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Journal of Neurology and Neurobiology

ISSN 2379-7150 | Open Access

CASE REPORT

Volume 7 - Issue 2

Two Cases of Encephalitis with Brainstem Involvement and Microglial Activation in SARS-CoV-2 Infection

Dimitar Metodiev[1]*, Yavor Toshev[2], Kamen Anachkov[2], Krasimir Minkin[3], and Sevdalin Nachev[1]

[1]Laboratory of Neuropathology, University Hospital, "St. Ivan Rilski," Sofia, Bulgaria
[2]Laboratory of Clinical Pathology, Nadezhda Hospital-Women's Health Hospital, Sofia, Bulgaria
[3]Department of Neurosurgery, University Hospital "Saint Ivan Rilski", Sofia, Bulgaria

***Corresponding authors:** Dimitar Metodiev, Laboratory of Neuropathology, University Hospital, "St. Ivan Rilski," Sofia, Bulgaria, E-mail: dr.dmetodiev@yahoo.com

Received: 12 Nov, 2021 | **Accepted:** 02 Dec, 2021 | **Published:** 09 Dec, 2021

Citation: Metodiev D, Toshev Y, Anachkov K, Minkin K, Nachev S (2021) Two Cases of Encephalitis with Brainstem Involvement and Microglial Activation in SARS-CoV-2 Infection. J Neurol Neurobiol 7(2): dx.doi.org/10.16966/2379-7150.180

Abstract

Corona Virus Disease 2019 (COVID-19) primary involves the respiratory system. However, as many other viral pandemics, the current severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is also characterized by nervous system involvement, mainly in elderly patients with comorbidity. The involvement of the nervous system is manifested by a variety of clinical symptoms, and results in morphology: encephalopathy, polyneuritis, brainstem encephalitis, etc. We present two PCR proven cases of patients who died after infection with the SARS-CoV-2 virus. The analysis of the inflammatory findings mainly manifested by perivenous lymphocytic infiltrates, also showed increase number of activated microglial cells. The blood supply of most venous vessels with different size and a pronounced "sludge" phenomenon made us a special impression, as in some sections these changes were demonstrated by a presence of thrombosis. Inflammatory manifestations were also observed in the brainstem near to the stem nuclei. We emphasize on the pathomorphological changes found in the brainstem, where inflammatory manifestations were also observed near to the stem nuclei.

Neuropathological examination of brain tissue from necropsy materials will be essential to establish the neuroinvasive potential of SARS-CoV-2 virus.

Keywords: SARS-CoV-2; Brainstem encephalitis; Microglial cells

Introduction

The SARS-CoV-2 virus induces a variety of immune system response. In some patients there is negligible or no reaction, while in others there is a "cytokine storm" with system damage of multiple organs-often including the brain. Recent scientific data confirm that this involvement of the nervous system is manifested by a variety of clinical symptoms, such as morphologically with: encephalopathy, encephalitis, polyneuritis, etc. However, the "morphology" is mostly represented by MRI. The first publication, focused on this problem is by Xiang P, et al. [1] as well as that of Moriguchi T, et al. [2]. Almost all cited conclusions by them are based on the diagnosis of MRI examination.

Some authors have diagnosed cases of brainstem encephalitis in COVID-19 positive patients [3].

In our two cases of patients who died after infection with SARS-CoV-19, we are focused mainly on the morphological changes found in the brainstem.

Materials and Methods

Case 1

A 63-year-old man, admitted as a matter of urgency in a soporific condition with evidence of respiratory failure and subsequent mechanical ventilation.

Accompanying diseases-obesity, liver cirrhosis, COPD, congestive heart failure.

In the course of the disease, a generalized edema with unstable hemodynamics appeared, which imposed catecholamine maintenance and administration of antiarrhythmics. There was a progressive deterioration and death 11 days after admission to hospital.

Leading morphological changes: COVID-19 associated pneumonia in subacute phase with foci of organization, fibrinous pleuritis; COPD-chronic bronchitis, obstructive emphysema; Chronic ischemic heart disease, nutmeg liver with transition to cardiac cirrhosis, anasarca.

From the CNS: serous, partially hemorrhagic meningoencephalitis. Common ischemia (including in the spinal cord), especially periventricular with multiple Amyloid bodies. Vascular stasis with "sludge" phenomenon, initial thrombosis, perivenous edema with erythrodiapedesis and some perivenous myelin fragmentation. Brainstem encephalitis with activated microglial cells.

Case 2

A 59-year-old man admitted with a 4-day history of shortness of

breath, fatigue, mild dry cough and fever up to 39°C. Accompanying diseases-gout, obesity, hepatic steatosis. In the course of the disease there was a progressive deterioration of lung mechanics and desaturation up to 69%. The patient was placed on command breathing. After cardiac conduction disorders, a lethal outcome occurred, 24 days after admission to hospital.

Leading morphological changes: desquamative pneumonia in regenerative, subacute phase, Acute Respiratory Syndrome in adults, focal lymphocytic pericarditis, pulmonary aspergilloma in the left lung base. On the part of the CNS: disseminated acute perivenous leukoencephalitis (including in the brainstem) with a pronounced thrombotic-hemorrhagic component of the inflammatory process, leading to older and more recent hemorrhage with a diameter of 2cm in the area of the cerebellar peduncles. Serous-hemorrhagic meningitis with vascular thrombosis.

Morphological changes were reported after necropsy examination of the following brain and spinal cord structures: Bulbus olfactorius; Frontal, parietal and occipital cortex, and underlying white matter-two levels; Temporal cortex; Subcortical nuclei (bilateral), incl. substantia nigra; III-ventricle (surrounding tissue); Mesencephalon; Pons; Cerebellum (including cerebellar peduncles); Medulla oblongata; Cervical part of the spine.

The emphasis was put on the pathomorphological changes in the brain stem. Prepared histological specimens were stained with HE and Methasol fast blue. Additional immunohistochemical studies were performed: CD3 (for T-lymphoid cells), CD68 (for microglial cells), Collagen IV (for basement membranes).

Results

The pathomorphological analysis of the inflammatory manifestations in both cases was demonstrated by perivenous infiltrates of lymphocytes, serodiapedesis and erythrocyte depots. Accumulations of Amyloid bodies periventricularly and also in the tectum of the brain stem (manifestations of ischemic process) were especially marked. The blood supply of most venous vessels with different size with a pronounced "sludge" phenomenon was impressive (Figures 1 and 2). In some areas, in case 2, these changes led to thrombosis, including the vessels in the meninges (Figure 3).

It should be noted that this finding were predominantly ubiquitous pronounced in the white matter of the brain. However, in the brainstem, inflammatory manifestations were also observed near to the stem nuclei (including nucleus dorsalis nervi vagi figure 4) with microglial activation (Figure 5), which may accelerate the lethal outcome of patients.

Another focus of interest was the changes in the substantia nigra: degenerative changes in neurons, in places with residual neuromelanin, and more importantly, in both cases, there was noticeable activation of microglial cells with a tendency to form nodules (Figure 6), giving a positive reaction in immunohistochemical examination for CD68 (Figure 7).

We observed an increased number of "string" blood vessels in various parts of the central nervous system, which indicated damage to the capillaries. Their basement membranes were immunohistochemically proven with Collagen IV (Figure 8).

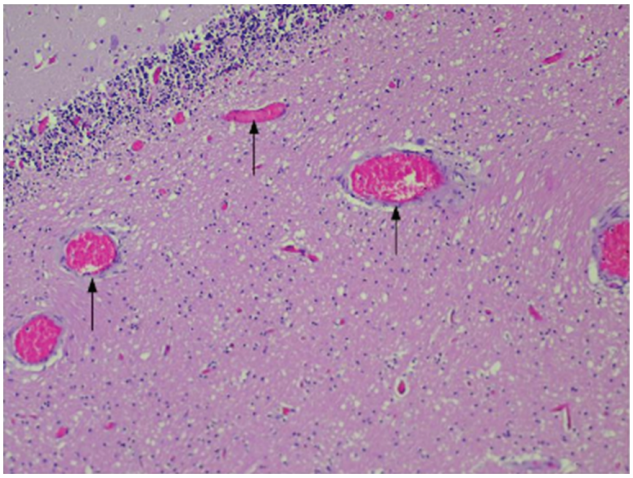

Figure 2: Erythrocyte aggregation with "sludge" phenomenon (arrows) in the cerebellum (HE, X200).

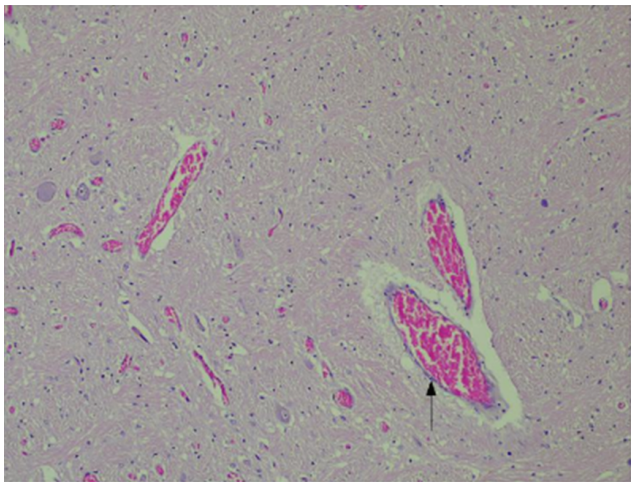

Figure 1: Erythrocyte aggregation with "sludge" phenomenon (arrow) in the medulla (HE, X200).

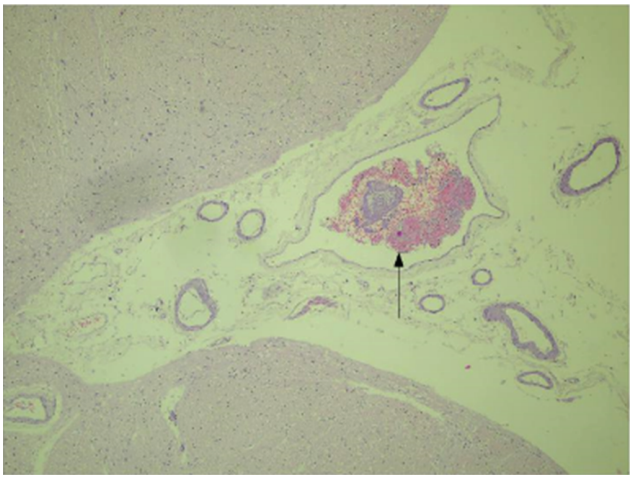

Figure 3: Thrombosis (arrow) in meningeal blood vessel of the medulla (HE, X100).

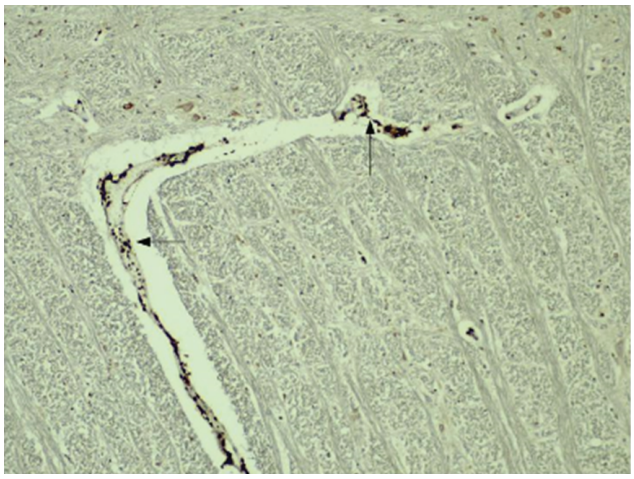

Figure 4: CD3-positive peryvascular T-lymphocyte infiltration (arrows) in the medulla (IHC-CD3, X200).

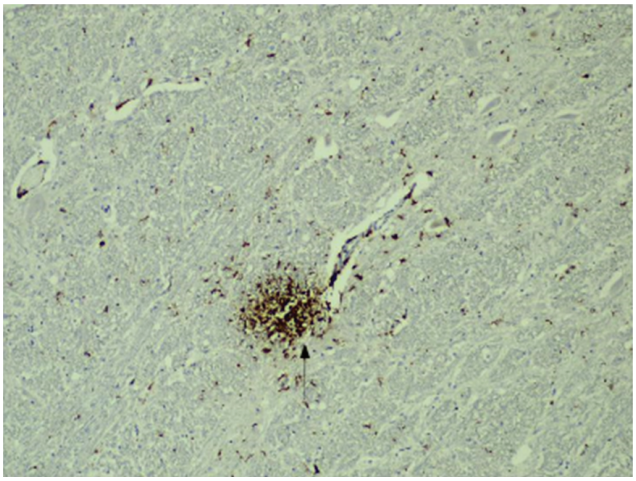

Figure 7: CD-68-positive activated microglial cells in the midbrain with a tendency to form nodules (arrow) (IHC-CD68, X200).

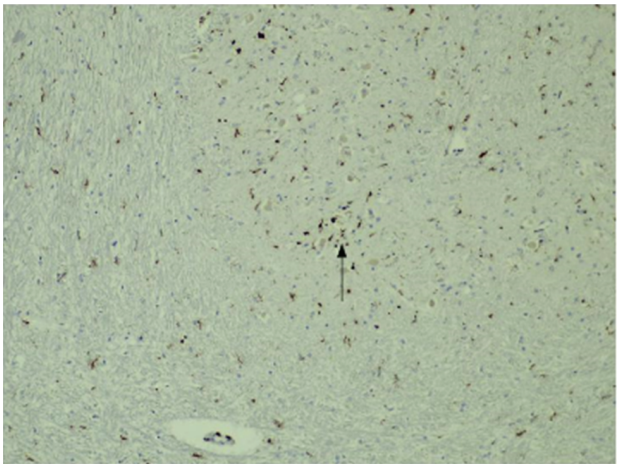

Figure 5: CD68-positive activated microglial cells (arrow) in the medulla (IHC-CD68, X200).

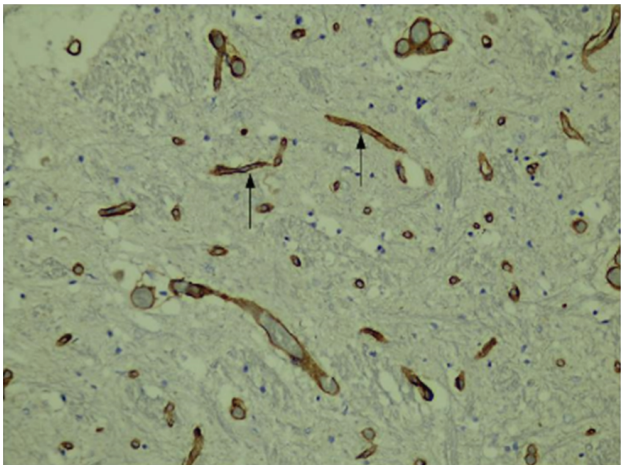

Figure 8: Collagen IV-positive "string" blood vessels (arrows) of the medulla (IHC-Collagen IV, X200).

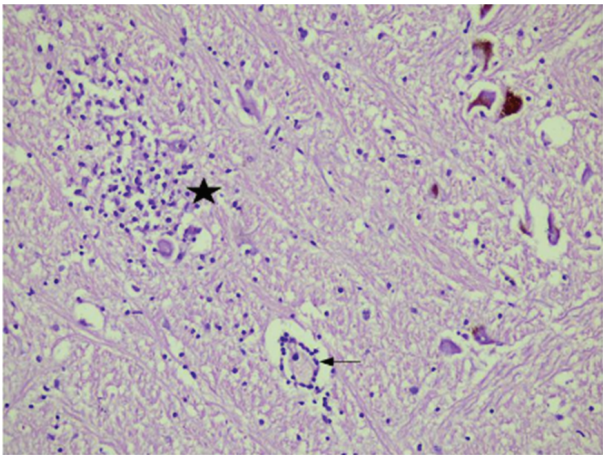

Figure 6: Activated microglial cells in the midbrain with a tendency to form nodules (asterisk), T-lymphocyte infiltration (arrow) degenerative changes in the pigment neurons of substantia nigra (HE, X200).

Case 2 was distinguished with a more pronounced thrombotic-hemorrhagic component of the inflammatory process leading haemorrhage with a diameter of 2cm in the area of the cerebellar peduncles. This was also the immediate cause of the patient's death.

In both cases, we observed a reduction in the number of Purkinje cells as well as a vascular stasis in the cerebellar cortex (Figure 9).

We also noticed degenerative changes in the motor neurons of the anterior horns of the spinal cord histologically demonstrated by marginalization of the Nissl substance.

It was likely that all these neuropathological findings were secondary to severe systemic infection with multi-organ failure and after mechanical ventilation. Moreover, we did not have the opportunity to experimentally prove viral RNA or protein in the brain tissue from our two patients.

Discussion

Like the virus H1N1 pandemic in 1918-1920, also known as "Spanish flu," the current SARS-CoV-2 pandemic is also characterized

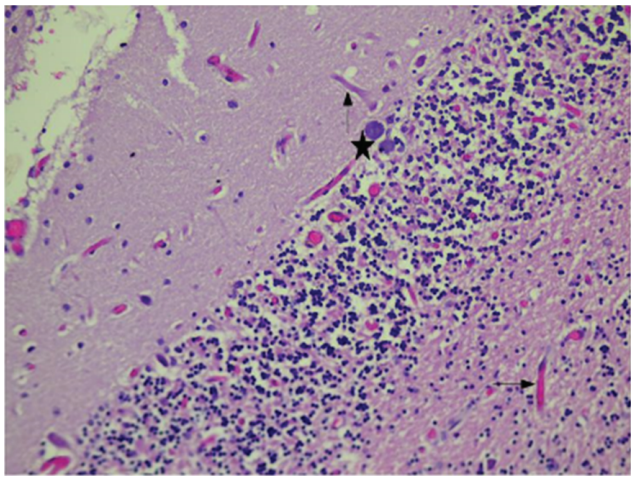

Figure 9: Reduced number of Purkinje cells (asterisk) and vascular stasis (arrows) in the cerebellar cortex (HE, X200).

by nervous system involvement, mainly in adults with concomitant, chronic diseases.

SARS-CoV-2 is known to possess neurotropism [4-7]. The mechanisms of CNS infection in human corona viruses have not yet been definitively elucidated. Different pathways for viral invasion in the nervous system have been discussed. This can be explained by the presence of Angiotensin Converting Enzyme 2 (ACE2) in combination with other components of the angiotensin system is expressed in the CNS, especially in endothelial cells, but also in neurons and glial cells [8]. The presence of the virus in the general circulation could provide a haematogenous route of entry to the CNS. SARS-CoV-2 may utilize the ACE2 receptors in the endothelial cells followed but subsequent budding of the viral particles from the capillary endothelium, damaging them, gaining access through the blood-brain barrier and initiating viral budding through interaction with ACE2 receptors in the neurons. The infection of the endothelial cells causes damage with rupture of the capillaries leading to bleeding or haemorrhagic infarctions, which have been recently reported in COVID-19 patients and can result in a fatal outcome [3]. We observed such a finding in case 2-a haemorrhagic infarction in the cerebellar peduncles.

Studies using experimental animals established that SARS-CoV-2 may enter the brain tissue *via* the olfactory nerve and initially spread to connected brain regions before proliferating more widely-including two areas such as the brainstem and cardiorespiratory centre in the medulla. The latter may potentially contribute to death [3].

Obviously SARS-CoV-2 induces a variety of immune system responses. Some patients have a weak or no immune response, while others have a "cytokine storm" with damage to many organs-often including the brain [9-11].

The causes of neurological/mental syndromes in patients with COVID-19 are numerous and include both generalized (including intracranial-brain) immune response and hypoxia, but also a need of intensive care [9-11].

These are the reasons for the development of both encephalitis/encephalopathy [12,13] and the appearance of psychotic syndromes, including delirium [14,15], which occur in COVID19.

As an immune-privileged structure, nerve tissue is particularly vulnerable to autoimmune attacks. This leads to various neurological diseases-MS, Guillain-Barre syndrome, as well as autoimmune encephalitis [16-18] and psychosis.

Antiphospholipid autoantibodies have been detected in patients with COVID-19 [19]. They can cause coagulopathies and cerebral infarctions, as have been commonly reported in deaths from COVID-19 [9-11]. We have also observed similar changes. A possible route of entry of SARS-CoV-2 into the CNS is *via* immune cells. A further mechanism of CNS involvement comes from reports of autoimmune encephalitis in COVID-19 patients [20], a condition which has been hypothesized to be related to a genetic susceptibility that leads to excessive self-response and antigen conditioned immune responses [21-23]. Patients with COVID-19 may produce antibodies against SARS-CoV-2 which also attack antigens in human endothelial cells in cerebral vessels or in neurons, resulting in cerebral oedema and autoimmune encephalitis [3].

The "string" blood vessels observed in our patients represent damaged microcirculatory cerebral vessels or more exactly-"residual basal membrane membranous structures" in which endothelial cells are not visualized. They are non-specific for COVID-19 and their number is significantly higher in other diseases, e.g. Hippocampal sclerosis, Alzheimer's disease, HIV infection, etc. [24].

The team of Al-Sarraj S, et al. [3] suggest the term "COVID-19 microglial encephalopathy"-pointing out that the activation of microglia play a role as a risk factor for the development or worsening of symptoms in MS and Alzheimer's disease.

Activated microglial cells play a role in the onset of: encephalopathies, cerebrovascular disease, epilepsy, neurodegenerative diseases and neuropsychiatric symptoms. Activated microglial cells were found in our cases, and the tendency to group in nodules, especially well expressed in the substantia nigra adjacent to degenerative changes of pigmented neurons there, made an impression.

It is possible the survivors of cerebral changes associated with COVID-19 infection may develop Parkinson's syndrome, as it was often been reported since the 1918-1920 pandemic.

Conclusion

The neuropathological changes in patients with COVID-19 may be caused by direct Cytopathic effects of SARS-CoV-2 replication in the brain or, more probable, indirectly by harmful immune response as a result of the "cytokine storm" induced by the viral infection.

Whether SARS-CoV-2 virus proteins can cause autoantibody formation and whether this is the essential mechanism for the observed demyelinating and psychotic states of patients with COVID19 provide us grounds for future investigations of material taken from patients and experimental animal models.

Moreover, in differential diagnostic aspect cases with autoimmune encephalitis or opportunistic viral infection have to be considered.

Conflict of Interest

The authors disclose no conflicts of interest.

Disclosure Summary

The authors have nothing to disclose.

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