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Case Report

Experimental Neurobiology

Blood-brain Barrier Damage is Pivotal for SARS-CoV-2 Infection to the Central Nervous System

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Transsynaptic transport is the most accepted proposal to explain the SARS-CoV-2 infection of the CNS. Nevertheless, emerging evidence shows that neurons do not express the SARS-CoV-2 receptor ACE2, which highlights the importance of the blood-brain barrier (BBB) in preventing virus entry to the brain. In this study, we examine the presence of SARS-CoV-2 messenger ribonucleic acid (mRNA) and the cytokine profile in cerebrospinal fluids (CSF) from two patients with a brain tumor and COVID-19. To determine the BBB damage, we evaluate the Q- albumin index, which is an indirect parameter to assess the permeability of this structure. The Q-albumin index of the patient with an intraventricular brain tumor suggests that the BBB is undamaged, preventing the passage of SARS-CoV-2 and pro-inflammatory molecules. The development of brain tumors that disrupt the BBB (measured by the Q-albumin index), in this case, a petroclival meningioma (Case 1), allows the free passage of the SARS-CoV-2 virus and probably lets the free transit of pro-inflammatory molecules to the CNS, which leads to a possible activation of the microglia (astrogliosis) and an exacerbated immune response represented by IL-13, IFN-γ, and IL-2 trying to inhibit both the infection and the carcinogenic process.

Key words: Blood-brain barrier, SARS-CoV-2, COVID-19, Cerebrospinal fluid, Brain tumor

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affects the pulmonary apparatus primarily [1]. Nevertheless, increasing evidence has confirmed SARS-CoV-2 infection to the central nervous system (CNS) in patients who also develop severe neurological symptoms with an incidence rate of 36.4% [2]. The most common neurological manifestations of SARS-CoV-2 infection are headache, anosmia, and dizziness; however, some patients can also display febrile seizures, loss of consciousness, convulsions, status epilepticus, and necrotizing encephalopathy that in turn may trigger the onset of multiple sclerosis [3].

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Several studies suggest that neurological symptoms in coronavirus disease 2019 (COVID-19) patients result from systemic inflammatory mediators that do not necessarily involve direct infection of the CNS. However, emerging evidence confirms that SARS-CoV-2 may also enter the brain through different routes [4]. The most accepted way for SARS-CoV-2 entry into brain tissue is via nasal mucosa [5], wherein SARS-CoV-2 binds to motor proteins along olfactory nerves by retrograde axonal transport and is transported to the brain [6, 7]. A second possible way is a hematogenous route, wherein after entering the respiratory tract, SARS-CoV-2 may spread to multiple tissues and organs such as the CNS. However, this hypothesis lacks support due to the blood-brain barrier (BBB), which is a semi-permeable barrier that protects the CNS from a wide variety of toxins, molecules, and microorganisms found in blood, making it difficult for the free passaging of pathogens such as virus to the brain [8].

To this respect, several studies have proposed three mechanisms through which the SARS-CoV-2 may enter the CNS via the BBB: transcellular migration, wherein the virus infects endothelial cells of the BBB via the Angiotensin-Converting-Enzyme 2 (ACE2), the primary cell receptor described for SARS-CoV-2; paracellular migration, characterized by viral invasion of tight junctions between endothelial cells of the BBB; and the so-called "Trojan horse strategy", wherein the virus infects macrophages, dendritic cells, and neutrophils that in turn can migrate across the BBB to the CNS [5]. However, all these hypotheses lack support due to the BBB integrity, and we propose that structural damage to the BBB elicits the SARS-CoV-2 infection to the CNS. Herein, we present the case reports of two patients with a brain tumor and COVID-19. Interestingly, we detected viral particles in Cerebrospinal Fluid (CSF) only from the patient with petroclival meningioma and an elevated Q-albumin index (an indirect parameter used to determine the BBB permeability), suggesting a possible BBB damage which highlights the importance of this structure in preventing SARS-CoV-2 infection to the CNS. Moreover, the direct infection of CNS showed an exacerbated cytokine response represented by interleukin (IL)-13, IFN-γ, e IL-2, compared to the CSF sample from the patient with an intraventricular tumor where we did not find viral particles.

CASES PRESENTATION

Case 1

Case 1 was a 43-year-old female patient with no previous chronic or metabolic disorders diagnosis. One month before hospital admission, she presented progressive onset of severe headache, nausea, and drowsiness. She was assessed by neurosurgery service, where a cranial magnetic resonance imaging was performed and allowed to conclude right petroclival meningioma. She was programmed one week later for a surgical procedure. At hospital admission, she had the following vital signs: blood pressure (BP) (120/80 mmHg), Heart Rate (HR) (78 bpm), Breath Frequency (BF) (17 bpm), body temperature (36.3℃), and Glasgow Coma Scale (GCS) of 13 points eye-opening: 4 points, verbal response: 4 points, and motor response: 5 points. Laboratory parameters at admission suggested total blood cell count abnormalities, including high leucocyte and neutrophil count and low monocyte count. After discarding any probable infection, ceftriaxone was given as antibiotic prophylaxis. We calculated the Q-albumin index by dividing the cerebrospinal fluid albumin by serum albumin and used it as a parameter of BBB damage (0.0341 g/dl/4.62 g/dl=7.3×10^{-3}). Retrosigmoid craniotomy with partial resection of petroclival meningioma (Fig. 1A) and high-pressure valve ventriculoperitoneal shunt system colocation was performed without any complication. After surgery, the patient was transferred to the intensive care unit (ICU) with advanced airway management. A day after, a cranial computer tomography (CT) was performed, revealing the persistence of the tumor accompanied by cerebral edema. The CT scan was extended to chest imaging with consistent data of SARS-CoV-2-related pneumonia (Fig 1B). The next day, she presented fever (38.6℃) and purulent respiratory secretions; bacterial cultures and SARS-CoV-2 specific detection through bronchoalveolar lavage were performed. Ceftriaxone was suspended, and an empirical antibiotic scheme was started with meropenem and vancomycin; dexamethasone was also added to the treatment. Quantitative polymerase chain reaction (qPCR) confirmed SARS-CoV-2 infection the same day, and *Acinetobacter baumannii* was isolated from cultures one week later, so the antibiotic scheme was changed to colistimethate. She remained with leukocytosis, fever, and neurological impairment during the next days. After 28 days of hospitalization, she died because of cardiopulmonary arrest.

Case 2

Case 2 was a 43-year-old male patient with a previous diagnosis of hypertension one year ago and treatment with ACE inhibitors. Three months before hospital admission, he began with progressive, intense headaches in the frontal region without medical treatment. After one month, he developed vomiting and syncope with progressive gait abnormalities and decreased alertness. Then, he was assessed in a primary care center, and cranial magnetic resonance imaging revealed a round and well-defined tumor in the fourth ventricle, causing a cerebrospinal fluid blockage (Fig. 1C). The patient started treatment with prednisone and dexamethasone and was referred to our hospital for neurosurgery assessment. He was admitted with the following vital signs: BP (130/70 mmHg),

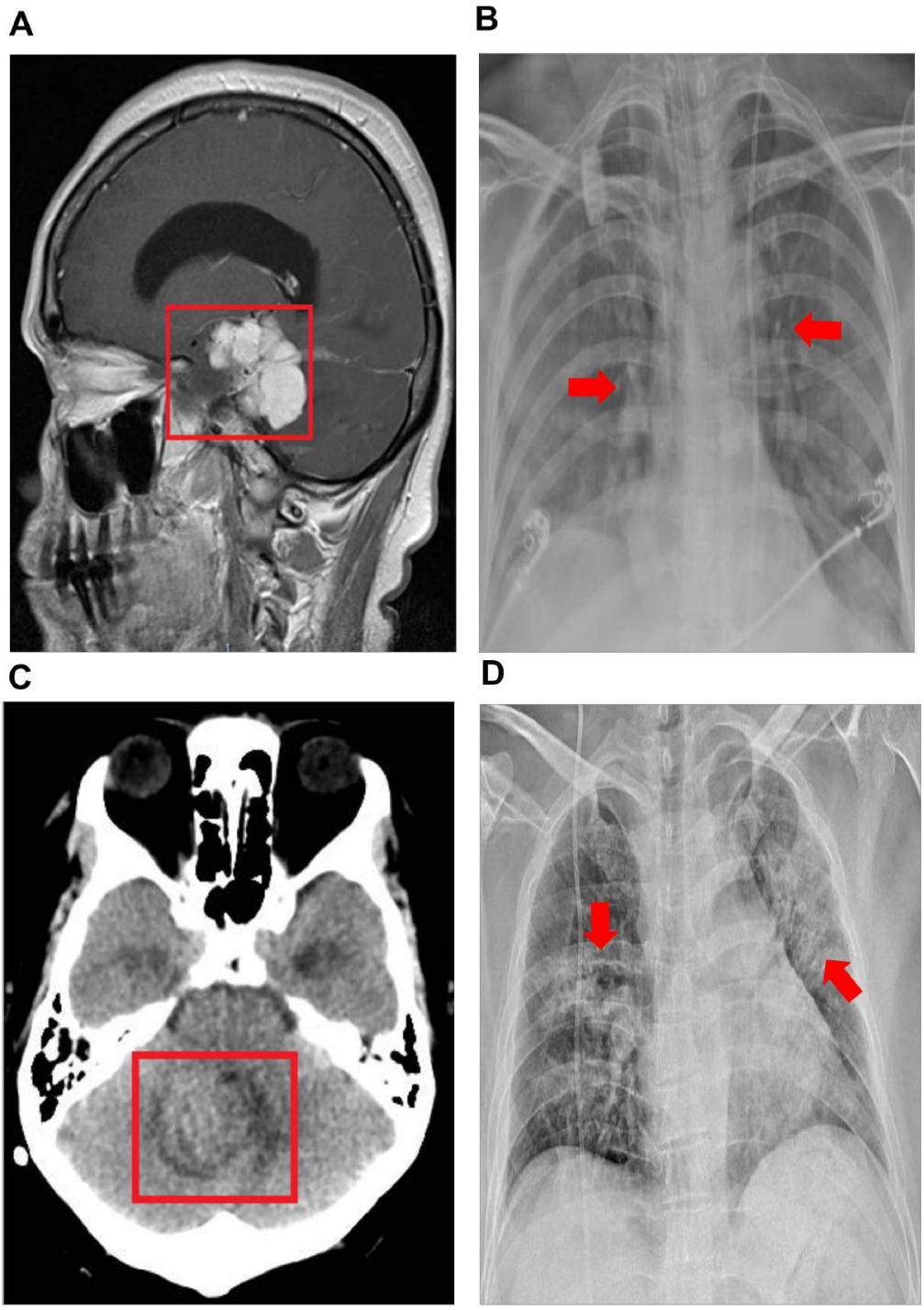

Fig. 1. Cranial and chest CT of patients with a brain tumor and COVID-19. (A) Case 1 magnetic resonance T1 sequence contrasted sagittal section petroclival lesion extending to a protuberance, enhancing the contrast medium compatible with meningioma. (B) Case 1 chest computed tomography (CT) with data suggestive of SARS-CoV-2 pneumonia. (C) Case 2 simple CT scan of the skull in coronal section showing lesion to the cerebellar vermis and right cerebellar hemisphere causing hydrocephalus. (D) Chest CT at admission showing severe pneumonia of Case 2.

HR (75 bpm), BF (18 bpm), body temperature (36.0℃), and GCS of 13 points (eye-opening: 3 points, verbal response: 4 points, and motor response: 6 points). Anosmia and peripheral oxygen saturation of 89% were also documented, and SARS-CoV-2 specific qPCR detection was performed, resulting positive. The relatives reported neurological impairment three days before admission,

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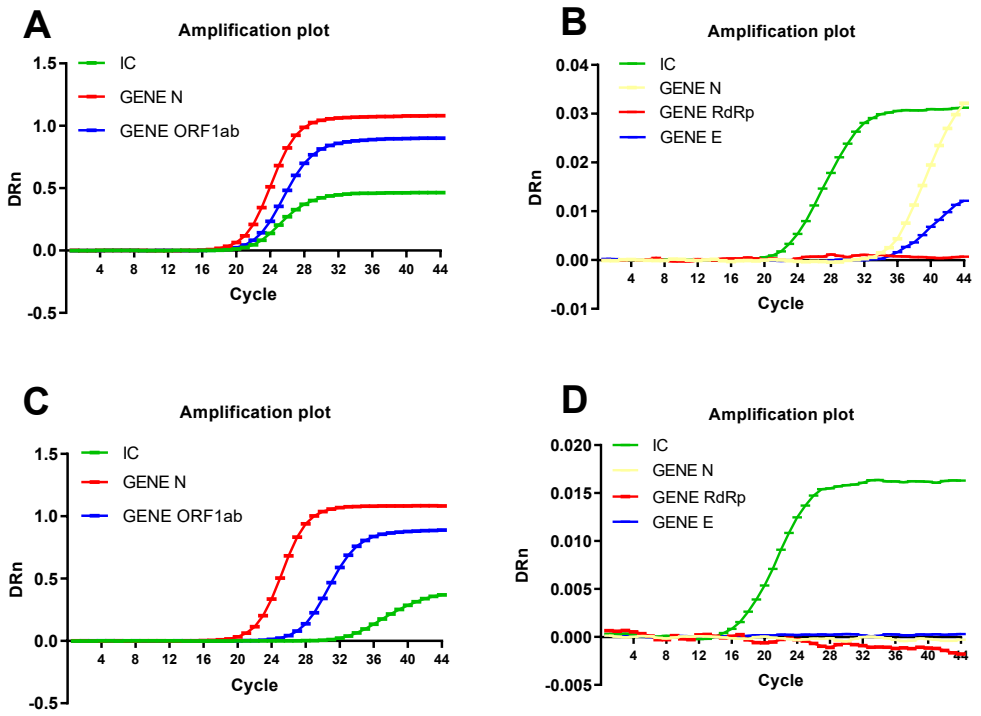

Fig. 2. Analysis of qPCR detection of SARS-CoV-2 viral particles. (A) Determination of viral infection in Case 1 by naso/oropharyngeal swab where N (CT=18.01) and ORF1ab (CT=19.6) SARS-CoV-2 genes were detected as well as the IC gene (CT=20.49). (B) Confirmation of CSF SARS-CoV-2 infection by the amplification of Gene N (CT=37.85) and the IC gene (CT=22.62). (C) Case 2 determination of viral infection by naso/oropharyngeal swab where N (CT=23.21) and ORF1ab (CT=24.86) SARS-CoV-2 genes were detected as well as the IC gene (CT=30.87). (D) Viral infection was not determined in CSF of Case 2; the IC gene amplification was CT=18.05.

without associated respiratory symptoms. Laboratory parameters revealed high leucocyte and neutrophil counts, whereas lymphocyte and monocyte counts decreased. For case 2, we found a Q-albumin index of 0.0016 g/dl/3.01 g/dl=5.3×10^{-4}. Fig. 1D shows a chest CT at admission revealing severe pneumonia. He was hospitalized in the pneumology department for COVID-19 management with supplemental oxygen therapy at 2 liters per minute using a nasal cannula, and oxygen saturation improved up to 95%. A high-pressure valve ventriculoperitoneal shunt system was placed the next day without any procedural complication. Ten days later, the patient was discharged with neurological improvement, GCS of 14 points (eye-opening: 4 points, verbal response: 4 points, and motor response: 6 points), and no supplemental oxygen needed.

The Institutional Ethical Committee of the General Hospital of Mexico guaranteed that the study was conducted in rigorous adherence to the principles described in the Declaration of Helsinki. Their relatives signed written informed consent. Both patients arrive at the emergency department because of neurological symptoms rather than respiratory complications associated with SARS-CoV-2 infection. The Carestream Viu Motion software v.12.1.5.7 from the digital electronic file of the General Hospital of Mexico was used to obtain cranial and chest CT scans.

The ORFlab and N genes of SARS-CoV-2 were detected by the kit for 2019 Novel Coronavirus (DADA0930-DA0932, DAAN Gene Co., Guangzhou, China) in naso/oropharyngeal swabs following the manufacture instructions. SARS-CoV-2 infection was confirmed in both patients by amplification of the N gen in Case 1 (CT=18.01) and Case 2 (CT=23.21), and the Orf1ab gene in Case 1 (CT=19.6) and Case 2 (CT=24.86), respectively. The internal control gene (IC) amplified at CT=20.49 in Case 1 and CT=30.87 in Case 2 (Fig. 2A, 2C respectively).

Both patients gave CSF samples at the beginning of the surgery by ventricular shunt. The serum of the patients was taken at admission for blood biochemistry analysis. The analysis of SARS-CoV-2 detection in CSF was performed following the instructions of the Gene Finder Kit™ COVID-19 Plus RealAmp Kit (Cat. Number IFMR-45, Gyeonggi-do, Korea), which can detect the presence of the E, N, and RdRp genes of SARS-CoV-2 and considering amplification of at least one of those genes as a positive result. Amplification of the N gene was detected only in Case 1 (N Gen CT=37.85 and endogenous gene CT=22.62) (Fig. 2B, 2D). CSF and serum were evaluated using the Beckman Coulter DxC 700 AU

Chemistry Analyzer (Beckman Coulter Inc., Brea, CA, USA) in adherence to the standard operating procedures to determine the values (g/dl) of albumin in both samples. Q-albumin index results from dividing the value of albumin in CSF by the albumin value in serum.

The CSF sample was centrifuged to 13,500 g for 60 minutes at 4℃. The RNA from mononuclear cells was isolated with TRIZOL reagent (Ambion by life technologies, Carlsbad USA Cat number 15596018) following the manufacturer's instructions. Total RNA samples were quantified and synthesized to complementary DNA (cDNA) using the kit M-MLV Reverse Transcriptase (Life Technologies, Carlsbad, USA Cat number: 28025-013). cDNA samples were used for amplification by qPCR (CFX96^{TM} Real-Time System, BIO-RAD) with SYBR Green Master Mix (Jena Bioscience, Jena Germany Cat number PCR-372L) according to the manufacturer's instructions. Specific primers for the cytokines were designed using the Primer-BLAST software from the National Center for Biotechnology Information, U.S. National Library of Medicine, following the thermocycling scheme: denaturation at 95℃ for 30 s, annealing at 61℃ for 30 s, elongation at 72℃ for 45s, 40 thermal cycles. The expression of the cytokines was normalized using the housekeeping gene control 18 s. The expression was reported as $2^{\Delta\Delta Ct}$. We used a control CSF sample taken by a ventricular shunt from a patient with non-communicating hydrocephalus and Wallenberg Syndrome. The control case had a negative nasopharyngeal exudate test for SARS-CoV-2 at the time of sample collection. We found an exacerbated cytokine response in Case 1with petroclival meningioma where we found viral particles. IL-13, IFN-γ, and IL-2 represented overexpressed cytokines. The expression of IL-13 increased by 2-fold in Case 2; meanwhile, in Case 1, this expression raises 19-fold compared to the Control Case. However, the expression of IFN-γ was 14-fold increased in Case 1 and decreased 0.6-fold in Case 2. mRNA levels of IL-2 increased in both patients 13 and 4.7-fold in Case 1 and Case 2, respectively. Similarly, the expression of TGF-β increased to 8 in Case 1 and 2.82 in Case 2. Finally, the IL-4 expression was 7-fold higher in Case 1 and slightly less in Case 2 (0.93-fold) compared to the Control Case. Cytokines such as IL-12, IL-1β, TNF-α, and IL-6 increased considerably (5-fold approximately) in Case 1, and the expression of these cytokines (exceptionally TNF-α) decreased in Case 2 to 0.3-fold compared to the Control Case (Fig. 3).

DISCUSSION

Several respiratory viruses such as HCoV-OC-43 and H1N1 can infect the CNS via transsynaptic transport. For this reason, a few studies suggested that SARS-CoV-2 could similarly reach the CNS. However, recent studies reported that ACE2 expresses in endothelial vascular cells, pericytes, and macrophages but not neurons [7], which reduces the chances of the transsynaptic transport as the main route of SARS-CoV-2 entry to the CNS. Moreover, the inability to detect viral particles in CSF from COVID-19 patients despite high titers of anti-SARS-CoV-2 antibodies [9, 10] remarks the possibility that BBB integrity plays a crucial role in SARS-CoV-2 neuroinfection. The BBB is an essential physiologic structure that selectively prevents the passage of pathogens such as viruses to the CNS. Consequently, it is feasible that SARS-CoV-2 can invade the CNS only after structural damage to the BBB.

Brain tumors can disrupt the BBB by releasing proinflammatory mediators, vasoactive cytokines, and growth factors with the ability to affect tight junctions and increase permeability, leading to edema and hemorrhage. Numerous studies have shown downregulation of tight junction protein expression such as claudin-1 and claudin-3 in specific brain tumors, including astrocytomas and glioblastoma multiforme [11]. Measurement of proteins typically found in serum but not in CSF unless BBB presents damage is an indirect method to estimate BBB integrity. When calculating the Q-albumin index, we obtained 7.3×10^{-3} g/dl for Case 1 and 5.3×10^{-4} g/dl for Case 2. Although reports indicate that a Q-albumin index $>8\times10^{-3}$ g/dl indicates BBB dysfunction [12], no patients exceeded this value. It is worth mentioning that the presence of a brain tumor triggers an inflammatory process where activation of microglia could decrease albumin levels due to albumin uptake from astrocytes [13]. However, the order of magnitude of the Q-al-

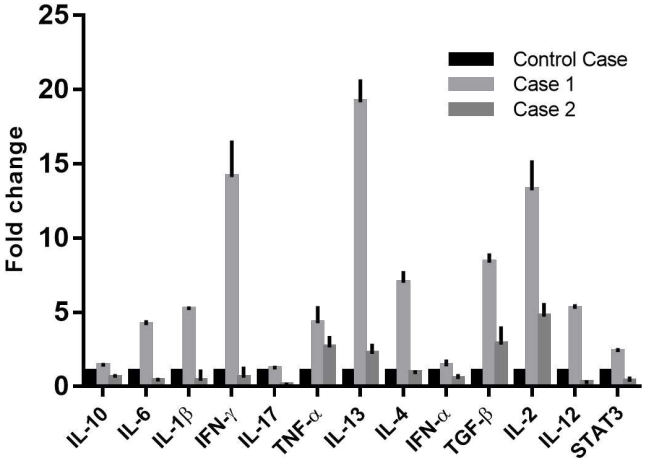

Fig. 3. Cytokine expression in CSF of patients with a brain tumor and COVID-19. IL-13, IFN-γ, and IL-2 represented the most overexpressed cytokines. These cytokines were more expressed in Case 1 (grey bars) compared to Case 2 (dark gray bars) and Control Case (black bars). The expression of cytokines such as TGF-β, IL-4, IL-6, IL-1β, TNF-α, and IL-12 was overexpressed around 5-fold in Case 1; meanwhile, in Case-2, these cytokines were under-expressed by 0.6-fold, except for TNF-α.

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bumin index between patient 1 is greater than patient 2, where we assume BBB integrity. Although Q-albumin is considered a valid parameter to evaluate the BBB permeability, it is indirect evidence which we consider a limitation of this study. Hence, the results presented in this manuscript should be taken with a reserve, and more studies should be conducted to determine the role of BBB in CNS infection by SARS-CoV-2.

In this study, we found viral particles in CSF only in the patient with petroclival meningioma, which causes BBB disruption as suggested by the Q-album index. Meanwhile, we did not find viral particles in the CSF of the patient with an intraventricular tumor, which is in line with our data in two patients with cerebrovascular disease [14]. Several authors, such as Bellon and cols., demonstrated that neurological symptoms in COVID-19 patients were not related to SARS-CoV-2 in CNS [10]. Conversely, they found intrathecal IG synthesis and signals of BBB disruption. These results suggest that virus invasion of the CNS may occur in patients with BBB damage. Moreover, the hypothesis of the neurological manifestations associated with COVID-19 are not necessarily supported by direct invasion of the CNS but through systemic inflammation that precedes the infection [15].

As mentioned earlier, the presence of a brain tumor activates the astrocytes surrounding the tumor-promoting the secretion of growth factors and cytokines trying to repair the damage. Astrocytes can also sense stimuli related to viral infection by expressing a cluster of proinflammatory genes in maladaptive reactive astrogliosis [16]. In this study, it is impossible to determine the observed inflammation source. This response could be due to the tumoral development, the infection by SARS-CoV-2, or by the BBB disruption allowing the free transit of proinflammatory molecules to the CNS. However, the patient with petroclival meningioma, positive for viral particles in CSF who probably had BBB damage, presents a higher expression of proinflammatory cytokines, which can be attributed to local viral infection. It is likely that the CNS infection by SARS-CoV-2 causes a more pronounced local (gliosis) immune response. Cytokine overexpression in these patients was represented by IL-13, IFN-γ, and IL-2, which have been used as immunotherapy to treat brain tumors, mainly in gliomas trying to inhibit tumor proliferation and angiogenesis. High levels of IL-13 were expected since the overexpression of the IL-13 receptor is an essential feature in brain tumors [17].

Moreover, recently IL-13 was recognized as the "driver" of COVID-19 severity, which neutralization in mice reduced both severity and death without affecting viral load [18]. Besides, IFN-γ is a central antiviral immune mediator that is abnormally downregulated in brain tumor cells. So, the overexpression of this cytokine could be exclusively due to viral infection. Initially, it was detected in respiratory swabs from COVID-19 patients with type I IFN genes (IFN alpha and omega) but not type II IFN genes (IFN-γ) [19]. However, recently was demonstrated that high levels of IFN-γ have a pivotal role in SARS-CoV-2 infection, inducing the expression of ACE2 in epithelial colonic organoid cells and enabling a higher virus replication; therefore, it is proposed that the pharmacological interference of IFN-γ may be a treatment for severe COVID-19 [20]. As well as IFN-γ, IL-2 is downregulated in brain tumors [21], but it is overexpressed in COVID-19 convalescent individuals [22]. Therefore, the overexpression of these cytokines seems to be a set of immune responses due both to tumor development and direct infection of CNS by SARS-CoV-2, specifically in Case 1. Since the CD4+ T lymphocytic origin of IL-2 and IFN-γ (helper and cytotoxic T cells) as a response to viral infection in the pulmonary epithelium, these cytokines or their producing cells may migrate to the CNS, allowed by the BBB damage, however more studies are needed to determine the source of these cytokines in the CNS in patients with a brain tumor, COVID-19, and their relationship with the integrity of BBB.

It is feasible that BBB damage is necessary for virus entry to the CNS, either through binding to ACE2 in endothelial cells or pericytes of the BBB. Due to ACE2 is not expressed in neurons, the integrity of the BBB would play a central role in allowing the passage of SARS-CoV-2 or infected immune cells to the CNS. Further studies are needed to examine ACE2 expression in other brain tissue cells that can host the virus. Accordingly, COVID-19 patients with documented structural disruption or suspected permeability of the BBB due to other diseases such as brain tumors should undergo a specific medical follow-up to monitor possible neurological effects associated with the presence of SARS-CoV-2 in the CNS. In conclusion, this study shows the presence of SARS-CoV-2 particles in the CSF only after damage to the BBB measured indirectly by the Q-albumin index, favoring the inflammatory response regulated by IL-13, IFN-γ, and IL-2, which highlights the possible key role of BBB integrity in SARS-CoV-2 infection.

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