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Viewpoint

Deleterious Outcomes in Long-Hauler COVID-19: The Effects of SARS-CoV-2 on the CNS in Chronic COVID Syndrome

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ABSTRACT: Amid our understanding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the mechanisms involved in the causation of acute-phase coronavirus disease (COVID-19), we have come across clinical cases that have been shown to run a protracted course of COVID-19 with complex clinical findings related to organ systems in general and the CNS in particular that deserve to be addressed in the COVID long-haulers, for which the more clinically-related term chronic COVID syndrome (CCS) has been coined recently. An in-depth understanding of the mechanism that forms the basis of CCS and neurological deficits in CCS is needed as this can help in determining the management of cases of neuro-COVID, which is emerging as a less lethal but more disabling disease state. This Viewpoint highlights this syndrome, the possible pathogenetic pathways involved, and the treatment approaches that can be taken to help manage COVID long-haulers in CCS.

KEYWORDS: *SARS-CoV-2, COVID-19, chronic COVID syndrome, long-haulers, neurological findings in COVID-19*

1. INTRODUCTION

The scientific community and healthcare professionals are faced with the dilemma of not only understanding diverse ways in which SARS-CoV-2 affects the host cells but also the capability of the virus in exerting prolonged enervating organ effects after an acute-phase SARS-CoV-2 infection in COVID-19. There have been reports from all over the world regarding patients who, after testing positive for COVID-19 and suffering the acute-phase of the disease, fail to revert to their normal daily routines and continue to exhibit symptoms.[1] This group of patients complains of an extended and complex list of signs and symptoms that had originated after the acute-phase of the disease. The syndromic picture of this group of patients has been called long-haulers, a term that had originated and has been seen to be extending into published literature during this ongoing pandemic. Though it has been suggested for long-haulers to have a better medical term like chronic COVID syndrome[2] and that staging and nomenclature[3] of COVID-19 based on the predominant organ involved are important to anticipate the complications in COVID-19, more significant is to dissect the underlying pathogenetic mechanisms that form the basis of the protracted patients affected by SARS-CoV-2. Although herein the focus is on the neurological aspects of chronic COVID syndrome, theories, research on the pathogenesis and follow-up of COVID-19 patients after the acute-phase are expected to unravel the mechanisms related to diverse organ involvement and therefore a better understanding of the long-haulers in CCS.

2. WHY DO ONLY A SUBSET OF LONG-HAULER PATIENTS EXHIBIT CHRONIC-PHASE OF COVID-19 WHILE OTHERS DO NOT?

In our encounter with SARS-CoV-2 causing COVID-19, there are more questions than answers, which is because of the novelty of the virus. In our experience with other viral epidemics that are capable of causing a chronic-phase of the disease, COVID-19 is difficult because of the diversity it exhibits in (a) evading and affecting the human immune system, (b) the tissue tropism it exhibits based on ACE2 receptor density, and (c) its capability to run amok with multiple organ and systems (Figure 1A2). The variation in viral load and a differential immune response (Figure 1) appears to be playing role in different clinical forms and phases of COVID-19.

Factors like the viral load, which may get eradicated or persist resulting from tissue budding of SARS-CoV-2, appear to be possibly playing the main role in long-haulers in CCS (Figure 1 B1). Other factors like ACE2 density in tissues, vascular permeability, coagulation, and cytokine activation cascade appear to determine an acute fatal outcome (Figure 1A2) or progression to a prolonged less lethal but more incapacitating clinical picture (Figures 1B1 and 2A). Our experience with the clinical picture that evolves in response to variable intensities of the immune response (Figure 1, top panel) has shown that the best outcome of an immune response is the one that eradicates the infection completely and makes the individual immune to future infection (Figure 1A1). Also, it is known with diverse viral infections that in the face of a qualitative or quantitative insufficient immune response, residual virus, and/or antigen load remains, and without a complete eradication, a chronic-phase does set in. A qualitative and quantitively adequate host

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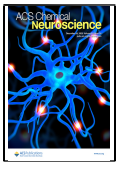

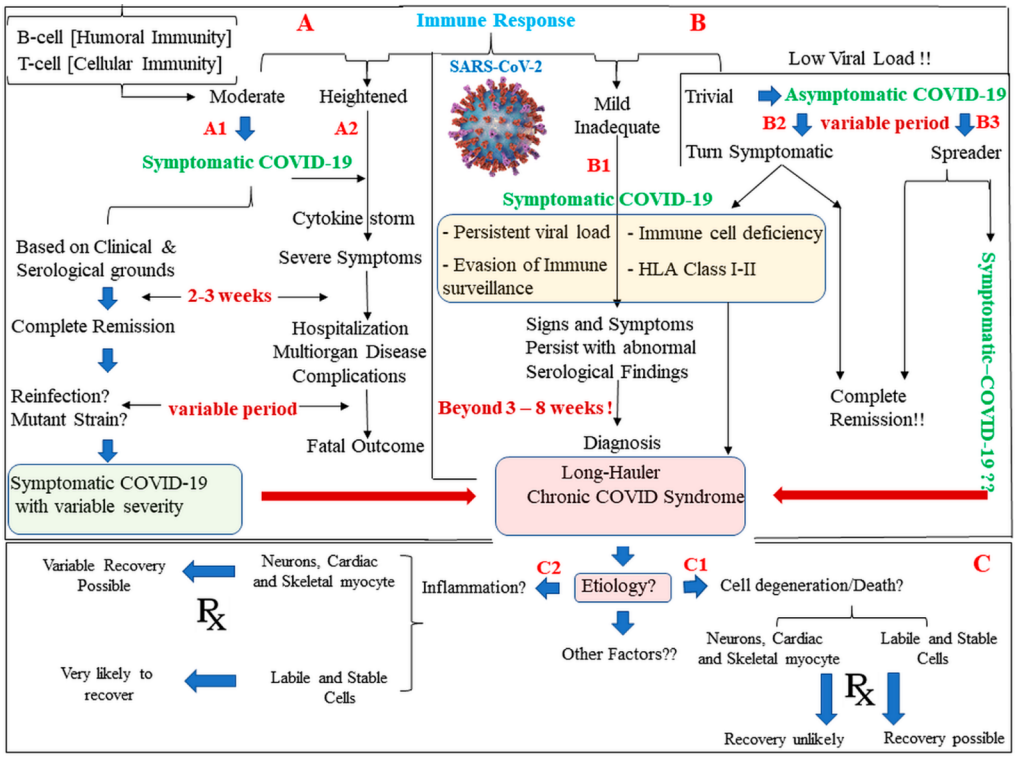

Figure 1. Humoral and cellular immune response and their sequelae in COVID-19. Variable viral load of SARS-CoV-2 coupled with a differential immune response provoke B and T cell-mediated immunity that can cause differential clinical manifestations resulting in symptomatic COVID-19 (A1), a fulminant syndromic COVID-19 with fatal outcomes (A2), a protracted course (B1) as seen in long-haulers with CCS, and asymptomatic/presymptomatic COVID-19 (B3). Note the diverse factors are hypothesized (yellow box) that can result in chronic COVID syndrome.

immune response, therefore, is the key player, and defects, diversity, or deficiencies in this element can determine a chronic-phase of COVID-19 in long-hauler CCS (Figure 2) with diverse organ complaints (Figure 2A) that persist even months[1] after the acute-phase of COVID-19 fades off. Out of curiosity, the next question would be how do we know which subsets of patients are more likely to have a susceptibility and continue into a chronic-phase in COVID-19? Human histocompatibility antigens (HLA) are known to determine a particular type of immune response (Figure 1B1) to a fixed dose of antigen, and therefore, screening the CCS patient with long-haulers for HLA subtypes is expected to resolve the mystery of why some patients are more prone to develop chronicity with COVID-19 while others are spared. A similar approach is expected to define the asymptomatic COVID-19 patients (Figure 1B3). There is also a need to have a consensus on the duration after which the diagnosis of CCS in long-haulers can be proclaimed,[2,3] which could prove to be of prognostic significance.

3. THE HYPOTHESIS OF THE PATHOGENETIC BASIS OF CHRONIC NEURO-COVID-19 SYNDROME

Much has been investigated on the pathogenetic mechanisms involved in the acute-phase of neuro-COVID in the past eight months.[1,3] Various routes of SARS-CoV-2 infection to the brain, the lobes of the brain involved, the finding of SARS-CoV-2 in the CSF, and derangements of the olfactory mucosa and bulb are a few of the many findings that surfaced after studies hinted that SARS-CoV-2 is a neurotropic virus. Not known at that time was that the findings observed in the CNS in the acute-phase of COVID-19 could extend into a prolonged symptomatic phase of neuro-COVID in long-haulers with CCS. Findings like brain fog, tremors, limb stiffness, confusion, and signs and symptoms involving cognitive functions of the brain are becoming apparent in long-haulers in CCS (Figure 2A) with multiorgan complaints.[4] The new challenge is to figure out the mechanisms involved at the molecular level that has become the basis of chronic neuro-COVID. Proposed here are some of the factors that can best explain the syndromic clinical picture of chronic neuro-COVID (Figure 2B, B1, and B2) with the rationale behind the different components of the hypothesis. Central to the concept of chronic neuro-COVID is possibly an ongoing low-grade smoldering inflammatory response to newly budding virions (Figure 2 B2) and/or degeneration of functional neuronal and glial cells (Figure 2B1) that are cardinal for the physiological function of the brain.

Vascular occlusions causing ischemia appear to be less likely contributors as they mostly have been reported to be involved in acute rather than chronic neuro-COVID. A frequently asked question that is of cardinal importance for the patient and also has been seen to puzzle the clinicians is will there be a partial or complete recovery to normal brain functioning in the near future in neuro-COVID? The answer to this question is difficult and will reside in the data collected from studies in long-term in patients with chronic neuro-COVID. One projection that can be made at this point is that if the basis of the signs and symptoms in neuro-COVID is inflammatory (Figure 2 B2), chances are there that they could improve with time. Given the very limited ability of neurons to regenerate at few sites in the brain, neuronal degeneration caused by viral budding from the infected neurons on the other hand (Figure 2 B1) is an ominous factor if it turns out to be the basis of chronic neuro-COVID in long-haulers with CCS. Neuronal loss by this mechanism can lead to a long-term

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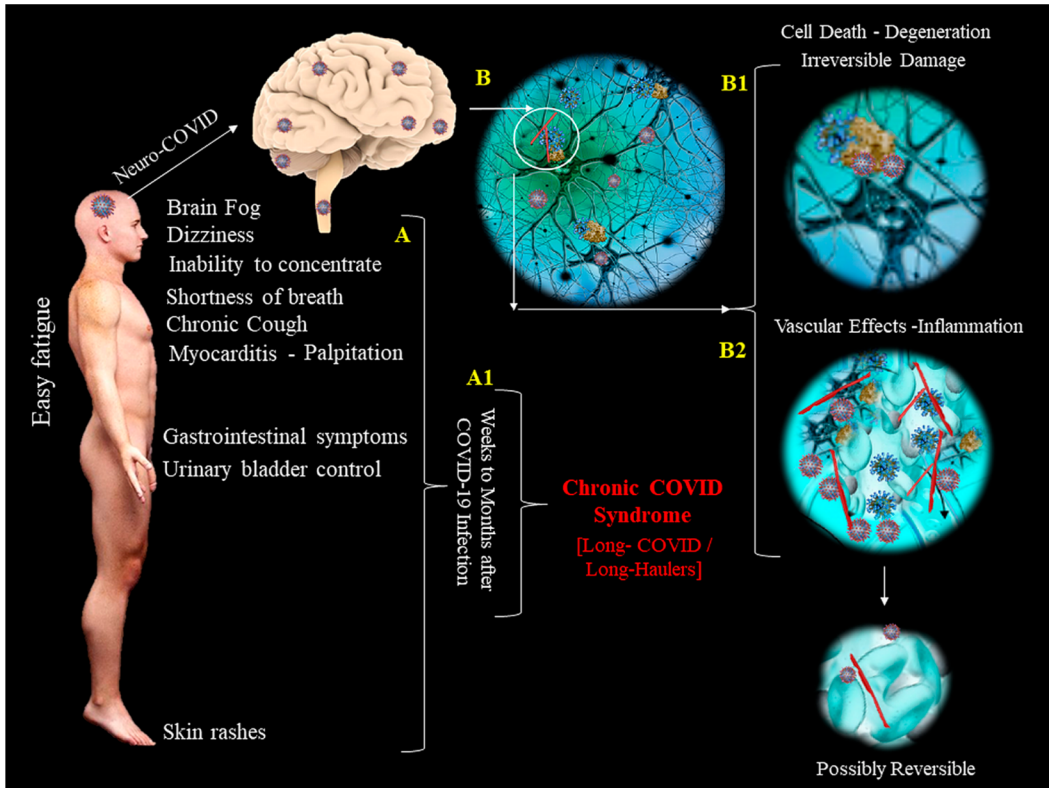

Figure 2. Chronic COVID syndrome and neuro-COVID in long-haulers. Patients who enter the chronic-phase of COVID-19 exhibit multiorgan (A) signs and symptoms. With the neurological syndrome seen in the long-haulers (first three feature in A), an underlying degeneration (B, B1) and/or a low-grade inflammation (B2) are the inferred mechanisms in neuro-COVID. The outcomes with cellular degeneration appear to be poor (B1), while with therapy (see text) the prognosis of an inflammatory cause of neuro-COVID without cell damage (B2) in effect could be better with a reversal to symptoms to normal.

deterioration in cognitive functions, and therefore, a complete recovery appears to be less likely the case.

4. POSSIBLE TREATMENT APPROACHES IN CHRONIC COVID-19 IN GENERAL AND NEURO-COVID IN PARTICULAR

Pathogenesis establishes the guideline for the treatment and management of any disease state in general. If the underlying mechanisms for neuro-COVID in CCS are known, we can outline a plan to win over the disease progression. In COVID-19, anticoagulant therapy in patients with high D-dimer levels is one example. Other examples are the management of the blood gases and blood-pH alteration seen in hospitalized COVID-19 patients. Attempts to rapidly neutralize the host cell binding S-protein of SARS-CoV-2 by infusion of monoclonal antibodies is another example where knowing the pathogenesis helps in determining treatment modalities. The long-haulers in CCS are new to the scientists and healthcare professionals, and it is expected to take some time before the underlying pathogenesis of this condition gets resolved. The hypothesis of the events occurring at molecular levels, with a plausible rationale, that possibly forms the basis of the clinical features observed in COVID-19 long-haulers in CCS in general and chronic neuro-COVID, in particular, is one of the ways forward to rule in or rule out the mechanisms involved. This approach provides us with a win−win situation, as the ruled-in hypothesis, if proven to be the case, makes the treatment regimens possible, and those that are ruled out are the ones on which we will not be wasting time researching in the future. Based on the proposed hypothesis here, if a low-grade inflammation is found to be a predominant cause, anti-inflammatory drugs that can be safely given (under supervision) for prolonged periods can be a regimen of choice in the long-haulers of CCS and patients with neuro-COVID-19. If found to be effective in clinical trials, nonsteroidal anti-inflammatory drugs and corticosteroids can be the next generation of drugs for long-haulers with CCS under clinical supervision. The untoward effects of the above drugs like gastric mucosal erosion with the former and immunosuppression and weight gain with the latter can be best managed by dose adjustments during a patient's follow-ups. The treatment of cellular degeneration, if found to be the cause of syndromic long-hauler in CCS, could turn out to be a particular problem in the organs made up of permanent cell types like cardiac/skeletal myocytes and neurons,[4] where regeneration of the native cells normally does not occur in adult life. The efficacy of cytoprotective therapy in these tissues in long-haulers remains to be established as clinical trials would be needed in long-haulers with CCS suffering cardiac and neuronal deterioration.

5. DISCUSSION AND CONCLUSION

Two things that have been learned in the past 8−10 months with SARS-CoV-2 causing COVID-19 are (a) the more time we take to understand the pathogenesis and factors related to SARS-CoV-2 spread, causation of organ injury, and mutations occurring in its genome, the more SARS-CoV-2 has turned into a die-hard virus; (b) the delays that are occurring in understanding the pathogenesis and cascade of multiorgan involvement in acute and chronic-phases of SARS-CoV-2

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infection are increasing the morbidity and mortality related to COVID-19. The rate at which the research on SARS-CoV-2 and COVID-19 has occurred in the past 10 months is a record by any standards. Even with limited access to wet laboratories and the fear of getting infected, the scientific community and healthcare professionals have been doing cutting-edge research and clinical management of COVID-19 patients to prevail over this virus. We have to remain ahead of the curve with SARS-CoV-2 if we wish to contain this virus, develop a vaccine, and outline a treatment plan to manage the affected patients. Innovative thinking, theorizing, and questioning our ideas and thoughts with critical self-reflection on the rationales we draw are the approaches needed to fight this pandemic. A few months back, no one knew that we would have a long queue of symptomatic long-haulers with CCS and this virus with a low mortality rate would prove to be disabling to previously healthy bodies and sharp minds. The long-haulers in CCS are new to us, and the best we can do is to compute the pathogenesis based on the clinical features consistently observed in long-haulers (Figure 2A). Though here chronic neuro-COVID in long-haulers is the focus, there is a need for understanding the pathogenesis related to pulmonary, cardiac, musculoskeletal, gastrointestinal, urogenital, and other organs that are involved in long-haulers seen in CCS.[3,4] Also, we need to have a consensus on the timeline on when a person with COVID-19 should be considered to have entered into the phase of chronic syndromic COVID and therefore a long-hauler state. For tissues in general, a period of 3 weeks[5] and, in some cases, a period of 3 months has been drawn to consider a disease as a chronic entity. The situation with CCS is expected to get worse with time as is evident with the scale of the current rate of spread documented with SARS-CoV-2. Even if a minority percentage of COVID-19 affected patients become victims of chronic illnesses, when calculated on a global scale the figures of long-haulers that will appear are expected to be alarming in the next few months to years. This Viewpoint stresses that we need to vigorously investigate the long-haulers clinically and with serological testings. It is needed that the funding agencies make grants available, with minimal paperwork (a major cause of delays) that can enable the scientists to research the pathogenesis of CCS in long-haulers. Long-haulers suffering syndromes like neuro-COVID are expected to cause an enormous increase in patient disability and economic burdens on the countries facing the COVID-19 pandemic.

6. FUTURE DIRECTIONS

Research niches in COVID-19 with data collection from long-haulers[4] in CCS are expected to uncover the molecular basis of the chronicity, as hinted in this Viewpoint, with the identification of other novel pathways and mechanics that form the basis of long-haulers in CCS. The open-access data on COVID-19 related research from almost all the scientific journals and the WHO policy on sharing the data are examples of how the research can be done in concert. Though already stressed above but deserves to be highlighted here again is the simplification needed in the provision of rapid funding and grants for research on this niche in particular as it will save billions of dollars that are expected to be spent on managing the affected patients in about two years from now, if the long-hauler CCS do not get the needed help in time.

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Notes

The author declares no competing financial interest.

REFERENCES

(1) Carfì, A., Bernabei, R., and Landi, F. (2020) Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. *JAMA 324* (6), 603−605.

(2) Baig, A. M. (2020) Need for an appropriate medical terminology for Long-COVID and COVID Long-Haulers. *J. Med. Virol*, DOI: 10.1002/jmv.26624.

(3) Hensley, L. (2020) *CORONAVIRUS NEWS, Experts Say COVID-19 'Long-Haulers' Need a New Name*, Verywell Health. https://www.verywellhealth.com/covid-long-haulers-need-new-name-5086429 [accessed 2020-11-10].

(4) Marshall, M. (2020) The lasting misery of coronavirus long-haulers. *Nature 585* (7825), 339−341.

(5) Kumar, V., Abbas, A. K., Aster, J. C., and Perkins, J. A. (2018) *Robbins basic pathology* (Tenth ed.), Elsevier, Philadelphia, PA.

https://dx.doi.org/10.1021/acschemneuro.0c00725
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