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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Letter to the Editor

Delirium and sleep disturbances in COVID−19: a possible role for melatonin in hospitalized patients?

Impaired consciousness ranging from somnolence to confusion, delirium, stupor and coma has been reported in almost 15% of hospitalized patients with Coronavirus Disease 2019 (COVID−19) [1]. These disturbances might depend on a direct effect of the SARS-CoV-2, but also on well-known precipitating factors such as prolonged hospitalization, pain, constipation, urinary retention and a broad range of metabolic abnormalities that occur during the course of a severe infection. Delirium has previously been estimated to occur in up to 50% of hospitalized elderly patients and 80% of critically ill patients who receive mechanical ventilation [2], and reported rates are likely to rise by the end of this ongoing pandemic. Although pathogenetic mechanisms of delirium are poorly understood, crucial contributing roles have been hypothesized for neurotransmitter imbalance, proinflammatory cytokines, tissue hypoxia and sleep deprivation.

Sleep deprivation is a modifiable risk factor but also a consequence of delirium itself. Administration of Melatonin or Melatonin Receptor Agonists (MRA) has been robustly associated with a shortened Intensive Care Unit (ICU) stay, reduced prevalence of delirium and improved sleep quality [3]. Given its safety, Melatonin should be considered a first−line agent to address sleep−wake rhythm and consciousness disturbances to minimize administration of molecules that can worsen delirium in the elderly or central respiratory depression such as benzodiazepines or antipsychotics.

It is noteworthy that, based on its anti-inflammatory, antioxidative and immune-enhancing features, a putative effect of melatonin in alleviating infection-induced acute respiratory distress has also been proposed [4]. In animal models, this natural hormone has been shown to improve acute lung injury by acting as a direct antioxidant and via melatonin receptor activation. The protective effect of Ramelteon (an MRA) against ventilator−induced lung injury, has recently been shown to depend on the upregulation of Interleukin (IL-10) in rats [5].

Melatonin's safety in doses up to 10 mg has been shown to be very high in ICU patients and should be used in the prevention and treatment of sleep disturbances and delirium in COVID−19. Although specific studies are needed, higher doses might also reduce the impact of the cytokine storm that is emerging as immunopathological pathway in a subgroup of patients with worse prognosis.

Conflict of interest

None declared.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.04.006.

References

[1] Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020. https://doi.org/10.1001/jamaneurol.2020.1127. Published online April 10.

[2] Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ 2015 Jun 03;350:h2538.

[3] Zhang Q, Gao F, Zhang S, et al. Prophylactic use of exogenous melatonin and melatonin receptor agonists to improve sleep and delirium in the intensive care units: a systematic review and meta-analysis of randomized controlled trials. Sleep Breath 2019;23(4):1059−70. https://doi.org/10.1007/s11325-019-01831-5.

[4] Wu GC, Peng CK, Liao WI, et al. Melatonin receptor agonist protects against acute lung injury induced by ventilator through up-regulation of IL-10 production. Respir Res 2020;21(1):65. https://doi.org/10.1186/s12931-020-1325-2.

[5] Zhang R, Wang X, Ni L, et al. COVID-19: melatonin as a potential adjuvant treatment. Life Sci 2020;250:117583. https://doi.org/10.1016/j.lfs.2020.117583 [Epub ahead of print].

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