Neurological Disorders in Hospitalized Patients with Covid-19: Clinical Symptoms, Treatment and Rehabilitation

Zaburzenia neurologiczne u hospitalizowanych pacjentów z COVID-19: objawy kliniczne, leczenie i rehabilitacja

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SUMMARY

Aim: To establish the spectrum of neurologic disorders in patients with coronavirus disease 2019, and to clarify what are their clinical peculiarities?

Materials and Methods: We analyzed retrospectively the clinical, radiological, and neuropathological findings of the patients who entered our clinics between October 2020 and the end of March 2021. Neurological syndromes developing during or after the disease, which were likely to be associated with COVID-19 on clinical and laboratory grounds, were included in the group of interest. Cases for which a more likely alternative pathology was found were excluded.

Results: In a case series of 515 patients with Covid-19, neurologic symptoms were observed in 173 (33.6%) patients and were more common in patients with severe infection (47.8%**)** according to their respiratory status, which included acute cerebrovascular events, impaired consciousness, and muscle injury. Encephalopathy (29/16.7), and neuropathy 36 (20.8) dominated among neurological syndromes.

Conclusions: Neurologic symptoms manifest in a significant part of patients with Covid-19. The most common were fever, fatigue, dyspnoea, and muscle-join pains.

Key words: SARS-CoV-2, COVID-19, Neurological Disorders

Słowa kluczowe: SARS-CoV-2, COVID-19, zaburzenia neurologiczne

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INTRODUCTION

In December 2019, a new infection, named Severe Acute Respiratory Syndrome (SARS)-CoV-2 causing severe acute respiratory syndrome, began in Wuhan, Hubei Province, China, and quickly spread around the world [1, 2]. SARS-CoV-2 virus is a novel, single-stranded RNA virus which was declared as the causative agent of coronavirus disease 2019 (COVID-19) in February 2020 and was recognized as a global concern (pandemic) by the World Health Organization (WHO) [3]. Preliminary data suggest that bats are the most probable initial source of the current coronavirus disease-19 (COVID-19), however worldwide spreading was apparently occurred from a "wet market" [1]. The COVID-19 pandemic represents the greatest global public health challenge since the pandemic influenza outbreak of 1918. According to currently available evidence, SARS-CoV-2 is transmitted to humans via respiratory droplets and aerosols [4, 5]. The most common signs and symptoms of COVID-19 are considered to be fever (temperature ≥37.8°C), cough, dyspnea (breathing difficulty), myalgia and fatigue, nasal congestion, smell and taste impairments (loss) [6]. Many of these symptoms and some others persist for a long time during and after acute COVID-19 [7]. The spike (S) protein of SARS-CoV-2 had a high affinity to angiotensin I–converting enzyme 2 (ACE2), which is responsible for the virus invasion. ACE2 is expressed in many types of the cells including nasal epithelial cells, as well as the blood vessel endothelial cells. Although the respiratory system involvement is the most common and life threatening in coronavirus disease 19 (COVID-19), there are increasing reports concerning neurological complications during and after disease. These neurological complications can affect both central, including encephalopathy [8], meningo-encephalitis [9], ischaemic stroke [10], acute necrotizing encephalopathy [11], and peripheral nervous system (Guillain-Barre´syndrome (GBS)

[12]. One of the most dramatic consequences of infectious diseases like severe acute respiratory syndrome and COVID-19 are respiratory muscle weakness and low exercise capacity that observed 1-4 month' and more after the initial infection. These SARS-CoV-2 experience has revealed the need for a multidisciplinary rehabilitation approach, especially for elderly patients with comorbidities, and organ failure. The International European Respiratory Society (ERS) and the American Thoracic Society (ATS) Task Force developed and implemented for COVID-19 survivors a comprehensive pulmonary rehabilitation (PR) program [13]. PR involves exercise training especially the inspiratory muscle training (IMT), and psychological support.

AIM

To study the detailed emerging spectrum of neurological disorders encountered in 173 patients admitted to the Center of Infectious Disorders of the Nervous System (CIDNS, Kyiv, Ukraine) and Sumy regional hospital because of acute respiratory distress syndrome (ARDS) due to Covid-19, and the frequency and severity of certain symptoms. We also intend to determine the proportion of COVID-19 survivors with a need for various rehabilitative intervention programs following hospital discharge.

MATERIALS AND METHODS

STUDY DESIGN, PATIENTS AND SITES

This prospective, observational study was carried out at 2 centers (Center of Infectious Disorders of the Nervous System, Kyiv, and Sumy Regional Infectious Hospital, Ukraine) which among others clinics were assigned by the government to treat patients with Covid-19. We analyzed consecutive patients from October 2020 until the end of March 2021, who had been diagnosed as having Covid-19, according to WHO interim guidance [14]: (i) definite (SARS-CoV-2 RNA PCR positive from nasopharyngeal swab, CSF or pathological specimen); (ii) probable (clinical and laboratory features highly suggestive of COVID-19: lymphopenia, raised D-dimer, suggestive chest radiology in the absence of PCR evidence) [6]; and (iii) possible, in whom temporal or laboratory features indicate an association but another cause was also found. Patients were admitted to our clinics if they have clinical or laboratory evidence of a Covid-19 infection: fever >38 °C, dry cough, headache, chest pain, general weakness, taste or smell impairment.

CLINICAL DIAGNOSIS AND FINAL DECISION

The final conclusion for the etiology of infection and recruiting the patient into the study was mainly based on the detection of SARS-viral RNA in nasopharyngeal swabs, however neuroimaging data and characteristic clinical signs also were taken into account. The diagnosis was considered to be Definite (confirmed) when the viral RNA was found by RT-PCR in the nasopharyngeal swab; Probable – when IgG/IgM antibody synthesis against specific viral proteins in blood were detected with the simultaneous presence of radiological or neurological symptoms; Possible (suspected) – when only antibodies against viral proteins were found in the blood [15].

INCLUSION/EXCLUSION CRITERIA

Patients below 18 years were not included in the study, since children with CNS infections are managed in other specialized centers. Patients with any neurological manifestations (confusion, altered mental status, seizures, focal deficiency, etc.) registered upon admission or developed during their hospital stay, as well as those who have been found to have cerebrospinal fluid (CSF) abnormalities (>four white blood cells per mm^3 or CSF proteins >0.4 g/L) were included in the study. Cases for which a more likely alternative pathology was found were excluded. Noninfectious CNS disease (cerebral tumor, cerebral abscess, and neurosurgery within the previous two-four months), and meningitis without clinical manifestation of brain involvement were also excluded.

Consequently, 515 patients were enrolled into the study. Written inform consent was obtained from all patients or from close relatives. Patients were managed by hospital physicians following routine clinical practice i.e. history, physical examination, hematology, biochemistry, blood culture, and radiology. Cerebrospinal fluid (CSF) examination was carried out when indications were present only. After lumbar punctures (LP) CSF samples were collected and immediately sent to lab for analysis.

The research was approved by Ethics Commission of Sumy State University University, according to the European bioethics and bio-rights, Helsinki Declaration of the World Medical Association.

STATISTICAL ANALYSIS

For statistical analysis continuous data were compared with Mann-Whitney U test. Proportions were analyzed by Fisher's exact test. A p value of ≤ 0.05 was considered statistically significant.

RESULTS

DEMOGRAPHY

Basic demographic information was collected from all patients using case report forms. Of all 515 Covid-19 infectious patients, 173 had the definite signs of NS disorders and consisted the group of interest. Their mean (SD) age was 54.9 (14.8) years, with ages ranging from 18 to 86 years, and 98 were men (56.6%), and 75 women (43.4%) (male/female 1.3). Of this patients, 71 (41%) had one or more of the following underlying disorders: cardiac or cerebrovascular disease including hypertension (65/37.5%), diabetes (19/11%), and overweight (37/21.4%). Seven patients had had previous neurologic disorders, including transient ischemic attack, partial epilepsy, and mild cognitive impairment.

CLINICAL FEATURES

According to patients, the incubation period (the time from the initial infection to the onset of the first symptoms) averaged 7-8 days (from 1 to 20 days). Although all humans are susceptible to infection, susceptibility to the virus appears to be largely determined by age, immune status, underlying medical conditions, etc. Apparently, people of mature and old age have an increased susceptibility to SARS-Cov-2-

infection. Preadmission period of illnesses lasted from 6 to 28 days, with an average of 21 days.

Clinical profiles observed among the patients are characterized by extreme diversity and a combination of several symptoms and signs. Most patients present with mild to moderate symptoms at onset of disease. Hospitalization has always been associated with a sharp deterioration. Almost all patients on admission had fever (≥38°C), dry cough and general weakness. Headache (93/53.7%) and cochlea-vestibular impairments (dizziness) (88/40.8%) were recorded also. Headache and dizziness have been also reported as two of the most common initial presentations in many patients with COVID-19 as well as others neurological pathologies such as encephalitis, meningitis, and vasculitis [16, 17]. Clinical symptoms were sometimes extremely intense, for example, weakness may be such that the patient cannot move independently. Over time, fatigue and dispnoea become the most common symptoms. Minority of the patients (10/1.9%) presented on admission the symptoms of "enteric" COVID only: abdominal pain, and diarrhea which spontaneously resolved.

As well as the symptoms, the severity of the COVID-19 disease varied from mild to critical. Mild disease accompanied usually by no pneumonia or mild pneumonia, severe disease with dyspnoea and hypoxia required oxygen supply, and critical disease accompanied by sharply decreased blood saturation with oxygen, septic shock or multi-organ failure. In a number of cases, the transition from mild to critical form occurred extremely quickly, sometimes within 24 hours the saturation dropped by tens of percent which forced the patient to be immediately transferred to the ICU. The patients presented with a wide range of CNS and PNS features including neuroinflammatory diseases and stroke from 3 days before and up to 19 days following the onset of the COVID-19 symptoms. CNS related symptoms included dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure, taste and smell impairment, audible and vision impairment (Table 1).

Vegetative dysfunction (45/26%), mental confusion (13/7.5%), pyramidal insufficiencies (38/21.9%), convulsions (32/18.5%), scattered neurological symptoms (29/16.7%), pelvic disorders (16/5.3%), reduced hearing (16/5.3%) were reported less frequently. Profound hearing loss was not detected. More severe neurological findings include stroke, impairment of consciousness, coma, seizures, neuropathy, and encephalopathy. In turn, impaired consciousness includes the change of consciousness level (somnolence, stupor, and coma) and consciousness content (confusion and delirium). Symptoms related to skeletal muscle injury as well as neuromuscular junction (NMJ) disorder also met quite often (31/17.9). Therefore, the correct diagnosis of neurological disorders strongly depends on the subjective assessment of the existing neurological symptoms and constant monitoring their changes during the course of the disease. Nevertheless, the dominant syndromes should be considered encephalopathy (29/16.7), and neuropathy 36 (20.8). Encephalomyelitis (11/6.3), and GBS (5/2.8) have also been reported.

Table 1. CNS related symptoms

Clinical signs	n %
fever	169 (97.7)
headache	170 (98.2)
weakness	173 (100)
meningism (stiff neck)	14 (8)
seizures	8 (4.6)
focal neurological sings	17 (9.8)
speech disorders	12 (6.9)
cranial nerve palsy	15 (8.6)
ataxia	19 (11)
sensory disorders	34 (19.6)
sleep disorders	18 (10.4 %)
diarrhea, abdominal pain	3 (1.7)
decline of consciousness/confusion	22 (12.7)
agitation/aggressiveness	25 (14.4)
apathy	30 (17.3)
hallucination	2 (≤1)

IMAGING

An important diagnostic and prognostic value has also neurovascular changes in the structure of the brain. Focal changes in the brain were observed more often – in 19 (51.3%) cases against 13 (35.1%) for diffuse disorders. In 5 patients (13.5%) no changes in MRI were detected. Findings include focal and diffuse changes of the limbic system around bilateral, temporal, occipital, and frontal areas. Signs develop gradually, but they are somewhat delayed as compared to the clinical symptoms. Encephalitis often involves the cortex, hippocampal, and extra hippocampal structures affecting the amygdala, tentorial cortex, thalamus, hypothalamus and deep forebrain structures, cerebellum, and brain stem. Edema, necrosis, and sclerosis are frequently found. These typical findings are subsequently resolved and brain atrophy is observed in the convalescent period.

TREATMENT

Treatment was essentially supportive and symptomatic since at this time there is no approved treatment for Covid-19. The first aim is to ensure adequate isolation to prevent transmission to healthcare workers. The main principles were controlling fever and blood oxygenation. In hypoxic patients, provision of oxygen through nasal prongs, face mask, high flow nasal cannula or non-invasive ventilation is indicated and was commonly used. Mechanical ventilation of the lungs was tried to be avoided due to the frequent complications. Routine use of antibiotics was mandatory in confirmed case of pneumonia due the high probability of bacterial co-infections.

In 15% of cases, when, against the background of prolonged use of antibacterial drugs (for 12-14 days or more), a high temperature, insufficient oxygenation, clinical signs of pneumonia persisted, a fungal co-infection (Candida albicans) was detected, which required the appointment of specific therapy. The Covid-19 Treatment Guidelines Panel

recommends now using dexamethasone alone either in combination with remdesivir for the treatment of Covid-19 in hospitalized patients on high-flow oxygen or noninvasive ventilation who have evidence of clinical progression or increased markers of inflammation [18]. Even before the start of this study, we were convinced of the complete uselessness of remdesivir and therefore avoided use it. So, we focused our efforts on maintaining oxygenation by any means, preventing coagulation and reducing excessive inflammatory response. Of 515 hospitalized patients with Covid-19 infection, oxygen was given to 71%, non-invasive ventilation in 15%, mechanical ventilation in 3%, antibiotics in 71%, antifungals in 15%, glucocorticoids in 29% and intravenous immunoglobulin therapy in 27%. The duration of non-invasive ventilation was 4–22 d [median 9 d].

OUTCOMES AND POST-COVID CONSEQUENCES

The mean duration of hospital stay was 19.7±15.3 days (range: 7-39). As a result of the treatment, 65 patients had a good outcome and after discharge they returned home. The condition of 55 patients improved significantly (a decrease of some neurologic symptoms, but with preservation of some manifestations of cerebrosthenic, vestibulo-atactic syndromes, pyramidal insufficiency). These patients were transferred to a convalescence facility. 46 patients, which condition worsened against the background of the therapy (dysfunction of the stem and cortical structures increased), were moved to ICU for further treatment. 13 patients died. It is necessary to emphasize complete recovery was observed only in a few of those who had been discharged. Poorly expressed dysexecutive syndrome consisting of inattention, disorientation, or erratic movements in response to a command was registered in almost 20% of them. Regular headaches, paresthesia with tingling in the arms and legs, constricted muscles, lack of smells and tastes persist for a long time after discharge. The main long-term complication of the previous illness, which almost all people face, is panic attacks which are a consequence of the transferred stress - lack of the oxygen.

REHABILITATION

Discharge from the hospital after treatment of COVID-19 does not mean complete recovery. Some of the symptoms especially late-onset ones may persist for a long time [19]. Among the long-term consequences of COVID-19 respiratory muscle weakness, low exercise capacity, and panic attacks were registered [20]. So, almost all surviving patients need for a long and multy-disciplinary rehabilitation approach, which should be started 3-4 weeks after discharge.

DISCUSSION

Potential Mechanisms of Neuroinvasion and Neuroinjury. Although SARS-CoV-2 is typically associated with respiratory tract disease, this virus, like others coronaviruses in this group (HCoV-229E, HCoV-OC43, and SARS-CoV-1), can probably infect neurons. Moreover, there are some reports of neurological complications in patients with COVID-19, which removes all doubts if SARS-CoV-2 is neurotropic in humans. The virus can enter the brain by several routes, including transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier (BBB) [21]. The dominant opinion was that human and nonhuman coronaviruses invade peripheral nerve terminals, spread retrograde along nerve synapses, and gain access to the CNS [22, 23]. However, a group of researchers in the brains of SARS-CoV-2-infected patients recently found an increase in string vessels, empty basement membrane tubes [24]. Their appearance is associated with the death of endothelial cells and leads, in turn, to damage to the BBB and cerebral ischemia. Authors postulate that death of brain endothelial cells in COVID-19 is secondary to their SARS-CoV-2 infection. Despite lack of ACE2 expression in certain cell types including brain endothelial cells others receptors primarily NRP1 and possibly BSG facilitates SARS-CoV-2 cell entry cells. After infection Mpro (main protease) cleaves host cell NEMO protein taking the central role in immunity. NEMO supports the survival of some but all cell types. The loss of NEMO induces an apoptosis of endothelial cells with following microvascular pathology. Subsequently, patchy hypoxia developed in the brain and the BBB became leaky.

CONCLUSIONS

To date, SARS-CoV-2 has infected millions and affected billions of lives. The understanding of neurologic disease in patients with Covid-19 is evolving, and clinicians should continue to monitor patients closely for neurological disease. Early detection of neurological deficits may lead to improved clinical outcomes and better treatment algorithms. Further laboratory and clinical data, including tests of CSF, brain imaging, and tests of CNS tissue, will be essential in elucidating the pathophysiology and potential for CNS injury. Lastly, longitudinal neurological assessments of patients after recovery will be crucial in understanding the natural history of Covid-19 in the CNS and monitoring for potential neurologic sequelae.

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