Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community

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Dear Sir,

The current COVID-19 pandemic has resulted in a cumulative total of over 34.8 million cases. Over 1 million deaths have now been reported globally, with the majority being reported in the region of the Americas (55%), followed by Europe (23%). Approximately 50% of cases worldwide are in the 25–64 age group (WHO situation report; accessed October 5,2020) though the majority of deaths have occurred in older persons.

Coronavirus disease-19 (COVID-19) is the disease caused by Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) and is firstly a respiratory disease. The pathobiology of COVID-19 begins with the virus targeting the angiotensin enzyme two (ACE-2) receptors which are ubiquitous throughout the body, including neural tissues. ACE-2 downregulation, as well as the recognition of the SARS-CoV-2 spike glycoproteins by the pattern recognition receptors (PPPs) on cell membranes, leads to activation of the innate immune system and local inflammation in the upper airway (or gastrointestinal system, depending on the entry point of the virus) and a generation of cytokines such as interleukin-10 (IL-10) and chemokines such as CCL4 (also known as Chemokine (C-C motif) ligands 4 as well as Macrophage inflammatory protein-1β (MIP-1β), CXCL-10 (C-X-C motif chemokine ligand 10 (CXCL10) also known as Interferon gamma-induced protein 10 (IP-10) or small-inducible cytokine B10). Neutrophils, effector T cells, monocytes and macrophages (key cells of the innate immune system) accumulate at the entry points of the SARS-CoV-2 virus resulting -in the generation of additional cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α). Viral downregulation of ACE2 receptors leads to endothelial dysfunction with associated hyperinflammation promoting further endothelial dysfunction culminating in endotheliitis not only at the entry points but also at the neuro-vascular units in the brain and other end organs. On-going hyperinflammation and endotheliitis contribute to the disruption of the blood-brain barrier, allowing entry of innate immune cells into the brain and further pro-inflammatory cytokine cascades [1,2]. The same cascade of events promotes a hypercoagulable state through thrombo-inflammation through mechanisms such as cytokine storm, endotheliitis and complement activation. At the same time, the virus itself can cause activation of the coagulation cascade. COVID-19 seems to be able to promote a hypercoagulable state through unique mechanisms and cross-talks between thrombosis and inflammation [3,4].

In view of the greater mortality among the aged, it is worth noting the presence of low-grade chronic inflammation and allready down-regulated ACE-2 levels in older individuals and those with chronic diseases such as hypertension, previous stroke, metabolic syndrome, diabetes, obesity. Such individuals are likely to suffer with a higher probability of disruption of the rennin-angiotensin-aldosterone system as well as endothelial dysfunction in the setting of COVID-19 and with even greater disruption of the blood-brain barrier as well as hyper inflammation [5]. Thus, the particular pathobiology associated with COVID-19 infection and inflammation predicts that acute and longer-term neurological manifestations are to be expected, especially in older individuals. Therefore, a better understanding of the biological development of COVID-19 and increased vigilance for any sign of neurological symptoms must become a priority for our global membership if successful acute and on-going interventions are to be achieved. In all cases, participation in translational research, including interventional clinical trials aimed at minimizing long term neurological damage will have long term benefits for the global community.

1. Post Covid-19 Neurological Syndrome (PCNS); a new syndrome with challenges and responsibilities the global neurology community

Past publications highlight that severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome coronavirus (MERS) infections culminated in a high prevalence of prolonged neurological impact [6,7]. Recent publications highlight the emerging evidence of a new syndrome- Post Covid-19 Neurological Syndrome (PCNS) with Chang and colleagues describing patients with prolonged muscle weakness and other forms of myopathy among SARS-CoV survivors in Hongkong [8]. It is also worth noting that the most delayed effects of SARS infection involve the nervous system and its associated impact on mood. A [9] study of more than 300 patients following earlier

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SARS epidemics reported active central nervous system involvement and chronic fatigue even after a period of four years from the initial infection [9].

In 2020 alone, the number of papers reporting longer-term Post COVID Neurological effects is increasing rapidly [10,11]. The neuropsychological impact of COVID-19 has been associated with varying degrees of depression, sleep impairment and anxiety, among seventy medical workers Post COVID-19 [12]. Another study on 714 COVID-19 patients in China has revealed that nearly 97% of the patients were displaying symptoms of severe post-traumatic stress disorder (PTSD) [13]. Lastly, a large study from Belgium and Netherland involving 112 hospitalized and 2001 non-hospitalized COVID-19 positive patients have noted that even among a large number of asymptomatic or very mildly symptomatic patients, prolonged symptoms such as muscle pain, dizziness, headaches, fatigue, and anosmia continued to experience for months, highlighting the need for on-going vigilance for PCNS by neurologists [18].

2. Conclusion

Currently, as we are still experiencing the pandemic and its effects, it is too early to describe the full clinical picture of PCNS. However, we believe published evidence has already made an undeniable case for medicine to recognize the increasing numbers of ex-patients with Post COVID Neurological Syndrome (PCNS) and the need for on-going neurological and cognitive/affective monitoring of all cases of COVID-19 (irrespective of the severity from asymptomatic, mild to severe) for PCNS. Special attention to the peripheral blood markers of inflammation such as neutrophil-lymphocyte ratio, C-Reactive protein, D-dimer, serum ferritin would appear to be warranted [14,15].

Global clinical registries with a meticulous systems-based approach to the assessment, management and reporting of post-COVID patients will aid in the exploration of the key clinical features of COVID-19 disease and any consequential PCNS as well as the efficacy of potential interventions in the coming months [16,17].

References

[1] S. Najjar, A. Najjar, D.J. Chong, B.K. Pramanik, C. Kirsch, R.I. Kuzniecky, et al., Central nervous system complications associated with SARS-CoV-2 infection: integrative concepts of pathophysiology and case reports, J. Neuroinflammation 17 (1) (2020) 231.

[2] South K, McCulloch L, McColl BW, Elkind MS, Allan SM, Smith CJ. Preceding infection and risk of stroke: an old concept revived by the COVID-19 pandemic. Int. J. Stroke.0(0):(1747493020943815).

[3] T. Wang, R. Chen, C. Liu, W. Liang, W. Guan, R. Tang, et al., Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19, Lancet Haematol. 7 (5) (2020) e362–e363.

[4] M. Ranucci, A. Ballotta, U. Di Dedda, E. Bayshnikova, M. Dei Poli, M. Resta, et al., The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome, J. Thromb. Haemost. 18 (7) (2020) 1747–1751.

[5] P. Verdecchia, C. Cavallini, A. Spanevello, F. Angeli, The pivotal link between ACE2 deficiency and SARS-CoV-2 infection, Eur. J. Int. Med. 76 (2020) 14–20.

[6] K.S. Hong, K.H. Lee, J.H. Chung, K.C. Shin, E.Y. Choi, H.J. Jin, et al., Clinical features and outcomes of 98 patients hospitalized with SARS-CoV-2 infection in Daegu, South Korea: a brief descriptive study, Yonsei Med. J. 61 (5) (2020) 431–437.

[7] S.M. Lee, W.S. Kang, A.-R. Cho, T. Kim, J.K. Park, Psychological impact of the 2015 MERS outbreak on hospital workers and quarantined hemodialysis patients, Compr. Psychiatry 87 (2018) 123–127.

[8] K. Chan, J. Zheng, Y. Mok, Y. Li, Y.-N. Liu, C. Chu, et al., SARS: prognosis, outcome and sequelae, Respirology 8 (s1) (2003) S36–S40.

[9] M.H. Lam, Y.K. Wing, M.W. Yu, C.M. Leung, R.C. Ma, A.P. Kong, et al., Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up, Arch. Int. Med. 169 (22) (2009) 2142–2147.

[10] P.J. Serrano-Castro, G. Estivill-Torrús, P. Cabezudo-García, J.A. Reyes-Bueno, N. Ciano Petersen, M.J. Aguilar-Castillo, et al., Impact of SARS-CoV-2 infection on neurodegenerative and neuropsychiatric diseases: a delayed pandemic? Neurología (English Edition) 35 (4) (2020) 245–251.

[11] M.T. Heneka, D. Golenbock, E. Latz, D. Morgan, R. Brown, Immediate and long-term consequences of COVID-19 infections for the development of neurological disease, Alzheimers Res. Ther. 12 (1) (2020) 69.

[12] Z.Q. Mei Junhua, Gong Xue, Li Lijuan, Zhang Zhongwen, Wang Jing, Chen Guohua, Wang Junli, Xu Jinmei, Shao Wei, Analysis of psychological and sleep state of medical stuff with novel coronavirus pneumonia, Herald Med. 39 (3) (2020) 345–349.

[13] H.-X. Bo, W. Li, Y. Yang, Y. Wang, Q. Zhang, T. Cheung, et al., Post-traumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China, Psychol. Med. (2020) 1–2.

[14] T. Wijeratne, C. Sales, S.G. Crewther, et al., First Australian case of good recovery of a COVID-19 patient with severe neurological symptoms post prolonged hospitalization, Cureus 12 (9) (September 10, 2020) 10366–10377, https://doi.org/10.7759/cureus.10366.

[15] T. Wijeratne, C. Sales, L. Karimi, S.G. Crewther, Acute ischemic stroke in COVID-19: a case-based systematic review, Front. Neurol. 11 (2020) (1031).

[16] G. Anderson, R.J. Reiter, Melatonin: roles in influenza, Covid-19, and other viral infections, Rev. Med. Virol. 30 (3) (2020), e2109.

[17] I.G. Garcia, M. Rodriguez-Rubio, A.R. Mariblanca, L.M. de Soto, L.D. Garcia, J. M. Villatoro, et al., A randomized multicenter clinical trial to evaluate the efficacy of melatonin in the prophylaxis of SARS-CoV-2 infection in high-risk contacts (MeCOVID Trial): a structured summary of a study protocol for a randomized controlled trial, Trials 21 (1) (2020) 466.

[18] Y.M. Goërtz, M. Van Herck, J.M. Delbressine, A.W. Vaes, R. Meys, F.V. Machado, et al., Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ Open Res. (2020).

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