

Neurologic aspects of COVID-19: a concise review

Matthijs C. Brouwer¹, Tiziana Ascione², Pasquale Pagliano³

¹Department of Neurology, Amsterdam UMC, University of Amsterdam, Amsterdam Neuroscience, Amsterdam, The Netherlands;

²Service of Infectious Diseases, Department of Medicine Cardarelli Hospital, Naples, Italy;

³Department of Medicine and Surgery, University of Salerno, Baronissi, Italy

SUMMARY

In addition to the conventional respiratory symptoms, patients with COVID-19 can exhibit neurological complications. In this concise review, we aim to report the most frequent neurologic manifestations related to Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV2) infection.

SARS-CoV2 can reach the central nervous system from the bloodstream or olfactory pathway by binding ACE-2 receptor and the spike protein protease TMPRSS2. Headache is reported in more than 10% of affected patients and loss of smell and taste disturbance are reported in a slightly smaller percentage of cases.

Acute cerebrovascular events are diagnosed in 3% of COVID-19 patients, but those with more severe manifestations have cerebrovascular events in more than 6% of the cases, as reported by two retrospective studies from Italy and China. Moreover, five cases of large-vessel stroke have been described in low-symptomatic COVID-19 patients aging less than 50

years suggesting that SARS-CoV2 can be associated with an increase of the risk of stroke in relatively young people.

Peripheral nerve diseases can be observed after an apparently uneventful SARS-CoV2. Based on a literature review, nine patients experienced Guillain-Barré syndrome (GBS) and 6 of these needed mechanical ventilation. Two more cases have been described with Miller-Fisher syndrome or polyneuritis cranialis, both had rapidly resolving symptoms.

In conclusion, nervous system symptoms can be observed during SARS-CoV2 infection of which headache and smell and taste disturbance are the main symptoms reported. Cerebrovascular complications can complicate the course of COVID-19 in apparently low-risk patients. GBS is a life-threatening manifestation of COVID-19.

Keywords: Covid-19, neurologic aspects.

Since April 2020 every two weeks 1 million new COVID-19 patients have been reported worldwide totalling 5 million by the end of May with a reported number of deaths of over 300.000 by mid-May. During this period physicians and scientist all over the world have started to explore the disease and report on the clinical characteristics, pathophysiology and outcome of the disease [1, 2]. Although initially the reports on clinical characteristics focused on the severe pneumonia

and need for mechanical ventilation that is the hallmark of COVID-19 infection, it quickly became clear the disease has multiple non-pulmonary features. A study investigating SARS-CoV-2 viral load in autopsy tissues demonstrated that significant viral amounts can be detected in kidneys, liver, heart and brain confirming preliminary investigations [3]. It has now become clear that there is a massive activation of the coagulation system through the severe inflammatory response [4]. This does not only cause deep venous thrombosis, pulmonary embolisms and renal failure, but also results in cerebral infarctions [5]. Besides strokes, every week new reports and reviews on neurological complications in COVID-19 are being published. Here we provide a

Corresponding author

Matthijs C. Brouwer

E-mail: m.c.brouwer@amsterdamumc.nl

summary of these findings now the first wave in Europe appears to have waned.

In the clinical presentation of patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) headache was reported in 11-34%, with the largest series reporting 14% [1, 6]. So far it is unclear what causes the headache, but hypoxia, metabolic disturbances or systemic inflammation may all be considered to contribute. Two studies available through the bioRxiv preprint platform suggest that SARS-CoV-2 can reach the Central Nervous System from the bloodstream or olfactory pathway by binding ACE-2 receptor and the spike protein protease TMPRSS2, but the clinical relevance of such brain invasion is unclear. An experimental model of SARS-CoV-1 infection did not report brain inflammation [7-9]. Direct infection of the central nervous system by SARS-CoV2 is considered unlikely, since cerebrospinal fluid (CSF) analysis is often normal. In the experience from our institutions at least eight patients with headache and PCR proven COVID-19 infection showed normal CSF composition (leukocyte count, total protein and glucose concentration) with negative COVID-19 PCRs in CSF. This complies with other case series in the literature [10]. So far, one case of acute necrotizing encephalitis (ANE) has been published, which is considered a post-infectious inflammatory syndrome rather than a direct infection of the brain by the virus [11]. Pending further publications on ANE following COVID19 a causal relationship is unsure.

A typical finding of COVID-19 is the loss of smell (or anosmia), which has been described in 40% of cases in a Spanish case control study and 34% in a Italian study [12, 13]. Although smell and taste disorders have been reported before in studies on other viral infections, the rate in COVID-19 patients is quite substantial. Although it has been theorized to be due to direct invasion of the olfactory nerve by the virus, further studies are needed to support this.

Infection is considered an important risk factor for stroke, based on large population-based studies and it is to be expected that a higher incidence of stroke during the weeks following a COVID-19 could be reported in otherwise low risk patients [14]. A large retrospective study from Wuhan investigating the neurologic aspects of COVID-19 found a total 2.8% incidence of acute cerebrovas-

cular events, with higher rate (6%) in patients with severe COVID-19 [15]. A similar incidence was reported in an Italian study where cerebral infarctions were diagnosed in 9 (2.5%) of 362 patients [5]. In only 2 of these 9 cases a definite risk of stroke (atrial fibrillation) was present. Two patients received systemic thrombolysis and one patient underwent a successful mechanical thrombectomy, with no relevant side-effects. These findings suggest that stroke has a significant incidence in COVID-19 and stroke treatment can be similar as in COVID-19 unrelated cases [5]. A recent study from New York, described 5 cases of stroke in COVID-19 patients aging less than 50 years during a 2-week period. Clot retrieval was performed in 4 cases and no procedure-related side-effect was reported. Comparing the incidence with the previous 12 months the authors found that the stroke incidence was about 6 times higher in the under 50 years of age group (0.73 cases every 2 weeks), suggesting an association between COVID-19 outbreak and stroke incidence in apparently low-risk cases [16]. The suggested explanation for the increased risk of stroke includes direct damage of the virus on the vascular endothelium and activation of coagulation through the systemic inflammatory response.

In addition to direct effects of the viral infection associated with stroke, post-infectious inflammatory neurological syndromes have also been identified after COVID-19. In Guillain-Barré Syndrome (GBS) an aberrant immune response triggered by a recent infection results in peripheral nerve injury. An association between GBS and COVID-19 has been suggested in a recent publication of 9 GBS cases in whom 8 patients developed GBS 5-10 days after fever and respiratory symptoms due to COVID-19 infection, while one case presented with ongoing fever and GBS [17]. Severe symptoms with respiratory failure needing mechanical ventilation were reported in 6 cases. No case tested positive for SARS-CoV-2 by PCR on cerebrospinal fluid and all patients had a positive nasopharyngeal PCR test and chest imaging characteristic of COVID-19. All cases received intravenous immunoglobulins. Similar findings were previously reported in 4 patients affected by SARS that developed symptoms more than 20 days after primary infection [17, 18].

Miller Fisher Syndrome (MFS) and polyneuritis cranialis, which are variants of GBS causing cra-

nial nerve and pharyngeal and facial weakness, have also been described in COVID-19. A Spanish study described two patients developing MFS and polyneuritis cranialis, respectively, 5 and 3 days after the symptoms of mild COVID-19 developed. PCR was positive in both cases by nasal swabs but was negative by CSF examination. Neurological features resolved in both cases within 2 weeks without relevant sequelae [19].

In conclusion, neurologic symptoms are frequently reported in COVID-19 patients, but no impact of SARS-CoV-2 as direct causative agent of an inflammatory disease of the brain has been currently demonstrated. Headache and anosmia are reported with the highest frequency and appear to improve with COVID-19 symptoms disappearance. The direct effect of the virus on the endothelium and the inflammatory cascade activation after COVID-19 increase the risk of stroke, which is also relevant in young patients and in those without any risk for cerebrovascular infection. In these cases, endovascular and systemic treatments have so far not been associated with an increased risk of bleeding. Also, peripheral nerve disease can be triggered by SARS-CoV-2 infection, but the low amount of data does not permit to draw specific conclusion in term of its prognosis and treatment.

Conflict of interest

None to declare

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