Introduction
Lymphocytic hypophysitis (LH) is a rare autoimmune disorder involving the destruction of the anterior pituitary due to lymphocytic infiltration. The disease shows a female predominance, commonly affecting women during late pregnancy into the postpartum period. The etiology of LH has not been well established and is presumed to be autoimmune based on the histopathological findings of lymphocytic infiltration and postpartum cases. Lymphocytic hypophysitis has yet to be studied in the context of a patient status post-recovery from COVID-19. Since the initial outbreak, additional information regarding the symptoms and outcomes has emerged on the virus’s effects on the nervous system.

Case: We present a novel case of post-COVID lymphocytic hypophysitis in a pediatric patient at Dayton Children’s Hospital. An 18-year-old previously healthy girl presented to the emergency department (ED) with acute onset headache and dizziness for 5 days. She had a history of symptomatic COVID-19 three weeks prior to the onset of current symptoms. Contrast enhanced magnetic resonance imaging (MRI) of the brain revealed diffuse thickening and enlargement of the infundibulum with homogenous contrast enhancement of the hypophyseal axis. Based on the suspicion for lymphocytic hypophysitis, she was started on Methylprednisolone 250 mg IV Q6hrs on day 1-3. Symptomatic clinical improvement was seen on day 3 with a significant decrease in the intensity of the headache.

Conclusion: The case illustrates the varied presentation and neurological sequelae associated with the COVID-19 virus. The case described here is the first ever reported post-COVID manifestation of lymphocytic hypophysitis.

Keywords
lymphocytic hypophysitis, COVID-19, headache

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mass effect and 85% of patients have varying degrees of hypopituitarism that may be associated with hyperprolactinemia. Symptoms include postpartum agalactia, amenorrhea, hyperprolactinemia, anterior pituitary insufficiency, diabetes insipidus, and associated autoimmune diseases.\(^3\)–\(^5\)

The definitive diagnosis of lymphocytic hypophysitis is made by biopsy; however, it poses a significant risk to patients and is accordingly not performed.\(^6\) Thus, radiologic abnormalities may be best able to suggest a diagnosis of lymphocytic hypophysitis. In the early phase of the disease, magnetic resonance imaging (MRI) is useful to exclude pituitary adenomas and the physiologic pituitary enlargement of pregnancy.\(^7\) The first MRI diagnoses of lymphocytic hypophysitis were reported by Levine 1988. The enlarged pituitary extends into the suprasellar region, displacing the optic chiasm upward in 64% of cases. The pituitary had low signal on non-contrast T1 imaging but a relatively high signal on T2, which may be a significant finding in the diagnosis of lymphocytic hypophysitis.\(^8\) Currently, contrast-enhanced MRI is the imaging of choice in elucidating a diagnosis of lymphocytic hypophysitis. Unfortunately, there is no standardized set of findings to definitively diagnose it. Gutenberg et al attempted to address this challenge by establishing a scoring system to aid in its distinction from a pituitary adenoma. Under this scoring system, any score greater than 1 is indicative of pituitary adenoma, while any score less than 0 is indicative of lymphocytic hypophysitis. The following findings on MRI earn a negative scoring (scores are in brackets): age less than or equal to 30 \([-1]\), current pregnancy or being less than or equal to 6 months postpartum \([-4]\), an increased stalk size \([-5]\), or increased gadolinium enhancement \([-2]\). The following findings on MRI receive a positive score: pituitary volume greater than 6 cm \([+2]\), sphenoidal mucosal thickening \([+2]\), heterogenous gadolinium enhancement \([+1]\), or asymmetrical sellar enlargement \([+3]\).\(^9\) It is important to highlight that this scoring system does not discriminate lymphocytic hypophysitis from non-adenomatous lesions, and thus does not exclude them.\(^9,10\) The management of lymphocytic hypophysitis remains varied, as the natural course of the disease process is also quite variable.

The etiology of LH is not well established and is presumed to be autoimmune based on the histopathological findings of lymphocytic infiltration and postpartum cases. LH has been associated with other autoimmune disorders including autoimmune thyroiditis, temporal arteritis, systemic lupus erythematosus, and post-infectious etiology bacteria, viruses, and other pathogens.\(^11\) Prevalence of lymphocytic hypophysitis is low with an incidence of 1 in 7-9 million.\(^6,9,10\)

The novel coronavirus causes an acute respiratory syndrome first diagnosed in December 2019 in Wuhan, China. The most common symptoms include fever, fatigue, and cough, but more severe cases result in respiratory distress, cardiac failure, and eventual death.\(^12\) Since the initial outbreak, additional information regarding the symptoms and outcomes has emerged on the virus’s effects on the nervous system. Lymphocytic hypophysitis has yet to be studied in the context of a patient status post-recovery from COVID-19. We present a novel case of post-COVID lymphocytic hypophysitis in a pediatric patient at Dayton Children’s Hospital.

**Case**

An 18-year-old previously healthy girl presented to the emergency department (ED) with acute onset headache and dizziness for 5 days. She had a history of symptomatic COVID-19 three weeks prior to the onset of current symptoms. Her COVID-19 symptoms were mild nasal congestion, cough, and fever for three days. She was asymptomatic for almost 2 weeks prior to the onset of current symptoms. She had an acute-onset, severe constant frontal throbbing headache radiating to

![Figure 1.](image-url)
the temporal head region which was progressively worsening. Her headache was unremitting, even with medications. Her vital signs including heart rate, respiratory rate, and blood pressure were normal. Glasgow coma scale was 15/15. Neurological examination was normal with no signs of meningitis. The rest of her physical examination was also normal. She never had headaches in the past and there was no family history of migraine or tension type headaches.

Contrast enhanced MRI of the brain revealed diffuse thickening and enlargement of the infundibulum with homogenous contrast enhancement of the hypophyseal axis. T2 hypointensity in the parasellar region was present with no other lesions. No other area of abnormal signal was present (Figures 1A, B and 2A, B). These findings are most consistent with lymphocytic hypophysitis. Cerebral spinal fluid (CSF) analysis showed no pleocytosis, 3/mm³ with 100% lymphocytes. Extensive CSF studies were performed including antibodies for arboviral encephalitis (West Nile, St. Louis, California, Eastern Equine, and Western Equine), polymerase chain reaction (PCR) for herpes simplex virus and enterovirus, Lyme antibodies, and oligoclonal bands which were negative. Systemic inflammatory markers including erythrocyte sedimentation rate and C-reactive protein were normal. An extensive hormonal workup including growth hormone, thyroid stimulating hormone, prolactin, estrogen, testosterone, and cortisol were within normal limits. An ophthalmology evaluation was performed which was reported within normal limits. Further workup for primary immunological disorders showed negative rheumatoid factor, antithyroid, antinuclear, antimitochondrial, and antineutrophil antibodies.

Based on the suspicion for lymphocytic hypophysitis, she was started on Methylprednisolone 250 mg IV Q 6 h on days 1-3. Symptomatic clinical improvement was seen on day 3 with a significant decrease in the intensity of the headache. The patient was switched to oral Prednisone 40 mg/day and was discharged. Repeat MRI on day 5 showed complete resolution of the initial lesion with no contrast enhancement of the hypophyseal axis. Based on the significant clinical and radiological improvement, trans-sphenoidal biopsy was not performed. A schedule for progressive reduction of the steroid dose and serial workup for panhypopituitarism was recommended.

**Discussion**

The case illustrates the varied presentation and neurological sequelae associated with the COVID-19 virus. The case described here is the first ever reported post-COVID manifestation of lymphocytic hypophysitis.

Acute onset headaches have a broad differential diagnosis in pediatrics. The incidence of acute onset headache in pediatrics is unknown, but in adults it is estimated to be 43 cases per 100 000 adults per year.¹³ The majority of cases remain unexplained or are diagnosed as primary headache disorders. Neuro-vascular diseases are considered one of the most common etiologies for acute sudden headache accounting for 17% of cases.¹⁴ Our case emphasizes the role of post-infectious acute inflammatory disorders as a rare etiology of acute onset headache. There should be a low threshold of performing neuroimaging in patients presenting with acute onset headache without any previous history of primary headache disorders.

As per previous studies, the hypothesis is that SARS-COV-2 gains entry by systemic vascular dissemination and across the cribiform plate of the ethmoid bone.¹⁵ The virus invades the CNS because of its unique interaction with angiotensin-converting enzyme (ACE2) receptors via spike proteins that bind the capillary endothelium.¹⁵ The pro-inflammatory properties leading to lymphocytic hypophysitis in our case can be explained by the direct targeting of hypothalamic and pituitary tissues, secondary to the high expression of ACE2 receptors.¹⁶ Multiple case series have been published correlating SARS-CoV-2 with demyelinating disorders, including Guillain-Barre Syndrome (GBS)¹⁷ and Bickerstaff’s encephalitis.¹⁸

The spectrum of neurological manifestations secondary to SARS-CoV-2 is still evolving and a wide array of neuropsychiatric manifestations, such as GBS, stroke,¹⁹ and encephalopathies²⁰ have been previously reported. SARS-CoV-2 predisposes patients to a thrombo-inflammatory response in critically ill patients.
Increases in fibrinogen, platelet, and D-dimer levels in addition to IL-6 are often present, indicating the causative relationship between the inflammatory response and thrombosis. The neurological manifestations from the COVID-19 virus can be secondary to the direct neuro-invasive properties or may be related to multiorgan dysfunction. Additionally, a recent article has been published describing the correlation between COVID-19 and central diabetes insipidus after SARS-CoV-2 infection.

In a study looking at neuroimaging findings in children with SARS-CoV-2, throughout all phases and presentations of COVID-19, the most prevalent neuroimaging manifestations observed in children resembled an immune-mediated parainfectious pattern of disease involving the brain, spine, cranial nerves, and nerve roots. The most common presentations were ADEM and myelitis in this study. In another study from Chile evaluating neurologic complications related to SARS-CoV-2, Guillain-Barre syndrome and demyelinating disorders were the two most common presentations. The prominence of immune mediated manifestations in children might explain the presentation in this case and the response to steroids. Hypophysitis is a rare condition and is usually associated with autoimmune conditions. In this patient we ruled out autoimmune conditions by performing a careful rheumatological workup. The temporal evolution of the symptoms post-COVID also suggests a para-infectious immune mediated process in this patient.

Conclusion
COVID-19 neurological manifestations are varied and clinically challenging. In symptomatic patients, the rare possibility of LH can be considered. As the underlying pathophysiology of neurological manifestations in SARS-CoV-2 remains to be fully determined, it is difficult to prove a direct cause and effect relationship between a single pathogen and the clinical manifestations. There is no previous literature associating SARS-CoV-2 with lymphocytic hypophysitis. Our case proposes a guide to explore this further in clinical practice. Increasing numbers of papers are reporting neurological involvement in patients, but more data are required to adequately correlate the two and the impact this has clinically.

Author Contributions
All authors made contributions towards drafting and critically revising the manuscript; they have all given final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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