A potential protective role of magnesium in neuroCOVID

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Abstract. Several recent studies support a role of dysregulated magnesium homeostasis in COVID-19. In the present narrative review, we focus on the neurological aspects of this disease, collectively known as neuroCOVID, and we propose some mechanisms by which alterations of magnesium may contribute to the involvement of the nervous system in the context of SARS-CoV-2 infection. Further fundamental, translational, and clinical research is needed to underpin the potential relationships between altered magnesium status and neuroCOVID, with potentially novel therapeutic implications.

Key words: magnesium, neuroCOVID, nervous system

The current coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in December 2019 and spread across the world causing, to date, more than 462,000,000 confirmed cases and 6,000,000 deaths [1], retrieved on March 18, 2022 SARS-CoV-2 is primarily a respiratory virus, whose main manifestations range from mild upper respiratory tract illness to severe pneumonia and death [2]. However, the virus also causes several extrapulmonary diseases, with cardiovascular, renal, gastrointestinal and neurological involvement [3]. In particular, when the disease affects the central or the peripheral nervous systems, it is referred to as neuroCOVID. Such a condition affects up to 82% of SARS-CoV-2-infected patients and in a minority of cases results in severe disease and even fatal outcomes [4-5].

Increasing evidence links insufficient or excessive serum magnesium levels with more severe COVID-19 manifestations [6]. Because magnesium dysregulation is involved in several neurological signs and symptoms [7], the present narrative review discusses the potential role of dysregulated magnesium metabolism in the clinical manifestations of neuroCOVID.

NeuroCOVID: from SARS-COV-2 neurotropism to neurological signs and symptoms

The mechanisms used by SARS-CoV-2 to invade the central nervous system (CNS) are the subject of intense studies [8] (*figure 1*). One possible way utilized by SARS-CoV-2 to access the brain is the haematogenous route. The virus reaches the CNS during the viraemic phase through the blood–brain barrier (BBB) or the blood-cerebrospinal fluid barrier located in the choroid plexus of the ventricles [8-9]. The virus may overcome these barriers *via* transcytosis, by infecting endothelial cells or using monocytes as a "Trojan horse". Paracellular invasion has been envisioned through increased permeability of the tight junctions of the BBB capillary endothelium due to inflammation [10-11]. Of interest, a recent study reported evidence of disruption in the basal membrane while the tight junctions seem to be spared [12]. It is also likely that the virus

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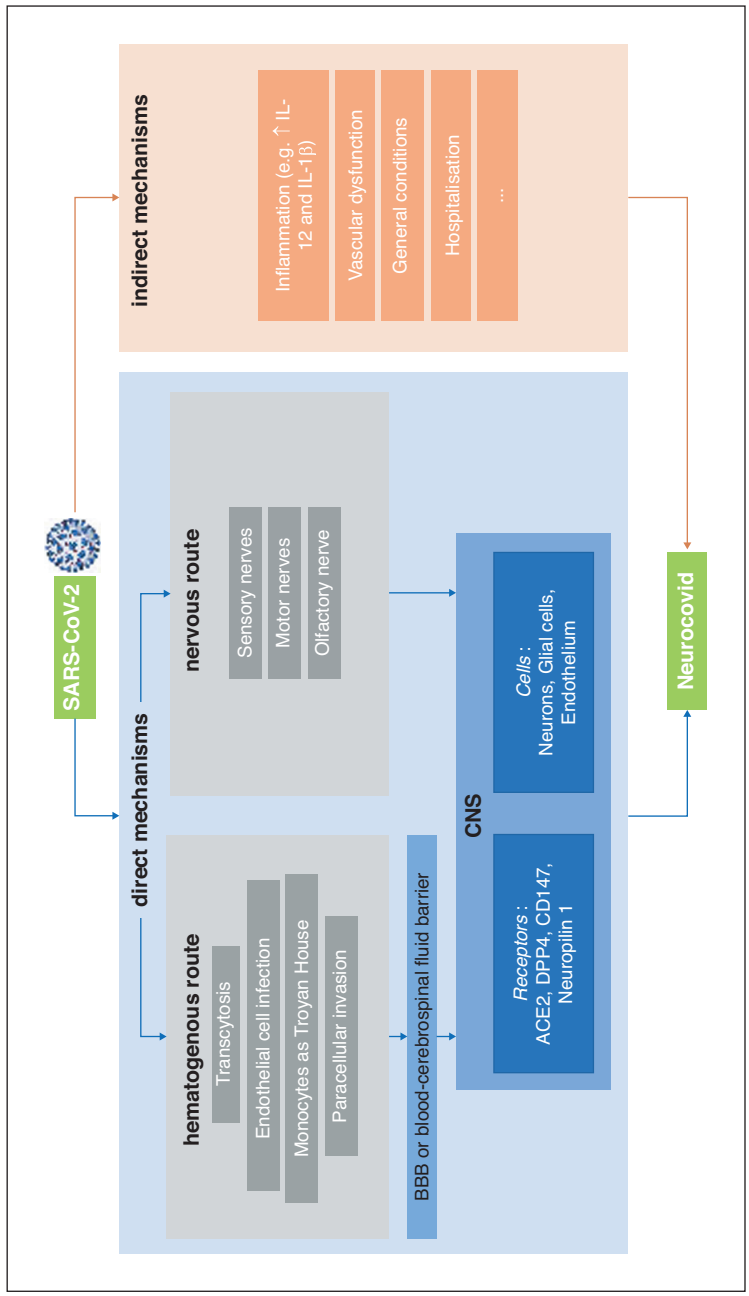

Figure 1. Summary of the possible (direct and indirect) mechanisms of neuro-invasion by SARS-CoV-2.

reaches the brain by travelling through motor and sensory peripheral nerves or through neurons originating in the cribriform plate and olfactory bulb, and subsequently spreads in the central nervous system across synapses. Of note, this is a common route for respiratory coronaviruses [11, 13-14]. Whatever the access route to the CNS, SARS-CoV-2 might enter neural cells via interaction of the viral spike protein with angiotensin converting enzyme 2 (ACE2) receptor, which mediates the invasion of SARS-CoV-2 in all infected tissues [3]. In the brain, the ACE2 receptor is expressed both on excitatory and inhibitory neurons and on non-neuron cells such as astrocytes, oligodendrocytes and endothelial cells [15]. Even though its overall level of expression is lower in the brain than in the lung, its uneven distribution leads to relatively high levels in regions that appear pivotal in the pathogenesis of neuroCOVID. For example, the ACE2 receptor is highly expressed in the olfactory bulbs and in the piriform cortex, a finding that reinforces the nervous route hypothesis [15]. Moreover, alternative coronavirus receptors might be utilized, such as DPP4 and CD147, and neuropilin 1 [16]. Of note, SARS-CoV-2 RNA or proteins were seldom detected in the brain of patients deceased due to acute COVID-19 [17-19] and viral RNA was often undetectable in the cerebrospinal fluid (CSF) from living patients with neurological symptoms [17]. It is noteworthy that increased amounts of IL-12 and IL-1β, cytokines that coordinate innate and adaptive immune responses, were found in the CSF but not in plasma. Therefore, controversy exists about a direct or indirect role of SARS-CoV-2 in neuroCOVID [19] (*figure 1*).

We now turn to the neurological manifestations reported in COVID-19 patients.

The Severe Acute Respiratory Syndrome (SARS), pandemic in 2003, and the Middle East Respiratory Syndrome (MERS), epidemic in 2012, proved that viruses belonging to the SARS-CoV species are capable of causing neurological manifestations [9]. Likewise, infection from SARS-CoV-2 can result in neurological signs and symptoms, especially in younger patients or those undergoing a more severe course of the disease [5]. The most common manifestations encompass dizziness, headache, vomiting, altered consciousness, ataxia, seizures and taste or smell impairment, while the most severe manifestations include polyneuritis, meningitis, encephalitis, Guillain-Barré syndrome, ischaemic stroke and intracranial haemorrhage [8, 20]. In an early review by Mao and colleagues, 36% of patients exhibited some sort of nervous involvement (25% presented with CNS manifestations, 9% peripheral nervous system manifestations, and 11% skeletal muscle injury signs) [20]. Other studies reported a prevalence of neurological complications in hospitalized COVID-19 patients ranging between 4% and 82% [5, 21-24], a variability that can be partially explained by the following limitations. First, the definition of "neurological symptoms" is unclear. Xiong and colleagues excluded patients with non-specific neurological manifestations such as headache, fatigue or dizziness, because they can be derived from systemic impairment, hospitalization and sedation [24]. Moreover, a mild neurological involvement may not be reported in the medical records, especially in patients with a severe form of COVID-19 [25]. Furthermore, some case series relied upon patients' subjective reports, because advanced diagnostic procedures such as MRI, lumbar puncture and electromyography were not available [25]. Finally, these data do not account for patients with COVID-19 who did not undergo hospitalization [25].

Magnesium and COVID-19

Magnesium is an abundant cation which plays a crucial role in energetic metabolism, intracellular signalling and enzymatic reactions, as well as in the normal function of immune, cardiovascular and neurological systems, among others [26-27]. Accordingly, magnesium was recently defined as a metabolite [6]. Despite the significant impact of magnesium on various physiological or pathological conditions, magnesemia is not routinely measured in clinical settings and magnesium supplementation is often overlooked [27]. In the context of the COVID-19 pandemic, a potential role of dysregulated magnesium homeostasis in the pathogenesis of disease was proposed [28-29], because certain hallmarks of COVID-19 resemble manifestations typically associated with hypomagnesemia. In addition, SARS-CoV-2 infection is more severe in people with known risk factors for magnesium deficiency, such as aging, comorbidities, polypharmacy and

malnourishment [28, 30]. A growing body of evidence links both hypo- and hypermagnesemia to disease severity [30]. Quilliot and colleagues observed that both hypo- and hypermagnesemia were associated with a poorer prognosis in patients with SARS-CoV-2 infection. Magnesium deficiency was common in patients with the moderate form of the disease, while high concentrations were common in patients with the critical form [30]. The same authors noted that in intensive care unit (ICU) patients, despite higher average magnesium levels, hypomagnesemia was more common than in other settings and was associated with a prolonged ICU stay and decreased survival [30]. Sarvazad and colleagues evaluated magnesium status at hospital admission in a sample of 134 patients with COVID-19 and found that almost half (48%) exhibited normal magnesium plasma levels, 32% were hypomagnesemic, 6% severely hypomagnesemic and 14% hypermagnesemic [31]. Normomagnesemia was more common among outpatients than in ICU patients [31]. In a study by Ouyang and colleagues, magnesium levels from the last laboratory tests of patients who died from COVID-19 were higher than those of patients who were discharged from the hospital, thus correlating hypermagnesemia with worse clinical outcomes [32]. All this evidence is in line with previous studies showing that magnesemia and in-hospital mortality are related in a dose-dependent manner [33]. Notably, the cut-offs defining hypo- or hypermagnesemic states vary across studies and a consensus is currently lacking [30, 34]. In fact, magnesium requirements depend on factors such as sex, age, race, body weight and the intake of other minerals, particularly sodium and calcium [27].

There are several possible physiopathological mechanisms that link abnormal magnesium serum levels with COVID-19 onset and severity. Hypomagnesemia is associated with chronic low-grade inflammation [25-36]. In COVID-19, a vicious circle may arise as low magnesium levels cause inflammation, which leads to local magnesium depletion, thus contributing to the potentially fatal cytokine storm [28]. On the other hand, hypermagnesemia could be the consequence of the release of intracellular components, including magnesium, in the bloodstream by soft tissues in septic patients exposed to distress [34, 37].

In hospitalized patients, hypomagnesemia is often accompanied by hypokalaemia [38]. The binding of SARS-CoV-2 to ACE2 receptors may directly contribute to the electrolyte imbalance [31]. Hypokalaemia, defined as serum potassium concentration lower than 3.5 mEq/L, is a common finding (up to 93%) among critically ill COVID-19 patients [31, 38]. This electrolyte imbalance is usually caused or exacerbated by magnesium deficiency, which alters the function of the sodium-potassium ATPase pump, and hence reduces intracellular potassium concentrations and promotes renal distal potassium excretion through the outer medullary potassium (ROMK) channels [39]. Potassium renal loss is further promoted by increased distal sodium delivery and higher aldosterone levels due to activation of the renin-angiotensin-aldosterone system (RAAS) in response to hypomagnesemia [39]. Moreover, the binding of SARS-CoV-2 to ACE2 receptors causes their internalization and down-regulation, which leads to hyperactivation of the RAAS [40].

Potential role of magnesium in neuroCOVID

In addition to the potential role of magnesium dysregulation in the pathogenesis of the systemic SARS-CoV-2 infection, disturbances in this electrolyte homeostasis may contribute to some neurological manifestations of COVID-19. Magnesium is, indeed, an essential cation for neuronal transmission and neuromuscular conduction. Among many other functions (summarized in *figure 2*), magnesium excites γ-aminobutyric acid receptors (GABA-R) and inhibits N-methyl-D-aspartate receptors (NMDA-R), induces the synthesis of BDNF, activates the transcription of genes involved in the synthesis of dopamine, and maintains the permeability of the BBB [7, 41-42]. Accordingly, low levels of magnesium promote excitotoxicity; disproportionate neural excitation that can lead to oxidative stress, neuroinflammation and eventually neuronal cell death [36]. Several neurological conditions, such as headache, stroke and mood disturbances, have been associated with a low magnesium status [27] and are briefly reviewed hereafter.

Headache is one of the most common neurological manifestations in COVID-19, reported in 6-25% of COVID-19 patients, often present at the

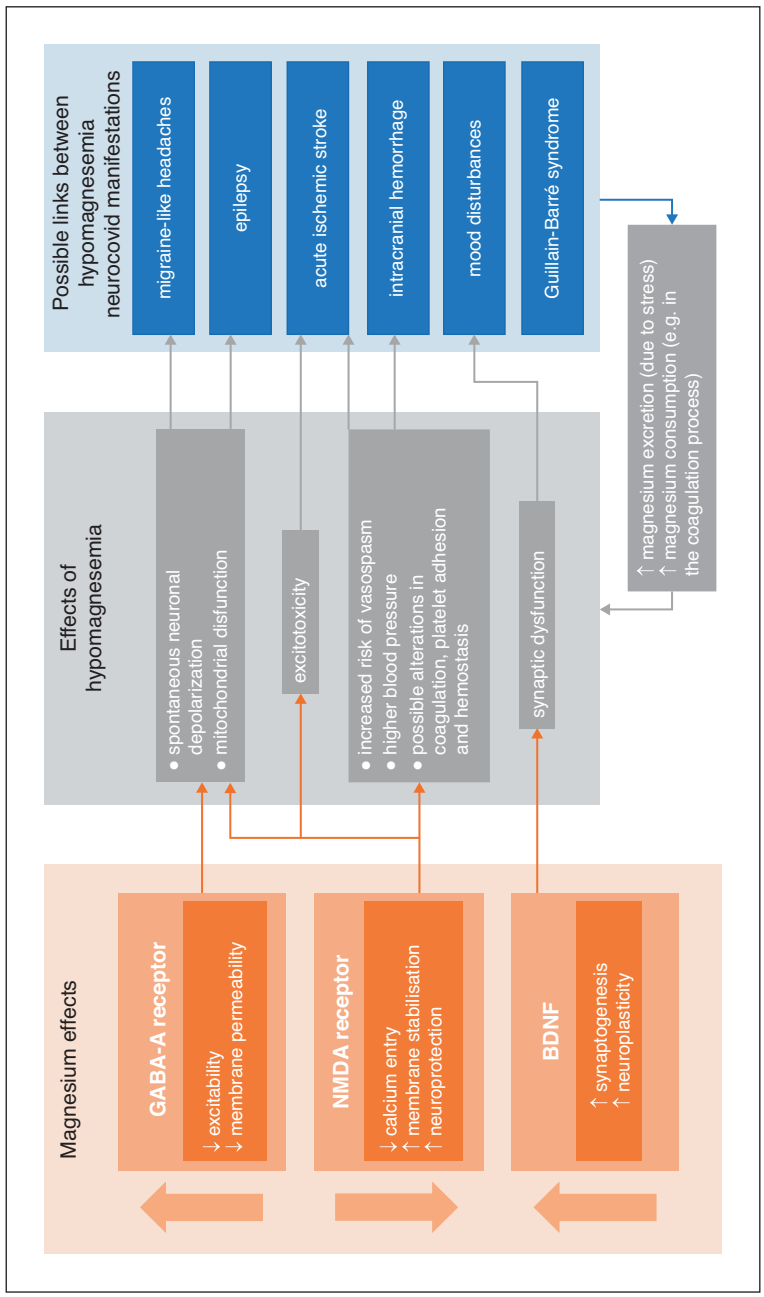

Figure 2. Overview of the possible influence of altered magnesium homeostasis on neuroCOVID. The principal actions of magnesium in the nervous system are depicted in the left panel, the effects of low magnesium on nervous functions in the central panel, and the association between low magnesium and some manifestations of neuroCOVID are presented in the right panel.

onset of the illness and persistent after the resolution of the infection [8, 43]. It can be interpreted as a symptom of systemic viral infection or attributed to various factors alone or in combination, such as infection of the trigeminal nerve nociceptive endings in the nasal cavity, infection of the endothelium in the trigemino-vascular system, the cytokine and chemokine storm irritating the trigeminal nerve endings, or certain psychological conditions such as stress, sleep deprivation, isolation and anxiety [8, 14]. Headache in COVID-19 often shows migraine-like features, with photo- or phonophobia, throbbing pain and vomiting [43]. In this instance, magnesium appears as a possible therapeutic option, since it is a key metabolic factor in mitochondrial function and lowers membrane permeability, therefore reducing the possibility of spontaneous neuronal depolarization which occurs in auras [44]. Moreover, it inhibits the glutamatergic excitatory NMDA-R system, which plays a crucial role in excessive CNS excitability, spontaneous neuronal depolarization and impaired mitochondria function reported in migraines [7]. Furthermore, migraine can also be the cause of lower magnesium levels in the brain, cerebrospinal fluid and serum, as people with headache are subject to stress that leads to greater magnesium excretion and subsequent magnesium deficiency [44].

In COVID-19 patients without a previous history of epilepsy, *de novo* seizures can occur, and the frequency and intensity of seizures increase in SARS-CoV-2-infected epileptic patients [8]. It is feasible that inflammation, fever, hypoxia, and metabolic and electrolyte alterations resulting from COVID-19, together with direct cerebral or meningeal involvement, reduce the seizure threshold. It should be recalled that some forms of epilepsy are associated with congenital or acquired hypomagnesemia [27]. Since magnesium exerts an inhibitory activity on NMDA-R, stabilizes the neuronal membrane, and helps to re-establish the electrolyte balance disrupted by SARS-CoV-2, magnesium salts might be administered as a second-line therapy after antiepileptic and anaesthetic drugs [8, 27].

Acute ischaemic stroke has been documented in 5% of COVID-19 patients [20]. COVID-19 is a strong independent risk factor for cerebrovascular accidents since it promotes oxidative stress, vasoconstriction, neuroinflammation and hypercoagulability [45-46]. Stroke in COVID-19 patients often shows atypical characteristics. It affects patients of all ages including those younger than 50 and may lack focal deficits, tends to involve multiple vessels and often causes simultaneous haemorrhages [14, 45]. Hypomagnesemia is often found in people suffering from ischaemic strokes and can contribute to the pathogenesis of such conditions through NMDA-R-mediated excitotoxicity and reduced vasodilation due to the relative lack of nitric oxide [27]. Magnesium supplementation has proven useful for this condition only if started within three hours from the accident, but studies linking magnesium and ischaemic stroke have yielded, to date, inconsistent results [27].

Intracranial haemorrhage has been documented in 0.5% of COVID-19 patients [17, 46]. Indeed, even though SARS-CoV-2 often results in a hypercoagulable state, haemorrhages can also occur as a result of consumption of coagulation factors, vessel fissurations due to elevated blood pressure, or anticoagulation therapy [8]. Low serum magnesium levels are associated with subarachnoid haemorrhages and worse functional outcomes in haemorrhagic patients [27, 47]. Hypomagnesemia may be merely a bystander due to comorbidities, as a result of magnesium consumption affecting coagulation, or actively contribute to the severity of the haemorrhage [47]. Some authors, in fact, argue that magnesium decreases the risk of vasospasm, lowers blood pressure, and possibly supports coagulation, platelet adhesion and haemostasis through an inhibitory action on intracellular calcium [47-48].

Depression, anxiety or other mood disturbances can be present during the course of COVID-19, and once the acute phase has resolved, often persist as components of post-COVID-19 neurological syndrome [8]. It is well accepted that magnesium deficiency contributes to synaptic dysfunction in mood disorders (primarily in depression), and magnesium supplementation has proven beneficial for the treatment of mild-to-moderate depression [41].

Albeit rare, Guillain-Barré syndrome (GBS) has been described in COVID-19 patients and is of great concern because it could potentially result in life-threatening paralysis [8]. GBS is caused by antibodies that cross-react with

antigens in the nervous system and is sometimes present in the initial stage of COVID-19, when respiratory failure has not yet occurred but serum levels of inflammatory cytokines are high [8]. Notably, hypokalaemia and hypomagnesemia have been reported in patients with GBS [49], but no data are available about the potential therapeutic use of magnesium in this setting.

Magnesium supplementation in COVID-19 patients

Magnesium supplementation may constitute a safe, accessible and cheap adjuvant medication, to be combined with other supportive therapies in patients with COVID-19, due to its multiple roles in anti-inflammation and antioxidant processes, immune system regulation, bronchial relaxation and vasodilation [50]. Oral magnesium intake with diet should be encouraged, but intravenous administration can ensure rapid regain of normal serum concentrations in emergency situations, such as the onset of a "cytokine storm" [6]. In patients with altered renal clearance and in those taking neuromuscular blockers, supplementation should be considered with caution and in all cases following evaluation of the magnesemia, since potentially resultant hypermagnesemia is a risk factor for more severe illness [30, 51]. Moreover, attention should be devoted to the first signs of magnesium toxicity such as loss of deep tendon reflexes (in particular, the knee tendon reflex), because these may indicate more serious consequences of excessive magnesium, including respiratory paralysis, cardiac conduction abnormalities and cardiac arrest [50].

Conclusions

SARS-CoV-2, despite being primarily a respiratory virus, can also cause or exacerbate a broad spectrum of neurological manifestations. Electrolyte alterations, including magnesium deficiency or excess, can favour SARS-CoV-2 dissemination and further aggravate neurological signs and symptoms. In summary, COVID-19 patients may benefit from constant monitoring of magnesium status, prompting its supplementation in magnesium-deficient patients.

Disclosure

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