Normal Pressure Hydrocephalus Associated with COVID-19 Infection: A Case Report

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Abstract

COVID-19 is a pandemic disease responsible for a large number of deaths worldwide. Many neurological manifestations have been described. We report a case of normal pressure hydrocephalus (NPH) two months after acute COVID19 infection, in a patient without other risk factors. A 45-year-old male patient presented an 8-month history of progressive gait disorder and cognitive impairment after being hospitalized for SARS-CoV-2 infection. Magnetic resonance imaging (MRI) was compatible with NPH. A spinal tap test was positive and there was progressive improvement after shunting, with complete resolution of symptoms. Other infections such Syphilis, cryptococcosis and Lyme disease have been associated with NPH. Possible mechanisms for NPH after COVID include disruption of choroid plexus cells by direct viral invasion or as a result of neuroinflammation and cytokine release and hypercoagulability leading to venous congestion and abnormalities of CSF flow. Given the significance of NPH as a cause of reversible dementia, it is important to consider the possibility of a causal association with COVID19 and understand the mechanisms behind this association.

Introduction

COVID-19 is a pandemic disease initially reported in Wuhan, China, in 2019, which has been responsible for a large number of deaths worldwide [1]. It is caused by an RNA virus named SARS-CoV-2 and is primarily a respiratory disease involving lower and upper airways, although many systemic manifestations have been described. Similarly to what has been reported with other coronaviruses, such as MERS-CoV and SARS-CoV-1, this pathogen has shown neurotropic and neuro invasive properties resulting in a wide range of neurologic manifestations [2].

The viral mechanism of cell invasion involves interaction of viral spike proteins with the angiotensin converting enzyme 2 (ACE2) receptor which is largely distributed in human tissues, including the central nervous system [3]. Recent studies indicate that these receptors are highly expressed in the olfactory tract, substantia nigra, posterior cingulate cortex and choroid plexus of lateral ventricles[4], leading to many neurologic manifestations.

Normal pressure hidrocephalus (NPH) is a condition characterized by a triad of cardinal symptoms composed by gait disorder, urinary incontinence and cognitive decline associated with dilated ventricles, in the absence of intracranial hypertension [5]: Initially described in 1965, it has been extensively studied as a potential cause of reversible cognitive decline [6]

Herein, we report a case of Normal Pressure Hydrocephalus, occurring two months after acute COVID19 infection.

Case Report

A 45-year-old male patient presented with a history of imbalance and progressive gait disorder for the last 8 months. During this period, his family also reported memory impairment and behavior changes. He had
a previous history of bipolar disorder and type II diabetes mellitus and reported a COVID19 infection 2 months before initial presentation of neurologic symptoms.

Initial symptoms of SARS-Cov-2 infection were fever, anosmia, disgeusia and anorexia. A real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay (Allplex™ SARS-CoV-2 Assay (N/RdRP/S genes) from nasopharyngeal swab confirmed the diagnosis of COVID19. In the tenth day of infection, he had respiratory distress and hypoxemia (SO2 87%), was admitted to a hospital and received oxygen via nasal cannula. He was hospitalized for seven days and treated with dexamethasone and antibiotics for suspected bacterial pneumonia. At discharge he was able to walk unassisted.

Two months after acute COVID19 infection the patient started a progressive gait disorder, complaining that he felt like his feet were glued to the ground. After a few weeks, he started forgetting recent facts and his family complained of excessive daytime sleepiness and blunted affect. They also reported a change in his personality, previously active and extroverted, became apathic and introverted. He progressed to executive dysfunction and difficulty in performing his labor activities, which led to him leaving his job. There was no history of head trauma, previous stroke or subarachnoid hemorrhage, meningitis, blood transfusions or substance abuse. There was also no family history of neurologic diseases.

Neurologic examination revealed short-term memory loss, slow processing speed, inattention, difficulty in planning and executive dysfunction. A mild tetraparesis was also perceived, with brisk deep tendon reflexes in four limbs. There was no clonus and flexor plantar responses were observed. There was mild rigidity of the upper limbs, without cogwheeling. Gait was slow and magnetic, with short steps, feet close to the ground and postural instability.

Laboratory evaluation did not reveal any abnormalities (Table1). Complete blood count, renal, hepatic and thyroid function were normal. Serology was negative for Syphilis and HIV. Vitamin B12 levels were also normal.

Brain magnetic resonance imaging (MRI) disclosed moderately dilated supratentorial ventricular system with callosal angle reduction, sulcal effacement near the interhemispheric fissure and aqueduct flow-void (Figure 1). A high-volume (40ml) diagnostic lumbar tap test was performed and revealed an opening pressure of 100mmH2O. There was marked improvement of gait and balance after the procedure. CSF analysis was entirely normal (Table2).

A diagnosis of Normal Pressure Hydrocephalus was made and a ventriculoperitoneal shunt was placed. Thirty days after the procedure there was significant improvement of cognitive functions with a Montreal Cognitive Assessment (MoCA) score of 28/30. Gait also improved substantially, now presenting normal speed and step and stride length. The patient returned to his previous work activities.

Discussion
We have described a previously healthy patient who developed NPH two months after a case of COVID19 infection of moderate severity, presenting with apraxic gait and cognitive impairment. Urinary incontinence was not reported, possibly because our patient was submitted to a ventriculoperitoneal shunt early in the disease course and urinary symptoms may present later in NPH [7].

Normal pressure hydrocephalus has been classified as idiopathic or secondary [8]. Many diseases have been implicated in its etiology, such as subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), meningitis, stroke and intracranial neoplasms [8]. Outcomes in patients with secondary NPH (sNPH) tend to be better than in those with idiopathic NPH (iNPH), with improvement after shunt in 50-70% in sNPH and only 30-50% in iNPH [9]. Some specific infectious diseases have also been reported as possible etiologies for NPH, including Lyme disease [10], neurosyphilis [11] and cryptococcosis [12], but as far as we know it hasn’t been associated with COVID-19 infection.

Some mechanisms could explain CNS invasion in COVID19. The main theory is that SARS-CoV-2 uses the olfactory nerves as a main input port through interaction of the viral S protein with the ACE2 receptor expressed on olfactory epithelium, invasion and transsynaptic retrograde transmission through the olfactory nerve into the brain [13]. Another proposed mechanism is infection of cerebral endothelium by viral particles in the bloodstream, leading to blood-brain-barrier dysfunction and viral invasion into the CNS [2]. The spatial distribution of ACE2 receptors in the CNS was studied using brain transcriptome databanks and high concentrations of these receptors were found in the choroid plexus of lateral ventricles suggesting that the choroid plexus could be a pathway for SARS-CoV-2 to enter the CNS [4]. It is possible that this interaction between the virus and the choroid plexus could alter the dynamics of CSF flow, contributing to NPH. An animal model study of hydrocephalus after SAH has demonstrated that inflammation of choroid plexus cells marked by increase in NF-kB results in dysfunction of these barrier cells leading to the production of increased abnormal protein-rich CSF, and consequentially in hydrocephalus due to excess CSF production [14].

Many neuroinvasive viruses such influenza A and B can initially trigger an innate immune response by activating microglia [15]. Ramified microglia (M0) are constantly scanning the neuropil through their highly motile processes and after encountering an insult signal change to an ameboid activated state and release cytokines. Short or moderate signals lead to a neuroprotective M2 phenotype, whereas intensive acute (such as a neurotropic viral infection) activation renders a proinflammatory M1 phenotype producing reactive oxygen species, nitric oxide, proteases, and proinflammatory cytokines, such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) [16]. Microglia also activates astrocytes that can modulate the recruitment and activation of additional microglial and other immunocompetent cells [17]. Microglial and astrocyte activation as well as massive cytokine release might lead to inflammation of arachnoid villi resulting in fibrosis and adhesion of these structures, reduction in CSF reabsorption, and consequently to hydrocephalus [18]. Another possible factor in the etiology of COVID19-associated NPH is a hypercoagulable state induced by the systemic response to SAR-CoV-2 [19], which could lead to venous congestion and CSF flow abnormalities [20].
In a case series of patients with persistent headache after COVID-19 infection 84.6% had an increased ICP in the absence of meningitis or encephalitis. A pro-thrombotic state was implicated in the disruption of normal CSF flow resulting in increased ICP in these patients [20]. It is possible that in patients with an increased intracranial compliance the same abnormalities might lead to an increase in CSF volume (resulting in normal pressure hydrocephalus), instead of raising ICP [21]. Another possibility is that some of these patients with initially elevated ICP might progress to NPH over time as the CSF compartment rearranges itself in a larger volume to maintain physiologic ICP according to Laplace’s law [22].

We have described the first case of normal pressure hydrocephalus possibly associated with COVID19 infection. Although pathophysiological mechanisms are still unclear and we cannot be certain that NPH occurred because of COVID19, there was a temporal correlation and the patient did not have other risk factors for NPH. Given the significance of this condition as a cause of reversible dementia, it is important to consider the possibility of a causal association with COVID19, as well as understand the mechanisms behind this association, leading to possible measures for preventing this complication in patients with initially elevated ICP. More reports, longer follow-up and perhaps histopathology of arachnoid granulation specimens are necessary to confirm this association and clarify its mechanisms.

**Declarations**

**Funding**

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**Competing interests**

The authors report that they have no competing interests.

**Ethics Approval**

The study was approved by the local ethics committee under the number 4092933

**Consent for publication**

The manuscript contains no any individual person's data in any form.

**Availability of data and material**

All materials used in this study will be made available subject to a material transfer agreement.

**Code availability**

Not applicable

**Consent to participate**
The patient has given informed consent to this report.

**Author’s contribution**

*Conception, Organization, and design of the work:* MASN, PBN and PRN

*Acquisition, analysis, or interpretation of data for the work:* TMFV, GMF, MLPS, ASV, PRN, PBN and MASN

*Writing the first draft:* TMFV and PRN

*Review and critique:* MASN, PBN, GMF, JDVC

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### Tables

Table 1 – Results of laboratory and cerebrospinal fluid analysis in a patient with normal pressure hydrocephalus after COVID19
| Variables                                      | COVID Symptoms Onset | Neurological Symptoms Onset | Reference values                  |
|-----------------------------------------------|----------------------|-----------------------------|-----------------------------------|
| **Serum tests**                               |                      |                             |                                   |
| Hemoglobin (g/dL)                             | 15,9                 | 14,5                        | 13 – 17,5                         |
| Leukocytes (cells/mm³)                        | 7640                 | 5600                        | 4000 – 11000                      |
| Lymphocytes (cells/mm³)                       | 770                  | 2420                        | 1000-3500                         |
| Platelets (number/mm³)                        | 259.000              | 255.000                     | 150.000 - 450000                  |
| C-Reative Protein (mg/dL)                     | 6,37                 | -                           | < 0,3                             |
| ESR (mm/HR)                                   | 27                   | -                           | <600                              |
| D-Dimer (ng/ml)                               | 300                  | -                           |                                   |
| Sodium (mMol/L)                               | -                    | 142                         | 136 - 146                         |
| Potassium (mMol/L)                            | -                    | 4,3                         | 3,5 – 5,1                         |
| Calcium (mg/dl)                               | -                    | 9,3                         | 1,16 – 1,32                       |
| Magnesium (mg/dL)                             | -                    | 2,3                         | 1,6 - 2,6                         |
| Blood Urea Nitrogen (mg/dL)                   | 21                   | 14                          | 7-20                              |
| Creatinine (mg/dL)                            | 1,1                  | 0,92                        | 0,5 - 1,3                         |
| AST (U/L)                                     | 39                   | -                           |                                   |
| ALT (U/L)                                     | 49                   | -                           |                                   |
| TSH (µlU/ml)                                  | -                    | 1,542                       | 0,550 – 4,780                     |
| HIV I, II                                     | -                    | Negative                    | Negative                          |
| Syphilis                                      | -                    | Negative                    | Negative                          |
| **Analysis of cerebrospinal fluid**           |                      |                             |                                   |
| Cell count (cells/mm³)                        | -                    | 2                           | 0-4                               |
| Differential cell count                       | -                    | 100% lymphocytes            | -                                 |
| Protein (mg/dL)                               | -                    | 26                          | 15-45                             |
| Glucose (mg/dL)                               | -                    | 74                          | -                                 |
| VDRL                                          | -                    | Negative                    | Negative                          |
| Gram stain                                    | -                    | Negative                    | Negative                          |
| Fungal stain (India-ink)                      | -                    | Negative                    | Negative                          |

PT- Prothrombin time; aPTT- Activated partial thromboplastin time; VDRL- Venereal Disease Research Laboratory; PCR- Polymerase chain reaction

Table 2 – Results of a spinal tap test in a patient with normal pressure hydrocephalus after COVID19
| Test parameter                     | Before spinal tap | After spinal tap |
|-----------------------------------|-------------------|------------------|
| ned up and go (10 meters)         | 18.4 seg          | 16.7 seg         |
| Number of steps                   | 32 steps          | 29 steps         |

**Figures**

**Figure 1**

![A](image1.png)  ![B](image2.png)  ![C](image3.png)
Brain MRI in a patient with Normal pressure hydrocephalus after COVID19 infection showing: (A) Axial T2-weighted image with dilated lateral ventricles, (B) Coronal T1-weighted image depicting acute callosal angle and upward bowing of the corpus callosum and (C) Sagittal T1-weighted image showing normal infratentorial ventricular compartment.