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Research Article

Neurological Sequelae in Idiopathic Intracranial Hypertension and COVID-19 Patients: A Novel Case Series

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Abstract

Neurological symptoms affect greater than one third of adult COVID-19 patients. Elevated Intracranial Pressure (ICP) findings have been noted increasingly in COVID-19 patients and associated with higher mortality amongst COVID-19 ICU patients. Yet, there is a dearth of literature discussing these disease processes and relevant detection and therapy. In this retrospective case series, six adult neurology patients who had both received a diagnosis of Idiopathic Intracranial Hypertension (IIH) and have had COVID-19 were interviewed using a standardized questionnaire that surveyed data regarding symptom types and length and treatment modalities. Three had an IIH diagnosis before contracting COVID-19, and three had findings of IIH only after contracting COVID-19. All patients who had an IIH diagnosis prior to contracting COVID-19 experienced vision changes or loss; no patients who had IIH only after COVID-19 reported symptomatic vision changes or loss. Patients with the preexisting IIH diagnosis more commonly experienced headache. All six patients had improvement of symptoms with treatment and over time.

Patients with IIH may be at increased risk for higher severity of COVID-19 neurological morbidity, specifically visual changes and loss. Detection of papilledema in patients at risk for elevated ICP who contract COVID-19 may be an important step in detection of new IIH diagnosis and early treatment. Acetazolamide and therapeutic lumbar puncture may present as useful tools to address ICP exacerbation in IIH and COVID-19 patients. Further study of COVID-19 and IIH therapy strategies is important for preventing vision loss and serious neurological damage.

Keywords: Idiopathic intracranial hypertension; Elevated intracranial pressure; COVID-19; Lumbar puncture; Headache; Papilledema

Abbreviations and Acronyms

IIH: Idiopathic Intracranial Hypertension; ICP: Intracranial Pressure; COVID-19: Coronavirus Disease 2019; ICU: Intensive Care Unit; pt: Patient; sx: Symptoms; dx: Diagnosis; LP: Lumbar Puncture; VP: Ventriculoperitoneal; MRI: Magnetic Resonance Imaging

Introduction

Although primarily a pulmonary disease, Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus is a systemic illness and evidence has demonstrated its involvement with the Central Nervous System (CNS). Neurologic involvement is linked to poor health outcomes such as ICU admission, mortality, and increased risk of disability among survivors, hence the importance of this research [1,2]. Regardless of severity, COVID-19 has the potential to present a multitude of neurologic signs and symptoms through its infection. Neurological manifestations of the virus can range from headache, dizziness, and anosmia to more critical cases involving musculoskeletal injury, encephalopathy, and cerebrovascular stroke [3]. While several COVID-19 patients may experience mild neurological symptoms, a small percentage of individuals can develop severe neurological disorders [4]. As growing literature illustrates COVID-19 as both a pulmonary and a vascular disease, neurological sequelae are frequently noticed but the complete pathophysiological mechanism behind neurological symptoms is not fully understood.

Headache is one of the most frequent neurological symptoms associated with COVID-19 infection. In a recent study, reports of headaches in patients with COVID-19 have been deemed as severe and persistent, as well as associated with elevated intracranial hypertension in a significant proportion of cases in the absence of meningitis or cerebrovascular disease [5]. These findings have been noted increasingly in COVID-19 patients and have been associated with higher mortality amongst COVID-19 ICU patients [6]. Yet, there is a dearth of literature explaining these disease processes and providing providers with standardized clinical recommendations for detection and therapy.

As the pandemic spread, the impact of COVID-19 on brain health became progressively pertinent. A large health network in the United States observed neurological manifestations in 82.3% of hospitalizations and outpatient care [7]. The true incidence of neurological manifestations, elevated ICP in particular, must be understood to characterize a unified pathophysiological methodology for effective treatment of symptoms affecting the CNS. Through a standardized case series, our study aims to better characterize COVID-19 and elevated ICP findings in patients, report treatment

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modalities and their outcomes, and discuss potential therapies and areas for further inquiry.

Methods

In this retrospective case series, adult neurology patients who had both received a diagnosis of idiopathic intracranial Hypertension (IIH) and have had COVID-19 were interviewed using a standardized questionnaire that surveyed data regarding symptom types, and length, and treatment modalities. Qualitative analysis and review of patients clinical and laboratory data was evaluated.

Results

Amongst eight patients interviewed, six successfully completed surveying and met all study criteria. The cohort comprises of five females and one male and BMIs ranging from 35 to 51. The most common elevated ICP symptoms included headache, vision changes or loss, tinnitus, dizziness, nausea, and auditory changes. Four had an IIH diagnosis before contracting COVID-19, and two had findings of IIH only after contracting COVID-19. Three out of the four patients diagnosed with IIH pre-COVID-19 patients experienced vision changes or vision loss; while none of the IIH post-COVID-19 cohort reported any visual abnormalities. Three out of four IIH pre-COVID infection patients also experienced headaches. All three patients who received Lumbar Punctures as a therapeutic intervention reported improvement in clinical symptoms. All six patients had improvement of symptoms over time regardless of intervention.

Discussion

This case series characterized the neurological symptoms experienced by multiple patients due to COVID-19 infection. Furthermore, more severe neurological morbidity was noted in patients with pre-existing IIH diagnoses. Therapies aimed at relieving ICP did lead to relief of IIH symptoms.

COVID-19 and Neurological Morbidity

Neurological morbidity is an increasingly common aspect of the COVID-19 disease experience; a 2020 study with a large cohort of hospitalized COVID-19 patients found over 57% displaying neurological symptoms [8]. They reported diverse symptoms including myalgias, dizziness, headaches, and changes in consciousness [8]. A large international survey conducted by the European Academy of Neurology [9] reported similar findings and included report of more serious manifestations such as acute cerebrovascular disorder and encephalopathy as well. The neurological symptoms experienced by patients during and after contracting COVID-19 within our case series included headaches, papilledema, vision changes, and auditory changes (Table 1). Headaches were the most reported symptom, which has been similarly found across other studies reporting neurological symptomology in COVID-19 [9-11].

Neurological morbidity within COVID-19 infection has been accounted for through several pathophysiological explanations. Firstly, the COVID-19 virus has been discovered to have potential capabilities to direct inoculate the central and peripheral nervous systems [12]. Central nervous system inoculation has been supposed *via* ACE2, a receptor found throughout the brain [12]. In fact, ACE2 receptor expression has also been shown in oral mucosa, specifically the tongue epithelia [13]. Thus, along with nasal inflammation impacting olfactory nerves, direct inoculation of these mucosal surfaces via ACE2 have served as another possible explanation for anosmia and ageusia symptoms [12]. However, there are many studies that report and not report COVID-19 RNA findings in the CSF, leading to a lack of a solid consensus amongst the literature regarding the strength of direct neuro invasion explanation [13]. Second, immune response dysregulation has also been given responsibility for neurological symptoms. Cytokine storm and even direct invasion of immune cells have been postulated to produce upstream effects leading to vascular and muscular damage as well as occasional reports of autoimmune neuropathies [12]. Lastly, neurological morbidity may be due to cerebrovascular damage. COVID-19 associated vasculitis has been attributed to the afore mentioned immune dysregulation as well as direct endothelial disruption and subsequently associated coagulopathies [12,14].

Furthermore, comorbidities may lead to greater risk for neurological morbidity in COVID-19 infection. In a large 2020 retrospective review [8] of over 800 hospitalized COVID-19 patients, researchers found diabetes, heart disease, hyperlipidemia, hypertension, and obesity to all is associated with severe infection; obesity was even found to be an independent predictor of severe disease. Romero-Sanchez et al. [8] discuss these findings in the setting of obesity and metabolic disease promoting immune dysregulation. Within our case series, all six patients had Body Mass Indexes (BMIs) of greater than 35. Further examination of patients with both higher BMIs and profound COVID-19 presentation to assess for ICP findings and potential undiagnosed IIH may add to our understanding of obesity's strong association with severe disease.

There is a dearth of literature describing IIH and its role as a condition that promotes severe COVID-19 disease presentation and neurological morbidity. This case series is the first to showcase and discuss patients specifically with prior IIH displaying neurological morbidity during COVID-19 infection, some of which warranted therapeutic interventions to relieve symptoms (Table 1). There are however several reports in the literature highlighting secondary IIH in the setting of COVID-19 infection [15-18]. Our case series also contributes to these novel reports of IIH diagnoses after COVID-19 infection. Comparing patients with prior IIH diagnoses to patients with secondary IIH in the setting of COVID-19 within our case series shows that both groups had instances of severe neurological presentation requiring invasive treatment (Table 1). This warrants specific attention to both patients with current IIH illness and patients with possible high disposition to getting IIH during COVID-19 illness. Further study with larger cohorts is needed to examine for potential differences in the presentations and needs of patients with prior *versus* secondary IIH.

Detection

As summarized above, ICP experienced by patients due to their primary IIH diagnosis or found after their COVID-19 infection most manifested as headaches, vision changes, dizziness, nausea, and auditory changes (Table 1). These findings are in line with ICP's impacts, which most commonly are characterized by the triad of worsening headaches, papilledema, and vomiting [19]. Detection of worsening neurological morbidity is important because it has been correlated with worsening morbidity and mortality in COVID-19 patients [20]. And, increased ICP specifically may be an important marker. Gultekin and Guven [21] found that detection of ICP severity *via* Optic Nerve Sheath Diameter (ONSD) on ultrasonography predicted in-hospital mortality amongst COVID-19 patients. In other neurologically impacting conditions, such as penetrating brain injuries, ICP monitoring has also been associated with decreased mortality [22]. Because COVID-19 infection has been seen to afflict

Table 1: Patients' reported IIH and COVID-19 experiences and symptoms.

Cohort	Pt	IIH Sx at Dx	IIH Interventions	Resolution of IIH	IIH Sx during COVID-19	Additional Relevant Comments
IIH Dx before COVID-19	1	Headache, Neck and Back pain, Transient Visual Obscurations	LP, Acetazolamide	Yes	Diminished Peripheral Vision	Required VP Shunt and Left Optic Nerve Fenestration due to elevated eye pressures
	2	Headache, Nausea, Dizziness, Blurred Vision, Double Vision	LP, Acetazolamide	Yes	Headache	Also experienced cough, chest pain, and shortness of breath
	3	Vision Loss, Pulsatile Tinnitus	Acetazolamide	Yes	None reported	N/a
	4	Asymptomatic, (however: during pregnancy she developed Headaches and Tinnitus)	LP	Headache resolved, Tinnitus still occurs intermittently	Headaches	Notes headaches became unbearable; received Tylenol, Motrin, and fluids, and sx resolved after 48 hours
COVID-19 before IIH dx	5	None reported	None	Yes	None reported	N/a
	6	Papilledema	Topiramate	Yes	Papilledema, Auditory whooshing sensation	Required confirmatory MRI and spinal tap after noticing of papilledema

IIH: Idiopathic Intracranial Hypertension; pt: Patient; sx: Symptoms; dx: Diagnosis; LP: Lumbar Puncture; VP: Ventriculoperitoneal; MRI: Magnetic Resonance Imaging

neurological morbidity, awareness of and attention to ICP findings and severity in patients may be an important step in preventing worsening disease and mortality.

The gold standard for ICP monitoring involves intraventricular catheters. However, more noninvasive methods have been found to also show promising efficacy and utility; these include use of computed tomography imaging, electroencephalography power spectrum analysis, ONSD ultrasonography, and optic disc evaluation *via* ophthalmologic examination among others [23]. Namely, ONSD *via* ultrasonography has been documented to be effective for ICP detection at the bedside [21,23]. And, as mentioned, this technique has already been effectively utilized for ICP detection in COVID-19 patients [11]. Within our case series, two patients were found to have ICP after findings of papilledema (Table 1). Optic disc evaluation is routinely used to assess for possible ICP since papilledema is a common ICP findings, and the ophthalmologic examination is relatively effective and noninvasive. However, papilledema is often noted to not be found in acute ICP elevations and not always be present despite increased ICP [23,24]. While awareness and detection of papilledema findings still serves as a useful screening tool for ICP detection especially in COVID-19 patients, use of ONSD monitoring for cases of more severe neurological presentations may aid in preventing serious morbidity and mortality. Further study and description of papilledema and ophthalmologic findings and detection methodologies in COVID-19 patients is needed.

Along with papilledema findings warranting further workup, such as optic disc evaluation or ONSD monitoring, severe headache and changes to vision may warrant assessment of ICP findings and potential IIH screening in patients with new or recent COVID-19 infection. Within our case series, headache was another very commonly reported symptom of COVID-19 and IIH (Table 1); and as discussed, headache is also the most common symptom found in COVID-19 patients experiencing neurological symptoms [8,19,20]. In their case report of secondary IIH in the setting of COVID-19, Sardar et al. [25] discuss setting a low threshold for IIH screening for COVID-19 patients with headache and vision abnormalities as important and valid because of COVID-19's ability to cause hyperimmune and hypercoagulable states. Our case series' findings further support this as not all patients had papilledema findings (Table 1). Moreover, during COVID-19 infection patients with comorbidities, such as obesity and metabolic disease, should be screened for IIH when severe headache symptoms are present without requiring papilledema findings to warrant workup and therapeutics.

Therapeutics

All study patients with prior IIH diagnoses had Lumbar Punctures (LP) as an intervention modality, and the majority was also taking acetazolamide for their diagnoses (Table 1). Acetazolamide is the first-line medical therapy and the mainstay of treatment for most IIH patients [26]. Weight management is also effective and a noninvasive component of IIH treatment regimens. On the other hand, LPs are also utilized to reduce elevated ICP; a single LP has been seen to significantly resolve a patient's IIH symptoms [26]. Cerebrospinal Fluid (CSF) diversion surgery *via* the placement of a Ventriculoperitoneal Shunt (VPS) is an invasive but more definitive treatment choice utilized in more serious cases IIH. Hamann et al. [27] point out that CSF shunts do have a high complication rate due to mainly infections or mechanical obstruction. These shunts are also negatively impacted by increased abdominal pressure often found in people with higher BMIs [27]. Nevertheless, direct reduction of ICP through techniques such as CSF shunts and lumbar punctures are important and effective at preventing blindness in patients with severe papilledema and elevated ICPs.

The patients in this case series report varying intervention modalities-from conservative management to LPs and optic nerve fenestration-in order to reduce ICPs and prevent worsening neurological morbidity, namely vision loss (Table 1). While all

effective, treatment modality differed on a case-by-case basis and severity of symptomology. Instead of acetazolamide, one of the included patients utilized topiramate, an often second-line IIH medical therapy (Table 1) [26,28]. Acetazolamide is a carbonic anhydrase inhibitor medication that alleviates elevated ICP by reducing choroid plexus' CSF production; topiramate works by enhancing GABA-channel activity that in-turn reduces the activation of carbonic anhydrase enzymes [26]. Increasing literature describes topiramate as comparably effective to acetazolamide and even effective at assisting with weight loss, which is important in IIH management [28,29]. Different from acetazolamide, topiramate is more optimal for patients with comorbid migraine disorders and recommended against in those with severe depression [29]. Further research comparing topiramate and acetazolamide for IIH management as well as larger-cohort studies observing each medication's efficacy for different IIH symptom profiles is needed. Furthermore, another patient reported use of optic nerve fenestration (Table 1). Optic nerve sheath fenestration is an effective method at reducing pressure on the optic nerves in severe cases of elevated ICP; this modality is most often utilized when there is specifically concern for unilateral vision loss.

Worsening neurological morbidity and vision loss are serious concerns in cases of elevated ICP. With increased risk of more severe symptomology in IIH patients after COVID-19 and reports of new IIH diagnoses after COVID-19 infection, more review and study of diverse treatment modalities and respective symptom profiles would be valuable for clinicians making therapeutic recommendations.

Disclosure Statements

The study protocol was reviewed and given approval by the St. Elizabeth's Medical Center IRB office on January 17th, 2023.

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