

# Post COVID syndrome: a new challenge for medicine

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**Abstract.** – The huge concern raised by SARS-CoV2 pandemic about public health management and social impact is still under debate, particularly because COVID-19 may affect infected people much longer than expected from a typical air-borne viral disease. The scientific community is actually wondering about the etiopathogenesis and clinical development of this “post-COVID” complex symptomatology, very close to symptoms typically observed in chronic fatigue syndrome, so recently named as “post-acute sequelae of COVID-19 (PASC)”. This commentary tries to focus on the most recent news about this issue.

*Key Words:*

COVID-19, PASC, Post-COVID syndrome, Chronic fatigue syndrome, Diagnosis and therapy, Long COVID.

## Introduction

The coronavirus 2019 disease (COVID-19) still represents a fundamental concern for medicine. This is not solely for the huge spreading of pandemic worldwide but for the complex pathogenesis, yet not fully elucidated, which thoroughly engaged medical science in retrieving sound responses towards this challenge. A recent contribution from Carli et al<sup>1</sup>, reported that in Italy at least 55% patients in the following 60 days after early COVID-19 onset, showed 3 or more post-COVID symptoms. Scientific research<sup>2,3</sup> about the long-lasting consequences of COVID-19 is becoming a straightforward topic of interest. Noticeably, Amy Watson’s case, the woman who suffered 344 days of fever because of COVID-19, is one of the most renowned examples of long-haulers still experiencing physical pain and debilitating symptoms after COVID-19. This did not find a sound pathogenetic explanation to date. A “post-COVID

syndrome” seems to characterize these apparently anecdotal, though rapidly increasing, new sickness cases, which are rapidly enhancing in their number. The term “post-COVID”, to indicate symptoms-sequelae subsequent to COVID-19, is currently replaced with “post-acute sequelae of COVID-19” (PASC), the most complete terminology of post-acute COVID-19 syndrome<sup>4</sup>. Amy Watson<sup>5</sup> herself in Oregon (USA) led a huge crowd of patients who, being discharged from COVID-19 and testing negative to molecular swabs yet continued to show symptoms. Actually, she gathered tens of thousands of post-COVID syndrome patients globally known as “long-haul COVID fighters”. The majority of these individuals were fairly young women, 40-45 years aged, therefore quite different from the typical elderly patients with pre-existing health problems upon a developing COVID-19<sup>5</sup>. Post-COVID syndrome has started its existence in the widest way.

## ***Post-COVID Syndrome: A Concern of the Utmost Importance for Healthcare and Caregivers***

Post-COVID syndrome shows symptoms, such as severe body aches, gastro-intestinal issues, chronic fatigue, intense migraine and “brain fog”, quite perfectly recalling the ones lamented by patients suffering from chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). For this reason, CFS patients started support and alliances with PASC ones. Furthermore, in the UK, a British “long-COVID aid group” started a solidarity campaign for recognition, research and support of PASC in the country, whereas in Italy a group called “post-COVID syndrome patients”, was recently set. The idea to join post-COVID syndrome patients altogether, creating a crowded group of people sharing the same puzzling symptomatology

gy, is fundamental for physicians and research experts<sup>6</sup>. Actually, numerous attorneys, lawyers for civil rights, scientists, disease experts and therapy drug developers have also joined together creating a network called “The Long COVID Alliance” (despite the term “long COVID” is currently dis-used) to leverage their collective knowledge and resources and educate policy makers. Therefore, our understanding of how to diagnose patients and manage them is still evolving.

What is certain is that patients’ condition can be very debilitating, having a serious impact on people’s ability to support their job life and have a normal social habit<sup>7</sup>. In this perspective, the WHO has now introduced post-COVID emergency using ICDs to support the implementation of a surveillance system in order to define and describe post-COVID events.

### ***PASC (Post-COVID Syndrome) Symptomatology: Two Classifications May Be Described***

A significant number of patients following their health recovery, keeps in having highly troublesome symptoms, at least three months later the onset of COVID-19, even if repeated molecular tests no longer showing SARS-CoV2 in the swabs<sup>5</sup>. The most common symptoms are exhaustion, generalized pain, shortness of breath, cognitive impairment, inability to exercise, headaches, and sleep disruption<sup>8,9</sup>. As COVID-19 is a novel, puzzling disease, burst in China at the end of 2019, we are not endowed with any sound and efficacious information about how to manage post-COVID syndrome. Moreover, we are unable to forecast who will develop a post-COVID syndrome. What we are becoming aware of, to date, is that both development and severity do not appear to correlate with the nature and extent of symptoms during the acute phase of the SARS-CoV2 infection. Therefore, even subjects who have only been affected by mild or moderate forms of COVID-19, can exhibit a post-COVID syndrome, whereas patients who were instead affected by the disease in a severe form can return to normality about two months later. Actually, post-COVID syndrome, with the aforementioned symptoms, is yet more likely to occur in people aged over 50, i.e., individuals with co-morbidity (two or three chronic diseases) and people who had experienced severe forms of COVID-19. So, there is no orthodox definition of what is known as post-COVID syndrome or PASC, yet. A reasonable definition would come from observing the condi-

tion that afflicts anyone who has been diagnosed with SARS-CoV2, developed COVID-19 and did not come back to the previous level of health and function. After six months, they may be included under the “umbrella” of symptoms pertaining to “post-COVID syndrome” or PASC.

Fundamentally, we can characterize two cohorts of patients who have been affected by the post-COVID syndrome: a) a first group who has experienced some form of damage to lungs, heart, liver, kidneys or brain, which we do not know if permanent or if it will resolve over time. These organs may have affected their ability to work at their best, b) people who continue to experience debilitating symptoms such as exhaustion, fatigue, even after small or moderate exertion, “brain fog”, muscle and joint pain, chronic flu-like symptoms, even if there is no direct evidence of organ damage, especially for lungs. The evidence that SARS-CoV2 targets epithelia expressing the highly ubiquitous ACE2 receptors, may explain the organic-systemic involvement of post-COVID syndrome. Upon some types of infectious diseases, there is lingering illness, and they altogether probably have the same common shared pathophysiology, as observed by Anthony Komaroff<sup>9</sup>, at the Harvard Medical School, Boston, MA (USA). Interestingly, this issue regarded coronavirus infections as a whole.

When SARS was discovered by the Italian physician Carlo Urbani, who at the time was living in Vietnam and died for SARS, viral spread was initially confined into China, Taiwan, Vietnam, Hong Kong and Canada (Toronto)<sup>10,11</sup>. About 5% of people infected still had visible changes in the lungs even after 15 years and 38% showed a reduced oxygen diffusion capacity<sup>12</sup>. Chronic fatigue was observed in SARS infected people<sup>13</sup> and a study, carried out in China, reported that SARS causes long-term symptoms, which could be classified as CFS/ME<sup>14</sup>.

### ***Post-COVID Syndrome: Sharing Patterns with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)?***

Dr Antony Fauci<sup>15</sup>, Head Director of the National Institute of Allergy and Infectious Diseases at NIH in Bethesda (US), was the first scientist who reported that most people of the second group (b) had developed a clinical condition very similar to what is called as CFS/ME. This condition can also emerge following other infectious diseases, as for instance mononucleosis<sup>16</sup>, Lyme disease, influenza and SARS. One of us (UT) has been seeing personally those patients for more than 30 years, after at-

tending various meetings at the CDC in Atlanta in 1993-1994, to formulate a new classification of the Chronic Fatigue Syndrome (CFS), then published on the journal *Annals of Internal Medicine*<sup>17</sup>.

Global estimations account for about 2,000,000 people affected from CFS/ME in USA, according to the National Academy of Medicine, and roughly the same amount can be estimated in the European Union, with about 500,000 individuals in the sole Italy. CFS/ME can be severely disabling and those subjects suffering from it report significant functional disabilities. Based on current evidence, the underlying pathology of CFS/ME involves energy metabolism, nervous function and the immune response, with alterations such as impaired NK cell function, increased number of CD8+ T cells, presence of various autoantibodies, particularly targeting CNS and ANS and abnormal production of cytokines<sup>17</sup>. We know that most patients with CFS/ME stay ill for many years. A policy statement published very recently in a WHO document (WHO ISSN 1997-8003) underscored how previous experience with CFS has also raised a great concern about the financial burden of job absence caused by long-term sickness, both for human society and economics.

### ***Future Remarks: Are There Therapy Options for Post-COVID Syndrome?***

The clinical sequelae of post-COVID-19 syndrome are still emerging and are therefore to be studied in depth. It is certainly a medical issue of potential serious impact on the population that is treated for COVID-19. A treatment, developed within the Italian Society of Oxygen Ozone Therapy (SIOOT), which uses oxygen-ozone therapy for COVID-19, provided encouraging evidence also in our clinical experience with numerous patients suffering from CFS/ME<sup>18-20</sup>. Ozone may act as a master tuner of the immune response and therefore it can be useful also in treating post-COVID-19 syndrome patients<sup>19</sup>.

Despite these promising suggestions, post-COVID syndrome yet remains a pathology to be further investigated alongside its treatment, as well, and new encouraging research evidence will fuel our knowledge about COVID-19.

## **References**

- 1) Carfi A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; 324: 603-605.
- 2) Khan NM, Sarker S. A review of coronavirus 2019 (COVID-19), a life threatening disease all over the world *WCRJ* 2020; 7: 31586.
- 3) Dönmez E, Temiz G, Dülger Z, Berker Döğler BN, Acar O, Demirci NS. The effects of COVID-19 phobia on quality of life: a cross-sectional study on cancer patients. *WCRJ* 2021; 8: e1965.
- 4) Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, Cook JR, Nordvig AS, Shalev D, Sehwat TS, Ahluwalia N, Bikdeli B, Dietz D, Der-Nigoghossian C, Liyanage-Don N, Rosner GF, Bernstein EJ, Mohan S, Beckley AA, Seres DS, Choueiri TK, Uriel N, Ausiello JC, Accili D, Freedberg DE, Baldwin M, Schwartz A, Brodie D, Garcia CK, Elkind MSV, Connors JM, Bilezikian JP, Landry DW, Wan EY. Post-acute COVID-19 syndrome. *Nat Med* 2021; 27: 601-615.
- 5) Seyed Alinaghi S, Afsahi AM, Mohsseni Pour M, Behnezhad F, Salehi MA, Barzegary A, Mirzapour P, Mehraeen E, Dadras O. Late complications of COVID-19; a systematic review of current evidence. *Arch Acad Emerg Med* 2021; 9: e14.
- 6) Al-Jahdhami I, Al-Naamani K, Al-Mawali A. The post-acute COVID-19 syndrome (Long COVID). *Oman Med J* 2021; 36: e220.
- 7) CDC-Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network – United States, March-June 2020 *Weekly/July 31, 2020 / 69; 993-998*.
- 8) Iqbal A, Iqbal K, Arshad Ali S, Azim D, Farid E, Baig MD, Bin Arif T, Raza M. The COVID-19 sequelae: a cross-sectional evaluation of post-recovery symptoms and the need for rehabilitation of COVID-19 survivors. *Cureus* 2021; 13: e13080.
- 9) Komaroff AL, Bateman L. Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? *Front Med (Lausanne)* 2021; 7: 606824.
- 10) Demmler GJ, Ligon BL. Severe acute respiratory syndrome (SARS): a review of the history, epidemiology, prevention, and concerns for the future. *Semin Pediatr Infect Dis* 2003; 14: 240-244.
- 11) Bitnun A, Read S, Tellier R, Petric M, Richardson SE. Severe acute respiratory syndrome-associated coronavirus infection in Toronto children: a second look. *Pediatrics* 2009; 123: 97-101.
- 12) Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology* 2010; 15: 543-550
- 13) Lam MH, Wing YK, Yu MW, Leung CM, Ma RC, Kong AP, So WY, Fong SY, Lam SP. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. *Arch Intern Med* 2009; 169: 2142-2147
- 14) Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, Ko FW, Chan MC, Chan DP, Tong MW, Rainer TH, Ahuja AT, Cockram CS, Sung JJ. Impact of severe acute respiratory syndrome (SARS) on

- pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 2005; 60: 401-409.
- 15) Fauci AS, Touchette NA, Folkers GK. Emerging infectious diseases: a 10-year perspective from the National Institute of Allergy and Infectious Diseases. *Emerg Infect Dis* 2005; 11: 519-525.
  - 16) Jason LA, Cotler J, Islam MF, Sunnquist M, Katz BZ. Risks for developing ME/CFS in college students following infectious mononucleosis: a prospective cohort study. *Clin Infect Dis* 2020: ciaa1886. doi: 10.1093/cid/ciaa1886. Online ahead of print.
  - 17) Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *International Chronic Fatigue Syndrome Study Group. Ann Intern Med.* 1994; 121: 953-959
  - 18) Tirelli U, Cirrito C, Pavanello M. Ozone therapy is an effective therapy in chronic fatigue syndrome: result of an Italian study in 65 patients. *Ozone Therapy* Sept 2018. DOI: 10.4081/ozone.2018.7812.
  - 19) Franzini M, Valdenassi L, Ricevuti G, Chirumbolo S, Depfenhart M, Bertossi D, Tirelli U. Oxygen-ozone (O<sub>2</sub>-O<sub>3</sub>) immunoceutical therapy for patients with COVID-19. Preliminary evidence reported. *Int Immunopharmacol* 2020; 88: 106879
  - 20) Tirelli U, Cirrito C, Pavanello M, Piasentin C, Lleshi A, Taibi R. Ozone therapy in 65 patients with fibromyalgia: an effective therapy. *Eur Rev Med Pharmacol Sci* 2019; 23: 1786-1788.