Neuropathological analysis of the brains of fifty-two patients with COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) poses a global challenge to healthcare and society in the early 21st century. We report neuropathological changes in 52 patients aged between 22 years and 88 years (median 58 years) who were infected with the CoV-2 coronavirus. Patients died under various circumstances and had various pre-existing diseases. The inclusion criteria for this study were: positive result for the nasopharyngeal swab for SARS-CoV-2 RNA, diagnosis of pneumonia of SARS-CoV-2 or nucleoproteins of SARS-CoV-2 in pulmonary tissue confirmed by immunohistochemical methods (IHC). Samples from all brain structures and lung specimens were taken for histopathological examinations. Brain and pulmonary samples were stained typically with histological and immunohistochemical methods and small tissue fragments were examined with the transmission electron microscope (TEM). The light and electron microscopy examination confirmed the numerous neuropathological changes in the brains of the patients infected with the CoV-2. Many of these changes were caused by pre-existing diseases of patients and/or by necessary treatment. However, vascular lesions and the inflammatory process seem to be characteristic of the CoV-2 infection. In all of the structures of 52 brains of patients, damage of the vessel walls and morphological feature of the damage to the blood-brain barrier were observed. Lymphocytic and microglial infiltrates, both perivascular and diffuse, were also observed. Hence, the brain changes due to COVID-19 infection, could be called COVID-19 cerebral angiopathy with diffuse inflammation.

Key words: COVID-19, CoV-2, SARS-CoV-2, neuropathology, ultrastructure.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a non-segmented positive-sense RNA virus belonging to the Coronaviridae family, first identified in Wuhan, China in December 2019 [10]. It is responsible for the ongoing global pandemic of coronavirus disease 19 (COVID-19), with recurrent waves in most countries, more than 130 million people infected and about three million deaths worldwide. Infections with SARS-CoV-2 primarily lead to the respiratory tract infection and its sequelae frequently dominate the clinical course [30]. Although, it was found that up to 36% of COVID-19 patients presented with nervous system symptoms, ranging from anosmia, dysgeusia, headache, dizziness, impaired consciousness, anxiety, agitation, to more
severe acute ischemic stroke, microhaemorrhages, meningoencephalitis, haemorrhagic posterior reversible encephalopathy syndrome (PRES), acute disseminated encephalomyelitis (ADEM), diffuse leukoencephalopathy or Guillain-Barré syndrome [6,12].

There is a growing body of reports describing pathological findings in the central nervous system (CNS) of patients with the SARS-CoV-2 infection. Although, most of them are autopsy case reports or case series with less than 50 subjects. In the systemic review of Pajo et al. [22] who analysed 14 publications with a total of 146 COVID-19 cases which underwent brain autopsy, the striking pathological changes included diffuse oedema (17.1%), gliosis with diffuse activation of microglia and astrocytes (35.6%), infarctions involving cortical and subcortical areas of the brain (2.7%), intracranial bleed (subarachnoid haemorrhage and punctate haemorrhages) (12.4%), arteriosclerosis (29.5%), hypoxic-ischemic injury (28.1%), and signs of inflammation (35.6%). Interestingly, 47.9% of cases tested negative in SARS-CoV-2 immunohistochemistry, 15.1% were positive and the rest was unreported (37%). Similarly, in a more recent review of Sieracka et al. [24], which summarizes 22 publications (more than 300 cases with brain autopsy), CNS pathology includes most frequently features of non-specific neuroinflammation with microglial activation and lymphoid infiltrations, ischemic/hypoxic encephalopathy, astrogliosis, acute cerebrovascular disease, secondary myelin injury, and microthrombi with some brains remaining unaffected or showing only non-specific changes.

Mechanisms responsible for the CNS invasion and brain damage of the SARS-CoV-2 are still unclear. Major hypotheses suggest that the virus can invade the CNS through neuronal-axonal transport or through the bloodstream, and angiotensin-converting enzyme 2 (ACE2) receptors play a crucial role as an entry route [5]. SARS-CoV-2 presents high affinity for the ACE2 receptor, which might lead to virion attachment to the cerebral capillary walls and distortion of the blood-brain barrier [1,2]. On the other hand, glial cells and neurons express ACE2 receptors, and attachment of the virus to the receptor could contribute to its neurotropism [1,2]. The olfactory tract seems to be the principal entry route to the CNS in the initial phases of the SARS-CoV-2 infection [5,20]. Thus, neurotropism and direct invasion of SARS-CoV-2 into the CNS, together with brain hypoxia caused by systemic respiratory failure and indirect mechanisms mediated by the macrophages and T-lymphocytes and cytokine storm induced by systemic SARS-CoV-2 inflammation seem to be major mechanisms that may contribute to a spectrum of neuropathological manifestations [5,12,22]. Interestingly, hypotheses emerge that SARS-CoV-2 can cause or accelerate neurodegenerative diseases, i.e., Parkinson’s disease, Creutzfeldt-Jakob disease [9,25,32].

In the present study we describe pathological changes in the brains of 52 patients with COVID-19.

Material and methods

The 52 patients with COVID-19 derived from the First Polish Brain Bank at the Institute of Psychiatry and Neurology, Warsaw, Poland. Criteria for inclusion in this study were: a positive result for the nasopharyngeal swab for SARS-CoV-2 RNA, diagnosis of pneumonia of SARS-CoV-2 and/or presence of SARS-CoV-2 nucleoprotein in pulmonary tissue was confirmed by immunohistochemical (IHC). Characteristics of cases are included in Table I. All brains were fixed in buffered 4% formaldehyde. Brain autopsies were performed in the Department of Neuropathology, Institute of Psychiatry and Neurology in Warsaw, Poland.

For neuropathological examinations, samples were taken from the olfactory bulb, frontal, parietal, temporal and occipital lobes, basal ganglia, midbrain,pons, medulla oblongata and cerebellum for each case. Lung specimens were also collected for examination. Tissue samples were processed and stained with haematoxylin and eosin and methods: Klüver-Barrera, Bielschowsky, using standard procedures. For microscopic examination, randomly selected sections of lungs and brain were analysed by immunohistochemical method with CoV-2 (Invitrogen, Ma1-7404, 1 : 100) but fragments from human brain were analysed by IHC with antibodies against GFAP (Bio-Rad, MCA4733GA, 1 : 300), CD68 (Cell Marque 1 : 250), ACE2 (Invitrogen, MA5-31395, 1 : 100), CD45 (Leica, NCL-L-UCHL1, 1 : 500), CD20 (NCL-L-CD20-L26, 1 : 100), LCA (Dako, 8B11-PD7/26, 1 : 75), PrP (Cayman Chemical Company, 189710, 1 : 250), TDP43 (Invitrogen, MA5-27828, 1 : 1000), α-SYN (Leica, NCL-L-ASYN, 1 : 30), β-amyloid (DAKO, 6F/3D8, 1 : 75), Ubiquitin (Invitrogen, PAS-16829, 1 : 90), and HLA-DR (Invitrogen, PAS-22279, 1 : 1000). Sections were incubated with antibodies and a chromogen, and
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Table I. Clinical description of study subjects

| Case No. | Sex | Age (years) | Place of death | Cause of death | Comorbidities |
|----------|-----|-------------|----------------|----------------|---------------|
| 1*       | Female | 80       | Hospital       | Pneumonia      | CAA, diabetes mellitus type 2, dementia, history of stroke, hypertension, goiter of the thyroid gland, epilepsy, history of limb vein thrombosis, history of staphylococcal sepsis |
| 2*       | Female | 60       | Emergency room | Pneumonia      | Hypertension, diabetes mellitus type 2, thyroid nodule |
| 3        | Male   | 88       | Home           | Pneumonia      | Cardiomyopathy |
| 4        | Male   | 61       | Hospital       | Pneumonia      | History of pulmonary embolism, peptic ulcer disease, hyperthyroidism, rheumatoid arthritis, history of lobectomy, hypertension |
| 5*       | Male   | 69       | Hospital       | Pneumonia      | Diabetes mellitus type 2, schizophrenia, epilepsy, benign prostatic hyperplasia, history of post-traumatic intracranial haemorrhage, parkinsonism |
| 6        | Male   | 72       | Hospital       | Acute myocardial infarction, pneumonia | Chronic heart failure, IHD, history of acute myocardial infarction, hypertension, dyslipidaemia, obesity, gout, benign prostatic hyperplasia, history of post-traumatic intracranial haemorrhage, acute pancreatitis |
| 7        | Female | 71       | Hospital       | Pneumonia      | Depression, rheumatoid arthritis, renal amyloidosis, osteoporosis, obesity |
| 8        | Male   | 23       | Car crash      | Head and chest trauma | Lack of data |
| 9        | Male   | 45       | Emergency room | Pulmonary embolism | History of intracranial bleeding, traumatic brain injury, acute pancreatitis, pneumonia |
| 10       | Male   | 59       | Hospital       | Pneumonia      | Urolithiasis, ischemic stroke |
| 11       | Male   | 45       | Emergency room | Pneumonia      | Lymphoma |
| 12       | Female | 74       | Hospital       | Burn, pneumonia | Thyroid nodules |
| 13       | Female | 50       | Hospital       | Pneumonia      | Hypertension, diabetes mellitus type 2, obesity |
| 14       | Male   | 74       | Hospital       | Pneumonia      | Benign prostatic hyperplasia, IHD, degenerative disease of the spine, TIA, CAA |
| 15       | Male   | 37       | Home           | Pneumonia      | Hypertension, diabetes mellitus type 2, obesity |
| 16       | Male   | 57       | Home           | Pneumonia      | History of stent grafting of ascending aorta aneurysm, cardiomyopathy |
| 17       | Male   | 66       | Hospital       | Pneumonia, intestinal obstruction | Colorectal cancer, benign prostatic hyperplasia |
| 18       | Male   | 52       | Hospital       | Suicide (abdomen stab wound) | History of lobectomy due to recurrent lung abscess and pleural empyema |
| 19       | Male   | 56       | Emergency room | Pneumonia      | Cardiomyopathy |
| 20       | Male   | 61       | Hospital       | Pneumonia      | Diabetes mellitus type 2, nicotine dependence, post-traumatic intracranial bleeding |
| 21       | Male   | 62       | Hospital       | Ischemic stroke, pneumonia | IHD, history of CABG, acute myocardial infarction, implantable cardioverter defibrillator, diabetes mellitus type 2, chronic renal failure, dyslipidaemia, hypothyroidism, hypertension, chronic heart failure |
| 22       | Female | 66       | Emergency room | Pneumonia      | Obesity, hypertension, diabetes mellitus type 2 |
| 23       | Male   | 75       | Emergency room | Pneumonia, alcohol withdrawal syndrome | Alcohol dependence, diabetes mellitus type 2, benign prostatic hyperplasia, hypothyroidism |
| Case No. | Sex | Age (years) | Place of death | Cause of death | Comorbidities |
|---------|-----|-------------|----------------|----------------|---------------|
| 24      | Male| 60          | Emergency room | Pneumonia      | Cachexy, malnutrition, CAA |
| 25      | Female| 71          | Hospital      | Pneumonia, acute myocardial infarction | IHD, urinary bladder cancer, history of bladder resection, hypertension, diabetes mellitus type 2 |
| 26      | Male| 63          | Emergency room | Pneumonia      | Ischemic heart disease, diabetes mellitus type 2, hypertension |
| 27      | Female| 56          | Hospital      | Pneumonia      | Asthma, hypertension, depression, urinary bladder cancer |
| 28      | Female| 59          | Home          | Pneumonia, acute myocardial infarction | Obesity, CAA |
| 29      | Female| 66          | ICU           | Suicide (drug poisoning) | Hypertension, diabetes mellitus type 2, obesity, pneumonia |
| 30      | Male| 54          | Street        | Choking        | IHD, alcohol dependence, pneumonia |
| 31      | Male| 78          | Hospital      | Acute renal failure, subarachnoid haemorrhage | Prostate cancer, obstructive uropathy, pneumonia |
| 32      | Female| 70          | Home          | Acute myocardial infarction, pneumonia | IHD, CAA, parkinsonism |
| 33      | Female| 36          | ICU           | Acute peritonitis, pneumonia | Acute pancreatitis, chest and abdomen trauma |
| 34      | Male| 35          | Home          | Pneumonia      | Atrial fibrillation, cardiomyopathy, scoliosis |
| 35      | Male| 72          | ICU           | Pneumonia      | Hypertension, schizophrenia, urolithiasis, benign prostatic hyperplasia |
| 36      | Male| 51          | Home          | Suicide (cutting the wrist arteries) | History of appendectomy, history of craniectomy, pneumonia |
| 37      | Male| 72          | Hospital      | Pneumonia      | Chronic kidney failure, kidney cystic disease, cardiomyopathy, hypertension, history of acute myocardial infarction, IHD, celiac disease, peptic ulcer disease, rectal varices, albinism, benign prostatic hyperplasia |
| 38      | Female| 60          | Hospital      | Pneumonia      | Lung cancer, depression, asthma, emphysema, sinusitis, IHD, history of acute myocardial infarction, atrial fibrillation, hypertension, mitral valve prolapse, epilepsy, hydrocephalus, cachexy, chronic kidney disease, hypothyroidism |
| 39      | Male| 71          | Hospital      | Suicide (suffocation) | Depression, hypertension, pneumonia |
| 40      | Male| 33          | Hospital      | Sepsis, pneumonia, meningitis | Traumatic brain injury, post-traumatic intracranial bleeding, post-traumatic hydrocephalus, ventricular-peritoneal valve implantation |
| 41      | Male| 22          | Home          | Pneumonia, acute myocardial infarction | No comorbidities |
| 42      | Male| 28          | Hospital      | Brain oedema   | Pneumonia, hyponatremia |
| 43      | Male| 29          | Home          | Pneumonia      | No comorbidities |
| 44      | Female| 69          | Hospital      | Pneumonia, sepsis | Lung cancer, depression, polyneuropathy, trigeminal neuralgia, thyroid nodules, degenerative disease of the spine |
| 45      | Male| 37          | Workplace     | Pneumonia      | Obesity |
| 46      | Female| 67          | Hospital      | Pneumonia      | Diabetes mellitus type 2, diabetic retinopathy, hypertension, dyslipidaemia, obesity, history of cholecystectomy |
| 47      | Male| 62          | Home          | Pneumonia      | Chronic limb ischemia, IHD, history of acute myocardial infarction |
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The ultrastructural studies were conducted on material from autopsy cases of three patients with COVID-19 of 69 (No. 5, taken on 72 hours after death), 80 (No. 1) and 60 (No. 2) years old respectively. Biological samples were collected from brain and lung lobe tissues. Small blood vessels in the brain and lungs were examined. For electron microscopic evaluation, most of the small fragments of tissues were fixed in 2.5% glutaraldehyde solution in cacodylate buffer pH 7.4. Other fragments of tissues were taken from paraffin blocks and after deparaffinizing with xylene and washing in water they also were fixed in 2.5% glutaraldehyde solution in cacodylate buffer pH 7.4. Then all the samples were postfixed in the 1% osmium tetroxide solution in the same buffer. After dehydration in a graded ethanol series and propylene oxide, specimens were embedded in Spurr resin. Semithin sections were stained with toluidine blue to choose appropriate areas. Ultrathin sections were contrasted with uranyl acetate and lead citrate. The sections were examined and photographed with transmission electron microscope (TEM), JEOL model 140 at the Nencki Institute of Experimental Biology, Polish Academy of Sciences in Warsaw, Poland.

Results

The median age of the 52 patients was 58 years (range 22-88), 15 (29%) patients were women and 37 (71%) were men. 48 (92%) had relevant pre-existing medical conditions, among them 25 patients (48%) had relevant cardiorespiratory problems, and 15 (29%) had pre-existing neurological and/or psychiatric diseases. 36 patients died in hospital (69%) and 13 (25%) patients died at home, the rest, patient number 8 died in a car accident, patient number 30 died on the street and patient number 45 died at the workplace and there were 3 suicides (Table I). Pneumonia was diagnosed in 49 (94%) patients, of which in 43 (83%) patients SARS-CoV-2 pneumonia was considered a cause of death. The diagnosis of pneumonia was made either during the lifetime or during a general autopsy. In some cases, IHC or ultrastructural (ME) tests for the presence of the virus (Fig. 1A, 11, 12) were conducted. IHC was use to examined receptors for the angiotensin-converting enzyme-2 (ACE2). In the brain, they were most abundant in the choroid plexus and the arachnoid meningeal (Fig. 1B, C).

In all of the 52 cases, microbleeds/petechial hemorrhages were observed in the subarachnoid space and around the blood vessels of the parenchyma (Figs. 2, 3). The microbleeds/petechial hemorrhages were of varying severity, over all hemispheres of the brain. Hemosiderin deposits were often observed, suggesting previous petechial haemorrhage (Fig. 4C). Distribution and morphology of patchy brain microbleeds and petechial haemorrhages were most prominent in the grey and white matter of the neocortex, but were also found in the brainstem and cerebellum (Fig. 3). Damage to the walls of blood vessels was observed in all examined specimens (Fig. 4). The damage mainly involved arterial vessels and was related to the proliferation and damage of the endothelium, as well as fibrosis and hyalinization of the vessel walls. We also observed diffuse and perivascular proliferation of mononuclear cells in all examined brains (Fig. 5). The greatest intensity of this process was observed in the white matter of the cerebral hemispheres and in the brainstem. The intensity of the process was of various degrees in different cases. In immunohistochemical tests, the diffuse infiltration consisted mainly of microglial cells, while the perivascular infiltration consisted of lymphocytic cells (of which from T lymphocytes) and macrophages (Fig. 6). Additionally, some cells showed IHC reactivity with a class II histocompatibility antigen (HLA DR) (Fig. 6C). Astrogial cell proliferation was also observed in all assessed regions (Fig. 7A). But most of the astrogial cells were damaged. Morphological changes in astrocytes were characterized by fragmentation of

| Case No. | Sex | Age (years) | Place of death | Cause of death | Comorbidities |
|----------|-----|-------------|----------------|----------------|---------------|
| 48       | Male| 63          | Home           | Pneumonia      | Lack of data  |
| 49       | Male| 44          | Hospital       | Pneumonia      | History of spleen removal |
| 50       | Male| 44          | Home           | Pneumonia      | Obesity       |
| 51       | Male| 64          | ICU            | Pneumonia      | History of fingers amputation |
| 52       | Male| 61          | Home           | Pneumonia      | Cholecystolithiasis |

*Case with electron microscopy examination. CAA – cerebral amyloid angiopathy, ICU – intensive care unit, IHD – ischemic heart disease, TIA – transient ischemic attack, CABG – coronary artery bypass grafting

Table I. Cont.
the distal processes and swollen cell bodies (clasmato
todendrosis). The most damaged cells were the peri
vascular, submeningeal and subependymal astroglia
(Fig. 7B, C).

Apart from the above-mentioned neuropathologi
cal changes, ischemic infarctions and haemorrhag
ic infarctions were observed in three patients (6%)
(Fig. 8). Perivascular or diffuse demyelination was
observed in 7 cases (13%, Fig. 9A, B). In these cases, swelling of the oligodendrocytes was also observed. Lewy bodies were observed in two cases (4%). They were present in the neurons of substantia nigra of mesencephalon (No. 5, Fig. 9C) or in the neurons of the locus coerules of pons (No. 32). Other pro-
teins, including α-synuclein, were also immunohistochemically controlled. β-amyloid was noticed in the vessel walls in 5 cases (10%, Fig. 10A). Positive IHC response for the TDP43 protein occurred in the cytoplasm of neurons in 2 cases (No. 1 and 3, 4%, Fig. 10B). In the same cases ubiquitin deposits in the cytoplasm of neurons were observed. The PrP prion protein in IHC reaction was observed in the proliferating Bergmann glial cells in the Purkinje cell layer (Fig. 10C). Bergmann glial cell proliferation was observed in cases of atrophy of the granular cell layer (cerebellopathy) (38% of cases). Ischemic changes in neurons were also observed in many cases.

The ultrastructural examination was performed on selected lung and brain tissue fragments obtained during autopsy of the patients with a positive diagnosis of COVID-19. An accumulation of osmiophilic nucleocapsids in vacuolar vesicles in type II pneumocytes was observed (Figs. 11, 12). Changes in the morphology of neurons, oligodendrocytes, astrocytes and microglia were found in the
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examined fragments of brain tissues (Figs. 13-16) and in the disturbed structure of small blood vessels (Figs. 17-20) under viral infection conditions. The neurons, often with damaged protoplasmic projections, contained swollen mitochondria and few lipofuscin inclusions visible in the cytoplasm (Fig. 13). The oligodendrocytes showed numerous densities of heterochromatin in rounded cell nuclei. The cytoplasm was electron dense and preserved projections were observed in most of these cells (Fig. 14). Astrocytes (Fig. 15), in comparison to the neurons, were surrounded by a dense network of neuropil elements, and in their cytoplasm, near the cell nucleus, osmophilic lipofuscin inclusions were found.
The greatest amount of lipofuscin deposits was found inside the projections of phagocytic astrocytes and/or macrophages. These inclusions were also observed in the vicinity of the microglia which showed presented rods' shapes (Fig. 16). The most advanced lesions were in the endothelial cells and basement membranes of capillaries (Figs. 17-20). The endothelium of most small vessels showed signs of degeneration, was heterogeneous, locally concentrated and in the cytoplasm, it contained vesicles of different size. Composition and osmophilicity as well as mitochondria with remnants of cristae were...
found there (Figs. 17, 18). In endothelial cells, damaged tight junctions were significantly widened (Fig. 20). The basement membranes of most capillaries showed a heterogeneous structure with pronounced local cavities indicative of loss of matrix components (Figs. 17, 18). In capillaries in the olfactory bulb, the basement membranes were thin, multi-layered, and locally folded (Figs. 19, 20).

Discussion

In our neuropathological diagnosis of brains of 52 patients with coronavirus disease 19 (COVID-19), and with pneumonia (SARS-CoV-2) in 94% of patients, subarachnoid and perivascular microhaemorrhages and/or petechial haemorrhages predominated. Subarachnoid/cerebral and perivascular microbleeds in brains of SARS-CoV-2 patients could be a consequence of damage to the endothelium and vessel walls, leading to the damage to the blood-brain barrier and an increase in vascular permeability [3,18]. Vascular permeability in COVID-19 patients could be also a consequence of cytokines storm, which induced endothelitis and general vasculopathy changes [15,18,26]. Only in one case (Table I, No. 10) a haemorrhagic infarction was observed and in two cases (No. 21 and 26) ischemic infarction. Intracranial haemorrhagic or ischemic infarcts may have occurred as a complication of necessary and/or not sufficient treatment. Ischaemic lesions followed and were likely caused by thromboembolic. Perivascular or diffuse demyelination occurring in several causes was probably caused by ischaemic changes and cerebral oedema caused by vascular disorders [18].

In the brains of patients with COVID-19, we also observed variable degrees of damage of astrocytes. The most common proliferating astroglial cells had short/fragmented processes or they were without processes. As is known, astrocytes are heterogeneous and multifunctional and they are part of the glymphatic system of the brain [14,17]. Damage to the glymphatic system may affect the removal of pathological proteins from the brain, the accumulation of which may be associated with neurodegeneration and the formation of inflammatory response [14,28]. Accumulation of α-synuclein was observed in two cases of clinical parkinsonism and accumulation of β-amyloid in the vessel walls was observed in five cases of cerebral amyloid angiopathy CAA (Table I). However, ApoE homozygous (e4e4) genotype, predispose to the more severe course of COVID-19 disease [16]. In three men aged between 75 and 88, the protein TDP43 was also observed in the cytoplasm of neurons. TDP-43 plays multiple roles in RNA metabolism including transcription, miRNA processing, RNA transport, nucleocytoplasmic shuttling and splicing, which can lead to dysfunction of both neurons and astroglial cells [7,31]. Cytoplasmic inclusions of TDP-43 in our patients were age-related changes rather than related to COVID-19 infection. The PrP prion protein was observed in the proliferating Bergmann glial cells in cases of atrophy of the granular cell layer (cerebellopathy, in 38% of our patients). The physiological function of the prion protein remains poorly understood, although it was suggested that PrP may have a normal function in maintenance of long-term memory and regulated cell death [21].

Also, Prion-like domains are critical for virulence in coronavirus disease and the development of therapeutic targets. Tetz and Tetz identified prion-like domains in the ACE2 receptors, interacting with the viral receptor-binding domain of SARS-CoV-2 [13,27].

We also observed diffuse and perivascular proliferation of mononuclear cells in all examined brains. The diffuse infiltration consisted mainly of microglial cells, while the perivascular infiltration consisted of lymphocytic cells and macrophages. We believe that macrophages, and mainly haemosiderophages, phagocytose perivascular blood cells participate in the process of cleaning up necrosis foci. However, most authors believe that the proliferation of lymphocytes and microglia is related to autoimmune processes and changes in the vascular walls, including inflammatory changes [11,15,18,23,29]. The authors believed that understanding the role of inflammatory cytokines, chemokines and the immune system could lead to the development of new therapeutic approaches.

Ultrastructural observations showed damage to the blood-brain barrier and energetic disturbances in all of the observed cells of the brain. The endothelial cells of small blood vessels were the most damaged ones. The astroglia and microglia/macrophage cells contained the phagocytic elements. Whereas accumulation of nucleocapsids in vascular vesicles was easier to be observed in type II pneumocytes than in brain structures [4,8,19].

In conclusion, it should be emphasized that many neuropathological changes in the brain are
caused by pre-existing diseases present in patients infected with the CoV-2 coronavirus and/or by necessary treatment. On the other hand, moderately severe neuropathological changes caused by infection with the CoV-2 virus cover all brain structures with the greatest intensity in the white matter. The lesions include damage to the vessel walls. The changes also included the morphological features of the damage to the blood-brain barrier (“open” tight junctions, clasmodendrosis, damage to elements of the vessel walls). The brain’s response to these changes was a diffuse inflammatory process (perivascular and diffuse proliferation of lymphocytes and microglia). Thus, the brain changes induced by SARS-CoV-2 could be called COVID-19 cerebral angiopathy with diffuse inflammation.

Disclosure
The authors report no conflict of interest.

Acknowledgements
This work is supported by the “Digital Brain – digital collection of the Institute of Psychiatry and Neurology” (Project No. POPC.02.03.01-00.0042/18-00). The project “Digital Brain” is co-funded by the European Union and the Polish budget. The authors are very grateful to the First Polish Brain Bank at the Institute of Psychiatry and Neurology, Warsaw, Poland.

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