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Review

Rehabilitation of severe neurological complications post SARS-CoV-2 infection

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ABSTRACT: Medical rehabilitation is a multi-professional / interdisciplinary process aimed at enhancing and restoring functional ability (activity and participation) and quality of life to people with impairments or disabilities. Rehabilitation is applied throughout the continuum of care. COVID-19 patients may develop a myriad of acute medical problems (linked to the virus per se, or as consequences of the invasive procedures), which can cause acute, post-acute and long-term consequences requiring rehabilitation. Information about short and long-term sequelae of COVID-19 indicate an increasing need for rehabilitation. The paper is focused on two main aspects: rehabilitation of the severe neurological disabilities that occurred during the acute phase and continuing in the chronic phase (i.e., different neurological sensory-motor and cognitive deficits secondary to stroke, encephalitis, seizures, encephalopathies). The other main issue is generated by the disruption of regular rehabilitation in people with neurological disabilities and chronic diseases (people living with sequels after stroke, Parkinson's disease, multiple sclerosis) due to quarantine, social isolation, movement restriction, and other healthcare systems 'disruptions. **Methods** Internet literature search (Lit Covid and PubMed) using the following keywords (Covid-19, Coronavirus, neurological complications, rehabilitation). During 2020-2021 were published 88 papers (in 2020 = 54, and in 2021= 54), with 21 reviewes (2020 = 15; 2021 = 8), and 2 systematic reviews, refearing neuroreabilitation in Covid-19 subacutre and long-term cases. **Discussion** REH-COVER Cochrane Rehabilitation WHO initiative ("Rapid Living Systematic Reviews Second Edition, called 2020"), contains the main cornerstones for a tailored rehabilitation programme, the best (current) available rehabilitation evidence on recovery interventions, for the patients living with sequelae of COVID-19. **Conclusions** More than two years since the outbreak of the COVID-19 pandemic, it is obvious that rehabilitation services play a crucial role in post-COVID recovery trajectories. A further achievement of research and evidence focussed on the clinical management, comprehensive treatments, and efficacy need to be targeted on short and long-term (neuro)-rehabilitation service models of care, for COVID-19 survivors.

Keywords: *Covid-19, rehabilitation, neurological disabilities, SARS-CoV-2*

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1. INTRODUCTION

Coronavirus (CoV) represents a large family of RNA viruses found in different animal species including birds, livestock, and mammals. These viruses are known to affect different human systems including the respiratory, hepatic, nervous, and gastrointestinal systems.

Subtypes of CoV which are known to be pathogenic to humans, usually cause mild clinical symptoms except for two subtypes: severe acute respiratory syndrome related coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).(1)

An internet literature search (Lit Covid and PubMed) using the following keywords (Covid-19, Coronavirus, neurological complications, rehabilitation). During 2020-2021 were published 88 papers (in 2020 = 54, and in 2021= 54), with 21 reviews (2020 = 15; 2021 = 8), and 2 systematic reviews, referring neurorehabilitation in Covid-19 subacute and long-term cases.

The catastrophic proportions of this pandemic is reflected in over 5.5 million deaths all over the world (fig 1) (2)

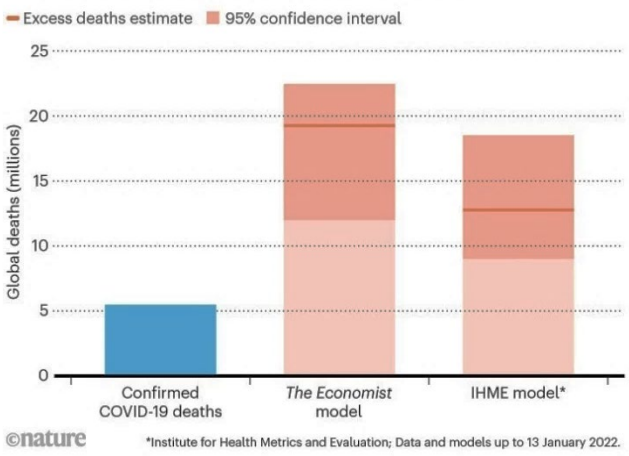

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Fig. 1 The total number of deaths from the beginning of the pandemic seems to be underestimated (28)

Covid-19 neurological manifestations and physiopathological mechanisms in the acute infectious phase are summarized in table I-II

Acute Neurologic Complications Of Coronavirus Infections

Para-infectious syndromes
Encephalopathy
Central hypoventilation
Viral meningitis
Anosmia and ageusia
Encephalitis
Stroke
Acute necrotizing hemorrhagic encephalopathy
Myositis

Postinfectious syndromes
Acute disseminated encephalomyelitis
Brainstem encephalitis
Transverse myelitis
Guillain Barre syndrome
Sensory neuropathy

PARAINFECTIOUS COMPLICATIONS

Stroke. Patients with SARS-CoV-2 and SARS-CoV-1 infection
- Hypercoagulable syndrome
- Elevated D-dimer levels and increased PT and aPTT
  - arterial and venous occlusions in the brain vasculature
  - DIC cases
- Elderly patients with other underlying cardiovascular risk factors
  - vascular occlusive syndromes
  - including stroke and deep vein thrombosis (Tsai et 2005)
  - myocarditis, which may be another risk factor for stroke
  - However, strokes are being reported an individuals who have no other risk factor other than COVID-19
  - cerebral vasculature presence viral receptor ACE2

Infection can cause neurologic symptoms such as headache, anosmia, ageusia, cerebrovascular accident,confusion, agitation, impaired consciousness, and encephalitis or encephalopathy, seizure, ataxia, neuropathies. (2- 4)

Dizziness and headache were the most common central nervous system (CNS) manifestations, found in 11.9% respectively 11.8% (5), followed by confusion/ decreased cognitive level (8%).
Common peripheral nervous system manifestations are taste and smell impairments found in 5.6% and found in 5.1%, respectively.

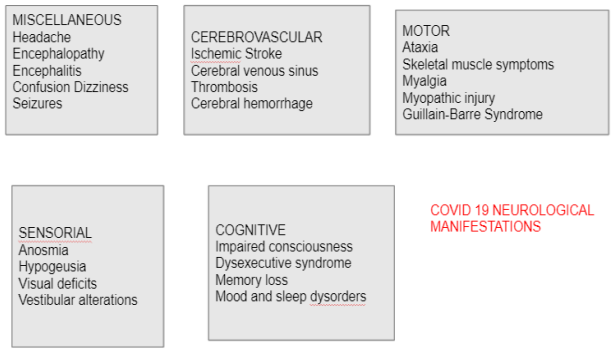

Fig 2, Neurological manifestations in coronavirus disease 2019 (COVID-19 (6)

In the acute stage multifocal areas of inflammatory encephalopathy can manifest with disturbance of consciousness, focal sensory-motor deficits, seizures. An illustrative case is depicted in fig 3

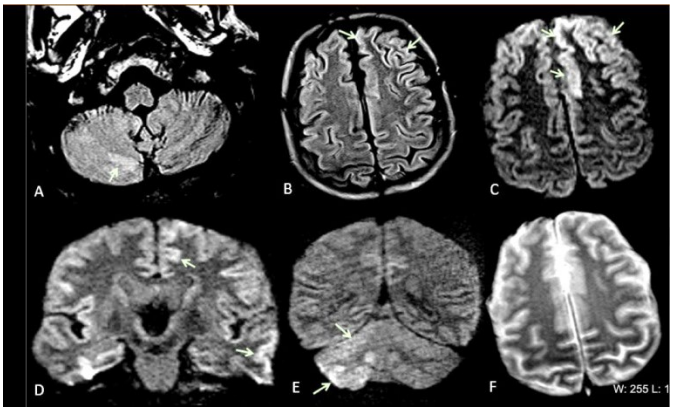

FIG 3 A 69 years-old-man presented with acute encephalopathy and seizures. (7) (A-B) Multifocal areas of FLAIR hyperintensity in the right cerebellum (arrows in A), left anterior cingulate cortex and superior frontal gyrus (arrows in B).
(C-D) Restricted diffusion in the left anterior cingulate cortex, superior frontal and middle temporal gyrus (arrows in D) and right cerebellum (arrows in E), consistent with cerebellar diaschisis. F) No hemosiderin deposits in gradient echo sequences((Modified and adapted from *How COVID-19 Affects the Brain in Neuroimaging* *https://www.itnonline.com/article/how-covid-19-affects-brain-neuroimaging*))
Thrombotic, hypotensive, and hypoxemic consequences of the viral infection can also contribute to longstanding, potentially painful neurological sequelae and disabling post-stroke neuro-psychomotor impairments.
Neurological acute and residual post-infectious complications may result from widespread neuropathological disturbances targeting major white matter bundle tracts, cortical gray matter, and subcortical gray matter. (8)
Direct or indirect invasion of the SARS-CoV-2 into CNS is involved in genesis and propagation of neurodegenerative processes via its systemic effects(9):

- migration and infiltration of peripheral leukocytes to the brain induces production of
- pro-inflammatory cytokines, activates microglia
- decline in ACE-2 activity, which acts as a neuroprotective factor

- acute respiratory distress syndrome (ARDS)-induced hypoxemia along with
- sepsis-induced hyper-coagulation generate hypercoagulable state and micro-thrombosis in brain vessels, leading to oxidative stress and neurodegeneration

SARS-CoV-2 can preferentially infect astrocytes explaining some of the neurological symptoms associated with COVID-19, especially fatigue, depression and 'brain fog', which includes confusion and forgetfulness.

Astrocytes might be vulnerable even if they are not infected by the virus.

A recent study compared the brains of eight deceased people who had COVID-19 with the brains of 14 controls. The researchers found no trace of SARS-CoV-2 in the brains of the infected people, but they did find that gene expression had been affected in some astrocytes, which were not working properly.(10)

Neuroinflammation may induce central GABA-ergic dysfunction, representing a common denominator for neuropsychological alterations neuromotor and cognitive fatigue, executive deficits, and apathy in post-COVID (11)

Chopra et al (2021) noticed that 33% of hospitalized patients had persistent symptoms at a 60-day follow-up after COVID-19. Residual effects from SARS-CoV-2 virus include fatigue, dyspnea, chest pain, persistent loss of taste and/or smell, cognitive changes, arthralgias, and decreased quality of life. (12)

About 87.4% of COVID-19 patients reported the persistence of at least one symptom, with fatigue being the most common reported symptom, followed by dyspnea (13)

Persistence or appearance of new symptoms after the recovery affects a multitude of organs. Systemic residual complications may extend beyond the duration of the initial illness during rehabilitation interval of SARS-CoV-2 infection.This persistent sequelae/ symptomatology is obvious multisystemic targeted and can be classified as(14):

(1) post-acute symptoms at 1-month after acute COVID-19 (short term),

(2) persisting and new clinical manifestations between 2 and 5 months after infection (intermediate term), and

(3) clinical manifestations present at least 6 months after COVID-19 (long term/ long haulers).

Most patients who survived after severe or even mild infection, had persisting (up to 12 weeks) of multiple disabling symptoms generically called postacute syndrome/long term covid. Persistence of post-acute disabling symptoms was noticed in half of Covid 19 survivors, mostly in those with mild form of infectious disease(15)

Aproximately 35% of patients with mild COVID-19 did not return to the baseline after recovery(16)

Long-Covid is outlined as a multisystemic post infectious complication/ entity, who summarizes(17):

- symptoms fatigue (92%),
- loss of concentration or memory (74%),
- weakness (68%),
- headache (65%)
- dizziness (64%)

Regardless of their direct neuroinvasive capacity SARS-CoV-2, like SARS and MERS, induce painful parainfectious neurological disease, polyneuritis, Guillain-Barre syndrome (potentially lethal).

COVID-19 infection is associated with painful symptoms, including myalgia, arthralgia, abdominal pain, headache, and chest pain (even in those not admitted to critical care environments) and may require even opioids for symptom management.(18)

Medical rehabilitation is a multi-professional process aimed at enhancing and restoring functional ability (activity and participation) and quality of life to people with impairments or disabilities. (19)

Hypoxia, systemic inflammation, sedation, fluctuations in level of consciousness, and neuromuscular blockade have negative repercussions on prognosis in acute care units

(ICU). Early neurorehabilitation begins in the ICU and is associated with improved outcomes, respectively longer-term neurologic recovery in patients with severe COVID-19 and disorders of consciousness. (20)

Rehabilitation of long-haulers (long Covid survivors) in our Clinic is an integrated, interdisciplinary medical endeavor, aimed mainly at respiratory and neurological sequels.

The physical kinetic rehabilitation of patients after COVID-19 infection cannot be separated from specialized medical assistance, focused on respiratory, neurological, and post-infectious pathologies.

The rehabilitation program requires a holistic approach that responds to the needs of the individual. Rehabilitation concerns several fundamental aspects/ objectives:

(a) Respiratory function and increase of cardio-pulmonary endurance, associated with

(b) postural hemodynamic rehabilitation

The first rehabilitation objective is to re-educate the patient`s postural cardio-vascular and respiratory parameters, from supine to lateral decubitus (rolling activity), then in sitting posture. These postures should be selected based on thoracic/CT imagery, ultrasound, clinical auscultation, and SpO2.

(c) Neuromotor rehabilitation techniques are aimed at restoring static and dynamic balance, and walking. These programs contain physical rehabilitation / re-education for peripheral muscle function (physical training at mild, moderate intensity, then aerobic training and strength.

The COVID-19 pandemic imposed social/physical distancing, lockdown measures and forced reorientation of the neurorehabilitation programs for people with neurological disabling sequels.

Telemedicine has turned virtual space into a new reality and may compensate for the restrictions imposed on face-to-face meetings. The regular and individualized physical-kinetic rehabilitation program can be achieved even in pandemic conditions, using modern telecommunication techniques. The European Foundation for health and exercise provides iPad and iPhone applications for telehealth and remote physical-kinetic motor rehabilitation in Parkinson's disease, for tbe therapists and patients. (https://apps.apple.com/us/developer/european-foundation-for-health-and-exercise/id473641733)

Further studies are necessary to identify the optimal web-based model of care, expand access to video-based care services (ie, remote consultation, patient education, and ongoing monitoring), establish best practices worldwide, and equitable access to this modern concept of neurorehabilitation. (21)(22)

Ozone therapy showed positive results in COVID-19 patients, besides its miscellaneous other benefic therapeutic applications, briefly summarized below:

-Non-healing wounds and ulcers, diabetic ulcers, surgical wound infections
-Circulatory disorders like varicose veins, Ischemia, atherosclerosis
-Skin conditions like eczema, infections, bedsores, ulcers
-Supportive treatment in cancer
-Gynecological infections (candida, endometriosis), and infertility
-Ear Nose Throat infections, sinus infections, bronchitis etc.
-Arthritis, Rheumatism, Backaches, Spondylitis
-Liver diseases, cirrhosis, hepatitis
-Brain disorders, Parkinson's, memory impairments, etc.
-Chronic infections due to viruses, bacteria, fungi, and other germs
- Neurological disorders (neuropathic pain, and hyperalgesia, headaches and facial pain)

A study of 46 patients (11 intubated and 35 non-intubated) showed that in 39 (84%) of the patients, respiratory improvement was obtained after ozone administration. (23)

In spite of the promising background data, indicating the effectiveness of ozone, there is still not enough evidence to confirm this as a viable treatment option for COVID-19. Its pathophysiological mechanism of action consists of influencing different hypoxia-inducible factors and cellular adaptation to hypoxia leading to activation of trophic proteins and specific biological processes, including erythropoiesis and angiogenesis.
Hyperbaric Oxygen Therapy (HBOT) is controversial. It seemed to be safe and effective in hypoxemic patients with COVID-19, but recent deadly accidents in some well known mass-media people in Romania questioned its efficacy and safety in (some ?) post-Covid patients.
Most studies used less than 1.5–2 absolute atmospheres (ATA) for 90 min sessions and thereafter sessions were decreased to 60 min. Trials demonstrated that most of the patients recovered after receiving HBOT, and blood oxygen saturation increased after several sessions of HBOT.
However, there is limited knowledge and evidence regarding the effects and mechanism of HBOT in COVID-19 treatment, and further evaluations require extensive well-designed studies. (24) Randomized controlled studies are mandatory (25)
The best (currently) available rehabilitation evidence on recovery interventions, for the patients living with sequelae of COVID-19 was synthesized in WHO initiative REHCOVER Cochrane Rehabilitation (Rapid Living Systematic Reviews Second Edition, 2020), contains the main cornerstones for a tailored rehabilitation program.(26)
The final pieces of the complex puzzle of rehabilitation interventions aim at improving autonomy, quality of life and reintegration of the individual into family and community / society. These aspects must be holistically integrated in a complex bio-psycho-socio-economic context. Somatic disabling symptoms (such as chronic pain post SARS-CoV-2 infection) may be exacerbated by multiple environmental barriers/ factors, including social threats, discontinuation of therapy, reduced access to treatments and concerns about health outcomes (27-31)
Conclusion Rehabilitation is applied throughout the continuum of care and is indicated in acute, subacute stages and in long covid survivors.
After two years since the outbreak of the COVID-19 pandemic, it appeared that rehabilitation services play a crucial role in post-COVID recovery trajectories.
A further achievement of research and evidence focussed on the clinical management, comprehensive treatments, and efficacy need to be targeted on short and long-term (neuro)-rehabilitation service models of care, for COVID-19 survivors.

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