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# Intracranial Hypotension after Severe COVID-19: Case Report and Literature Review

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## Abstract

**Background:** Despite the lack of published clinical studies, new mutations of COVID-19 are travelling worldwide, and sooner or later, unexpected consequences will be reported. At the middle of October 2020 new variant of SARV-CoV-2 (known as 20H/501.V2, B1.351 or variant β) were identified in South Africa. This variant has multiple mutations in the spike protein, including K417N, E484K, N501Y. Soon after another variant from India was also reported which is the predominant variant now? We did an extensive search of the medical literature, looking for all publications regarding intracranial hypotension, subdural effusions SARS-CoV-2/COVID-19.

**Case presentation:** We report a 46-years-old-male with severe COVID-19 admitted in the intensive care unit preceded by gastrointestinal manifestations; all performed investigations confirmed the severity of the infection caused by SARS-CoV-2. PMH refers chronic vascular headache, CSF analysis was normal, and MRI of the brain three months before admission reported no abnormalities. The patient recovered from the respiratory disorder and went back home, but he developed a postural headache two weeks later. We suspect spontaneous intracranial hypotension, and the CSF pressure (5.5 cm of $H_2O$) confirmed it. In addition, a CT scan of the head showed bilateral frontal subdural effusion.

**Conclusion:** We did not find a published report related to COVID-19, subdural effusion, and intracranial hypotension. We delivered comments and hypotheses to explain its pathophysiology based on the role of zonulin and the microbiota-gut-brain axis.

**Keywords:** Intracranial hypotension • Subdural hygroma • Subdural effusion • SARS-CoV-2 • Cytokine storm • ACE-2 • Post-COVID-19 manifestations • Gut-brain-axis • Microbiota • Zonulin • Cytokine storm

**Abbreviations:** ACE-2: Angio Converting Enzyme; CNS: Central Nervous System; COVID-19: Coronavirus Disease 2019; CSH: Chronic Subdural Hematoma; CT: Computer Tomography; ECGF1 Endothelial Cell Growth Factor 1; HCoV-229E: Human Coronavirus 229E; HCoV-OC43: Human Coronavirus OC43; HCoV-NL63: Human Coronavirus NL63; HCoV-HKU1: Human Coronavirus HKU1; IH: Intracranial Hypertension; INFγ: Interferon-Gamma; MERS-CoV: Mild Encephalitis /Encephalopathy with a Reversible Splenial Lesion and Coronavirus; PMH: Past Medical History; SARS-CoV-2: Severe Acute Respiratory Syndrome; Coronavirus 2; SHg: Subdural Hygroma; SIH: Spontaneous Intracranial Hypotension; TNF-α: Tumor Necrotic Factor Alpha; TYMP: Thymidine Phosphorylase; VEGF-A: Vascular Endothelial Growth Factor-A

## Introduction

Next to the end of 2019, a new variant of coronaviruses affected many peoples causing viral pneumonia of unknown sources in Wuhan, which belong to central China's Hubei province. Later, this virus is named SARS-CoV-2 because some authors found similarities with the virus in 2003 that caused the SARS [1]. From December 2019, the number of cases of 2019 coronavirus (COVID-19) infected subjects has been increasing exponentially up to date, accumulating more than 214,468,601 confirmed cases, 4,470,969 fatalities and a total of 4,953,887,422 vaccine doses have been administered worldwide. (August 25, 2021) [2]. SARS-CoV-2 is a highly contagious virus transmitted from person to person through respiratory droplets, direct contact of mucous membrane with contaminated hands, or even *via*l fecal-oral contamination [3]. Despite the lack of clinical studies done, it has been confirmed that some new mutations of COVID-19 are travelling worldwide, and sooner or later, unexpected consequences will be seen despite the vaccination program.

Since the first published study in Wuhan, every month, an increasing number of cases presenting COVID-19 and neurological manifestations have appeared in the medical literature. COVID-19 can cause severe neurological conditions. According to the information from CDC in Atlanta (United States of America) and other authors, the most standard clinical features include cough, general malaise, fever, dyspnea, diarrhea, chest pain, and muscle pain [4,5]. On the other hand, some neurological manifestations of COVID-19 include non-vascular headache, dry cough, sore throat, anosmia, ageusia, fatigue, myalgia, breathlessness and symptoms, and signs secondary ischemic and hemorrhagic stroke, cerebral sinus venous thrombosis, epileptic seizure, epilepsy, status epilepticus, Bell's palsy, Guillain-Barre-Syndrome including Miller Fisher variant, and encephalopathies among others [5-29]. In the medical literature is reported that 88% of severe COVID-19 patients develop neurological complications with an associated lymphopenia, increased ferritin, and LDH level in blood [30]. Seems to be that the main entrance of the SARS-CoV-2 to the brain is *via* the systemic blood flow, mainly in severely infected patients. Another way of entry is passing the cribriform plate at the upper nasal fossa, causing hyposmia/anosmia, and then continuing *via* a retrograde axonal pathway to reach the brain [31].

The virus takes another path from mechanoreceptors and chemoreceptors in the infected lung tissue and then ascent vias synapse-connected route to the cardiorespiratory centre at the medulla oblongata [32] and from there most probable it disseminates to other areas of the brain and the cerebrospinal fluid (CSF). Some authors from Beijing Ditan Hospital (China) confirmed the SARS-C0V-2 genome's presence in the CSF this year [33]. Other authors demonstrated the presence of COVID-19 in a case of necrotizing encephalopathy with damage to the blood-brain-barrier (BBB), leading to hemorrhagic encephalopathy [34]. Finally, other

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authors also confirmed SARS-CoV-2 in CSF of a child with encephalitis and endothelial vascular damage from virus invasion *via* angiotensin-converting enzyme II (ACE-2) receptors [35]. In a recent large study about the aggressivity of SARS-CoV-2, the authors found two significant virus types of modalities that they called L type and S type being the first one the most aggressive compare with the second one [36]; these mutations can provide some impacts on the pathogenesis of the viruses. At the same time, other authors found a relationship between the severity of COVID-19 and chromosome 3p21.31 [37]. In the meantime, other publications have been trying to explain the pathogenic mechanism behind the complications caused by COVID-19 [38-47]. One of the tools is the invasion of the brain *via* the ACE-2 receptor [38], and the structural and biophysical evidence 2019-nCoV S protein binds ACE2 (inhibited by ACE inhibitors) with higher affinity than does SARS-CoV S, which suggests that antibody cross-reactivity is limited amongst the two receptor-binding domains [39]. Recently, Want K and colleagues reported from their finding that SARS-CoV-2 invade host cells *via* a novel route of CD147-spike protein, which is bound to CD147 (a receptor on the host cells) [43]. In addition, another author. suggested that S protein-specific T cells in average persons may be cross-reactive clones developed after previous exposure to person endemic coronaviruses [44]. The severity of COVID-19 is directly proportional to the concentration level of tumour necrosis factor-alpha (TNF-$\alpha$), macrophage inflammatory protein 1 alpha (MIP-1A), granulocyte colony stimulating factor (GCSF), interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), and inflammatory cytokines like interleukins (IL-2, IL-6, IL-7, IL-10) [47]. There is also an additional pathological process caused by programmed cell death protein 1 (PD-1), T-cell immunoglobulin mucin-3 (Tim-3), and natural killer group 2 A (NKG2A) at the beginning of the disease [45,46]. It is essential to highlight that NKG2A is an inhibitory component of the NKG2 group manifested on NK cells (natural killer T cells) and a subset of CD8+ T cells. The interactivity of NKG2A with histocompatibility antigen alpha chain E (HLA-E) can suppress NK cells and T cells [47,48]. T lymphocytes and NK cells are an expression of PD-1. These cells support the immune responses and promote self-tolerance, reducing T cells' activity, stimulating regulatory T cells [49]. T-cell immunoglobulin mucin-3 (Tim-3) (a co-inhibitory receptor) plays a crucial role in inhibiting T helper 1 cells (Th1) responses and the expression of TNF-$\alpha$ and IFN-$\gamma$ [49].

In the last trimester of last year, a new variant of SARV-CoV-2 (known as 20H/501.V2, B1.351 or $\beta$-variant) had been found in our province (Eastern Cape), South Africa. This variant has multiple mutations in the spike protein, including K417N, E484K, N501Y. Today, June 7, 2021, we have no idea when this pandemic will end and what kind of sequelae will occur.

Intracranial hypotension (IH) is a clinical entity characterized by low CFS pressure ≤6 cm of $H_2O$ measured at the lateral recumbency position without pillow by lumbar punction (LP), presenting clinical manifestations of postural headache, which is a positional headache that usually improves by lying in a recumbent position for 15-30 minutes [50], neck pain, nausea, vomiting, dizziness, and visual and hearing disturbances [51]. In many cases, the most typical cause is CSF leak at the setting level along the spine are due to: Perineural cyst, which is the spontaneous dehiscence of dura matter. Degenerative dural tears caused by the protrusion of calcified intervertebral disc. Focal agenesia of dura matter (bare nerve root). CSF-venous fistula [52].

IH can also be secondary to iatrogenic procedures, craniospinal injury, over-shutting (diversion devices). Sometimes IH presents with unknown aetiology (Primary). This process is usually named spontaneous intracranial Hypotension (SIH) or craniospinal Hypotension. IH is more frequent in females around 30-50 years of age with a past medical history (PMH) of idiopathic intracranial hypertension, according to some author's report [53]. The same investigators refer to a PMH of clear rhinorrhea or otorrhea in traumatic or iatrogenic aetiology or even pituitary surgery through nasal fossa, sinus surgery basal skull fractures. Anecdotal IH presentation in the comatose stage was reported in the literature [54]. Other less common exhibitions include medial sphenoid meningocele, Marfan syndrome, autosomal dominant polycystic kidney disease, idiopathic intracranial hypertension, Ehlers-Danlos syndrome (type II) [55]. Other conditions associated with SIH are subdural collections or hematomas. There is a predisposition of the bridging veins to broken and tear when they pass through the subarachnoid space, mainly in patients under anticoagulant therapy, causing chronic subdural hematoma (CSH) in around 5%-20% of the population [56,57]. Sometimes, the CSF volume loss may cause a compensatory enlargement of the subarachnoid/subdural space and occur a subdural hygroma (SHg) or a chronic subdural haematoma (CSH) if there is tearing of the engorged cortical veins even bilaterally [58]. Bilateral CSH also happens in SIH cases [58-60] or circumstances without IH. In cases of underlying IH, the CSH/SHg will not improve until IH resolve.

Nevertheless, if the CSH/CHg receives surgical treatment and disappears, then soon after, it may recur because of CSF underlying dynamics abnormalities [61]. Therefore, the primary treatment is to

Correct the leak instead of evacuating the subdural collection. This collection usually resolves following the appropriate IH therapy [62] The most relevant IH features on MRI are diffuse pachymeningeal enhancement and "brain sag" signs, although these images are present in several clinical processes [63].

### Our research questions

- What frequent is IH in COVID-19 patients?
- How COVID-19 can influence the pathogenesis of IH?

We systematically reviewed almost all publications about COVID-19 and associate subdural effusions and their pathophysiology and management written in English, Spanish, and Portuguese to answer the previous research questions using the procedure mentioned below and present our patient.

## Literature Review

### Literature search strategy

We included all publications like case reports, case series, and observational cohort studies that reported intracranial hypotension, Covid-19, and subdural effusion. The initial search included all articles published before May 31, 2021. We reviewed the following databases for published studies: Medline, EMBASE, Scopus, Google Scholar, Science Direct, Scielo, LILACS, BIREME, Search of Sciences, and Cochrane library to identify articles evaluating COVID-19/IH. All items about spontaneous intracranial hypotension, intracranial hypotension, subdural hygroma, subdural effusion, neurological manifestations of COVID-19, coronavirus disease, cytokine storm, Neuro-COVID, pachymeningeal enhancement, subdural collection, Neuro-COVID, SARS-CoV-2, zonulin", microbiota, gut-brain axis, where is the PubMed Central wild card for every possible word beginning or ending. We did not include other neurological manifestations beyond the current work scope.

### Study selection

We select all publications (case reports, case series, cross-sectional studies, clinical trials, and observational cohort studies) reporting IH, SH, SHg, and COVID-19 patients during the initial search. Later we progressively s excluded all duplicate studies and those publications not meeting inclusion criteria because they reported only COVID-19 separately or articles reporting IH, SH, SHg not related to COVID-19 apart from some manuscripts written in other languages or abstracts without English translation.

Between December 1 of 2019 and May 31, 2021, our literature search yielded 215 publications. After removing duplicate articles, unsuitable manuscript we retained 59 unique records. Considering the title and abstracts, we discarded 21 journals, 38 items, screening the complete text, and selected 32 publications regarding COVID-19/Neurological complications. Finally, we found a total of cero publications referring to COVID-19/IH. From all groups, we did not find any published study about post-COVID-19/IH/SH/SHg (Figure 1).

**Figure 1.** Flow diagram of publications searched in the medical literature.

## Case presentation

A 46-years-old-male admitted in our hospital in June 2020 presented a four-day history of fever, dry cough, dyspnea, nausea, vomiting, abdominal pain, decreased taste and smelling sensation. He also complained of recurrent diarrhea on an alternating day for seven days duration. A fifth day from the beginning, he developed severe respiratory distress with severe hypoxemia, requiring a long stay in the intensive care unit where neuromuscular blockade, mechanical ventilation, and deep sedation were provided.

Three months before the admission, he complained of recurrent and severe non-vascular headache without focal neurological signs. CFS was complete normal and CT scans of the brain (MX16 evo. Philips South Africa Health System) done showed no abnormalities. Because the ELISA test came positive for cysticercosis, we requested MRI (1.5T Siemens Healthineers. Forcheim, Germany) of the brain looking for intraventricular neurocysticercosis, which showed no abnormalities. He never smoked, consumed alcohol or recreational drugs.

On examination, moderate obesity is present with no noticeable body asymmetry. The patient had mild cyanosed mucous membranes, but he was well hydrated and afebrile with a GCS 15/15. Motor examination revealed a 5/5 muscle power and no focal neurological signs. Patient was in respiratory distress with tachypnea of 30 breaths/minute saturating at 84% on a 40% venture face mask. The rest of the vital signs showed a BP of 125/85 mmHg, a pulse of 100 bpm. Hgt of 22 mmol/l She had fine crepitation on both lower part of the chest, and blood test on admission revealed: Hb: 13.1g/dl, white cell counts 13.30 x 109 /L, lymphocytes:741 µL (1,000 to 4,800), platelet count 365 x 109 /L, CRP 23 H mg/L. nasopharyngeal PCR confirmed SARS-CoV infection. Blood group A-positive, Na 141 mmol/L, k 2.8 mmol/L, Cl 118 mmol/L, Urea 8.8 mmol/L, Creatinine 122 umol/L, level of D-dimer:0.85, determination of serum level interleukine-6 was not available. Counts of CD4+ T cells: 310/µL, ferritin 250 ng/mL (10 to 120), creatine kinase 612 units/L (30-135), procalcitonin: 0.94 ng/mL (0.10 – 0.49). Albumin: 7.8 g/dL (3.4 to 5.4 g/dL), CD4 count 325/µL. On arrival to ICU, he also received high flow nasal oxygen (60% at 15 L/min), dexamethasone 8 mg IV daily, Clexane 60 mg SC 12 hourly, ceftriaxone 1g IV daily, azithromycin 500 mg PO daily, vitamin D 50000 u PO weekly, vitamin C 250 mg PO 8 hourly, amlodipine 10 mg orally daily, Ridaq 25 mg orally daily and Intravenous fluids (1L Ringer's lactate IV 8 hourly).

Two weeks later, the patient improved and was discharged home, only complaining of occasional mild headaches, and referred to the outpatient neurology clinic for follow-up. However, during the second week after discharge, he complained of a generalized and severe headache that improves rapidity in the recumbent position and worsens around 15 minutes of assuming the upright position with complete recovery after 15 to 20 minutes in supine position. This pain increased by coughing, laughing, and defecation. The patient returned to the neurology clinic, where focal neurological signs or meningeal signs were not found, fundoscopy was utterly ordinary, but the Valsalva maneuver exacerbates the headache remarkably. A lumbar punction show an opening pressure of 5.5 cm of H20, and a CT scan of the brain confirmed a bilateral SHg in the frontoparietal region. PCR for SARS CoV-2 back negative. The patient did not respond well to oral analgesic. The improvement was obtained after resting in a flat position without a pillow for no less than 12 hours, generous caffeine intake (stimulating CSF production?) and increasing oral hydration. We made a 48-hour Flat Test, which confirmed our diagnosis. The patient improved gradually, there wasn't indication to perform any invasive procedure, and he never presents a sign of rebound intracranial hypotension. Four and a half months later a new CT scan of the brain revealed a 50% reduction of SD effusion with mild to moderate headache sporadically.

## Comments

On the flow diagram (Figure 1), we did not identify any publication regarding IH/SD effusion/COVID-19 despite of our extensive research of the available medical literature. Therefore, we consider that this comorbidity/tardive neurological manifestation of COVID-19 is exceptionally uncommon. Our patient did not present clinical manifestations of long-COVID-19. Later, we discuss possible pathophysiology for this finding and deliver our hypothesis for answering question two.

Brief comments about the investigation done: Our second comment is related to an elevated white cell count, low lymphocyte count, elevated D-dimer level, and creatine kinase during her ICU admission, suggesting severe illness. Other authors also reported these findings when comparing these parameters among in and out ICU admissions [64]. We found abnormal albumin levels, lactate dehydrogenase, and C-reactive protein in our case probably

associated with the lungs' acute injury during ICU admission. We could not check the status of angiotensin in plasma which abnormalities have been reported by other authors as well [65]. Our patient belongs to blood group A, which has been related with severe COVID-19 and respiratory failure as well [66, 67]. Findings of CD4 count below 400/µL associate with the severity of the SARS-CoV-2 infection have been reported too [46]. These authors also confirmed that T cell numbers related to IL-6, IL-10, and TNF-αconcentration in the serum of COVID-19 patients were negative. When the total T cells account is below 800/µL, those patients need urgent management, including patients with no apparent critical illness because sooner or later, they will develop remarkable deterioration. It is essential to highlight that a notable lymphocytes' levels are part of the cases' characterization, presenting a severe COVID-19 [45,46, 68]. Hypokalemia is the most relevant electrolyte imbalance seen in COVID-19 [47].

Apart from those above-mentioned, other laboratory abnormalities are important to determine the severity of the patient's condition and predictors of death, such as neutrophil/lymphocyte ratio, ferritin level, and hypophosphatemia, hypofibrinogenemia, and platelet/lymphocyte ratio [47]. Other authors established that around 50% of the critically ill COVID-19 patients present cytokine elevation, fever, high ferritin levels, and cytopenia [69,70]. It has known that SARS-CoV-2 causes an immunosuppressive effect on the body by exhausting and diminishing T lymphocytes working with inhibitory receptors on natural killers and NKG2A, TIM-3, and PD-1 (T cells), as we commented before. Therefore, immunomodulators plus immunostimulant and anti-inflammatory activities can influence the severity of COVID-10 and minimize the risk of multiorgan failure and death [47]. Severe COVID-19 causes neuronal and glial cells dysfunction and can develop other neurovascular complications and leptomeningeal injury [70].

Considering that IH is a frequent consequence of CSF leak at any level along the neuroaxis, and this situation can alter the necessary equilibrium between the volume of arterial and venous blood, CFS, and brain parenchymal. That mechanism referred to the relationship between the intracranial components' pressure-volume inside the skull's no expansible compartments. It had been explained magisterially by Alexander Monro (1733-1817), a Scottish physician, and George Kellie (1720–1779). a Scottish general surgeon [71,72]. Their hypothesis combines the intracranial volume of the brain (~1400 mL) with the total volume of the venous and arterial blood (~150 mL) and the volume of the CSF (~150 mL) to keep a

dynamic equilibrium. When the volume of any component diminishes, the other two volumes increase to keep the intracranial volume average (~ 1700 mL) [73]. Another mechanism controls the low-pressure venous system that displaces blood volume [72]. Suppose we apply the Monro-Kelly hypothesis to our patient. It is easier to understand the mechanism of low intracranial pressure and why upright posture leads to the dilation of the nociceptive cerebral venous system explaining why orthostatic headache. The Figure 2 shows a list of the commonest causes of IH (Figure 2).

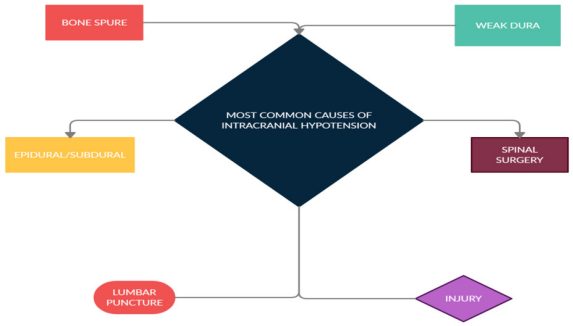


**Figure 2.** The most typical cause of IH.

Recently some authors found more evidence of neuronal degeneration, neuronophagia, mild oedema around nerve cells, and the small veins within the COVID civets' brain [74]. Based on this information, we hypothesize about the subdural effusion mechanism caused by SARS-CoV-2 facilitated by a cytokine storm.

In critically ill COVID-19 patients, if possible, to see cerebral microbleeds (CM) damaging different areas of the brain, mainly the corpus callosum. The complete pathogenesis of this process remains unknown, but the direct and indirect effect of SARS-CoV-2 on the endothelial tissue caused by the cytokine cascade is certain, apart from the hypoxemic injury caused by disruption of the blood-brain barrier (BBB) [75]. The best investigation to visualize CM is the MRI of the brain. Unfortunately, we could not perform a new MRI study looking for CM because of limitation of our COVID-19 protocol.

The pathogenesis of the brain lesions is related to astrocyte's disorder. This glial cell is the brain's primary homeostatic cell from one side. Other activated astrocytes (AA) release chemokines to activate specific receptors from invading microglia and macrophages, attracting them to the lesions. In addition, these astrocytes may modulate the immune response delivering TNF-α, IL-12, IFN-γ, TGF-β, IL-10 and controlling the pro-/anti-inflammatory phenotype of macrophage [76].

The neuroinflammatory reactive astrocytes can stimulate naïve precursor T-cells and produce pro-inflammatory (Th1) or anti-inflammatory (Th2) phenotypes *via* pro-inflammatory cytokines (IFN-γ, TNF-α, IL-17) and anti-inflammatory cytokines (IL-10, TGF-β).

Nonetheless, Th1 cells stimulate macrophages activation and worsening the inflammatory reaction by releasing IL-2, IFN-γ, TNF, while Th2 cells cause inhibition of the macrophage's inflammatory activity by releasing IL-4, IL-5, IL-6, IL-10, and IL-13 through humoral immunity. The BBB integrity also depends on the astrocyte function by secreting VEGF, TGFα, bFGF, TNF-α, IL-1β, IL-3, IL-6, Ang-1, and BAFF endothelial cell control from one side of the barrier and the other by glial-derived neurotrophic factor. The nervous system's large glutamate sink is in the astrocytes, which control its function [76] (Figure 3).

Undoubling, astrocytes play an essential role in the mechanism of brain damage in human beings, depending on the predominance of cytokines released. It has also known that many pathogenic agents cross the BBB by paracellular path *via* transcytosis mechanism inside, entering monocytes according to the Trojan Horse hypothesis or by the hijacking of β-adrenergic receptors [77]. The two BBB alterations are called non-disruptive and disruptive. The first one happens when there is molecular damage and its permeability if affected increasing or decreasing regulations of receptors and transportation across the barrier associate to astrocyte dysfunction, cytokine production and augmenting neuroinvasion of pathogen agents and the disruptive modalities follow to anatomical modifications, including mitochondrial lesion, loss of tight-t junctions' integrity, breakdown of glia limitans, degradation of the glycocalyx, increased vehicular traffic, re-induction of fenestrae, astrocytopathy, and apoptosis [78,79]. Astroglia-produced cytokines [IL-1β, IL-6, TNF-α] and prostaglandins mediate both BBB modalities [80]. Astroglia cells may release both anti/pro-inflammatory factors that can provoke and control the neuroinflammatory brain process.

Among these anti-inflammatory agents' astrocytes released are cytokines and growth factors (IL-6, IL-10, IL-11, IL-19, IL-27, TGF-β, SHH), intracellular signaling factors (CRYAB; Gal9, STAT3, and A20), C.-receptors (Dopamine D2 receptors, estrogenic receptor-α, glycoprotein 130, D.-small intercellular effector molecules (MicroRNAs, retinoic acid: miR-181, miR-17-5p, and Dicer1). Pro-inflammatory activity is listed here: (See Figure 3), chemokines: monocyte chemoattractant protein-1 (MCP-1/CCL2), CCL5 (RANTES), CCL7, CCL8, CCL12, CXCL1, CXCL8 (IL-8), CXCL9, IFN-γ-inducible protein-10 (IP-10/CXCL10), CXCL12, CXCL16. Cytokines and growth factors: IL1-β, IL-6, IL-11, IL-15, IL-17, TNF-α, BAFF, vascular endothelial, and growth factor (VEGF). Intracellular signaling factors: NF-κB, SOCS3, Act1. Small intercellular effector molecules: PGE and NO [81,82].

Without a doubt, SARS-CoV-2 cause brain inflammatory reaction as has been mentioned-before; in that situation, astrocytes tend to up-regulate the production of IL1-β, IL-6, IL-11, IL-15, IL-17, TNF-α, BAFF, VEGF and develop remarkable delayed pro-inflammatory phenotype, even more than activated microglia activation (MA) [83,84].

One of the most relevant pro-inflammatory activity in the pathogenesis of the septic process is provided by IL-1β inducing astroglia cells to produce thymidine phosphorylase (TYMP)/endothelial cell growth factor 1, (ECGF1). Vascular endothelial growth factor A (VEGF-A) contribute to the downregulation of TJ protein expression in BECs, leading to BBB breakdown [85]. At the same time, astroglia cells attenuate MA releasing TGF-β as well [86]. The before-mentioned AA with IL-1β supports the up-regulation of mRNA plus protein expression of IL-6 and TNF-α [87]. On the other hand, some authors found in transgenic model that overexpression of IL-6 (constitutive astrocytes) linked with a breakdown of the BBB, angiogenesis, increased expression of complement proteins, astrogliosis, and neurodegeneration [88,89]. Other researchers also reported that SARS-CoV-2 infection increase levels of cytokines such as TNFα, interleukin (IL)-1β, IL-6, IL-12, and INFγ, a phenomenon known as "cytokine storm" (See Figure 4a) [90-92]. Based on previous reports, SARS-CoV-2 cause neurodegeneration, demyelination, and cellular senescence, which accelerate the ageing process of the brain and increase neurodegenerative pathology [93-97]. Therefore, we have hypothesized that the damage persists beyond the acute phase of SARS-CoV-2 infection apart from later intensive care syndrome, autoimmunity dysfunction, post-viral fatigue syndrome, permanent organ damage and persistent virus infection leading to long-COVID-19. After searching the medical literature, we could not identify a suitable mechanism able to reverse these processes, accelerate the neurogenesis all over the brain and repairing the covering of the brain. Notwithstanding, the enunciated postulates about direct/indirect damage on the brain caused by SARS-CoV-2 through pro-inflammatory cytokines, chemokines, and growth factors, we want to comment on other CNS damage seen in post-acute SARS-CoV-2 infection without long-COVID. In this regard, some authors have confirmed enlargement of Rolandic operculum, insular lobes, hippocampi, olfactory cortices, Heschl's gyrus, and cingulate gyrus by MRI images and concluded there is a general decline of mean diffusivity, axial and radial diffusivity accompanied by an increase of fractional anisotropy in the white matter of the right corona radiata, superior frontal-occipital fasciculus, and external capsule. Based on these findings, same authors suggest a disruption of the brain's micro-structural components and functionality in the recovery stages of COVID-19 [98]. To answer our second research question is necessary first to review the most acceptable pathophysiologic of SH. A dural tear is the cause of

the IH in patients presenting connective tissue disorders like autosomal dominant polycystic kidney disease, Ehrler Danlos' syndrome (Type II), or Marfan Syndrome. In the case of dural ectasis leading to CSF leakage into the epidural or subdural space, this mechanism can explain why orthostatic headache and cranial nerves (V-VIII) disorders accompany this process [99]. Other conditions cause IH like diabetic coma, hyperpnea, uremia, dehydration, and even severe systemic illness [100]. Nevertheless, there are not coronavirus' cases reported during the previous or current pandemic.

Based on observation of patients presenting clinical manifestations of IH with normal CSF pressure, we believe that reducing the CSF volume rather than a reduced CSF pressure is the primary pathophysiology of this syndrome but can be both processes and it is our first hypothesis: "Decrease CSF volume can be a consequence of the arachnoid membrane's rupture, leading to CSF leakage into the subdural space" which probably happened in other patients [101] (See Figure 3). However, if this theory is correct, why there are not more similar COVID patients reported?

We can consider that this presentation may be a simple coincidence. Besides that, we still hypothesize that SARS-CoV-2 present in the CSF cause damage to the arachnoids membrane until proven otherwise, but it is essential to investigate other mechanisms.

As we know, CSF's buoyancy plus pain-sensitive structures is the primary support of the brain. These structures are the meninges layers and blood vessels (cerebral and cerebellar veins), some cranial nerves (5th, 9th, and 10th), and C1-C3 spinal nerves [102]. Considering the CSF's buoyancy effect may diminish when its volume decreases, leading to the brain sag downwards, which causes headaches with worsening by an

upright position, like our case. Moreover, this is the exact mechanism that explain postural headache in other patients or cases with reduced brain volume [103]. Furthermore, it is opportune to recall that SARS-CoV-2 cause brain atrophy, as we point out before. Finally, headaches can be secondary to the intracranial blood vessels pathology [104]. The Valsalva maneuver was joyous in our case. However, this test diminishes the venous return to the cardiac chambers and increases the venous volume intracranially, causing headaches even in a flat position like our case. In addition, some authors reported the presence of mononuclear pleocytosis, reticulocytes, elevated protein concentration, and xanthochromia in CSF of patients with IH caused by diapedesis of protein and cells into the subarachnoid space [105], but we did not find such CSF abnormalities. Here we briefly highlight some relevant signs seen on MRI in IH cases. In this regard, Nadir Ali, and colleagues [99] proposed a Mnemonic: SEEPS to remembering the five most relevant signs of IH visible on MRI: Sagging of the brain or downward displacement of the brain. Engorgement of venous structures. Enhancement of the pachymeninges. Pituitary hyperemia. Subdural fluid collection and the presence of extrathecal CSF, apart from reducing the Galen vein diameter, internal cerebral vein angle, collapsed superior ophthalmic vein and spinal meningeal diverticula. However, IH's typical characteristic MRI signs is a linear, thick, and non-nodular enhance of meninge without the leptomeninges' involvement, which serves to differentiate IH from meningitis [99].

Around 50% of patients with IH have bilateral subdural effusion without any appreciable mass effect resulting in a remarkable meningeal enhancement caused by a compensatory effect of dilatations of the cerebral veins secondary to huge CSF volume loss [106]. In this bibliographic research, we found that leptomeningeal enhancement is present in COVID-19 associated with the presence of oligoclonal bands [107,108], and prominent subarachnoid spaces are quite common (47%) around the optic nerves adding another interrogation about intracranial pressure in SARS-CoV-2 infected patients, apart these volumetric and micro-structural pathological changes in the olfactory cortices and white matter of recovered COVID-19 cases as previously cited [93].

One crucial issue that needs to be deeper investigate is the distribution of the ACE-2 receptors all over the brain and its relationship with the affected brain regions considering that SARS-CoV-2 penetrate CNS cells by attaching to ACE-2 through spike glycoprotein indicating more severe brain damage where the ACE-2 is largely expressed. In these regards, the expression of ACE-2 is higher in the substantia nigra, brainstem, the spinal cord, followed by the hippocampus, lentiform nucleus, caudate nucleus, thalamus, limbic system, and lastly frontal lobe cortex [109].

Probable the coincidence of an elevated expression of ACE-2 in the frontal lobe leading to more concentration of SARS-CoV-2 is related to the proximity to the direct penetration of the virus into the brain through olfactory gyrus, as the first functional area in the nervous system invaded by SARS-CoV-2 [110], and microstructural and functional integrity changes at the recovery stages [93] plus the damage caused by the pro-inflammatory cytokines over the meninges layers including arachnoid rupture [70] which may explain the subdural effusion and IH present in our patient. Almost finishing this part of the manuscript, another question arises: why the frontal lobe is more affected than the other?

Because there is more expression of ACE-2 in the frontal lobe than the others cerebral lobes therefore, more concentration of SARS-CoV-2 resulting in more regional pathology leading to frontal subdural effusion and IH. The Figure 3 (SARS-CoV-2/ CT scan) also has the intention to bring into your attention that coronavirus can affect the brain after respiratory syndrome recovery.

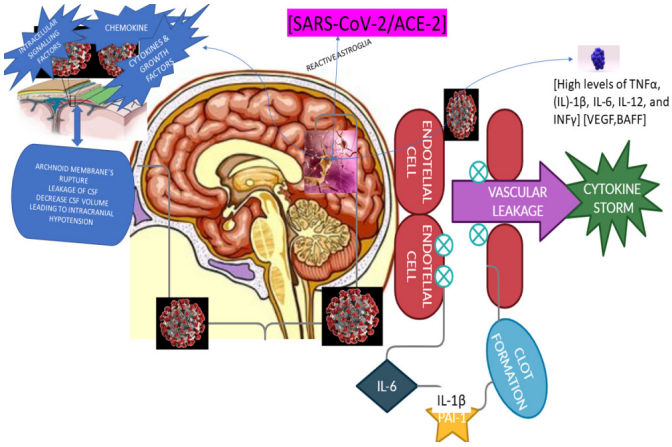


**Figure 3.** Schematic representation of the proposed hypothesis for a SIH mechanism in patients presenting severe COVID-19 from reactive astrocytes, Zonulin, cytokine storm and MGBA.

Our patient presented a combination of respiratory, gastrointestinal (GI), and neurological signs. Looking for one common factor for this association and thinking in the close relationship between the respiratory system, nervous system, and GI manifestations seen in many COVID-19 patients, we agreed that it could be due to an augmented expression of ACE2 and high expression of TMPRSS2 in intestinal epithelial/endothelial cells, and other systems. We believe that one of the elements to explain that relationship may be the role to be played by Zonulin (Znl).

In 2000, Znl was described by Wang and colleagues [111] as a 47 KDa protein whose primary function is to provide an endogenous regulation of intestinal paracellular permeability by disassembling tight junctions (TJs) of epithelial and endothelial cells. This Znl can be found in the GI tract [112], lungs

[113] and CNS [114], increasing the permeability of the BBB [115]. Another essential issue to consider is the results obtained with the new AT-1001 (Znl peptide antagonist), which is currently listed as a specific medication (Larazotide Acetate) against SARS-Cov-2 [116].

The presence of anosmia and ageusia in our case is caused by the neurotropism of the SARS-Cov-2 on the olfactory, facial, glossopharyngeal nerves (retrograde neuronal route), leading to viral replication and CNS invasion. The respiratory involvement is secondary to the direct invasion of the lungs from the infected naso-oral region (mixed with saliva), which moved to the esophagus binding enterocyte surface ACE2 and replicates. From this level, *via* the laryngopharynx-trachea, it moved to the lungs and return to the CNS mainly through a hematogenous route with disruption of

the BBB. Another route to and from the CNS is through the vagal nerve (VN) [117]. The VN components include parasympathetic efferent and viscera-sensory afferents to and from the lateral wall of the medulla oblongata (MO). The VN viscera-sensory afferents fibres sources are in thoracic and abdominal organs as ramified and free terminals nerve belonging to glutamatergic neurons located in the nodose ganglion and project nucleus tractus solitarius (NTS) in the MO (See Figure 4a and 4b).

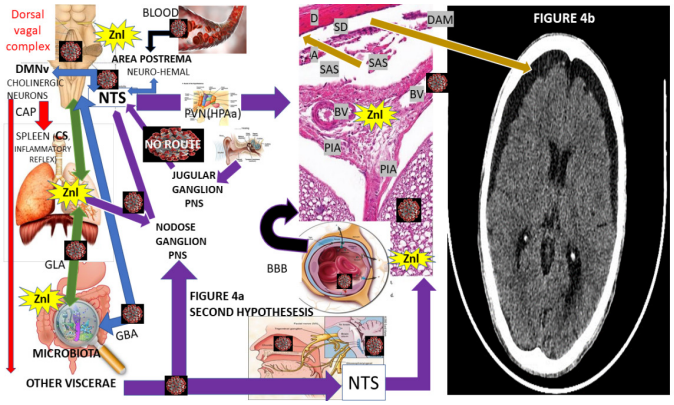


**Figure 4.** (a) Hypothesis on the mechanism for bilateral subdural effusion after severe COVOD-19. Red arrows: Motor pathways. Blue arrows: Sensory pathways. A: arachnoid membrane, BBB: Blood- brain-Barrier, BV: Blood vessel, CAP: cholinergic anti-inflammatory pathway, CS: Cytokine storm, D: Dura mater, DMNv: Dorsal motor nucleus of the vagus nerve, GBA: Gut-brain-axis, GLA: Gut-lung-axis, HIPAA: Hypothalamus-pituitary-adrenal axis, NTS: Nucleus tractus solitarius, PIA: Pia mater, PNN: Paraventricular nucleus of the hypothalamus, RAM: Rupture of the arachnoid membrane, SAE: Subarachnoid space, SD: Subdural space, Znl: zonulin. (b) CT scan of the brain shows a bilateral frontoparietal subdural effusion more prominent in the frontal/parietal lobe.

Nevertheless, the efferent fibres of the VN are composed of axons of the large cholinergic neurons in the dorsal motor nucleus (DMN) of the VN (immunosuppressor component), which project to all thoracoabdominal viscera *via* local cholinergic neurons in intravisceral ganglia. Thus, all efferent and afferent VN fibres are strongly interconnected within the dorsal vagal complex included the area postrema (AP) of the MO, which provides the necessary anatomical substratum to regulate vital homeostasis (See Figure 4a). On the other hand, regulating the cardio-respiratory system is strongly dependent on the chemoreflex and baroreflexes through the VN and medullary centres. One "take away" knowledge from this review is the absence of BBB in the AP, which probably allow a direct invasion of SARS-CoV-2 straight to the medullary centers including pre-Bötinger neuronal complex with associated breathing disturbances. The gastric α-synuclein immunoreactive inclusions located in the submucosal Meissner and the myenteric Auerbach plexuses from the gut moves to the brain through the VN. However, based

on the proposal of Llorens and colleagues, another pathway can be considered from the infected GI tract, involving Znl, Toll-like receptor 4 (TLR4), protease-activated receptor 2 (PAR2), and Znl brain receptor to explain how the GI system, upper and lower respiratory apparatus, CNS, and systemic damage due to cytokine storm (CS) happens simultaneously [117]. The positivity of the PCR tested in the CSF confirm that neurological disorders are not primarily caused by direct spread of the virus in the CNS [118]. Some authors reported that GI symptoms are risk factors for developing mild nervous system complications such as headache, myalgia, anosmia, or dysgeusia [117], and Znl can reach the CNS and increase BBB permeability [119]. In summary, Znl activated complement system (the first response of the immune system against any foreign invasion) together with the CS secondary to viral replication, causing disruption of the BBB and the neurological manifestation seen in COVID-19 patients. However, this mechanism is not good enough to explain dural effusion and IH yet. Last year we were convinced that SARS-CoV-2 did not pass from the esophagus to the gut passing across the stomach because of pH level. Today, we support the hypothesis that GI system is another entry place of SARS-CoV-2 from oropharyngeal region toward the brain in patients with reduced gastric pH level by viscous sputum, nasal discharge, mucus, and bile [117] allowing the virus to reach the intestine. After the virus trespass this natural barrier, it invades the host cell *via* ACE-2, serine proteases TMPRSS2 and TMPRSS4 [120], then proteins and virus-specific RNS (synthesized in the cytoplasm) assemble a new virion [121] released to the GI system and disseminating through the paracellular pathway leading the immune response, and CS in the brain. SARS-CoV-2 protected by airway-borne mucus can survive gastric pH, reaches the gut where its protein S bind TLR4 and, *via* MyD88, induces a high expression of IL-6, which promote elevated expression of Znl opening paracellular pathways *via* PAR2, allowing virus entry, infect the vascular endothelial cells and spread to the brain through a hematogenous route [117] and neurogenic pathway. At this level, SARS-CoV-2 binds the Znl receptor and induce Znl release with consequent BBB damage and dissemination to the nervous tissue, including its coverings as happens in multiple sclerosis (MS) and experimental autoimmune encephalomyelitis involving the PAR2 [122]. It is well known that the highest IL-6 level is seen in critically ill COVID-19 patients with acute respiratory failure [123,124], and promoter of Znl is under IL-6 control [125] then overexpression of Znl and IL-6 expression are MyD88 related.

Propose the role of the gut-brain axis (GBA) in our case: Apart from the remarkable role played by CS and other mechanisms in our patient, we also consider another hypothesis to explain the pathogenesis of subdural effusion and IH, and it will be discussed below.

The GI system has its nervous tissue, also known as the enteric nervous system (ENS), where many hormones and immune functions are exchanged. The GBA allow strategic communication among the gut and the brain in both directions; therefore, any disturbance in the gut is present in the brain and vice versa. This is one of the reasons we encourage and promote specialist in neurogastroenterology. It has been proved that the GBA is involved in the pathogenesis of stroke, epilepsy, and neuroinflammatory disorders, including MS [126]. Other paths of invasion of the SARS-CoV-2 to the brain *via* the vagal afferents from the intestine have been discussed, highlighting the relevant mechanism of GBA in the pathogenesis of brain disorders [127]. The previous postulate included infectious diseases like COVID-19 based on updated knowledge on the interconnection between the enteric glial cells and the ENS. It represents the more critical histocompatibility complex class II, which acting antigen-presenting cells (immune cells) of the gut-associated lymphoid tissue (GALT) composed by the appendix, lymphoid follicles of the intestinal mucosa and the Peyer's patches. The immune response mechanism is initiated by GALT activated by SARS-CoV-2 infection, increasing the permeability of the endothelium and elevated expression of almost all pro-inflammatory mediators (mainly IL-6). We also agreed that increased gut permeability (secondary to overexpression of Znl) opens the doors for SARS-CoV-2 entry. From this location, SARS-CoV-2 reaches the blood flow/lymphatic system invading local tissues, endothelial cells, lymphatic vessels, and disseminates through endogenous channels and retrograde afferent vagal route to the brainstem and all over the brain [117]. It is important to recall that increased permeability of the BBB is usually seen in other viral infections [128,129] and both BBB and the intestinal epithelial barrier (IEB) are composed of endothelial and epithelial cells; both are similar and are regulated by glial cells. These cells (BBB/IEB) are in charge to seal TJs that can be disrupted by external stimulus [130]. As we said, the increased permeability of the BBB plays a remarkable role in the pathogenesis of many neurological disorders, including haemorrhage stroke allowing passage of plasma factors into the nervous system that leads to inflammation of the brain, blocking off the endothelial pericyte interaction, increasing immune cells migration into the CNS plus astrocyte activation [131]. Zonulin works as the physiological mediator of TJs permeability in the GI tract, involved in the pathogenesis of neurological features caused by SARS-CoV-2 throughout the disruption of the BBB (leaky brain). Both barrier (BBB/IEB) under normal circumstances stops stressors (undesirable particles) from entering and causing damage on the GI system (into the lamina propia) and the CNS (into the astrocytes). Znl allows these undesirable particles to enter the blood flow, including zonulin itself, leading to the activations of C3 and C5 components of the complement system [132]. As mentioned, TLR4 and

PAR2 presence (in glial cells and neurons) are mandatory for functional and overexpression of Znl, which contribute to the inflammatory component of neurodegenerative disorders [133]. The human brain receptor for Znl (PAR2) is a glycoprotein enriched by sialic acid residues [134], which are receptors for SARS-CoV-2 as well, expressed in the capillaries endothelium (brain) and able to dissemble TJs *in vivo* [135]. When the TJs opens, it may develop a leaky gut which depends on augmented exposure to stressor leading to inflammation and immune response, creating a vicious cycle where the inflammation increases intestinal permeability, the passage of stressor (toxins, pathogens, endotoxins, antigens, and inflammatory markers) aggravating the situation and interacting with neurotransmitter metabolism and the hypothalamus-pituitary-adrenal axis (HIPAA) (Figure 4b).

Recently has been proved the reciprocal relationship between Parkinson Disease (PD) and GI through the gut-brain axis recognized as an "intestinal syndrome." Many factors included leaky gut/endotoxemia, microbial dysbiosis, and swelling of the intestine, cause peripheral αsynucleinopathy and gut dysfunction [136]. These interactions xplain the relationship between the intestinal syndrome in our patient and his neurological manifestation. Furthermore, our patient complained of GI manifestation related to SARS-CoV-2 infection, and modification of the gut microbiome could increase the expression of local pro-inflammatory elements. This increased gut permeability, could expose ENS neurons to bacterial infection from the mentioned pro-inflammatory products. Furthermore, activated enteric glial cells (EGC) in the GI tract might

contribute to the spread of α-synuclein across the ENS locally and CNS *via* VN. In the brain, α synuclein disseminates all over and cause loss of nigrostriatal dopaminergic neurons leading to PD, Alzheimer's disease (AD) and other neurological conditions [136].

Propose role of micro biota in our case: The role of the gut-brain axis related to homeostasis and pathogenesis of several neurological conditions have been mentioned, and over the past 15 years, the role of microbiota has been under investigations. Our scientific community has long ignored one hundred trillion microorganisms living in our body. Today we know that it is the most important regulators of the GBA function. Apart from the retrograde VN and the ENS route, other paths serve to communicate the microbiota with the brain, including tryptophan metabolism and the immune system involving microbial metabolites like branched-chain amino acids, peptidoglycans, and short-chain fatty acids, which stimulate the CD103+ dendritic cells facilitating proper migration of activated T cells to the intestinal lumen, plus butyric, and acetic acid as well [137]. On the other hand, the microbiota-gut-brain axis (MGBA) composition can be modified by infections, environmental stressors, nutrition, medications, plus genetic factors in early life, and later in life by ageing process and during all stages of life by stress. Many researchers have reported the implications of MGBA on many neuropsychiatric disorders such as anxiety, depression, schizophrenia, PD, AD, and regulation of neural process in animal models like microbiome activation of microglia, neurogenesis, and myelination [138].

The interaction of immune cells of the GALT and gut microbiota is mandatory to modulate the immune system. The balance between the regulatory T cell and the effector T cell is elucidated by gut microbial products [139]. Nevertheless, these cell from GALT and immune factors can be moved to the bronchial-associated lymphoid to deliver protection against respiratory infections [140], known as the "gut–lung axis," these are another element to be considered in the pathogenesis of our patient's condition and late development of neurological complications.

The gut-lung axis also works in both directions, as has been proven by Wang and colleagues in their research. They found lung derived CCR9+CD4+ T cells migrating from the lung to the gut after the influenza virus infection. These authors confirmed gut microbiota dysbiosis leading to aberrant Th17 response, gut damage, and consequent gastroenteritis [137,141]. This process could be present in our case as well. Previously, we discussed the role of CS on the pathogenesis of the neurological manifestation present in our case; now, we will comment on the role of MGBS in the pathophysiology of COVID-19/ CS. The main point to comment is the diversity of gut microbiota is not affected by ageing. However, in erdely peoples affected by COVID-19 enhance chemokine and cytokine production contribute SARS-CoV-2 to induce hyper-inflammation (CS) and called macrophage activation syndrome, leading to poor prognosis [142] In experimental models, selected patients have been observed chemokine CXCL10 playing a crucial role capturing inflammatory cells to the place of inflammation-inducing CS. Some of these authors documented aberrant expressions of chemokines and pro-inflammatory cytokine in infected cases by SARS-CoV-2 presenting severe COVID-19 like our case.

## Conclusion

As far we know this is the first reported case presenting intracranial hypotension secondary to subdural effusion after severe COVID-19 without long-COVID. The review of the medical literature leads a creation of the novel list of causes of IH. Based on our bibliographic research seems to be that severe COVID-19, cause neuronal and glial cells dysfunction leading to neurovascular complications and leptomeningeal injury. We hypothesize on the subdural effusion mechanism caused by SARS-CoV-2 facilitated by cytokine storm, dysbiosis, zonulin hypothesis, MGB axis and other elements graphically represented in Figures 3 and 4. Undoubling, astrocytes play an essential role in the mechanism of brain damage in COVID-19 patients depending on the predominance of cytokines released. More investigations should be done to support or deny our hypothesis, to bring better comprehension of the pathogenic mechanism behind these disorders and providing better therapeutic approach with suitable medication and promptly.

## Limitations

We acknowledge that our extensive review has several limitations. Firstly, many studies reviews are either case series or case reports, with no observational cohort studies and no cross-sectional investigations. Most of these studies are considered relatively lower in quality with publication and reporting bias.

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## Declarations

### Ethical issue and consent to publish

We obtained written informed consent to publish clinical details and patient's images. The Institutional Ethical committee did not consider this report for additional ethical approval. The corresponding author has copy of consent form signed by this patient by request.

### Consent for publication

We got additional written consent for publication of patient clinical information and images.

### Availability of data

All material, data that support the findings of this study are used for this publication is available by request to corresponding author.

### Competing interest

The authors have not any conflict of interest to disclose and declare they did not get of any commercial or financial relationships construed as a potential conflict of interest.

### Funding

The author declares that he did not receive financial support or personal collaboration that could have influenced the results reported in this paper.

### Declaration of anonymity

The author certifies that he did not reveal the names, surnames, initials, or other identity issues of this case in this publication, and complete anonymity is guaranteed.

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