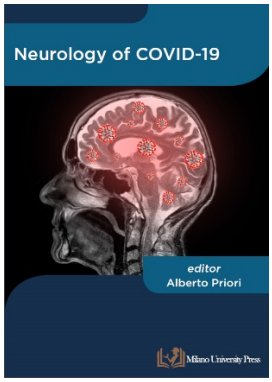

Neurology of COVID-19
Editor Alberto Priori
DOI: https://doi.org/10.54103/milanoup.57

Published by: Milano University Press
Via Festa del Perdono 7 - 20122 Milano
URL: https://milanoup.unimi.it/
E-mail: redazione.milanoup@unimi.it

Chapter 16. **Impact of COVID-19 on pre-existing neurological diseases**

DOI: https://doi.org/10.54103/milanoup.57.31

List of Contributors

Paola Alberti
School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;
NeuroMI (Milan Center for Neuroscience), Milan, Italy;
San Gerardo Hospital, ASST Monza, Monza, Italy.
Email: paola.alberti@unimib.it

Simone Beretta
School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;
NeuroMI (Milan Center for Neuroscience), Milan, Italy;
San Gerardo Hospital, ASST Monza, Monza, Italy
Email: beretta.simone@gmail.com

Laura Brighina
NeuroMI (Milan Center for Neuroscience), Milan, Italy;
San Gerardo Hospital, ASST Monza, Monza, Italy.
Email: brighina.laura@asst-monza.it

Valeria Isella
School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;
NeuroMI (Milan Center for Neuroscience), Milan, Italy. Email: valeria.isella@unimib.it

Carlo Ferrarese
Professor of Neurology
School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy;
NeuroMI (Milan Center for Neuroscience), Milan, Italy;
San Gerardo Hospital, ASST Monza, Monza, Italy.
Email: carlo.ferrarese@unimib.it

Chapter 16. Impact of COVID-19 on pre-existing neurological diseases

Paola Alberti, Simone Beretta, Laura Brighina,
Valeria Isella, Carlo Ferrarese

Introduction

Neurological sequelae and complications have been reported as being related to COVID-19[1-3]. Yet light should still be shed on the exact impact of COVID-19 on neurological diseases as well as on patients with an underlying neurological condition. To solve this unmet clinical and scientific need, large observational multicenter studies are warranted; one good example is the NEUROCOVID study proposed by Members of the Italian Society for Neurology (Società Italiana di Neurologia, SIN)[4].

In this chapter we address some potentially highly interesting topics related to COVID-19 and neurological patients.

Neuroinflammatory and neuro-oncological diseases

In this section we discuss issues related to some categories of frail neurological patients: those affected by neuroinflammatory and neuro-oncological conditions. As a general indication, basic safety rules apply. Social distancing is crucial, and given these are mainly chronic patients, appropriate logistic solutions should be put in place by the treating physician/center: minimizing trips to pharmacies, relying on telemedicine if appropriate and switching to home infusion of selected drugs (e.g., home-base intravenous immunoglobulin subcutaneous administration). In the next section we will examine the specific issues related to COVID-19 in categories of fragile patients.

Multiple sclerosis

Epidemiological studies are addressing the potential effects of COVID-19 in multiple sclerosis (MS) patients. A European multicenter trial reported 21.8% of 399 MS patients suffered from an infection clinically suggestive of COVID-19, and reported major symptoms of COVID-19[5]. MS is a chronic

immune-mediated demyelinating disease of the central nervous system which involves inflammation, blood-brain-barrier disruption, and autoreactive lymphocytes. Its treatment relies on disease-modifying therapies (DMTs) aiming at immunomodulation, immunosuppression, or cell depletion and/or alteration of inflammatory cell trafficking[6]. Relapse treatment is based on glucocorticoids and, occasionally, plasmapheresis cases of corticosteroid failures, with, of course, only short-term administration. Instead, DMTs are administered chronically to help prevent relapse and to slow progression. In basic terms, DMTs can be divided into[6]: *immunomodulatory drugs*, such as interferon-beta-1 (IFN-β1), glatiramer acetate (GA), and fumarates (i.e., dimethyl fumarate); *cell trafficking alterations molecules*, like S1P receptor modulators (i.e., fingolimod), and natalizumab, an anti-α4-integrin antibody; *cell depletion* (anti-CD20 antibodies [i.e., ocrelizumab, rituximab, ofatumumab], cladribine, and *anti-CD52 antibodies* [i.e., alemtuzumab]); *systemic immunosuppressants* (i.e., teriflunomide). The immunocompetence status of patients might play an important role in COVID-19 associated risks. It has been suggested that MS patients not receiving DMTs have the same risk of suffering from COVID-19 as the general population[7] and that the greatest risk of contracting the disease can be related to dosage and medication administered, in particular for second-generation therapies[8]. However, these observations were conducted on a relatively small cohort possibly biasing the results[8, 9]. From case series studies, immunosuppression has emerged as a risk factor for severe forms of COVID-19[10]. *Dimethyl fumarate*, for example, could potentially induce lymphopenia, mainly in the early treatment course[11], eventually increasing susceptibility to SARS-CoV-2 in case of moderate-to-severe lymphopenia, but it is considered likely to be safe in patients with no or mild lymphopenia (absolute lymphocyte count > 800/mm^3)[12]. Another drug, *natalizumab*, is considered to be low risk for severe forms of COVID-19[13] since it does not interfere with lymphocyte function. Other drugs with, however, a possible moderate risk for COVID-19 are those with a modulatory effect of the S1P receptor (*fingolimod, siponimod, and ozanimod*) and anti-CD20 monoclonal antibodies (*ocrelizumab and rituximab*)[13]. S1P modulators are capable of reducing peripheral lymphocytes, increasing susceptibility to coronavirus infection, as evidenced by the increased predisposition to other viral infections[13]. Anti-CD20 monoclonal antibodies could impair the anti-viral long-term immunity and increase the risk of reinfection[13]. For the same reasons, the greatest infection risk might be suggested for treatments acting on the lymphocyte population, such as alemtuzumab or cladribine; moreover, they potentially affect the early and long-term immunity against SARS-CoV-2, increasing infection susceptibility and re-infection rate[13].

Given these reflections, caution should be exercised when managing each individual patient both for acute relapse treatment, and management of confirmed COVID-19 cases. In case of acute relapse, single cases should be carefully

evaluated given that corticosteroids are associated with an increased risk of infections, including (of course) SARS-CoV-2 infection, and these accelerate the onset of relapses[11]. In patients with a relapsed MS and, at the same time, an ongoing COVID-19, the use of plasmapheresis was suggested[13]. However, in case of COVID-19 in a MS patient without an active neuroinflammatory status, it is generally suggested to continue DMTs if infection is mild. Suspension is to be evaluated in those with greater immunosuppressive effects or in patients with other risk factors for development of a more severe form of COVID-19. Careful risk assessment of rebound activity should always be considered in case of suspension of S1P modulators and natalizumab[11]. However, it should be noted that we are still gaining inferences on COVID-19 and MS patients as well as DMTs, therefore, it should be strongly encouraged to stay carefully updated on the indications of regulatory agencies and scientific societies on these products (see as an example those released by Associazione Italiana Sclerosi Multipla [AISM][14]).

Myasthenia gravis

Myasthenia gravis (MG) is a chronic autoimmune disorder characterized by fluctuating muscle weakness affecting ocular, bulbar and limb skeletal muscles[15]. The onset of MG has been related to several triggering factors including hepatitis B and C, herpes simplex, HIV, Epstein-Barr virus, West Nile and Zika virus. SARS-CoV-2 virus has given rise to some possible challenges in MG patients since it can lead to variable symptoms, ranging from mild to severe pneumonia, subsequently leading to acute respiratory distress syndrome (ARDS) and death in many cases[16]. The risk can be higher in MG patients for many reasons: a potential immunocompromised state related to MG therapies and possible respiratory muscle weakness[16]. Several reports in literature are available on MG patients suffering from COVID-19; Camelo-Filho et al.[17] published a large series of patients, revealing a rather severe disease course, requiring intensive care admission in 87% of cases, mechanical ventilation in 73%, and with a fatal outcome in 30%. However, clinical response of MG patients to COVID-19 represents a major challenge and outcome predictors are still lacking. Most notably, it has been pointed out that Treg/Th17 imbalance in the course of COVID-19 might increase or even trigger an excessive autoimmune response, and a possible role for hyper-inflammatory responses in COVID-19 might be crucial in respiratory failure[16]. Therefore, respiratory muscle function evaluation is crucial in deciding the timing of endotracheal intubation in MG patients affected by COVID-19. A non-invasive ventilation trial can be indicated and could avoid endotracheal intubation. But, in cases of excessive distress in breathing, or in case of the development of bulbar dysfunction or ARDS, early intubation and mechanical ventilation could be required. The current state of knowledge on the interaction between MG and COVID-19 is changing rapidly due to growing

experience with patients. The ongoing international registries will soon provide greater insight on this matter[18, 19]. For the moment, the best approach is for MG patients to continue their current treatment, unless specifically discussed with and approved by the treating physician; when deciding whether altering or stopping an existing immunosuppressive therapy, the increased disease activity and/or MG exacerbation or crisis, should be considered.

Inflammatory neuropathy

The relationship between COVID-19 and inflammatory neuropathies is quite complex. On one hand, patients affected by inflammatory neuropathies might be undergoing an immunomodulatory treatment, raising the same concerns discussed for other diseases so far; on the other hand, COVID-19 itself might trigger an immune reaction resulting in potential damage to the peripheral nervous system. Regarding chronic conditions, such as chronic inflammatory demyelinating polyneuropathy, a reflection is in order. Some standard treatments are not expected to increase the risk of COVID-19 or severe disease: immunoglobulin (either intravenous or subcutaneous), complement inhibitor therapy (e.g., eculizumab), therapeutic plasma exchange.

Notably, the inflammatory response driven by COVID-19 has started to raise concerns related to acute polyradiculoneuritis occurrence. Case reports and case series were reported at the beginning of the first COVID-19 outbreak[20,21]. As pointed out by Sheikh and co-authors[22] in a recent systematic review, acute polyradiculoneuritis could be considered one of the many presentations of COVID-19. However, there is no definite agreement on the robustness of the association between COVID-19 and acute polyradiculoneuritis. A recently published study by Keddie and collaborators[23] argues against SARS-CoV-2 as being causative. They based this statement comparing cases in the UK from 2016 to 2019 and cases reported during the COVID-19 outbreak. Nevertheless, authors recognized it is not possible to entirely rule out the possibility of a link, since acute polyradiculoneuritis incidence has fallen during the pandemic, probably due to lockdown measures reducing transmission of other pathogens associated with this condition. In general, despite the reported conflicting studies, it is highly important not to underestimate a diagnosis of acute polyradiculoneuritis related to COVID-19; acute polyradiculoneuritis raises specific challenges the treating physician should be aware of, especially in an intensive care setting.

Neuro-oncological patients

The COVID-19 pandemic has created major issues for cancer diagnosis and treatment, as well as in access to care; this is particularly true in the field of neuro-oncology. In the case of brain tumors, the perceived benefit of therapeutic interventions is often low, although this view is not always correct. As a consequence of the pandemic, the risk/benefit ratio has altered and major challenges

have been posed to health-care providers. In order to reduce risks to patients, different responses were evaluated: brain scans intervals were increased and radiotherapy schedules were adapted to hypofractionation. Another issue was raised by systemic chemotherapy given its immunosuppressive potential, raising some concerns, for example, on proposing temozolomide to glioblastoma patients lacking MGMT promoter methylation, given the risk of lymphopenia and repeated access to the hospital facilities (e.g., for blood tests), thus increasing the risk of developing COVID-19[24]. For brain cancer patients symptomatic for COVID-19, withholding systemic chemotherapy, unless entirely non-immunosuppressive, could be suggested until full recovery from COVID-19[24]. A careful evaluation of risk/benefit is needed, and moderate delays of systemic chemotherapy may be a preferred option, in case of patients positive for SARS-CoV-2, as part of a screening program, but asymptomatic. In any case, there is an urgent need to ensure treatment of neuro-oncological patients is not significantly delayed and initiating therapy should not be outweighed by COVID-19. Therefore, multidisciplinary initiatives are being undertaken to better navigate through pandemics and learn/adapt practice. As an example, Bernhardt and collaborators[25] proposed detailed consensus-based practice recommendations based on experts' opinion, including neuro-oncologists, neurosurgeons, radiation oncologists, and medical physicists. They suggest adapting treatments, proposing hypofractionated radiotherapy, and modifying chemotherapy to minimize immunosuppression.

Cerebrovascular diseases

COVID-19 patients with pre-existing cerebrovascular disease have been shown to have a significantly higher risk of in-hospital death, compared to COVID-19 patients without cerebrovascular comorbidity (relative risk 2.18)[26]. Moreover, patients with previous cerebrovascular disease had higher risk of severe COVID-19 than those without (relative risk 2.07) and requiring intensive care (relative risk 2.79). Both pharmacological and non-pharmacological therapies used for COVID-19 have increased risks or are less practicable in patients with previous stroke. Dexamethasone and tocilizumab increase the risk of bacterial infections,[27] hydroxychloroquine has a potential cardiac toxicity[28] and prone positioning is difficult to apply in conscious patients with previous motor disability.

The risk of first or recurrent stroke associated with COVID-19 is a matter of debate. The first studies during the early phase of the pandemic indicated an apparent increase in the number of stroke patients who were younger and with a lower vascular risk factor burden, as well as an apparent increase in stroke severity, but other cohorts did not identify this different patient profile.[29-34]

For patients with pre-existing cerebrovascular disease, who are more vulnerable to secondary events as a result of their poor vascular condition, the risk of recurrent stroke among individuals with COVID-19 remains to be determined. This issue is even more difficult to ascertain due to the approximately 30% decrease in the volume of stroke patients accessing hospitals during the COVID-19 pandemic, with an even larger decrease (up to 40-60%) for patients with transient ischemic attacks (TIA) and mild strokes.[35-37] Despite a true decline in stroke incidence that may be related to a reduced exposure to common viruses (well-known triggers of acute cerebrovascular events), during the lockdown periods,[38] the most likely explanation is that the reduced stroke presentation is a direct consequence of social distancing, decreasing early identification of stroke and patients' fears about coming to the hospital in the midst of a pandemic.[39] Hospital avoidance may have created a cohort of untreated stroke patients at risk of poorer outcomes and recurrent events. Notably, an alarming increase in lifestyle risk factors for cerebrovascular diseases, such as smoking, alcohol and physical inactivity was noticed during the months of confinement.[40, 41]

COVID-19 highlighted the long road that still has to be run towards a satisfactory education of the population for stroke. The World Stroke Organization issued an important campaign highlighting the importance of not wasting time in suspected first or recurrent stroke during the COVID pandemic.[42]

In particular, for patients who had already suffered a stroke and were likely to have reduced access to secondary prevention clinics and neurological rehabilitation therapies, the pandemic has highlighted the enormous potential of telemedicine in stroke care. Although still in their early stages, novel models of care have been implemented for telemedicine neurological consultations of TIA patients[43] and for video-guided telerehabilitation using home exercise programs.[44]

Epilepsy

Epilepsy is one of the most common chronic neurological conditions, with a prevalence of approximately 1% and a high incidence among elderly individuals and children[45]. Various factors surrounding epilepsy and epilepsy care may be affected by COVID-19.

A systematic review article showed that the rate of COVID-19 severity in people with epilepsy is lower than other neurological disorders such as dementia, cerebrovascular disease, and multiple sclerosis[46]. However, epilepsy is not a single disease; it has many causes and associations, some of which may debilitate the patient and increase the risk of respiratory impairment. Notably, patients with epilepsy associated with learning and developmental disabilities are exposed to a significantly higher risk of death due to a severe form of COVID-19 compared to other epilepsy patients[47].

Current evidence indicates that the incidence of acute symptomatic seizures due to COVID-19 is less than 1%,[48] suggesting that acute symptomatic seizures caused by COVID-19 are not particularly common compared with other viral diseases. However, a change in seizure frequency among patients with chronic epilepsy during the COVID-19 crisis has been reported, regardless of whether these patients were infected with COVID-19[49]. The proportion of patients experiencing increased seizures varied from 8% to up to 30%, and may reflect several contributing factors, besides COVID-19 infection itself: reduced compliance to antiepileptic drug schedule, difficulty in obtaining medicine due to lockdown or reduction in income, increased psychological stress and sleep problems. Indeed, the impact of the COVID-19 pandemic on psychological effects in epilepsy patients showed a high prevalence of depression (29%), anxiety (38%) and insomnia (29%)[50].

The social impact of COVID-19 has been seen also in epilepsy care facilities. Patient access to healthcare facilities has been greatly restricted because of the potential for patient-to-patient or healthcare provider-to-patient transmission of SARS-CoV-2. In a survey from 49 countries, more than 90% of physicians responding stated that in-person outpatient visits had decreased and use of telemedicine had increased[51].

The use of virtual epilepsy appointments became the standard of care in the lockdown periods in most countries and allowed an unprecedented assessment of this new care system, from both the patient's and the physician's perspective. Two large studies enrolling over 1,300 patients showed no backlog of appointments or loss of care continuity and strong levels of satisfaction expressed by clinicians for routing follow-up appointments, including adjustment of antiepileptic drugs and prescriptions of diagnostic testing[52, 53]. On the other hand, most physicians doubted the suitability of telemedicine for patients with newly diagnosed epilepsy and drug-resistant epilepsy. Up to 75% of patients reported positive experiences of telephone appointments comparing them favorably to face-to-face encounters. Beyond the pandemic, most patients reported a preference for continuing telemedicine if their epilepsy symptoms remained stable, while only 44.4% chose telemedicine should their symptoms worsen.

Dementia and movement disorders

Coexistence of coronavirus disease with degenerative cognitive and movement disorders has represented the crossroad of two pandemics. Neurodegenerative diseases like Parkinson's disease (PD) or, and above all, Alzheimer's disease (AD), are extremely frequent in older people, who were also the main target of COVID-19 infection. The impact of the virus in these clinical populations has been massive and diverse: during the quarantine these patients have shown a higher risk of contagion and a worse outcome of the infection, have suffered

the consequences of physical confinement and social deprivation, and also of greater caregiver burnout, and have experienced discontinuity in assistance due to overload or lockdown of medical and support services.

Results from meta-analyses and systematic reviews have shown that, compared with individuals with no dementia, dementia patients were at higher risk of COVID-19 infection, showed a more severe disease course, and had a higher mortality rate (with ORs ranging from 1.54 to 5.17)[46, 54-62]. Various elements have been indicated as causes of this increased vulnerability[63, 64]. Some were related to age (increased viral shedding, atypical presentations, such as lack of fever, that delay the diagnosis, or heavy comorbidity), while others were more specific to dementia. A case in point was delirium, which is particularly frequent in patients with a neurodegenerative disease in the course of an infection; this is a serious, potentially lethal condition. A second element was the fact that measures to prevent contagion, like wearing masks, frequent handwashing or avoiding social contact, are difficult to introduce to individuals with cognitive impairment. Third, potential biological mediators of major vulnerability to COVID-19 in AD were hypothesized[61, 62, 64-66]. For instance, Apolipoprotein E allele ε4, a known risk factor for AD, has been associated with increased COVID-19 severity, and expression of the ACE2gene, coronavirus binding protein for cell entry, has been found to be upregulated in the brain tissues of AD subjects. Moreover, and more importantly, cytokine-mediated neuroinflammation plays a central role in the pathogenesis of AD, and COVID-19 is known for causing a 'cytokine storm' that affects multiple organs, including the central and peripheral nervous system. These observations on biological common links between coronavirus and AD, however, are for the moment highly speculative, and will need to be verified empirically.

As far as PD is concerned, it remains unclear whether there was a major incidence of coronavirus disease in this disorder. Reports on prevalence of the infection varied greatly (according to geographical area, inclusion criteria, etc.), ranging from 0.6% to 8.5%[67], but in most studies it was below 1%, therefore equivalent to that of the general population. Risk factors for COVID-19 infection in PD were also similar to those seen in control populations, i.e., age, male gender, smoking, cardiovascular and chronic obstructive pulmonary diseases[67]. However, data are still insufficient to establish whether the similar prevalence was related to the same predisposition for COVID-19 infection, or to a higher level of attention and self-isolation in PD patients as an at-risk population[68, 69]. Interestingly, a few studies have actually reported that a subgroup of PD patients were less likely to be infected by COVID-19, namely those receiving amantadine[70, 71]. This finding has also received support from an *in vitro* drug screen gene expression study showing that amantadine decreased the virus rate of replication and degree of infectivity[72].

With regard to the prognosis, mortality rates were also highly variable (from 5% to 75%) according to sample size, and patients' socio-demographic and clinical characteristics (e.g., disease stage, involvement of community-dwelling, hospital-based or long-term care facilities series). However, they were generally higher in PD patients than in age-matched non-PD individuals[73], mostly because of restricted pulmonary capacity due to axial akinesia, and impaired cough reflex[74]. Interestingly in PD the detrimental interaction between coronavirus infection and neurodegeneration has appeared to be bi-directional, in the sense that the virus also seemed to have a negative impact on the course of the motor disorder, through various mechanisms. Dopamine neurons have in fact been shown to highly express the ACE2 receptor, which mediates COVID-19 entry to cells, and immune activation in the olfactory system, targeted by the virus, has been shown to eventually lead to the misfolding of α-synuclein in the central nervous system, possibly causing the development and/or progression of PD. In support of this hypothesis, four cases of parkinsonism have been reported, which manifested between five to 32 days from coronavirus infection and showed asymmetric decrease of dopamine uptake in the putamina and good response to dopamine replacement therapy[75, 76]. These cases of new-onset parkinsonism might have been related to unmasking subclinical PD. Large cohort studies will be needed to determine whether COVID-19 will also increase the incidence of PD in the long term.

The pandemic has had heavy consequences on patients with dementia and movement disorders also indirectly, through quarantine and isolation. During the lockdown declared in Italy as a containment measure of the first wave of the coronavirus pandemic, the COVID-19 Study Group of the Italian Society of Neurology for Dementia (SINdem) carried out a nation-wide survey on the impact of quarantine on cognitive, neuropsychiatric and motor symptoms of dementia, using a telephone interview with patients' family caregivers. Clinical worsening was reported in approximately two patients in three for behavioral aspects (mainly irritability and apathy), in one patient in two for cognitive functions (especially memory), and in one patient in three for motor disturbances (above all, in walking)[77, 78]. These findings are in line with a large bulk of literature also showing exacerbation of pre-existing neurological symptoms of dementia during and after quarantine[78]. Such an exacerbation appeared to be linked to multiple factors: movement restriction, reduced social interaction and activities that usually stimulate cognition and have a beneficial effect on mood and behavior, disruption of daily routine. A negative effect was also observed in terms of greater caregiver burnout, which has been reported repeatedly in the pandemic literature[79, 80], and quarantine due to the coronavirus disease 2019 (COVID-19, and this set off a vicious cycle with worsening of the patient's clinical condition.

Very similar findings have been reported for PD patients. Worsening of motor and non-motor symptoms has also been described in these patients, and attributed mainly to psychological distress, depression and anxiety, a reduction in physical activity, and social isolation, besides fear of being infected by COVID-19[81, 82]. A behavioral disturbance very typical of PD, Impulse Control Disorder (ICD), has also been found to increase during the COVID-19 lockdown[82].

The SINdem COVID-19 Study Group's report on the impact of quarantine on family caregivers of patients with dementia identified discontinuity in assistance as one of the main determinants of caregiver stress, causing a three-fold increase in feelings of isolation and abandonment and a two-fold increase in a sense of being overwhelmed and helpless[83]. This element has in fact emerged as one of the main causes of the extra burden resulting from the pandemic on patients with dementia[83], mostly on patients with PD[81, 82.] Redeployment of hospital units and lockdown of medical and assistance services (outpatient clinics, diagnostic departments, cognitive and motor rehabilitation centers, elderly day-care facilities, social support services) created a real emergency, with problems in the supply of medications and postponement of appointments for follow ups and for new referrals, leading to delays in diagnosis and initiation of appropriate management. PD patients seem to have been the most heavily penalized by this situation, due to the fact that, unlike other neurological groups, they need routine visits to the hospital for physical assessment and medication adjustments by movement disorder specialists. In particular, during the peak phases of the COVID-19 pandemic a significant decline was observed globally for PD Multimodal Complex Treatments (MCT), including levodopa/carbidopa intestinal gel, continuous subcutaneous apomorphine infusion and Deep Brain Stimulation (DBS). Patients treated by MCT require regular follow-up visits in highly specialized and multidisciplinary clinical settings, which appear to have been massively affected by social distancing and lockdown measures[84]. Beside reporting concern about problems of hospital access and the interruption of pharmacological and non-pharmacological treatments, patients treated with MCT were also worried specifically about management of stimulation devices. First of all, PD patients with implanted DBS systems require replacements of the Implantable Pulse Generator (IPG), especially if not rechargeable, every three to five years. More crucially, battery malfunction due to exhaustion or other device-related issues may occur unexpectedly and become an emergency requiring surgical intervention to avoid the risk of life-threatening complications such as malignant subthalamic nucleus-DBS withdrawal syndrome (similar to a neuroleptic malignant syndrome), acute dystonic crisis, and the reappearance of disabling PD symptoms, which can be refractory to medication. During the pandemic, both pre-planned and urgent hospitalizations for interventions on the device were extremely problematic.

Possible role of telemedicine

These issues lead straight to reflections about the need to identify and implement interventions aimed at providing care in current and future situations of physical distancing Telehealth must represent a very promising solution, as it helps in limiting virus circulation by decreasing person-to-person contact, while allowing remote delivery of a full spectrum of services to patients and caregivers[85, 86]. Indeed, a recent study showed that telemedicine was as efficacious as in-office visits, and PD patients even expressed an increased likelihood of participating in future clinical research studies if some visits could be conducted remotely[87]. Along these lines, the International Parkinson and Movement Disorder Society has developed a guide on how to set up telemedicine practice as a valid alternative method for consultations and remote assessments of PD patients[88]. History-taking, aspects of the neurological examination, a brief cognitive assessment, and medication reviews can be performed via videoconferencing. Virtual cognitive and also physical stimulation programs may also be arranged, and counseling or psychological support may be provided to patients, caregivers and family members through telephone or web meetings. Furthermore, PD patients may efficiently be assessed with wearable devices to complement remote MDS-UPDRS scores. However, telehealth has some limitations: the impossibility of performing a complete neuropsychological evaluation or physical examination (e.g., to assess rigidity, or to perform balance-related maneuvers, especially without the supervision/assistance of a trained caregiver); the lack of validation and norms for neuropsychological tools; the inability to conduct 'difficult conversations' (e.g., on palliative care) on the screen, or to check in with the caregiver without the presence of the patient; the problems in using audio-visual devices for older people and for subjects with major neurocognitive disorders or severe neurosensory deficits, or even the unavailability of such devices.

Patient and caregiver education programs

When and where telehealth is not a feasible or efficient solution, other interventions might help reduce the overall impact of coronavirus disease on neurological disorders, and particularly on dementia and PD populations[64, 89]. Patients and caregivers should first of all be educated to keep home a "clean zone" (e.g., contacts should receive an anti-COVID vaccine, have regular COVID-19 testing, wear appropriate personal protective equipment, strictly follow recommended prevention rules). Family members and caregivers should also be encouraged to monitor patients' clinical changes (including, for instance, worsening or onset of ICD in PD patients), and be advised on how to organize home-based activities like cognitive stimulating tasks (including arts and crafts or games) or simple exercise (e.g., walking, stretching). In fact, although the majority of physical rehabilitation programs for PD patients are conducted outside

the home in supervised settings (e.g., non-contact boxing programs, assisted aerobic or functional strength activities, yoga), many activities can be done at home[90]. Most of them have been shown to effectively reduce off-state motor signs even with minimal remote supervision, at least in patients with mild disease severity[91]. For PD patients, web-based exercise initiatives such as online singing and exercise or dancing classes have indeed been implemented during the pandemic, often initiated or supported by large patient associations.

Pharmacological interactions

On their part, clinicians should keep on the alert for atypical presentations of coronavirus infection, to promote timely diagnosis of the disease, and be able to adopt a targeted approach in those patients who do become infected. Special efforts should be made to monitor and prevent delirium, given the high prevalence and poor outcome of this condition in patients with a neurodegenerative disorder, and close attention should be paid to possible pharmacological interactions. Patients with dementia are often on a cocktail of cholinesterase inhibitors/memantine, antidepressants and antipsychotics that interact with liver enzymes and cause adverse events similar to those of antirheumatic (chloroquine and hydroxychloroquine), antiviral (ritonavir in particular) or antibiotic (e.g., azithromycin) drugs used for treating COVID-19[62]. Pharmacological choices should be guided by these observations. As an example, cholinesterase inhibitors might require adjusting, or replacing with memantine (which has lower hepatic interaction) if used in conjunction with antirheumatics, and ribavirin or favipiravir should be preferred to other antivirals as they can be administered more safely alongside treatments for AD. As to patients with PD, several case series and observational studies have reported a worsening of motor and non-motor symptoms during COVID-19 infection, which may be linked to acute systemic inflammatory response, or to changes in pharmacokinetics of oral therapy (e.g., reduced absorption due to diarrhea)[92]. Clinicians should be prepared to increase levodopa dose in these circumstances[92]. For patients treated with MCT, it is recommended to gradually reduce stimulation amplitude and increase levodopa dosage accordingly to avoid acute cessation when end of IPG life is approaching. Routine management of the device should also be reorganized, for instance through supplementation of programming-related follow ups with video teleconsultations, and with the use of patient-controlled programmers. Decision algorithms for patients with advanced therapies are available in the literature to improve PD work up in these difficult circumstances[93].

Reflections on COVID-19 vaccination in frail neurological patients

The ultimate defense against coronavirus infection is, of course, represented by vaccines.

Specialists managing patients with dementia should be aware that vaccination against COVID-19 is recommended to these patients above and beyond the general elderly population. Participation of patients with cognitive impairment or dementia in clinical trials on anti-COVID vaccines was probably null or negligible, since such conditions were explicit reasons for exclusion in the Oxford-AstraZeneca trial, and could be reasons for exclusion upon investigator's judgment in the Pfizer/BioNTech and Moderna trials[94], but without a doubt the risk-benefit ratio favors vaccination of patients with dementia against coronavirus. This has also been clearly confirmed in PD patients (see MDS/MDS COVID-19 Vaccine Statement for Patients[95]) since the benefits and risks of approved COVID-19 vaccinations do not appear to differ in individuals with this disorder from those observed in the general population, while the risks of life-threatening complications of the infection do appear to be higher for persons living with advanced PD. Moreover, no changes in PD symptoms or responses to PD treatments following COVID-19 vaccination have been reported, whereas PD symptoms may worsen after COVID-19 infection. Finally, although longitudinal studies are warranted to explore the impact of vaccines on PD progression, no evidence has been found thus far suggesting a direct interaction of vaccine-induced immune response with the neurodegenerative process and, in particular, with inflammation associated with the pathogenesis of PD[96].

Some concern might arise in patients with underlying neuroinflammatory conditions when it comes to COVID-19 vaccines; the fear is that vaccination would trigger the immune system and lead to neurological adverse events. One of the main concerns is related to the possible onset of an acute polyradiculoneuritis following vaccination. Weighing the evidence to date, the potential COVID-19 specific consequences outweigh the risks of vaccination. The general recommendation is that patients with inflammatory neuropathies should be encouraged to have the vaccination[97] and, as stated by such experts as Lunn and co-authors[98], although an association of any vaccination to acute polyradiculoneuritis cannot be ruled out and we should stay vigilant, it is not necessarily to be expected. On the other hand, regarding those patients who are actively receiving an immunosuppressive/immunomodulatory treatment, such as, for example, MS patients, some concerns might arise as to the effect of these treatments on vaccine efficacy, reducing the ability of the individual patient to have an adequate immune response[99], especially for those which interfere with B-cell activity and antibody production. This gave rise to some indications by different scientific societies, for example the SIN, suggesting to wait 4-6 weeks after

the completion of the whole vaccination cycle before starting drugs such as alemtuzumab, rituximab, ocrelizumab, ofatumumab, cyclophosphamide, mitoxantrone[100]. However, this is just an example, and given that we are still obtaining evidence on COVID-19 and COVID-19 vaccination management (taking into account novel vaccines might be soon available), the best course of action is to rely on indications given by regulatory agencies, such as the European Medicine Agency (EMA) in Europe and the Food and Drug Administration (FDA) in the US, and to keep constantly updated on changes on data reported in the technical description of both DMTs and COVID-19 vaccine.

Take-home message

- SARS-CoV-2 virus, known to cause COVID-19, is having a dramatic impact on neurological patients, highlighting older and new frailties.
- Careful updates on growing evidence should be recommended for patients undergoing immunomodulatory/immunosuppressive treatments, relying on indications that continue to be released by regulatory agencies and scientific societies.
- There have been problems in treatment/care/follow up of frail patients (e.g., dementia patients) suggesting a possible role for telemedicine.
- COVID-19 should be carefully monitored for potential neurological complications and their exact impact will only be evaluated through large observational trails, such as the NEUROCOVID study proposed by the SIN.
- The ultimate defense against coronavirus infection is represented by vaccines. Considering the evidence so far, the potential COVID-19 specific consequences outweigh the risks of vaccination. Careful planning of vaccine administration should be undertaken for patients undergoing immunomodulant and/or immunosuppressive treatments.

References

1. Vakili K, Fathi M, Hajiesmaeili M, et al. Neurological Symptoms, Comorbidities, and Complications of COVID-19: A Literature Review and Meta-Analysis of Observational Studies. Eur Neurol 2021:1-18.
2. Yadav R, Srivastava DK, Bajpai PK, Kumar R. Systemic review of CNS involvement and its manifestations in SARS-CoV2 positive patients. *J Infect Public Health* 2021;14:734-739.
3. Camargo-Martínez W, Lozada-Martínez I, Escobar-Collazos A, et al. Post-COVID 19 neurological syndrome: Implications for sequelae's treatment. *J Clin Neurosci* 2021;88:219-225.
4. Ferrarese C, Silani V, Priori A, et al. An Italian multicenter retrospective-prospective observational study on neurological manifestations of COVID-19 (NEURO-COVID). *Neurol Sci* 2020;41:1355-1359.
5. Dalla Costa G, Leocani L, Montalban X, et al. Real-time assessment of COVID-19 prevalence among multiple sclerosis patients: a multicenter European study. *Neurol Sci* 2020;41:1647-1650.
6. Chaudhry F, Jageka C, Levy PD, Cerghet M, Lisak RP. Review of the COVID-19 Risk in Multiple Sclerosis. *J Cell Immunol* 2021;3:68-77.
7. Berger JR, Brandstadter R, Bar-Or A. COVID-19 and MS disease-modifying therapies. *Neurol Neuroimmunol Neuroinflamm* 2020;7.
8. Willis MD, Robertson NP. Multiple sclerosis and the risk of infection: considerations in the threat of the novel coronavirus, COVID-19/SARS-CoV-2. *J Neurol* 2020;267:1567-1569.
9. Wijnands JMA, Zhu F, Kingwell E, et al. Disease-modifying drugs for multiple sclerosis and infection risk: a cohort study. *J Neurol Neurosurg Psychiatry* 2018;89:1050-1056.
10. Boziki MK, Mentis AA, Shumilina M, Makshakov G, Evdoshenko E, Grigoriadis N. COVID-19 Immunopathology and the Central Nervous System: Implication for Multiple Sclerosis and Other Autoimmune Diseases with Associated Demyelination. *Brain Sci* 2020;10.
11. Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. *Neurology* 2020;94:949-952.
12. Zheng C, Kar I, Chen CK, et al. Multiple Sclerosis Disease-Modifying Therapy and the COVID-19 Pandemic: Implications on the Risk of Infection and Future Vaccination. *CNS Drugs* 2020;34:879-896.
13. Diaz de la Fe A, Peláez Suárez AA, Fuentes Campos M, et al. SARS-CoV-2 Infection and Risk Management in Multiple Sclerosis. *Diseases* 2021;9.
14. https://www.aism.it/raccomandazioni_aggiornate_sul_covid_19_le_persone_con_sclerosi_multipla_sm.
15. Gummi RR, Kukulka NA, Deroche CB, Govindarajan R. Factors associated with acute exacerbations of myasthenia gravis. *Muscle Nerve* 2019;60:693-699.

16. Galassi G, Marchioni A. Myasthenia gravis at the crossroad of COVID-19: focus on immunological and respiratory interplay. *Acta Neurol Belg* 2021.
17. Camelo-Filho AE, Silva AMS, Estephan EP, et al. Myasthenia Gravis and COVID-19: Clinical Characteristics and Outcomes. *Front Neurol* 2020;11:1053.
18. Muppidi S, Guptill JT, Jacob S, et al. COVID-19-associated risks and effects in myasthenia gravis (CARE-MG). *Lancet Neurol* 2020;19:970-971.
19. Jacob S, Muppidi S, Guidon A, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci* 2020;412:116803.
20. Paola, Maria ASBMPAK, Ferrarese LPPSMVGGFPDAMIAC. Guillain-Barré syndrome related to COVID-19 infection. *Neurol Neuroimmunol Neuroinflamm* [serial online] 2020;accepted paper.
21. Filosto M, Cotti Piccinelli S, Gazzina S, et al. Guillain-Barré syndrome and COVID-19: an observational multicentre study from two Italian hotspot regions. *J Neurol Neurosurg Psychiatry* 2020.
22. Sheikh AB, Chourasia PK, Javed N, et al. Association of Guillain-Barre syndrome with COVID-19 infection: An updated systematic review. *J Neuroimmunol* 2021;355:577577.
23. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. *Brain* 2021;144:682-693.
24. Weller M, Preusser M. How we treat patients with brain tumour during the COVID-19 pandemic. *ESMO Open* 2020;4:e000789.
25. Bernhardt D, Wick W, Weiss SE, et al. Neuro-oncology Management During the COVID-19 Pandemic With a Focus on WHO Grade III and IV Gliomas. *Neuro Oncol* 2020.
26. Siepmann T, Sedghi A, Barlinn J, et al. Association of history of cerebrovascular disease with severity of COVID-19. *J Neurol* 2021;268:773-784.
27. Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis* 2018;77:905-910.
28. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers YM. Cardiac Complications Attributed to Chloroquine and Hydroxychloroquine: A Systematic Review of the Literature. *Drug Saf* 2018;41:919-931.
29. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med* 2020;382:e60.
30. Wang A, Mandigo GK, Yim PD, Meyers PM, Lavine SD. Stroke and mechanical thrombectomy in patients with COVID-19: technical observations and patient characteristics. *J Neurointerv Surg* 2020;12:648-653.
31. Escalard S, Maïer B, Redjem H, et al. Treatment of Acute Ischemic Stroke due to Large Vessel Occlusion With COVID-19: Experience From Paris. *Stroke*

2020;51:2540-2543.

32. Akhtar N, Abid FB, Kamran S, et al. Characteristics and Comparison of 32 COVID-19 and Non-COVID-19 Ischemic Strokes and Historical Stroke Patients. *J Stroke Cerebrovasc Dis* 2021;30:105435.
33. Rothstein A, Oldridge O, Schwennesen H, Do D, Cucchiara BL. Acute Cerebrovascular Events in Hospitalized COVID-19 Patients. *Stroke* 2020;51:e219-e222.
34. Bekelis K, Missios S, Ahmad J, et al. Ischemic Stroke Occurs Less Frequently in Patients With COVID-19: A Multicenter Cross-Sectional Study. *Stroke* 2020;51:3570-3576.
35. Sacco S, Ricci S, Ornello R, et al. Reduced Admissions for Cerebrovascular Events During COVID-19 Outbreak in Italy. *Stroke* 2020;51:3746-3750.
36. Siegler JE, Heslin ME, Thau L, Smith A, Jovin TG. Falling stroke rates during COVID-19 pandemic at a comprehensive stroke center. *J Stroke Cerebrovasc Dis* 2020;29:104953.
37. Hsiao J, Sayles E, Antzoulatos E, et al. Effect of COVID-19 on Emergent Stroke Care: A Regional Experience. *Stroke* 2020;51:e2111-e2114.
38. Schlachetzki F, Wilfling S, Hubert ND, et al. Decline and Recurrence of Stroke Consultations during the COVID-19 Pandemic Lockdown Parallels Population Activity Levels. *Cerebrovasc Dis* 2021;50:317-325.
39. Jasne AS, Chojecka P, Maran I, et al. Stroke Code Presentations, Interventions, and Outcomes Before and During the COVID-19 Pandemic. *Stroke* 2020;51:2664-2673.
40. Koopmann A, Georgiadou E, Reinhard I, et al. The Effects of the Lockdown during the COVID-19 Pandemic on Alcohol and Tobacco Consumption Behavior in Germany. *Eur Addict Res* 2021:1-15.
41. Chambonniere C, Lambert C, Tardieu M, et al. Physical Activity and Sedentary Behavior of Elderly Populations during Confinement: Results from the FRENCH COVID-19 ONAPS Survey. *Exp Aging Res* 2021:1-13.
42. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. *Int J Stroke* 2020;15:361-364.
43. D'Anna L, Ellis N, Bentley P, et al. Delivering telemedicine consultations for patients with transient ischaemic attack during the COVID-19 pandemic in a comprehensive tertiary stroke centre in the United Kingdom. *Eur J Neurol* 2021.
44. Wang CC, Chao JK, Wang ML, et al. Care for Patients with Stroke During the COVID-19 Pandemic: Physical Therapy and Rehabilitation Suggestions for Preventing Secondary Stroke. *J Stroke Cerebrovasc Dis* 2020;29:105182.
45. Correction: Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology* 2017;89:642.
46. Kubota T, Kuroda N. Exacerbation of neurological symptoms and COVID-19 severity in patients with preexisting neurological disorders and COVID-19: A systematic review. *Clin Neurol Neurosurg* 2021;200:106349.
47. Cummins L, Ebyarimpa I, Cheetham N, Tzortziou Brown V, Brennan K, Panovs-

ka-Griffiths J. Factors associated with COVID-19 related hospitalisation, critical care admission and mortality using linked primary and secondary care data. *Influenza Other Respir Viruses* 2021.

48. Lu L, Xiong W, Liu D, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. *Epilepsia* 2020;61:e49-e53.
49. Kuroda N. Epilepsy and COVID-19: Updated evidence and narrative review. *Epilepsy Behav* 2021;116:107785.
50. Lallana S, Fonseca E, Restrepo JL, et al. Medium-term effects of COVID-19 pandemic on epilepsy: A follow-up study. *Acta Neurol Scand* 2021.
51. Wirrell EC, Grinspan ZM, Knupp KG, et al. Care Delivery for Children With Epilepsy During the COVID-19 Pandemic: An International Survey of Clinicians. *J Child Neurol* 2020;35:924-933.
52. Banks J, Corrigan D, Grogan R, et al. LoVE in a time of CoVID: Clinician and patient experience using telemedicine for chronic epilepsy management. *Epilepsy Behav* 2021;115:107675.
53. Datta P, Barrett W, Bentzinger M, et al. Ambulatory care for epilepsy via telemedicine during the COVID-19 pandemic. *Epilepsy Behav* 2021;116:107740.
54. Smorenberg A, Peters EJ, van Daele P, Nossent EJ, Muller M. How does SARS-CoV-2 targets the elderly patients? A review on potential mechanisms increasing disease severity. *Eur J Intern Med* 2021;83:1-5.
55. Hariyanto TI, Putri C, Arisa J, Situmeang RFV, Kurniawan A. Dementia and outcomes from coronavirus disease 2019 (COVID-19) pneumonia: A systematic review and meta-analysis. *Arch Gerontol Geriatr* 2021;93:104299.
56. Izcovich A, Ragusa MA, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PLoS One* 2020;15:e0241955.
57. Liu N, Sun J, Wang X, Zhao M, Huang Q, Li H. The Impact of Dementia on the Clinical Outcome of COVID-19: A Systematic Review and Meta-Analysis. *J Alzheimers Dis* 2020;78:1775-1782.
58. Numbers K, Brodaty H. The effects of the COVID-19 pandemic on people with dementia. *Nat Rev Neurol* 2021;17:69-70.
59. Mok VCT, Pendlebury S, Wong A, et al. Tackling challenges in care of Alzheimer's disease and other dementias amid the COVID-19 pandemic, now and in the future. *Alzheimers Dement* 2020;16:1571-1581.
60. Emmerton D, Abdelhafiz AH. Care for Older People with Dementia During COVID-19 Pandemic. *SN Compr Clin Med* 2021:1-7.
61. McAlpine LS, Fesharaki-Zadeh A, Spudich S. Coronavirus disease 2019 and neurodegenerative disease: what will the future bring? *Curr Opin Psychiatry* 2021;34:177-185.
62. Yamamoto V, Bolanos JF, Fiallos J, et al. COVID-19: Review of a 21st Century Pandemic from Etiology to Neuro-psychiatric Implications. *J Alzheimers Dis*

2020;77:459-504.

63. Gil R, Arroyo-Anlló EM. Alzheimer's Disease and Face Masks in Times of COVID-19. *J Alzheimers Dis* 2021;79:9-14.
64. Meshkat S, Salimi A, Joshaghanian A, Sedighi S, Aghamollaii V. Chronic neurological diseases and COVID-19: Associations and considerations. *Transl Neurosci* 2020;11:294-301.
65. Wouk J, Rechenchoski DZ, Rodrigues BCD, Ribelato EV, Faccin-Galhardi LC. Viral infections and their relationship to neurological disorders. *Arch Virol* 2021;166:733-753.
66. Rahman MA, Islam K, Rahman S, Alamin M. Neurobiochemical Cross-talk Between COVID-19 and Alzheimer's Disease. *Mol Neurobiol* 2021;58:1017-1023.
67. Artusi CA, Romagnolo A, Ledda C, et al. COVID-19 and Parkinson's Disease: What Do We Know So Far? *J Parkinsons Dis* 2021;11:445-454.
68. Papa SM, Brundin P, Fung VSC, et al. Impact of the COVID-19 Pandemic on Parkinson's Disease and Movement Disorders. *Mov Disord* 2020;35:711-715.
69. Artusi CA, Romagnolo A, Imbalzano G, et al. COVID-19 in Parkinson's disease: Report on prevalence and outcome. *Parkinsonism Relat Disord* 2020;80:7-9.
70. Cortés-Borra A, Aranda-Abreu GE. Amantadine in the prevention of clinical symptoms caused by SARS-CoV-2. *Pharmacol Rep* 2021.
71. Cortés Borra A. Does amantadine have a protective effect against COVID-19? *Neurol Neurochir Pol* 2020;54:284-285.
72. Fink K, Nitsche A, Neumann M, Grossegesse M, Eisele KH, Danysz W. Amantadine Inhibits SARS-CoV-2 In Vitro. *Viruses* 2021;13.
73. Fearon C, Fasano A. Parkinson's Disease and the COVID-19 *Pandemic. J Parkinsons Dis* 2021;11:431-444.
74. Zhang Q, Schultz JL, Aldridge GM, Simmering JE, Narayanan NS. Coronavirus Disease 2019 Case Fatality and Parkinson's Disease. *Mov Disord* 2020;35:1914-1915.
75. Cohen ME, Eichel R, Steiner-Birmanns B, et al. A case of probable Parkinson's disease after SARS-CoV-2 infection. *Lancet Neurol* 2020;19:804-805.
76. Makhoul K, Jankovic J. Parkinson's disease after COVID-19. *J Neurol Sci* 2021;422:117331.
77. Rainero I, Bruni AC, Marra C, et al. The Impact of COVID-19 Quarantine on Patients With Dementia and Family Caregivers: A Nation-Wide Survey. *Front Aging Neurosci* 2020;12:625781.
78. Cagnin A, Di Lorenzo R, Marra C, et al. Behavioral and Psychological Effects of Coronavirus Disease-19 Quarantine in Patients With Dementia. *Front Psychiatry* 2020;11:578015.
79. Mioshi E, Foxe D, Leslie F, et al. The impact of dementia severity on caregiver burden in frontotemporal dementia and Alzheimer disease. *Alzheimer Dis Assoc Disord* 2013;27:68-73.
80. Tsapanou A, Papatriantafyllou JD, Yiannopoulou K, et al. The impact of COVID-19 pandemic on people with mild cognitive impairment/dementia and

on their caregivers. Int J Geriatr Psychiatry 2021;36:583-587.

81. Helmich RC, Bloem BR. The Impact of the COVID-19 Pandemic on Parkinson's Disease: Hidden Sorrows and Emerging Opportunities. *J Parkinsons Dis* 2020;10:351-354.
82. Salari M, Zali A, Ashrafi F, et al. Incidence of Anxiety in Parkinson's Disease During the Coronavirus Disease (COVID-19) Pandemic. *Mov Disord* 2020;35:1095-1096.
83. Zucca M, Isella V, Lorenzo RD, et al. Being the Family Caregiver of a Patient With Dementia During the Coronavirus Disease 2019 Lockdown. *Front Aging Neurosci* 2021;13:653533.
84. Richter D, Scherbaum R, Bartig D, Gold R, Krogias C, Tönges L. Analysis of nationwide multimodal complex treatment and drug pump therapy in Parkinson's disease in times of COVID-19 pandemic in Germany. *Parkinsonism Relat Disord* 2021;85:109-113.
85. Geddes MR, O'Connell ME, Fisk JD, et al. Remote cognitive and behavioral assessment: Report of the Alzheimer Society of Canada Task Force on dementia care best practices for COVID-19. *Alzheimers Dement (Amst)* 2020;12:e12111.
86. Gosse PJ, Kassardjian CD, Masellis M, Mitchell SB. Virtual care for patients with Alzheimer disease and related dementias during the COVID-19 era and beyond. *CMAJ* 2021;193:E371-E377.
87. Tarolli CG, Andrzejewski K, Zimmerman GA, et al. Feasibility, Reliability, and Value of Remote Video-Based Trial Visits in Parkinson's Disease. *J Parkinsons Dis* 2020;10:1779-1786.
88. https://www.movementdisorders.org/MDS/About/Committees--Other-Groups/Telemedicine-in-Your-Movement-Disorders-Practice-A-Step-by-Step-Guide.htm.
89. Barry HE, Hughes CM. Managing medicines in the time of COVID-19: implications for community-dwelling people with dementia. *Int J Clin Pharm* 2021;43:275-279.
90. Vaartio-Rajalin H, Rauhala A, Fagerström L. Person-centered home-based rehabilitation for persons with Parkinson's disease: A scoping review. *Int J Nurs Stud* 2019;99:103395.
91. van der Kolk NM, de Vries NM, Kessels RPC, et al. Effectiveness of home-based and remotely supervised aerobic exercise in Parkinson's disease: a double-blind, randomised controlled trial. *Lancet Neurol* 2019;18:998-1008.
92. Cilia R, Bonvegna S, Straccia G, et al. Effects of COVID-19 on Parkinson's Disease Clinical Features: A Community-Based Case-Control Study. *Mov Disord* 2020;35:1287-1292.
93. Fasano A, Antonini A, Katzenschlager R, et al. Management of Advanced Therapies in Parkinson's Disease Patients in Times of Humanitarian Crisis: The COVID-19 Experience. *Mov Disord Clin Pract* 2020;7:361-372.
94. Antonelli Incalzi R, Trevisan C, Del Signore S, et al. Are vaccines against COVID-19 tailored to the most vulnerable people? *Vaccine* 2021;39:2325-2327.

95. https://www.movementdisorders.org/COVID-19-Pandemic-MDS/MDS-COVID-19-Vaccine-Statement-for-Patients.htm.

96. Bloem BR, Trenkwalder C, Sanchez-Ferro A, et al. COVID-19 Vaccination for Persons with Parkinson's Disease: Light at the End of the Tunnel? *J Parkinsons Dis* 2021;11:3-8.

97. Doneddu PE, Spina E, Briani C, et al. Acute and chronic inflammatory neuropathies and COVID-19 vaccines: Practical recommendations from the task force of the Italian Peripheral Nervous System Association (ASNP). *J Peripher Nerv Syst* 2021.

98. Lunn MP, Cornblath DR, Jacobs BC, et al. COVID-19 vaccine and Guillain-Barré syndrome: let's not leap to associations. *Brain* 2021;144:357-360.

99. Otero-Romero S, Ascherio A, Lebrun-Frénay C. Vaccinations in multiple sclerosis patients receiving disease-modifying drugs. *Curr Opin Neurol* 2021;34:322-328.

100. (http://www.neuro.it/web/lib/Download.cfm?dirdownload=E%3A%5Cgruppotesi%5Cdatasite%5Cnephromeet%5CDocs%5CNWSNEURO%5CATT%5C&filename=190%5FAggiornamentoRaccomandazioniSMeCovid%5F17052021%2Epdf&filesavename=Aggiornamento%20Raccomandazioni%20SM%20e%20Covid%5F17%2E05%2E2021%2Epdf&typeattach=inline.