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ORIGINAL ARTICLE

Possible consequences of Covid-19 on the nervous system

Miron Sramka[1], Ján Slavik[2], Jan Masan[3], Eugen Ruzicky[4]

1 Department of Stereotactic Radiosurgery, OUSA and St. Elizabeth University of Health Care and Social Work in Bratislava, Slovak Republic
2 Agel Hospital Košice-Šaca and AGEL ACADEMY, Košice, Slovak Republic.
3 Faculty of Health Sciences, University of Ss. Cyril and Methodius in Trnava, Slovak Republic.
4 Faculty of Informatics, Pan-European University in Bratislava, Slovak Republic.

Correspondence to: Assoc. Prof. Eugen Ruzicky, PhD.
Faculty of Informatics, Pan-European University, Tematinska 10, 851 05 Bratislava, Slovak Republic
e-mail: eugen.ruzicky@paneurouni.com

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Abstract

OBJECTIVES: The aim of the survey was to find out what the possible consequences are of the COVID-19 disease on the nervous system and to propose a method of using artificial intelligence.
MATERIAL AND METHODS: Recent research has shown that the risks to patients due to severe acute coronavirus 2 respiratory syndrome (SARS-COV-2) differ most significantly depending on age and the presence of underlying comorbidities such as: cardiovascular disease, hypertension, diabetes and others. The consequences of COVID-19 on the nervous system are especially important. We performed a detailed selection of articles describing the effects of COVID-19 on the nervous system.
RESULTS: We made a clear summary of the main consequences of COVID-19 on the nervous system and suggested a way to use artificial intelligence.
CONCLUSION: We confirmed research that artificial intelligence methods have the potential to accelerate prediction, especially for the possible consequences of COVID-19 on the nervous system.

Abbreviations:

CT	- Computer Tomography
MR	- Magnetic Resonance
COVID-19	- Coronavirus Disease 2019
SARS-CoV-2	- Severe acute respiratory syndrome coronavirus 2
WHO	- World Health Organization
SpO2	- Peripheral oxygen saturation
CNS	- Central nervous system
PNS	- Peripheral nervous system
SRS	- Stereotactic Radiosurgery
EEG	- Electroencephalography
AI	- Artificial Intelligence
ML	- Machine Learning
CAD	- Computer-aided Diagnosis
VR	- Virtual Reality
AR	- Augmented Reality

INTRODUCTION

The World Health Organization declared the outbreak of COVID-19 a threat to international public health on 30 January 2020 and a pandemic on 11 March. World research laboratories have found that the risks in patients due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vary most significantly with age and the presence of an underlying comorbidity (Fang *et al.* 2020). Comorbidities have been observed in the global population as follows by significance: cardiovascular disease, hypertension, diabetes, chronic obstructive pulmonary disease, cancer,

and chronic kidney disease. Observations of frequent hypercoagulable conditions in patients with COVID-19 lead more frequently to stroke. Neurosurgical treatment of the consequences of Spanish influenza (Dvorak *et al.* 1973) also drew attention to the study of infectious, para-infectious, and post-infectious consequences (SARS-CoV-2).

Influenza is a viral disease. It affects the respiratory system, causing symptoms such as coughing, fever, sore throat, tiredness, muscle pain, and a runny nose. One of the complications of influenza is pneumonia which, along with infections of the sinuses and ears, is more common in infants and the elderly. The influenza virus changes its genetic material, so influenza vaccines are not very effective and change almost every year. Influenza vaccines are not a protection against Covid-19, but they reduce the vulnerability of people to coronaviruses, which often have similar symptoms.

COVID-19 is similar to influenza. Common symptoms include fever, cough, fatigue, shortness of breath or difficulty breathing, and loss of smell (WHO 2019a). Complications may include pneumonia and acute respiratory distress syndrome. In most people, coronavirus (SARS-CoV-2) causes mild disease, while in others it can cause severe pneumonia; in some cases, it can lead to death. If a patient shows symptoms of COVID-19, then they should take a coronavirus test and must be isolated at home. The patient should have a pulse oximeter (Tobin *et al.* 2020) with which he/she can identify a worsening condition. If the patient tests positive for the coronavirus and his/her condition worsens, then he/she must contact the Institute of Public Health or call a general practitioner.

The pulse oximeter measures blood oxygenation (SpO2) and heart rate. The normal SpO2 value is higher than 95%. An SpO2 value of less than 92% means that the blood is weakly saturated with oxygen (hypoxemia). A drop in SpO2 below 92% can severely impair heart and brain function. No symptoms of respiratory distress were observed in some COVID-19 patients with low SpO2. Their brains responded to low oxygen levels with silent hypoxemia (Tobin *et al.* 2020; Couzin-Frankel *et al.* 2020). Patients with such low blood oxygen levels should be unconscious, but patients are able to talk and have minimal anxiety. During the expected second wave of a pandemic, such patients will not need to undergo unnecessary intubation and pulmonary ventilation.

If a person has hypoxemia and symptoms of infection, they must be hospitalized immediately. In the hospital, the patient needs to have detailed blood tests, lung X-rays, and a clinical examination carried out by a pulmonologist. When the SpO2 oxygen level falls below 92% and the patient has symptoms of pneumonia, it is advisable to perform a lung CT on the patient and initiate treatment in the intensive care unit or prepare the patient for pulmonary ventilation. In the case of neurological symptoms, it is advisable to give the patient a brain MR examination.

COVID-19 and comorbidities. Patients with comorbidities of hypertension, diabetes mellitus, coronary heart and cerebrovascular diseases are at increased risk of COVID-19 infection (Fang *et al.* 2020). Cerebrovascular ischemic strokes often occur in COVID-19 (Avula *et al.* 2020; Beyrouti *et al.* 2020; Morassi *et al.* 2020), as well as intracerebral haemorrhaging (Morassi *et al.* 2020; Al Saiegh *et al.* 2020) cerebral sinus thrombosis (Li *et al.* 2020; Lodigiani *et al.* 2020; Oxley *et al.* 2020) and transient ischemic events (Benussi *et al.* 2020).

Hypercoagulable conditions and cerebrovascular diseases are rare in some acute viral infections but are often a neurological complication of COVID-19. COVID-19 patients with cardiovascular comorbidities are more likely to die of coronavirus.

The following Table 1 summarizes COVID-19 publications for Cerebrovascular diseases.

Tab. 1. List of publications dealing with the Covide-19 for Cerebrovascular diseases

Cerebrovascular diseases	COVID-19 publications
Intracerebral haemorrhaging	Morassi; Al Saiegh
Ischemic strokes	Avula; Benussi; Beyrouti; Morassi
Cerebral sinus thrombosis	Li; Lodigiani; Oxley

(Source: own research)

POSSIBLE CONSEQUENCES OF COVID-19 ON THE NERVOUS SYSTEM

Protecting the population from COVID-19 and its consequences requires the necessary clinical, diagnostic, and epidemiological studies. A distinction needs to be made between non-specific complications such as hypoxic encephalopathy, acute neuropathy, including infectious, para-infectious, and post-infectious encephalitis, as well as hypercoagulable conditions causing stroke, from those caused by the new coronavirus SARS-CoV-2. Recognition of neurological disease associated with COVID-19 patients in whom the respiratory infection is mild or asymptomatic will be challenging. If primary COVID-19 has occurred with smell and taste disorders, the patient should be isolated as soon as possible (Moein *et al.* 2020). These patients can have serious neurological consequences. Neurological disorders are increasingly occurring in the central nervous system (CNS) and the peripheral nervous system (PNS) and may occur in the absence of other clinical signs. Acute cerebrovascular disease is another serious complication of COVID-19.

Clinical signs of neurological disease associated with COVID-19 and the effects of coronavirus on the nervous system lead to neurological and psychiatric diseases (Varatharaj *et al.* 2020). Published changes and diseases are reported as being mental status, encephalopathy,

encephalitis, neuropsychiatric diagnoses, psychosis with a neurocognitive dementia-type syndrome, and affective disorders (Ellul *et al.* 2020).

Encephalitis. Inflammation of the brain parenchyma is caused by an infection or immune defence of the body associated with COVID-19. Neurological symptoms begin mostly from the onset of respiratory symptoms, preceded by cough and fever with irritability, confusion, and decreased consciousness, sometimes associated with seizures (Bernard-Valnet *et al.* 2020; Sohal *et al.* 2020) and psychotic symptoms (Vollono *et al.* 2020), or rhombencephalitis (Wong *et al.* 2020). A patient with ataxia had a brain lesion that extended to the spinal cord (Craik *et al.* 2020).

Encephalopathy. Changes in personality, behaviour, cognition, disorders of consciousness, including clinical manifestations of delirium or coma, have been reported (Slooter *et al.* 2020). In patients with encephalopathy and COVID-19 who have not been reported to have brain inflammation, it can be caused by hypoxia, drugs, toxins, and metabolic disorders (Solomon *et al.* 2012). CNS symptoms including dizziness, headaches, and impaired consciousness of patients with symptoms of CNS who had severe respiratory disease. It has occurred as acute disseminated encephalomyelitis (Zanin *et al.* 2020; Zhang *et al.* 2020), multifocal demyelination syndrome (Dugue *et al.* 2020; Helms *et al.* 2020; Mao *et al.* 2020; Paniz-Mondol *et al.* 2020; Zhou *et al.* 2020) acute hemorrhagic necrotizing encephalopathy (Poyiadji *et al.* 2020) and myelitis (Zhao K *et al.* 2020). The following Table 2 summarizes publications that address the various symptoms of COVID-19 disease for the Central Nervous System.

Tab. 2. List of publications dealing with the Covide-19 disease for Central nervous system

Diseases of CNS	COVID-19 publications
Encephalitis	Bernard-Valnet; Sohal; Wong; Craik; Zanin; Zhang; Zhao; Ellul
Encephalopathy	Dugue; Helms; Mao; Paniz-Mondol; Zhou; Slooter; Dugue; Helms; Mao; Paniz-Mondol; Zhou; Poyiadji
Parkinsonism's	Cohen ME; Vaira
Psychiatric diseases	Vollono; Slooter; Bernard-Valnet; Sohal

(Source: own research)

PNS disorders and muscular disorders. Guillain-Barré syndrome is an acute polyradiculopathy characterized by rapidly progressive symmetrical limb weakness and sensory disturbances. Neurological symptoms that began after respiratory or systemic disorders in COVID-19 patients with Guillain-Barré syndrome included limb weakness, and loss of sensation (Toscano *et al.* 2020). Excluding Guillain-Barré syndrome, the symptoms also included facial nerve involvement, dysphagia, (Camdessanche *et al.* 2020), respiratory failure (Zhao H *et al.* 2020), ophthalmoplegia (Gutiérrez-Ortiz *et al.* 2020, Dinkin *et al.* 2020), ataxia with areflexia, acute vestibular syndrome (Escalada-Pellitero *et al.* 2020), and rhabdomyolysis (Jin *et al.* 2020). Fischer Miller syndrome is included among other neuropathies (Gutiérrez-Ortiz *et al.* 2020).

Disorders of sensory functions

Disorders of sensory functions. Loss of smell (anosmia) and taste (ageusia), frequent symptoms of COVID-19, combined with other symptoms or in isolation could be useful diagnostic markers (Lodigiani *et al.* 2020). Unusual smell and taste in patients are linked to COVID-19. Patients report a loss of smell and taste 7 days before the appearance of fever and respiratory difficulties (Ellul *et al.* 2020; Sedaghat *et al.* 2020). Such patients should be quarantined. Patients with viral infections of the upper respiratory tract also have a temporary or permanent loss of smell and taste. These symptoms are more common in COVID-19 cases with a subjective loss of smell or taste. A higher percentage of smell loss is detected when the testing is done using objective methods that measure the smell function. Most patients first notice problems with smell, but because smell is often necessary as a supplement to taste, these symptoms are often linked. Patients with COVID-19 who did not have smell problems had a worse course of the disease and were more often hospitalized and placed in the intensive care unit. Patients with smell dysfunction had a milder course of the COVID-19 disease. The loss of smell in patients infected with COVID-19 may be the first or the only symptom of the disease. Loss of smell and taste could serve as a screening tool because these symptoms appear earlier. Loss of smell is one of the first and sometimes the only one symptom in up to 25% of COVID-19 patients. The ability of the SARS-CoV-2 coronavirus to enter olfactory tissue may be a pathway for brain infection (Ellul *et al.* 2020).

Olfactory epithelium and smell test. A standardized questionnaire on the loss of smell was used. Patients' loss of smell was evaluated using 8 questions from a standard olfactory identification test called "Sniffin Sticks", which includes 16 scented pens that patients identified every 30 seconds. Patients labelled the scents from a choice of three descriptive terms: normosmic (normal odor), hyposmic, or anosmic. In studies, the loss of smell occurred in 87% of COVID-19 patients compared to in only 56% of patients who detected taste disorders. The most common symptoms were loss of smell and headaches. Half of the patients did not have the ability to recognize the basic tastes (salty, sweet, bitter, sour) and also experienced headaches, myalgia, cough, loss of appetite, and abdominal pain with diarrhoea. Patients experiencing loss of smell and taste also had ear-, nose- and throat-related symptoms. Anosmia could be a reliable way to predict whether

a patient will have a cough and fever. Patients with COVID-19 regained their sense of smell within a few weeks. Specific cell types in the olfactory epithelium were restored much faster than the lower airway cells, which were restored in a couple of months. Temporary loss of smell (anosmia) is the main symptom and one of the first and most frequently reported indicators of COVID-19. Loss of smell and taste may be caused by diseases other than coronavirus, but to determine the cause it is necessary to test patients for COVID-19 (Ellul *et al.* 2020).

Now, in September 2020, the first case was published online that a patient after infection with severe acute respiratory syndrome with coronavirus 2 (SARS-CoV-2) was subsequently diagnosed with Parkinson's disease without a previous family history of this disease (Cohen ME *et al.* 2020). Within isolation period of 3 weeks, this patient noticed that his handwriting had changed and was harder to read it than before. Immune activation in the olfactory system can eventually lead to misfolding of α-synuclein and the development of Parkinson's disease (Lema *et al.* 2013) which is often preceded by anosmia, a common feature of SARS-CoV-2 infection (Vaira *et al.* 2020). The following Table 3 summarizes the publications that address the various symptoms of COVID-19 disease for the peripheral nervous system and sensory functions.

Tab. 3. List of publications dealing with the Covide-19 disease for Peripheral nervous system and Sensory functions

Diseases of PNS and Sensory	COVID-19 publications
Guillain-Barré syndrome	Toscano; Camdessanche; Zhao H; Gutiérrez-Ortiz; Dinkin; Escalada-Pellitero; Jin;
Anosmia	Lodigiani; Ellul; Sedaghat
Ageusia	Lodigiani; Ellul; Sedaghat

(Source: own research)

Stereotactic radiosurgery

In brain surgery, stereotactic radiosurgery (SRS) is an ideal non-invasive treatment modality in the current pandemic environment. It is used in the treatment of intracranial malignancies, benign tumours, vascular malformations, and neuropathic pain (Liaw *et al.* 2020). It is performed as an outpatient procedure with minimal personal protective equipment, usually requiring only one session. SRS does not require endotracheal intubation or the use of high-performance devices, thus reducing the risk of exposure to infectious aerosols and bone dust present in open surgery (Liaw *et al.* 2020; Zacharia *et al.* 2020).

In the long term, we assume that, as a result of the post-infectious autoimmune disease COVID-19, changes in the nervous system may develop over the course of 10 years and longer, up to the rest of the patients' lives, as a result of the pandemic. Similar results occurred with Parkinson's disease after Spanish influenza (Dvorak *et al.* 1973).

Data analysis and artificial intelligence

In the years since the onset of SARS, supportive tools using artificial intelligence have been developed to diagnose, monitor, and predict the disease. Many publications on the use of artificial intelligence (AI) for neurodegenerative diseases appeared (Belic *et al.* 2019; Raghavendra *et al.* 2019). Applying deep-learning-based medical image analysis to computer-aided diagnosis (CAD) provides better decision support to clinicians and improves the accuracy and efficiency of various diagnostic and treatment processes (Chan *et al.* 2020). AI and machine learning (ML) created numerous applications in computer-aided monitoring and diagnostics of neurodegenerative movement disorders (Belic *et al.* 2019). An overview of research using ML methods to perform quantitative analysis of MR image data indicates using the study of Parkinson's disease (Xu *et al.* 2019). Fast and automated analysis of CT and MR scans with the support of artificial intelligence enabled the optimization of diagnostic processes, to recognize the patient's condition quickly and reliably, and propose other treatments.

Currently, the use of MR and CT scans is as one of the possible effective and useful tools for the diagnosis of COVID-19 and its possible consequences. Methods of analysis of radiological image data obtained from COVID-19 patients showed the need to perform a CT scan of the brain after a sudden stroke. MR brain scans are suitable for the analysis of pathological changes in patients with neurological symptoms (Moriguchi *et al.* 2020; Wong *et al.* 2020) and their use evaluated the effects of COVID-19 on the brain. MR examination revealed lesions that enhanced the haemorrhagic margin within the bilateral thalamus, median temporal lobes, and subinsular areas (Poyiadji *et al.* 2020). Brain MR scans revealed abnormal findings (Kandemirli *et al.* 2020). COVID-19 is associated with metabolic and coagulative disorders. EEG studies of focal central nervous system (CNS) lesions showed a general slowing of EEG and their results have evaluated the effects of COVID-19 on the brain.

Recently, there have been rapid advances in computerized technology, including wearable devices, virtual reality (VR) and augmented reality (AR), mobile internet, and robot assistant systems. These new-generation assessment tools can produce real-time, programmable, and safe measurements of neurological deficits (Asakawa *et al.* 2019). New technologies using Virtual Reality (VR) and Artificial Intelligence (AI) changed the processing and interpretation of the medical data on central nervous system diseases such as for diagnosing Parkinson's disease and stroke (Ruzicky *et al.* 2020). The Virtual Reality methods have the potential to accelerate rehabilitation and increase the motivation

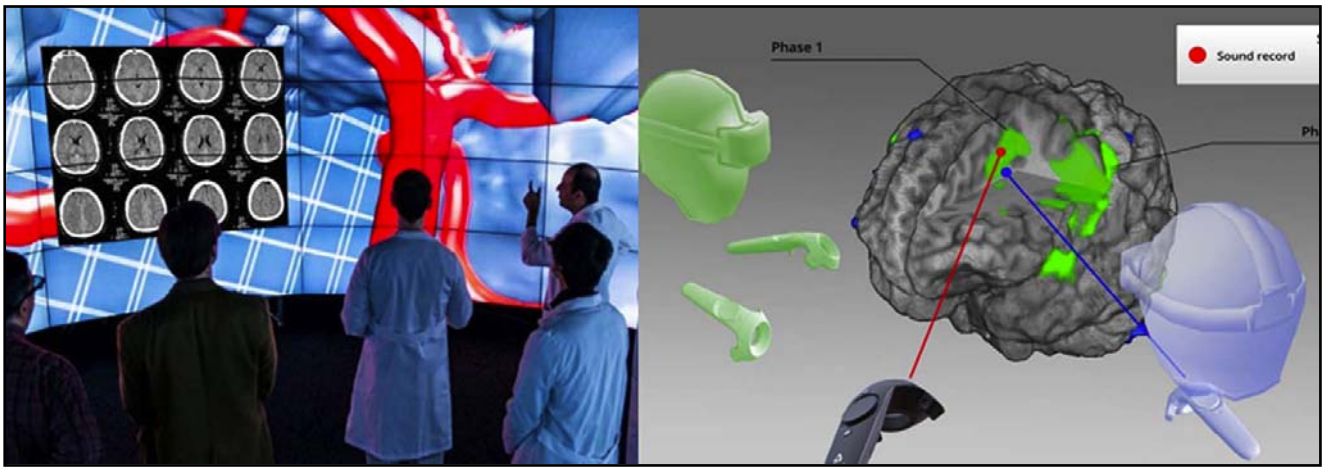

Fig. 1. Using of the Virtual reality for real-time communication of physicians from various departments with the modeling of the patient's brain. (Source: own research)

of selected groups of patients after stroke (Sramka *et al.* 2020). Figure 1 shows the virtual reality capabilities for physicians to communicate with medical imaging technologies in real time. The left part of the picture shows the communication of, for example, neurologists and radiologists in one workplace, while the right part of the picture shows the use of virtual reality with a 3D virtual model of the patient's brain. Physicians communicate from two different departments about treating a patient using VR devices displayed on a model.

The exercise unit using Imoove has positive effects on increasing the load of the paretic lower limb in patients after overcoming ischemic stroke (Masan *et al.* 2020). In recent years, very few studies have helped quantify the motor properties of Parkinson's disease, which have evaluated the disease in a "free-living" environment using mobile devices (Dorsye *et al.* 2020). This phenotyping could help us to use artificial intelligence to evaluate the possible consequences of COVID-19 objectively and effectively in the future.

CONCLUSION

The ongoing COVID-19 pandemic and the expectation of the development of collective immunity of the world's population suggest that the total number of patients with a neurological disease could increase in the future. Neurological complications, especially encephalitis and stroke, can cause lifelong disability in patients. This will involve long-term care needs and potentially major health and social problems, as well as economic costs.

In the context of public health protection, prevention and treatment, as well as the need for long-term care in these areas, it is important to focus on the following research activities: to analyse current solutions for monitoring the course of COVID-19 disease in patients with mild, moderate and severe courses; to design subjective and objective parameters implementable in a database divided into structured text and image data; to find comprehensive applications for the acquisition, evaluation, and interpretation of patient data and implement comprehensive applications, including the necessary testing; to evaluate the proposed applications for their usability in real life; to design methods of image processing and statistical analysis of input image and text data; to implement artificial intelligence methods to predict the development of COVID-19 disease based on the generated data; to use the proposed methods of artificial intelligence to predict the development of COVID-19; and, to use all these results for other similar diseases and pandemics.

Neurodegenerative diseases such as Parkinson's and Alzheimer's are a global health and social threat. The aim of the newly implemented project "Early warning of Alzheimer's disease" is research into the detection of neurodegenerative diseases through the analysis of speech and language patterns using artificial intelligence methods. The main benefit of the project is the implementation of the mobile application using speech recordings of the tested person. This approach makes it possible to identify people at risk of cognitive impairment (e.g. for Parkinson's disease too) and to start treating the patient as soon as possible. The project is implemented mainly in the company AXON PRO in cooperation with the Faculty of Informatics of the Pan-European University (with the Faculty of Medicine at P.J. Safarik University) and the Institute of Informatics of the Slovak Academy of Sciences.

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