thus, ACE inhibition, which results in a decrease in bradykinin degradation, causes 'bradykinin storm'[13] and contributes to the appearance of symptoms driven by its effects.

2. AIM

The purpose of this publication is, using the example of a clinical case, to draw attention to the need for further study of the pathogenesis and clinical manifestations of COVID-19 and post-COVID-19 syndrome, considering the assessment of various theories, including the hypothesis of bradykinin storm.

3. CASE STUDY

We analysed the data of the white (Caucasian) male patient, 29 years old, who referred to a consultant of the Ukrainian Military Medical Academy at the National Military Medical Clinical Centre 'Main Military Clinical Hospital' in February 2021 regarding complaints of muscle weakness, a feeling of fear, hypochondria, sleep disturbances, body temperature of 36.9°C–37.2°C, reduced working performance and quality of life. However, the primary complaints that led the patient to seek medical help were palpitations, especially in an upright position, as well as during minimal physical exertion, and an increase in systolic blood pressure (SBP) to 140 mmHg, diastolic blood pressure (DBP) to 92 mm Hg (with maximum single increase of SBP up to 160 mm Hg and DBP up to 100 mm Hg).

Four months before (October 2020) the index visit, the patient experienced a laboratory-confirmed case of COVID-19 (real-time PCR) in a hospital setting. Due to unstable blood pressure with a tendency to hypertension and signs of postural orthostatic tachycardia syndrome (POTS), patient was carefully examined to exclude cardiovascular as well as endocrine pathology. All examinations at that period were performed in accordance with the routine principles of differential diagnosis.

At the moment of consultation (4 months after the disease, February 2021), his level of IgG antibodies to SARS-CoV-2 was normal (1.04, the reference value for a negative result is less than 1.3). The patient was not vaccinated against COVID-19 because such vaccines were not yet available during that period.

The selection of the patient for this publication was based on thorough dynamic examination after COVID-19 as well as data on the period preceding this disease (the patient had no harmful habits or any comorbidities before COVID-19, led a healthy lifestyle, regularly undergoing preventive check-ups).

All examinations were carried out once in the first 20 days after the onset of COVID-19; only those laboratory tests were repeated, for which abnormal values were obtained during the first assessment. The list of conducted before the index consultation examinations included:

- blood and urine tests;
- endocrine panel: adrenocorticotropic hormone, active renin, aldosterone, aldosterone-renin ratio, prolactin, testosterone, thyroid-stimulating hormone (TSH), free thyroxine (T4) and free triiodothyronine (T3), antibodies to thyroperoxidase, parathyroid hormone, total metanephrines in daily urine, cortisol in urine;
- liver markers: blood levels of alkaline phosphatase, alanine and asparagine transaminases, bilirubin, total protein;
- blood level of fasting glucose and glucose tolerance test;
- blood levels of creatinine, urea, and uric acid;
- lipid profile;
- serum vitamin D and folic acid levels;
- blood electrolytes;
- homocysteine blood level;
- ultrasound examination of the abdomen and kidneys, carotid vessels, and thyroid gland;
- magnetic resonance imaging of the kidneys;
- X-ray examination of the thoracic organs;

Table 1. Dynamics of thyroid function laboratory tests of the patient.

Parameter	October 28, 2020	December 18, 2020
TSH, μU/mL	1.48 (0.38–5.33)	2.06 (0.40–4.00)
T3, pg/mL	4.50 (2.50–3.90)	3.87 (2.30–4.20)
T4, ng/dL	1.06 (0.61–1.12)	1.29 (0.59–1.76)

Comments: all numbers are given as test result (normal range of the laboratory tests).

- ambulatory blood pressure monitoring (ABPM);
- electrocardiography (ECG);
- echocardiographic examination (EchoCG).

Holter ECG monitoring with assessment of heart rate variability (HRV) was carried out and analysed in accordance with the standard methodology using gender and age standardized indicators proposed by Umetani et al.[16]

The results of patient's physical examination did not reveal any significant deviations from the normal parameters. Thyroid ultrasound examination revealed no pathology.

According to the laboratory tests made 10–20 days after the onset of COVID-19, there was a decrease in the plasma level of aldosterone (3.27 ng/dL at normal range of 7.00–30.00 ng/dL), a significant increase in both homocysteine blood level (30.8 μmol/L, normal range of 3.7–11.0 μmol/L) and free cortisol in urine (228.9 μg / 24 h, normal range of 1.5–63.0 μg / 24 h). All these parameters turned to normal after 3 months from the onset of COVID-19. We also found a mild transient increase in free T3 blood level without pathological values of TSH and near to high blood level of normal range of free T4 (Table 1).

During Holter ECG monitoring, the average heart rate was 82 bpm (range 51–150 bpm) with 3 isolated premature atrial depolarizations identified, 52 episodes of sinus tachycardia, and a circadian index of 1.42. According to EchoCG data, the end-diastolic volume of the left ventricle (LV) was 87.7 mL (end-diastolic volume index – 45 mL/m^2), LV ejection fraction – 60%, LV stroke volume – 52.7 mL, LV myocardial mass index – 71.5 g/m^2. Regarding the cardiovascular system, there were signs of incomplete right bundle branch block according to ECG, no clear signs of stable hypertension but non-dipper state for night-time blood pressure levels (ABPM) (Figure 1). Moreover, we determined sympathetic, central, and humoral-metabolic dysregulation (HRV).

Based on the results of testing on the hospital anxiety and depression scale during index consultation, the patient was diagnosed clinically significant anxiety (12 points) with the absence of signs of depression (5 points) and a high degree of vegetative disorders on Veyn scale (31 points).

The patient was diagnosed with post-COVID-19 syndrome characterized by a high degree of autonomic dysregulation (predominantly sympathetic hyperactivation) accompanied by POTS and inappropriate sinus tachycardia, anxiety, and sleep disorder.

Recommendations for this patient encompassed a gradual increase in physical activity, avoidance of cardiac stimulants, control of consumption and, if necessary, an increase in the consumption of liquids and salt to manage POTS. Low dose of a selective β1-blocker was prescribed to address dysautonomia and sinus tachycardia symptoms. Additionally, we suggested seeking expert psychological assistance.

4. DISCUSSION

Schematically, the bradykinin storm within COVID-19 can be represented as a sequential chain of events (Figure 2).

The contradictions that exist in the literature regarding the state of the RAS in COVID-19 are closely linked to the bradykinin storm hypothesis.[14,15,17] Changes in RAS are associated with the expression of ACE2, which counterregu-

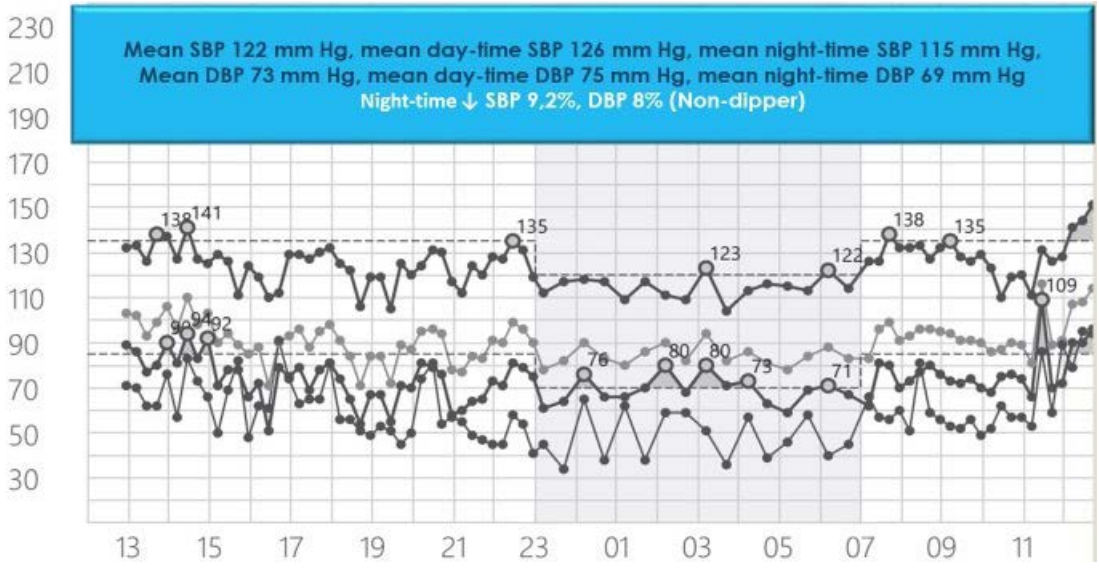

Figure 1. Ambulatory blood pressure monitoring data of the patient. Comments: SBP – systolic blood pressure; DBP – diastolic blood pressure.

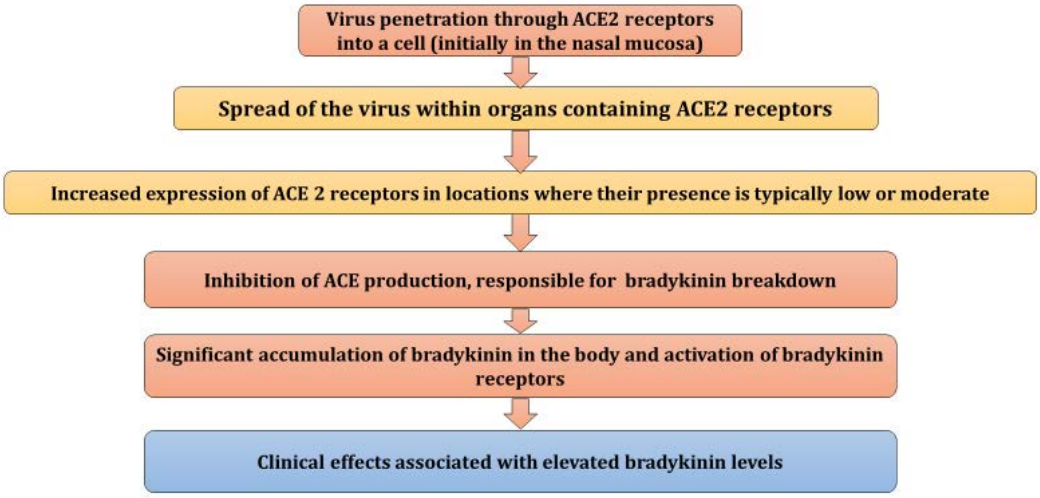

Figure 2. Bradykinin storm hypothesis.

lates ACE and is caused by SARS-CoV-2.[14,15] So, bradykinin storm and expression of ACE2 may contribute to supression of ACE and thus RAS in acute phase of the disease.[12]

Currently, it is not possible to verify the clinical state of bradykinin storm due to the lack of appropriate and clinically reproducible markers of this condition.[12] Nevertheless, in the presented clinical case, the majority of clinical symptoms and several laboratory and instrumental findings may be attributed to the impact of bradykinin (Table 2). In the case of patient, we did not observe RAS expression according to laboratory tests, and there was a decrease in the aldosterone level during the early post-COVID-19 period. This decrease may be linked to RAS disorders, thus, indirectly confirming the bradykinin storm hypothesis (the elevated bradykinin levels, coupled with increased sensitivity of bradykinin receptors, are associated with suppression of ACE activity, and subsequently impact the synthesis of angiotensin II).

Thyroid and parathyroid involvement has been described in COVID-19.[18–20] Adherents of the 'bradykinin storm' hypothesis have considered the potential involvement of this phenomenon in the development of the pathological changes within the thyroid among COVID-19 patients or those with post-COVID-19 syndrome, which has been described in numerous publications. Early experimental studies have demonstrated the effect of bradykinin on thyroid function through activation of Ca^{2+}-phosphatidylinositol cascade of human thyrocytes.[21] This activation may, to some extent, explain our finding of isolated T3 level elevation in the presented patient with post-COVID-19 syndrome. This patient showed transient fluctuations in free T3 without any increase in thyroid inflammation markers. This gives reason to consider an increase in T3 level augmentation through the lens of the known effects of bradykinin (see Table 2). Remarkably, when describing a parathyroid disease in a post-COVID-19 patient, Grigoravičius et al. analyzed TSH and T4 levels, but omitted T3 level, which is quite a common practice.[20] Consequently, our case demonstrates the need to control the entire panel of hormones that reflect thyroid function among patients with post-COVID-19 syndrome.

Table 2. Some clinical parallels of patient's symptoms and bradykinin effects.

Occurrences associated with bradykinin	General clinical appearance	Symptoms of the described patient
Inadequate vascular dilatation	Decreased blood pressure, inappropriate sinus tachycardia and POTS, weakness, fatigue, cardiac arrhythmias	Inappropriate sinus tachycardia and POTS, weakness, fatigue, cardiac arrhythmias
Effect on blood clotting	Thrombus formation	Hyperhomocysteinemia
Breach of the blood-brain barrier	The appearance of neurological symptoms and cognitive impairment	Several psychological symptoms, including muscle weakness, feeling of fear, hypochondria, sleep disturbance, anxiety
Effect on the thyroid gland	Thyroid dysfunction, hyperthyroidism	Mild thyroid dysfunction with transient T3 elevation only

We attribute the increase in urinary free cortisol level in this case to the patient's stress and anxiety, since other potential triggers were excluded during a rigorous examination. Attention should be paid to the elevated homocysteine level in this patient, since an indicator of more than 10 μmol/L is considered to be a risk factor for thrombosis[22] and a complicated course of COVID-19.[23]

Thus, the clinical symptoms and changes in laboratory parameters, which we have identified, may be associated with the consequences of bradykinin storm. No other convincing reasons for the change in these indicators were identified during a thorough examination of the patient.

5. CONCLUSIONS

(1) This clinical case suggests continuing the discussion about the potential role of bradykinin storm in the clinical course of COVID-19 and post-COVID-19 syndrome.

(2) Cardiovascular and psychological symptoms of patients after COVID-19 may be associated with dysregulation of autonomic nervous and neuroendocrine systems, and their persistence is associated with such triggers as stress, anxiety, and slight transient isolated increase in T3 blood levels.
(3) Further research is needed to improve knowledge of the pathogenesis of COVID-19 and its consequences.

Conflict of interest
None to declare.

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Ethics
Informed consent was obtained from the patient.

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