

Melatonin at the crossroads: Commentary on COVID and cognition

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Abstract

In this commentary, we explore the frontier edge of the emerging potential role of the chronobiotic agent melatonin, in both the prevention and treatment, and in the amelioration of some of the newly identified pathological neurocognitive sequelae, of SARS-2-CoV infection (COVID-19 disease). In the process we review clinical evidence of benefit in these domains, suggesting the strong promise that melatonin appears to provide, with a highly favorable benefit/harm ratio of excellent tolerability, affordability and safety, and sufficiently compelling evidence of efficacy as to be actionable, in the here and now.

Melatonin in SARS-2-CoV (COVID-19) disease

The ubiquitous pineal indolamine molecule melatonin is a chronobiotic, playing a critical role in the regulation of the human circadian rhythm, and exhibiting pleiotropic activity via its well-established anti-inflammatory, antioxidant and free radical scavenger, antiapoptotic, and immunomodulatory properties, with potential cytoprotective, neuroprotective, nephroprotective, cardioprotective, anti-hypertensive, anti-nociceptive, and antiviral effects consequent to immunomodulation, with emerging evidence of benefit in neurocognitive disorders [1,2], these latter two capabilities we discuss more fully below.

Given the epidemiologic observation of high levels of melatonin in children and the significant decline with advanced age that may in part contribute to the vulnerability and high lethality of SARS-2-CoV (COVID-19) infections in the elderly [3] in conjunction with modest impact in exposed children who exhibit appreciable relative resistance, and from the observation of its potential in recent previous Ebolavirus Disease (EVD) outbreaks starting in 2013 to limit or counter oxidative stress and immuno-inflammatory injury [4-8], there has been a strong burst of interest and research in the deployment of melatonin for the prevention and treatment of COVID-19 disease. This is motivated by its spectrum of established antiviral activities consequent to its suppression of multiple inflammatory pathways [9] and its strong immunostimulatory activity through production of multiple interleukins (IL-1/2/6/12), and of interferon γ (IFN- γ), cytotoxic T cells, and B- and T-cell precursors among others, especially relevant against a disease COVID-19 whose pathophysiological hallmarks include excessive inflammation, oxidation, and an hyper-exaggerated immune response that can culminate in a "cytokine storm" and can progress to and trigger acute lung injury (ALI) / acute respiratory distress syndrome (ARDS) and multiple organ failures, such progression not infrequently proving fatal [10].

Melatonin's antiviral activities via the suppression of inflammatory pathways [9] is of special interest given the known pathophysiological lung characteristics of severe COVID-19 patients. Melatonin's mechanism of action may also help to explain the epidemiologic observation that children, who have naturally high melatonin levels, are

relatively resistant to COVID-19 disease manifestations, whereas older individuals, who have decreasing melatonin levels with age, are a very high-risk population. In addition, exogenous melatonin administration / supplementation may be of particular benefit to older patients given the aging-related reduction of endogenous melatonin levels and the vulnerability of older individuals to the high lethality of SARS-CoV-2 [10].

In terms of clinical studies, based on these considerations a potential therapeutic regimen has been hypothesized for COVID-19 patients, 3 - 10 mg for elderly and high-risk patients, escalated up to 40 mg for health care workers, administered 30 to 60 min pre-bedtime [11], in substantial agreement with UT Texas San Antonio researchers in collaboration with CIBER de enfermedades CardioVasculares (CIBERCV) (Madrid). In addition, a retrospective descriptive case series at Manila Doctors Hospital (Manila, Philippines) of patients admitted with COVID19 pneumonia treated with high-dose melatonin at doses of 36-72mg/day in 4 divided doses as adjuvant therapy [12] found clinical stabilization and/or improvement within 4-5 days after initiation of high-dose melatonin in all patients treated with it, all surviving, (including 3 with moderately severe ARDS, 1 with mild ARDS), and with none requiring mechanical ventilation. The only adverse event was sleepiness which patients deemed favorable. This small (n=10) case series suggests that melatonin may provide shorter time to clinical improvement, reduced need for mechanical ventilation, shorter hospital stay and possibly lower mortality. And a recent single-center, double-blind, randomized clinical trial of patients hospitalized with confirmed mild to moderate COVID-19 found that those who received standard of care plus melatonin dosed at 3 mg three times daily for 14 days, when compared to the control group without melatonin, had significantly improved clinical symptoms (cough, dyspnea, and fatigue), more optimal levels of C-reactive protein (CRP), and reduced

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pulmonary involvement, and with significantly shorter mean time of hospital discharge and return to baseline health [13].

Melatonin - neurocognitive impact and issues

Although we must grant that our knowledge of melatonin's complex kinetics and dynamics continues to evolve [14], nonetheless there is wide consensus on core functional, operational and molecular principles including those relating to neurocognitive activity, and given that melatonin binds to and exerts its biological / physiological activities through the high-affinity G protein-coupled membrane receptors MT1 and MT2 expressed throughout the body, including in the central nervous system, and its biosynthesis is predominantly via the suprachiasmatic nucleus (SCN) with the limiting synthesis enzyme being the arylalkylamine N-acetyl transferase (AANAT) [15,16], there has been intense interest in melatonin's neurological mechanisms and potential benefits. In addition, melatonin synthesis is in part modulated by the brain renin-angiotensin system (RAS) that is critical in blood pressure regulation and in several cardiovascular disorders and in the pathogenesis of pulmonary diseases, and which is also implicated in the complex pathologies of acute respiratory distress syndrome (ARDS) seen in COVID-19 disease, part of which can be countered via angiotensin converting enzyme (ACE) 2 (ACE2) activity that may attenuate inflammation [17]. We note in this connection that there have been questions raised as to the potentially adverse impact on the susceptibility to and severity of SARS-CoV-2 infection of ACE inhibitors (ACEIs) and AT1R blockers (ARBs) that are deployed in both pulmonary inflammatory and cardiovascular diseases, but more recent robust meta-analytic data fail to support this [18,19] although there is some suggestion there may be some geographic dependencies as to benefits versus harms [20].

In parallel, there is thus a growing literature documenting the potentially long-term neurocognitive sequelae / impairment that may be engendered by the neuroinflammatory cascade associated with COVID-19 [21-25] and in confirmation, recent postmortem findings have shown SARS-CoV-2 virus in neural tissue: in the cerebrospinal fluid (CSF) and in parts of the brain's frontal lobe [26-28].

Noting these potentially negative neurocognitive impacts of acute respiratory distress (ARD) and hypoxia, and especially the hyper-elevated levels of proinflammatory cytokines released in COVID-19 infections, researchers at the University of Bonn, and others, have hypothesized that patients may experience post-infection cognitive decline [29], not altogether surprising given high rates of memory impairment reported in the aftermath of two previous coronavirus outbreaks, SARS in 2002 - 2003, and MERS in 2012 [21]. These concerns have led to the establishment of the international Consortium for Chronic Neuropsychiatric Sequelae of SARS-CoV-2, aka the "CNS SARS-CoV-2 Consortium", founded by The Alzheimer's Association and with representatives from 30+ countries under technical guidance from the World Health Organization (W.H.O) [22]. Also recently launched is GCS-NeuroCOVID, the Global Consortium to Study Neurological dysfunction in COVID-19, under endorsement of the Neurocritical Care Society (NCS) that is focusing on the prevalence, pathophysiology and prognostic implications of neurological complications among hospitalized COVID-19 patients [30], with many others of comparable intent being formed at national and regional levels.

In light of the data supporting the underlying dysregulated neuro-inflammatory processes engendered by SARS-CoV-2 infection, we note that melatonin has demonstrable cross-BBB (blood-brain barrier) capabilities, and benefits on both cognitive function and sleep quality

[31]. And although it is true that one meta-analysis of seven studies concluded that Alzheimer's Disease patients receiving melatonin therapy showed no improvement in cognitive abilities as assessed by the mini-mental state examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) [32], we hazard this may in part have been due to the formulation, immediate release (IR) versus prolonged release (PR): in a randomized, placebo-controlled, multicenter trial using 2 mg of prolonged release melatonin as adjunct to the existing treatment regimen for Alzheimer's Disease, there was in fact a statistical improvement in median ADAS-Cog values [33]. Furthermore, recent data supports the amelioration of neuroinflammation and of amyloid-beta protein (A β)-induced neurotoxicity [31], which when diminished alleviates many of the pathological symptoms of Alzheimer's Disease [34,35]. Thus a recent study [36] explored the effect of six-months of melatonin therapy (0.15 mg/kg) on the thickness of the lamina cribrosa in patients with minimal cognitive impairment, finding significantly augmented thickness and hippocampal volume. CSF tau levels were reduced along with improvement in the mini mental score, compared to the untreated group, suggesting the efficacy to melatonin in the reduction of brain degeneration and its clear potential in the neurological sequelae of COVID-19.

In this connection, based on their recent review of the evidence, the Recommendations of the French Medical and Research Sleep Society (SFRMS) categorized as Level A results showing that melatonin as add-on treatment provides beneficial effects both in mild cognitive impairment (MCI), and in the improvement of sleep quality in Alzheimer patients [37]. Indeed, a randomized controlled trial found that 2 mg of prolonged (time-released) melatonin in Alzheimer's Disease patients improved cognitive function with significant reversal of circadian disruption [33].

Tellingly, from a variety of malignancies, we know that chemotherapy is neurotoxic and that there are both acute and delayed adverse side effects of chemotherapy on cognitive function, with the resulting cognitive impairment a source of considerable distress, compromising the patient's QoL - with as much as 75% of breast cancer patients affected [38] in part mediated by oxidative stress associated with chemotherapy and by decreased hippocampal volume and cytokine-mediated blood brain barrier disruption [38-40], with some of these contributory neuroinflammatory cascades being triggered in many cases both by the cancer itself as well as the chemotherapy regimens deployed. It is important to note that optimal dosing matters, this being set at 20 mg nightly [39], as witness an earlier RCT [41] that failed to find any effect of melatonin on cognitive function, but the difference being it dosed at 6 mg. In sum, a rich body of literature in oncology strongly supports 20 mg as the optimal dosing level [42,43].

Finally, we note that we have cross-discipline validation. Chemotherapy-related cognitive impairment in breast cancer patients receiving chemotherapy engenders both acute and/or delayed complications, with 52% of those treated experiencing peri- and post-treatment chemotherapy-related cognitive function decline (compared to just 23% pre-chemotherapy) [44], these persistent cognitive deficits widely known among patients as "chemo-brain" or "chemo-fog", confirming the neurotoxicity of chemotherapy. A recent randomized, double-blind, placebo-controlled trial examined the effects of melatonin therapy on cognition, sleep, and depression in breast cancer chemotherapy patients, finding that melatonin, when dosed at 20 mg nighttime before and during the first cycle of adjuvant chemotherapy in breast cancer patients exerts a neuroprotective effect on the neuroplasticity process, significantly offsetting the well-known

phenomenon of chemotherapy-related cognitive function decline, as well as improving sleep quality and depressive symptoms compromised by chemotherapy exposure [45].

Conclusions

Given the continued relative scarcity of preventive agents as well as treatment regimens for SARS-2-CoV (COVID-19), and the staggering toll that this pandemic continues to exact across the globe, we are not sanguine that the current rather fitful rollout of COVID vaccines will be sufficient in the near term to control this wily and highly lethal (especially in vulnerable populations) infection, so there is a moral imperative to leverage available / repurposed tools like melatonin (and likely synergistically, Vitamin D3) that have demonstrable safety and tolerability, are affordable and easily accessible, and with provisional but strongly compelling evidence of efficacy that may serve as beneficial adjuncts in our continued efforts to stay the devastation that this disease continues to bring in its wake, especially so, but not only, in resource-constrained regions of the world.

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