Features and Management of Acute and Chronic Neuro-Covid

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Dedicated to all colleagues and friends who are engaged at the forefront of this long-standing battle against an invisible but terrifying enemy

Foreword

At the beginning of the pandemic, in the middle of the night, I received a message from Marco asking for my opinion on a clinical case of COVID-19. He was excited because the patient's conditions rapidly improved after he received one dose of tocilizumab. As an immunologist, I understood that the pathophysiology of the disease was largely attributable to the cytokine storm and this evidence could be exploited for therapeutic purposes. In other words, what we learned over the years in immuno-oncology could be translated to the treatment of COVID-19, particularly the host inflammatory response phase of the disease. In this critical situation, it was evident that not only the lung, but all the organs were affected by the hyperinflammation with subsequent damage. In this context, the acute and long-lasting neurological manifestations of COVID-19 configure a chapter of paramount importance.

The authors have comprehensively addressed all the problems related to neuro-COVID, from the neuropathogenesis of SARS-CoV-2 infection, to the acute clinical pictures, and diagnostic approaches, to the post-acute neurological, psychiatric, and neurocognitive issue. The result is a book that is enjoyable to read and full of information. I appreciated, for example, the authors' choice to summarize the therapeutic suggestions into highlights. This strategy facilitates rapid consultation by those who may have difficulty navigating into the plethora of scientific literature on the subject and search for rapid practical suggestions. The efforts of the authors will certainly be rewarded, and I am sure that both experienced readers and those who intend to deepen their knowledge in the field will appreciate this book.

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Preface

Similar to other epidemic-induced coronaviruses, the SARS-CoV-2 seems to be neuroinvasive, neurotropic, and neurovirulent. A Chinese study published in the first weeks after the onset of the pandemic reported neurological symptoms were present in 36% of COVID-19 patients. Subsequently, thanks to the growing number of data reported in the literature, clinicians and researchers deduced that the neurological manifestations could represent a separate chapter of the disease. The term "neuro-COVID" was coined. Nevertheless, further data must be produced to characterize its profile and obtain a precise taxonomy. In the meantime, we realize that neuro-COVID is an umbrella that collects disparate clinical manifestations. In this set, neurological effects, psychological/psychiatric aspects, and neurocognitive phenomena are included. The pathophysiology of these processes is very complex. Besides a potential direct viral damage, other mechanisms, such as immune-mediated reactions, hypoxia, effects of multiorgan dysfunction, could be involved. Furthermore, the consequences of long-term intensive care treatment, such as psychological sequelae derived from isolation in critically ill patients, should not be underestimated. These arguments also concern non-hospitalized patients who have been subjected to a high burden of psychological distress.

In neuro-COVID, a logical distinction concerns the acute forms from those that occur at a distance (Fig. 1). Although for narrative aims this approach is valid, it has many limitations. Most of the clinical pictures recognize pathophysiology that determines a trigger in the acute phase and that can clinically manifest itself within the acute manifestations of the disease, or at a distance. Therefore, there is an overlapping and difficulties in temporally placing most phenomena often arise. For example, changes in taste and smell, pain, headache, and dizziness may begin when COVID-19 explodes and persist as respiratory symptoms resolve. Nevertheless, the same clinical manifestations can occur after a free interval. Since several diagnostic and therapeutic aspects must necessarily be kept separate, in this book the distinction between acute and chronic forms is maintained.

Another issue concerns the correlation between the clinical expressions of neuro-COVID and the features of the underlying pathology. Myalgia, joint pain, sore throat, abdominal pain, chest pain, and headache usually accompany respiratory symptoms but they can also occur as isolated clinical findings, or can be expressed regardless of the severity of COVID-19. Research on pathophysiology will clarify this and other doubts. The angiotensin-converting enzyme 2/renin–angiotensin

system pathway and the direct virus-induced damage, the exuberant immune-mediated inflammation, and disease-related factors represent a thriving field of research that borders on the fields of neurology and embraces multiple disciplines.

The diagnostic phase plays a very important role. Given that the different expressions of neuro-COVID can have a deleterious impact on the patient's prognosis, a high index of clinical suspicion for neurological complications is mandatory. Thus, every effort should be done to reach a definitive diagnosis. In this contest, besides a complete clinical evaluation, it is often necessary to utilize a battery of neuroimaging, laboratory, and electrodiagnostic tests. Nevertheless, organizing diagnostic pathways can be very difficult. For example, in the case of in-hospital patients, some diagnostic procedures, such as neuroimaging techniques or electrophysiological tests, could be a challenge due to the increased risk of virus transmission to other patients and staff.

A chapter of enormous interest in COVID-19 concerns the post-acute effects of the disease. The implications, in fact, are manifold and range from the need to accurately and urgently characterize the spectrum of clinical conditions that are involved, to the healthcare needs, and obviously to the health costs associated with them. An amount of scientific evidence is showing that COVID-19 is not only a pathology that affects the physical health of those who contracted it, but it can induce a series of non-negligible psychological consequences. Some symptoms related to the contracted infection such as fatigue, weakness, and pain rarely disappear immediately once the critical phase of the disease is overcome but also occur in the periods following COVID-19, impacting the quality of life of patients who have contracted the SARS-CoV-2 infection. In particular, symptoms such as fear, mood changes, states of anxiety, depression, sleep disorders, and insomnia can occur alone or in combination by structuring a variety of psychological syndromes. In the context of long-COVID, risk factors should be carefully addressed. It seems, for instance, that middle-aged women are more prone to develop debilitating long-term symptoms.

The therapy of many clinical forms of neuro-COVID is often addressed by the individual specialist according to the type of symptom, or clinical manifestation,

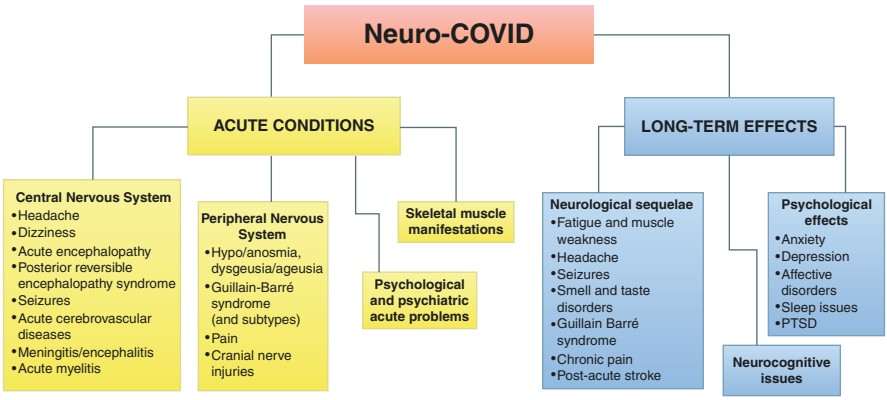

Fig. 1 Neuro-COVID: Synopsis

who follows the rules of good clinical practice. Very often, however, this approach is not enough and a multidisciplinary, or preferably interdisciplinary, strategy is desirable. It is a further challenge that launches the disease. It seems appropriate to create synergies between medical and non-medical branches that are apparently distant and to intensify efforts in the field of translational medicine.

Since research on SARS-CoV-2 and COVID-19 is advancing at unprecedented speed, much data reported in this book on the pathophysiology, clinic, diagnosis, and therapy will soon become obsolete. However, another lesson this pandemic has taught us is to speed up the timing of science disclosure. It provides the implementation of translational research and building of research programs starting from synthetic, but exhaustive, pathways, on specific topics. It is the real purpose of this manuscript. To write it, we raced against time for providing an agile and useful book to be consulted by clinicians, researchers, and even non-expert readers.

Napoli, Italy Marco Cascella
Napoli, Italy Elvio De Blasio

Acknowledgments

The list of people we should thank is particularly long. They are all those doctors, nurses, health workers who, since the beginning of the pandemic, have thrown all of themselves into the arena fighting against this indomitable beast. This book is dedicated to all of them, and from them, we have obtained a wealth of data, suggestions, most of which are not collected in scientific publications, but are an integral part of a wealth of experience that will remain indelible. This wonderful inspiration enhanced our determination and creativity.

We are especially grateful to colleagues who materially assisted us in drafting the text, especially when we faced topics that went beyond our areas of competence. In particular, we have to extend our heartfelt thanks to two doctors and researchers of the San Pio Hospital (Benevento, Italy). Dr. Marco Sparaco, a neurologist from the Division of Neurology and Stroke Unit performed an excellent revision of the chapter on clinical features of neuro-COVID. Moreover, Dr. Carmine Franco Muccio, neuroradiologist from the Division of Neuroradiology of the same hospital has offered an invaluable contribution in drafting the chapter on diagnostics.

We thank Dr. Andrea Ridolfi, Editor Clinical Medicine Books, Responsible Editor, Intensive Care Medicine, Anesthesiology, Neurology at Springer for his kind and professional coordination. The experience accumulated in the field of scientific publications allows us to affirm that his competence is far above the average. He provided us with valuable advice at each stage of our project development. These requirements are what an author expects when the best publisher to entrust his/her manuscript is sought.

Finally, special thanks go to Laura and Vincenzo Cascella, medical students. They have critically read the text and provided us with important suggestions to make it accessible not only to expert readers, but also to those who are confronted with these issues for the first time.

Contents

Abbreviations

^{18}F-FDG	^{18}F-fluorodeoxyglucose
ACE	Angiotensin-converting enzyme
ADC	Apparent diffusion coefficient
ADEM	Acute disseminated encephalomyelitis
AHLE	Acute hemorrhagic leukoencephalomyelitis
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
AMAN	Acute motor axonal neuropathy
AMSAN	Acute motor and sensory axonal neuropathy
ANE	Acute necrotizing encephalitis
Ang	Angiotensin
ANM	Acute necrotizing myelitis
ARDS	Acute respiratory distress syndrome
ASL	Arterial spin labelling
AT	Ang type
BBB	Blood-–brain barrier
BBE	Bickerstaff brainstem encephalitis
BCSFB	Blood–cerebrospinal fluid barrier
BDNF	Brain-derived neurotropic factor
BFP	Bilateral facial palsy with paresthesia
BMS	Brain midline shift
CAM	Confusion assessment method
CAR-T	Chimeric antigen receptor T
CBF	Cerebral blood flow
CBV	Cerebral blood volume
CendR	C-end rule
CNS	Central nervous system
COVID-19	Coronavirus-induced disease 2019
CRP	C-reactive protein
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTA	CT-Angiography
CTP	CT perfusion
DCE	Dynamic contrast enhancement

DPP4	Dipeptidylpeptidase 4
DRG	Dorsal root ganglia
DSC	Dynamic susceptibility contrast
DWI	Diffusion weighted imaging
EEG	Electroencephalography
EMG	Electromyography
FLAIR	Fluid-attenuated inversion recovery
GBS	Guillain-Barré syndrome
GCS	Glasgow Coma Score
GFAp	Glial fibrillary acidic protein
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HCoV	Human coronavirus
HEV	Hemagglutinating encephalomyelitis virus
HIV	Human immunodeficiency virus
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
IFN	Interferon
IL	Interleukin
IP10	Interferon gamma inducible protein-10
IVIG	Intravenous IG
MCP1	Monocyte chemoattractant protein 1
MERS	Middle East respiratory syndrome
MFS	Miller Fisher Syndrome
MHV	Murine hepatitis virus
MIP1A	Macrophage inflammatory protein 1A
MIS-C	Multisystem inflammatory syndrome in children
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
nEVs	Neuronal-enriched extracellular vesicles
NICE	National Institute for Health and Care Excellence
NIHSS	National Institutes of Health Stroke Scale
NIRS	Near-infrared spectroscopy
NK	Natural killer
NRP	Neuropilin
OB	Olfactory bulb
ORN	Olfactory receptor neuron
PAG	Periaqueductal gray
PD	Parkinson's disease
PET	Positron emission tomography
PICS	Post-intensive care syndrome
PNC	Polyneuritis cranialis
PNS	Peripheral nervous system
PP2A	Protein phosphatase 2A

PRES	Posterior reversible encephalopathy syndrome
PTSD	Post-traumatic stress disorder
RAS	Renin–angiotensin system
ROS	Reactive oxygen species
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAH	Subarachnoid hemorrhage
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SSE	Shannon's spectral entropy
STIR	Short tau inversion recovery
SWI	Susceptibility weighted imaging
TCCD	Transcranial color-coded duplex
TCD	Transcranial cerebral Doppler
TF	Tissue factor
TLR	Toll-like receptors
TMPRSS	Transmembrane serine protease
TNF-α	Tumor necrosis factor α
US	United States
WBC	White blood cell count

Pathophysiology of COVID-19-Associated Neurotoxicity

1

1.1 Introduction

The clinical spectrum of COVID-19 (coronavirus induced disease 2019), the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), varies from paucisymptomatic forms to clinical conditions ranging from different degrees of respiratory insufficiency to multiorgan/systemic manifestations such as sepsis, septic shock, until multiorgan failure.

Similar to SARS-CoV which is another member of the family *Coronaviridae* and responsible for the severe acute respiratory syndrome (SARS) outbreak, from 2002 to 2003, SARS-CoV-2 can spread through active pharyngeal viral shedding. In turn, extrapulmonary manifestations of COVID-19 are encompassed among the clinical features of the disease. Nevertheless, a key aspect of the COVID-19 pathophysiology is understanding whether this extrapulmonary involvement is produced by damage from viral spreading (direct damage). Moreover, it should be advisable to distinguish alterations produced by an aberrant inflammatory response to the viral attack (indirect damage) from organ damage that is the expression of advanced disease with multiorgan dysfunction or failure. The latter picture has complex pathophysiology including invasive therapies, drugs, severe hypoxia, and other causes.

Regardless of the precise underlying pathogenic mechanisms, it is remarkable that in COVID-19 several extrapulmonary manifestations frequently occur [1]. Evidence suggests that hematologic [2], cardiovascular [3], renal [4], gastrointestinal, hepatobiliary, and pancreatic [5] systems, and other organs [6–8] can be affected by the disease.

Within the context of the COVID-19-related extrapulmonary manifestations, the neurologic aspects of the disease represent a special chapter [9, 10]. The term "neuro-COVID" is useful for encompassing these neurological manifestations. Notably, neurological issues were also described in other coronavirus-induced diseases including the SARS and the Middle East respiratory syndrome (MERS), in

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2012 [11]. It was demonstrated, for instance, that SARS-CoV can provoke a wide range of lesions to the neurons, such as demyelination, and glial cells, mostly expressed as glial hyperplasia; these lesions were localized in several brain areas [12]. Previously, in 1993, and thus before the emergence of SARS and MERS, some authors conducted in vitro and in vivo experiments for evaluating the neurotoxicity of the human coronavirus HCV-229E on oligodendrocytes [13]. Later, it was also proved that primary cultures of human neural cells, adult astrocytes, and adult microglia can be infected by coronaviruses [14]. Interestingly, the awareness that many coronaviruses, not just human coronaviruses (HCoVs), can infect the central nervous system (CNS) of animals has long been known. In 1962, Greig et al. [15] isolated the hemagglutinating encephalomyelitis virus (HEV), which is a β-coronavirus, in the brains of pigs. Furthermore, in the early 1980s, two different coronaviruses were detected in autopsy neural tissues of two patients suffering from multiple sclerosis. The viruses, generically indicated with the initials of the patients and not further characterized, were also isolated in their cerebrospinal fluid (CSF) [16].

Thus, similar to other epidemic-induced coronaviruses, the SARS-CoV-2 seems to be neuroinvasive, neurotropic, and neurovirulent. Nevertheless, given the magnitude of the COVID-19 pandemic, these phenomena can have considerable importance.

Despite the great interest of the scientific community in the neuropathogenesis of SARS-CoV-2 infection, there are many open questions. The potential route of entry of the virus to the nervous tissue, the ability to damage cells, and the induction of immune-mediated processes are all issues that must necessarily be well elucidated. As mentioned above, the question is whether the clinical manifestations of neuro-COVID are the effect of direct viral damage or they are caused by an excessive immune-mediated response of the host. Is it possible an association between both mechanics? Similarly, it would be appropriate to distinguish between events that characterize acute damage to central and peripheral nervous tissue from processes that could clinically manifest at a distance. The pathophysiology of the latter could be very complex to explain. In addition to direct viral damage, other mechanisms such as immune-mediated reactions, hypoxia, effects of multiorgan dysfunction, could be involved. Furthermore, the consequences of long-term intensive care treatment, such as psychological sequelae derived from isolation in critically ill patients, should not be underestimated.

On these premises, a worrying scenario is opened and further research is needed to better clarify if the neurotoxicity can induce long-term sequelae probably manifested in terms of post-infectious neurodegenerative and neuroinflammatory complications. Previous studies, indeed, suggested that coronaviruses can provoke processes of demyelination, neurodegeneration, and cellular senescence. These changes could also accelerate brain aging and/or exacerbate neurodegenerative conditions [17].

Starting from experimental elements that come from different branches such as molecular biology, virology, neurophysiology, the study of pathophysiology must

be able to arrive at an overall vision, as it happens for the construction of a mosaic. Although we are a long way from this goal, the road seems to have been drawn.

Moreover, the vast spectrum of neurological manifestations involves two types of problems. The former concerns the need for clinical care of patients who can be extremely complex to treat. On the other hand, the latter issue concerns the need to strengthen the preclinical research aimed at identifying the pathogenic mechanisms underlying the pulmonary and extrapulmonary involvement of the disease for offering clinicians better therapeutic choices [18–21].

This chapter is aimed at dissecting the pathologic mechanisms of COVID-19-associated neurotoxicity. The issue of pain mechanisms (COVID-pain) is discussed and updates on preclinical findings, ongoing clinical investigations, as well as perspectives for conducting preclinical and clinical investigations are also proposed.

1.2 Overview on Neurological Manifestations

The neuro-COVID chapter encompasses clinical manifestations of varying severity, incidence, and significance. They can manifest before fever and respiratory symptoms, or be the unique clinical manifestation of COVID-19. Additionally, clinical manifestations may also occur after the resolution of the acute phase (long-COVID). Although in most cases there are isolated neurological symptoms (e.g., headache, dizziness), complex scenarios can occur. Therefore, the term neuro-COVID is an oversimplification as it appears to be a great umbrella that collects disparate clinical conditions.

According to the location of symptoms, neurologic manifestations of COVID-19 can be grouped into three categories including central nervous system (CNS) manifestations, peripheral nervous system (PNS) manifestations, and skeletal/muscular clinical expressions. Furthermore, the onset time of the clinical presentations can help differentiate infective (acute) from post-infective complications. A classification based on the pathophysiology of the symptoms seems to be more appropriate. It should differentiate clinical conditions produced by direct damage from others related to indirect injury (e.g., neuroinflammation and cytokine-related injury), or disease-related (e.g., ischemic, multiorgan impairment) damage. Nevertheless, it is often difficult to separate the mechanisms and overlap phenomena exist.

Headache is one of the most common signs of COVID-19 (often associated with fever). It usually has a non-specific meaning. Clinically it is manifested as tension-type or migraine without aura, migraine-like headache (less commonly), with long-lasting duration and analgesic resistance. Dizziness is frequently combined with headache (and tinnitus), and is often observed in the earlier disease.

Data from literature and clinical experience suggest that olfactory and gustatory dysfunction is considered an early manifestation of COVID-19 infection [1].