

## **Chronic post-Covid syndrome with neuro-cognitive symptoms in a patient with multiple comorbidities**

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### **Abstract:**

Chronic forms of Covid-19 represent a distinct pathology, in relation to the acute form of the disease, with a polymorphic symptomatology that persists for weeks or even months. Recent literature describes several types of post-Covid-19 syndromes, some with detectable lesion substrate, in several organs, and others without organ damage detectable by the usual methods of investigation. The present study aims to explore this form of disease which is often extremely debilitating affecting the quality of life of patients and their ability to work and in some cases being followed by permanent sequelae that require the application of special rehabilitation programs. The present case describes a patient with multiple comorbidities who, after an acute episode of Covid-19, developed a symptomatology dominated by intense physical and mental fatigue, vertigo, cognitive disorders and sleep disorders. To these were added respiratory and cardiac symptoms. The evolution was progressive in the first months, which determined the patient to request specialized consultations. On this occasion, the patient underwent laboratory tests, imaging examinations (native and contrast-enhanced brain MRI) and video-EEG. The results of these investigations led to the discovery of a de novo atheroma plaque in the cerebral arteries and a desaturation of oxygen during sleep that suggests the presence of a sleep apnea syndrome. As a result of these findings, a number of therapeutic indications have been formulated as well as recommendations for the adoption of a recovery program in order to increase the patient's quality of life, restore work capacity and reduce chronic fatigue. The case study concludes with a series of recommendations for clinical research that the authors consider necessary in order to increase the level of understanding of these chronic forms of post-Covid-19 pathology.

**Keywords:** Post-Covid, neuropsychiatric symptoms, atheromatosis, sleep apnea

### **Introduction**

An increasing number of cases of persistent symptoms in patients who have been diagnosed with COVID-19 for weeks or even months after the acute episode have been reported in the literature in the last two years (J. K. Logue et al. 2021; A. Nalbandian et al. 2021). More than 30% of individuals affected by COVID-19, and approximately 80% of patients hospitalized for COVID-19, may experience post-COVID sequelae, according to a recent systematic review and meta-analysis (F. Ceban et al. 2022). Several terms have been proposed for these cases, such as "long-COVID", "post-COVID syndrome", "chronic COVID syndrome" or "post-acute sequelae of SARS-CoV-2 infection (PASC). Recently, however, observational studies have noted the existence of several different syndromes, under the umbrella term of post-Covid, which has led to the classification of clinical cases into several categories. For example, T. Greenhalgh et al. (2020) classified the long-term clinical picture of Covid-19 into two broad categories: the post-acute form with persistent symptoms for 3-12 weeks and the chronic form with symptoms lasting more than 12 weeks.

The case study presented in this article aims to draw attention to the chronic forms of Covid-19, insufficiently studied, internationally and almost completely ignored nationally (V. A. Voicu ed. 2021; V. A. Voicu 2021). Retrospective studies that have been performed so far in other countries indicate a neurological and sometimes psychiatric impairment, even six months after the onset of acute disease (J. P. Rogers et al. 2020). These are confirmed by cross-sectional studies which show that already in the first weeks after the acute episode of the disease, significant and persistent neuro-psychological symptoms set in (K. Matsumoto et al. 2022). A recent cohort study, conducted in the United Kingdom, published by A. K. Clift et al. (2022) showed that the severe neuropsychiatric sequelae of Covid19 infection were similar to those of other severe acute respiratory infections (SARI): anxiety, depression, dementia, bipolar disorder, psychosis (A.K. Clift et al. 2022).

The following section will describe the evolution of the symptoms of a patient with a history of allergic asthma, chronic rhino-sinusitis, stage I essential hypertension (high risk), dyslipidemia and obesity (stage I), diagnosed with COVID-19 in December 2020 and which, for several months, showed an altered general condition, physical and mental fatigue of above average intensity as well as repeated episodes of vertigo when switching from clinostatism to orthostatism. The persistence of the symptoms for more than six months allows the inclusion of this case in the category of post-Covid syndromes, the chronic type. Against the background of a long-term suffering, the temporary improvement of which was followed by episodic worsening of symptoms, the patient underwent specialized examinations in several clinics and underwent laboratory investigations, imaging and electroencephalographic investigations. The following is a brief description of the evolution of the clinical picture and the medical examinations, to which the patient underwent, in the period elapsed from hospitalization, from December 2020, and up to present. The case description will be completed with a series of therapeutic recommendations aimed at reducing symptoms and increasing the patient's quality of life.

### **Description of the clinical case**

The 51-year-old patient from Bucharest, a scientific researcher by profession, was found positive for SARS Cov2 virus infection, following the administration of an RT-PCR test, in December 2020. Between December 23 and December 29, 2020 the patient received treatment at home with non-steroidal anti-inflammatory drugs (Paracetamol 500 mg). He was hospitalized, urgently, at the Clinical Hospital for Infectious Diseases "Matei Balș", being diagnosed with Covid 19. At the time of hospitalization, the following investigations were performed: 1) blood tests indicating the presence of a severe inflammatory syndrome and high blood sugar of 108 mg / dl; 2) EKG examination with normal electrical pattern; 3) CT chest (29.12.2020) with the following result: a medium severity bilateral interstitial pneumonia. During the five days of hospitalization, the patient was given the standard treatment with antivirals, non-steroidal anti-inflammatory drugs, anticoagulants and analgesics as needed. During the entire period of hospital stay, oxygen saturation ranged from 94% to 97%. The patient was given oxygen through the nasal prongs (low flow) in the first 48 hours after hospitalization.

Throughout the hospital stay, the patient continued his treatment with Symbicort 160 / 4.5 micrograms for a pre-existing lung condition (allergic asthma), cardiology treatment with Prestarium (2.5 mg / day) and Nebilet (2.5 mg / day) and prophylactic treatment with Sortis (20mg / day). After discharge, the patient continued the anti-coagulant treatment with Eliquis (2.5 mg tablets twice a day) for 30 days.

### *The evolution of the case during January-March 2021*

After being discharged from the hospital, the patient presented, for several months, a polymorphic symptomatology in which the neurological, neuro-psychiatric, respiratory and cardiac aspects dominated the clinical picture. Among the neurological symptoms the most prominent were: mental fatigue, dizziness, visual disturbances (decreased visual acuity), sleep disturbances. Neuro-psychiatric symptoms were dominated by cognitive disorders (attention deficit, concentration problems, short-term memory impairment). From the respiratory point of view, the patient presented with dyspnea at minimal exertion, unproductive cough, pain in the right hemithorax accentuated by inspiration and which sometimes reduced the expansion capacity of the thorax. From the point of view of cardiac activity, palpitations and hypertension broke out, but they responded immediately to treatment.

From a somatic point of view, it was also found that, after an initial weight loss, during the acute illness, the patient began to progressively gain weight, within five months reaching from 100 kg to 113 kg. The state of intense physical fatigue, dyspnea at minimal effort and frequent dizziness caused the patient to have a reduced mobility and to spend many hours a day in clinostatism. An abnormal increase in the sensation of hunger, associated with diurnal - and sometimes - nocturnal hyperphagia, also contributed to this weight gain. The family doctor advised the patient that he should consult a specialist at a Diabetes and Nutrition clinic. In the period immediately following his discharge from the hospital of infectious diseases, the patient was registered at the Diabetes and Metabolic Diseases Clinic in Bucharest. The diagnosis made on this occasion was Class 2 (moderate-risk) obesity, metabolic syndrome and prediabetes.

### *Immunization against Covid19 by vaccination*

The patient was vaccinated with the Pfizer BIONTech vaccine, Comirnaty (a COVID-19 mRNA vaccine with modified nucleosides) on February 22, 2021. The second dose, with the same type of vaccine, was given on March 15, 2021. The third, booster dose of vaccine was administered on October 2, 2021. From the patient's report, it appears that severe side effects have not occurred at any of the doses given.

### *Thoracic imaging examination*

The imaging examination, by performing a chest CT on 25.02.2021, indicated the following: minimal right posterior apical pahypleuritis and small bilateral axillary lymphadenopathy, the largest of 15mm / 9mm. A specialist consultation was recommended at the pneumology clinic, but the patient was not scheduled with a pulmonologist during the present study. However, he continued his treatment for asthma with Symbicort Turbuhaler 160 / 4.5 (160 micrograms / 4.5 micrograms), two puffs a day, in the morning.

### *Neurological examination*

The clinical neurological examination, performed on 20.01.2021 did not reveal anything abnormal. However, given the state of persistent mental fatigue, brain fog, and repeated episodes of vertigo, in the process of transition from clinostatism to orthostatism, the neurologist recommended to perform additional investigations of brain imaging (native brain MRI + contrast agent). The exam revealed the existence of focal supratentorial lesions with vasculo-degenerative substrate associated with moderate cerebral atrophy.

The persistence of the symptoms in the following period determined the patient to request a new neurological consultation on 17.03.2021. The reasons for the consultation were described as follows: a clinical picture that started after the SARS-Cov-2 infection in December 2020 and which consisted of fatigue, attention and concentration deficit, executive dysfunction, difficulty remembering new events, sleep disturbance and dizziness. From the personal pathological antecedents, the following can be retained: an echo vascular Doppler

examination (05.06.2020). Conclusions: average intimate thickening at the ACC level, without meeting the criteria for an atheroma plaque. The echo-Doppler examination of the cervico-cerebral arteries performed on 17.03.2021 showed the following pathological aspects: right carotid atheromatosis (small atheroma plaque at the right ACC bifurcation with a thickness of 0.15 cm). Possible interpretation: the appearance of atheroma plaque as a post-Covid sequelae. Clinical neurological examination did not indicate any other changes. Conclusions: post-Covid syndrome, cerebral micro-angiopathy, right incipient carotid atheromatosis, mixed dyslipidemia.

## Discussions

In the recent literature (Aly & Saber 2021; F. Ceban et al. 2022) a form of post-Covid has been described that is symptomatically similar to the chronic fatigue syndrome (formerly called myalgic encephalomyelitis). Apparently, the case described by us has similarities with the clinical picture of chronic fatigue with the three essential criteria (fatigue, post-exercise malaise, unrefreshing sleep) and two other common symptoms in this condition (cognitive impairment, orthostatic intolerance). On the other hand, studies that have focused on the direct or indirect effects of the virus on organs have shown that acute infection with SARS Cov2 virus causes multiple organ damage: lungs, kidneys, liver, brain, pancreas, etc. (C. Del Rio et al. 2021; B. Bowe et al. 2021). These can create conditions for long-term damage, possibly with permanent sequelae. Starting from the presence or absence of organ damage, U. Tirelli et al. (2021) proposed a classification of cases of post-Covid syndrome into two major categories: 1) the group of patients who suffered a multi-organ impairment that led to a decrease in work capacity; b) the group of patients who, although they continue to describe persistent symptoms of fatigue, exhaustion or “brain fog”, joint pain, etc., do not show organ lesions detectable by the usual methods of investigation. The important question is whether the presence of lesions in the brain, lesions of the walls of the large cerebral vessels, as a result of a de novo formation of an atheroma plaque, as well as pleuro-pulmonary lesions, discovered at the CT examination, two months after the onset of the disease, are sufficient arguments for us in order to classify the case described in the category of post-Covid syndromes with multiple organ injuries, from the first category of Tirelli et al. (2021).

In our opinion, the presence of these organ injuries is not sufficient to classify the case we studied in the first category of Tirelli et al. However, two important factors cannot be overlooked. On the one hand, it is the formation of a new atheroma plaque and, on the other hand, it is the presence of a sleep apnea syndrome accompanied by significant levels of oxygen desaturation. It has already been shown that the infection with SARS CoV 2 virus can contribute to the onset of a process of atheromatosis by several mechanisms: a) first, the virus can directly infect endothelial cells, binding to the angiotensin converting enzyme (ACE2) and causing endothelial dysfunction and renin-angiotensin system; b) in addition, excessive inflammation caused by infection (a known risk factor for atherosclerosis) can cause additional endothelial dysfunction, which in turn is pro-inflammatory, thus triggering a vicious circle. Although this association is explicable, so far there are no conclusive studies to prove it, and our case presentation can be an argument in starting a larger study.

During the EEG examination, a decrease in oxygen saturation of up to 91% during sleep was observed, even if the recording was made over a short period of only 2 hours and 26 minutes. This may indicate the presence of apnea syndrome during the sleep. Sleep apnea has been described as an independent risk factor in severe forms of Covid-19, and in these cases a higher frequency of hospitalization has been observed. Sleep apnea syndrome can exacerbate fatigue and impaired concentration. Fatigue is also a common symptom of post-Covid-19, with approximately 50% of patients experiencing severe fatigue two months after infection (C.

Huang et al. 2021). Ceban et al. (2022) for instance, recently discovered that „a third of individuals experienced persistent fatigue and over a fifth of individuals exhibited cognitive impairment 12 or more weeks following confirmed COVID-19 diagnosis” (F. Ceban et al. 2022). According to a longitudinal study, which examined the health status of Covid-19 survivors, in a recovery program, between May and October 2020, 70.8% of patients had some form of sleep apnea syndrome, much more than the prevalence in the general population (i.e. 3-7 %). Therefore, it might be useful to apply the Epworth questionnaire, a subjective test to determine the degree of drowsiness, as well as the objective investigation, by night polysomnography, to this category of patients with prolonged post-Covid-19 fatigue, especially if they show relevant risk factors for this pathology.

## Conclusions

The present study aimed to explore a form of pathology that is gradually beginning to gain international recognition. It is about those chronic forms of Covid-19 disease that present themselves, extremely variable, in the form of several syndromes whose symptomatic constellation is still being specified and whose pathophysiological substrate is still uncertain. Some chronic forms of the disease that are accompanied by multiple organ lesions have been described and on the other hand some other forms of clinical long-Covid have been described whose lesion substrate is undetectable by current means of investigation and will probably be specified following more extensive studies on the mechanisms of chronic Covid-19 disease. The case we presented, with multiple comorbidities, was included in the class without major organ damage, following the acute episode of the disease, which makes it very similar to the chronic fatigue syndrome. As we have shown above, this similarity has been more intensively studied in recent months, allowing some authors to make a series of therapeutic recommendations for the recovery of patients with post-Covid-19 syndrome, especially those with significant neuro-cognitive disorders (B.A. Sabel et al. 2021). However, it is known that there is no specific treatment for myalgic encephalomyelitis / chronic fatigue syndrome. Each of the symptoms can be alleviated by pharmacological and nopharmacological treatments depending on the particularities of the respective cases. In the present case, the hypothesis of a sleep disorder was also formulated, based on clinical data and video-EEG investigations performed.

For the treatment of sleep disorders, if the clinical picture is associated with a sleep apnea syndrome, treatment with continuous positive airway pressure (CPAP) is recommended. Sleep can also be improved by sleep hygiene measures to which medication can be added if needed (eg trazodone, clonazepam). Modafinil may be used to relieve the concentration problems described by the patient. As for orthostatic intolerance, it can be improved by proper hydration and a regular diet, to which can be added the wearing of stockings with elastic compression (M. Stahlberg et al. 2021). If these measures are not effective, fludrocortisone may be recommended. In case of weakness after minor physical or mental exertion (i.e. post-exercise malaise), it is recommended to dose the effort and guide the patient to resort to medical rehabilitation services and cognitive behavioral therapy.

We believe that, first of all, it is necessary to better inform patients about this pathology (myalgic encephalomyelitis / chronic fatigue syndrome) which can be associated with the chronic form of SARS Cov2 virus infection (F. Ceban et al. 2022). In many cases, it is misdiagnosed as anxiety, depression, or hypochondria (R. V. Woodward et al., 1995). However, the correct diagnosis can lead to a better acceptance of the condition and, later, to the development of adaptation mechanisms. Laboratory studies, brain imaging studies and clinical trials of cerebral sequelae that may lead to long-term cognitive impairment (i.e. post-Covid-19 dementia) are also needed. These forms of pathology can occur in the post-pandemic period in young people, or in adults under the age of 65, who have previously had one or more acute episodes of viral disease caused by the SARS Cov2 virus. Finally, we consider it necessary that

for this category of heterogeneous disorders with polymorphic symptoms, multidisciplinary clinics be opened with experts specialized in the early diagnosis, treatment, and rehabilitation of post-Covid-19 patients. Ideally, these institutions should be associated with universities or medical research centers that allow the application of the latest results of scientific research in an evidence-based practice.

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