Clinical Correspondence

Tolosa-Hunt syndrome after COVID-19 infection

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Abstract

Tolosa-Hunt syndrome (THS) is a rare, idiopathic, non-specific inflammation within the cavernous sinus and/or superior orbital fissure leading to painful ophthalmoplegia. The authors describe the first case of a 12-year-old otherwise healthy girl who presented with painful ophthalmoplegia after a documented COVID-19 infection. Neuroimaging revealed inflammation within the ipsilateral cavernous sinus, Meckel’s cave, and orbital apex. After a comprehensive work-up was negative, the patient experienced prompt clinical and radiographic improvement with high-dose corticosteroids, and a diagnosis of THS was made.

Keywords

COVID-19, ophthalmoplegia, SARS-CoV-2, Tolosa-Hunt syndrome

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Introduction

Painful ophthalmoplegia is associated with a variety of etiologies localizing to the cavernous sinus, including Tolosa-Hunt syndrome (THS). The constellation of unilateral, periorbital headache and painful ophthalmoplegia was first characterized by Eduardo Tolosa in 1954, with additional cases in 1961 by Hunt et al.1,2 THS, so named by Smith and Taxdal in 1966,3 is a rare disease with an estimated incidence of one case per million per year.4 Although the non-specific inflammation of the cavernous sinus and/or superior orbital fissure of THS is idiopathic, there are numerous reported triggers, including COVID-19 vaccination.5 However, to the authors’ knowledge, this is the first report case of THS following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Case report

The patient was a 12-year-old otherwise healthy girl who presented to the emergency department (ED) with right eye pain and periorbital swelling. She was diagnosed with COVID-19 by polymerase chain reaction (PCR) 3 weeks prior to presentation with minimal symptoms. Three days prior to presentation, she developed an elevated temperature to 100.3 degrees Fahrenheit, right-sided facial pain, headache, and eye pain. The patient had a telemedicine visit 1 day prior to presentation and was prescribed amoxicillin for possible acute sinusitis. The morning of presentation the patient awoke with right periorbital swelling, worsening right facial pain, and right upper eyelid ptosis prompting her parent to bring her to the ED.

In the ED, the patient was afebrile. CT orbits and sella with contrast was obtained and demonstrated post-contrast enhancement of the right cavernous sinus without cavernous sinus thrombosis and signs of chronic non-obstructive paranasal sinus disease. Ophthalmology was consulted, given binocular diplopia and ptosis of the right upper eyelid. Her visual acuity (VA) was 20/20 both eyes (OU). Color vision by Ishihara color plates was 13/13 OU. There

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was no red desaturation. Visual fields were full to confrontation and red target testing. Pupils were brisk, symmetric, and without relative afferent pupillary defect OU. Extraocular motility showed supraduction and adduction deficit of the right eye with associated pain. Intraocular pressure (IOP) was 18 and 13 mm Hg. There was right upper eyelid ptosis with a marginal reflex distance 1 of 0 mm. The ptosis and extraocular motility deficits were consistent with a partial right cranial nerve (CN) three palsy. Dilated fundus and complete neurological exams were normal. The patient was admitted for further evaluation.

MRI brain, face, neck, and orbit with and without contrast demonstrated an inflammatory process involving the right cavernous sinus, Meckel’s cave, and orbital apex with minimal asymmetric thickening and enhancement of the dura overlying the right cavernous sinus, Meckel’s cave, and planum sphenoidale (Figure 1). There was narrowing of the right internal carotid artery (ICA) in corresponding regions, as well as asymmetric enhancement of the right petro-occipital venous plexus along the course of the petrous segment ICA. The MRI findings were highly suggestive of THS.

Lumbar puncture was performed, and cerebral spinal fluid (CSF) showed 1 white blood cell with 64% lymphocytes and 36% monocyte/macrophage, no red blood cells, normal protein 18 mg/dL, and elevated glucose 99 mg/dL (normal 40–70 mg/dL) with negative meningitis-encephalitis panel, HSV IgG and IgM, VZV IgG and IgM, angiotensin-converting enzyme (ACE), Lyme serologies, and FTA-ABS. The elevated CSF glucose was interpreted as a physiologic response to their dextrose 5% intravenous (IV) drip and initiation of IV methylprednisolone 250 mg given their serum glucose was 143 mg/dL. CSF bacteria, fungi, and mycobacteria cultures showed no growth. Complete blood count and comprehensive metabolic panel were normal. ESR and CRP were elevated at 43 mm/hr and 9.6 mg/dL respectively. Autoimmune work-up was negative, including ANA, ACE, ds-DNA antibody, Smith antibody, SSB (La) antibody, SSA (Ro) antibody, ANCA, and anti-GQ1b antibodies. Serum protein electrophoresis was without monoclonal spikes. Hemoglobin A1c was 5.0%.

SARS-CoV-2 by PCR was positive and SARS-CoV-2 IgG antibodies were elevated at 570.1 AU/mL. Infectious work up was otherwise negative, including CMV, Enterovirus, Influenza, Parainfluenza, HSV, VZV, RSV, Adenovirus, Human parechovirus, Human herpesvirus 6, Bordetella parapertussis/ pertussis, Borrelia Burgdorferi antibodies, Chlamydiophila pneumoniae, Human metapneumovirus, Rhinovirus, Syphilis...
IgG, Group B Streptococcus, Listeria monocytogenes, Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitides, Escherichia coli K, and cryptococcus neoformans/gattii.

The patient was started on IV methylprednisolone 250 mg every 6 hours with follow-up neuroimaging 2 days later showing decreased enhancing soft tissue proliferation within the right orbital apex, cavernous sinus, and Meckel’s cave, but persistent asymmetric narrowing of the right ICA (Figure 2). Following 4 days of IV methylprednisolone the patients’ symptoms resolved, and she was transitioned to oral prednisone with slow taper. Follow-up inpatient exam showed normal afferent visual function, normal pupil exam, along with full extraocular motility and essentially normal ocular alignment. IOP was 19 mmHg OU. CN, anterior segment, and posterior segment exams were otherwise normal. Prior to discharge, otolaryngology evaluated the patient and concluded that her asymptomatic chronic non-obstructive sinusitis was unlikely to be contributing to her THS presentation. Outpatient neuroophthalmology follow-up exam was normal.

Figure 2. MRI Coronal T1 post-contrast images following corticosteroid administration demonstrating interval improvement of enhancement at (A) the medial orbital apex and (B) resolution of asymmetric right Meckel’s cave enhancement. (C and D) Axial Time of Flight MRA showing persistent asymmetric narrowing of the right internal carotid artery (arrow).

Discussion
Since December of 2019, COVID-19, caused by SARS-CoV-2, has become a global pandemic often with many systemic health consequences. Reported ophthalmic manifestations have been broad, including a variety of neuroophthalmic phenomena, ranging from optic neuritis to Miller Fisher syndrome.6 Although THS is idiopathic, there have been case reports of its association with autoimmune diseases, such as systemic lupus erythematosus.7 Recently, Chuang et al. reported a case following mRNA COVID-19 vaccination, citing the vaccines association with other autoimmune phenomena, including immune thrombocytopenia, as a potential association.5 Our patient presented with signs and symptoms concerning for THS after being diagnosed with
COVID-19. There has been one other report of probable THS that co-occurred with COVID-19 infection; however, the case did not meet the International Headache Society (IHS) diagnostic criteria for THS as the MRI was reportedly normal and no biopsy was obtained.8 Given THS has not been associated with an infectious disease, our patient’s THS was most likely due to COVID-19 related immune dysregulation.

The IHS diagnostic criteria for THS includes unilateral headache with granulomatous inflammation of the cavernous sinus, superior orbital fissure, and/or orbit identified on biopsy or MRI with ipsilateral oculomotor nerve palsy (CN III, IV, and/or VI).9 CN palsy within 2 weeks or occurring simultaneously with a headache on the ipsilateral side, which is not better explained by another headache etiology, further corroborates the diagnosis. These criteria have a sensitivity that approaches 100%, but a low specificity of 50%. Our patient met the IHS criteria for THS with right-sided headache, binocular diplopia, ophthalmoplegia, and eyelid ptosis concerning for CN III involvement with MRI findings showing inflammation of the ipsilateral cavernous sinus. CN III involvement is seen in approximately 80% of cases, being the most common CN affected.4 It is unclear if the presentation of THS is different in the pediatric population, but pediatric cases have shown the constellation of signs and symptoms seen in our patient, including ptosis.10

MRI brain with contrast can help exclude other etiologies of painful ophthalmoplegia and show characteristic findings of THS, including thickening of the cavernous sinus that is isointense on T1, isointense or hypointense on T2, and enhances with contrast. However, these MRI findings may also be seen with lymphoma, meningioma, and sarcoidosis.11 Neuroimaging is also important to exclude cavernous sinus thrombosis. Our patient’s neuroimaging was without signs of meningioma or cavernous sinus thrombosis. Ruling out cavernous sinus thrombosis in this patient was imperative given the association of COVID-19 and thrombosis.12 Our patient’s MRI brain showed a typical inflammatory process with associated narrowing of the right ICA and asymmetric enhancement of the right petro-occipital venous plexus along the course of the petrous segment ICA. All of these findings were highly suggestive of THS.

As THS is a diagnosis of exclusion, extensive serum and CSF testing should be obtained to rule out other etiologies, including autoimmune, infiltrative, and infectious processes. Our patient had a negative workup, except SARS-CoV2 PCR positivity and elevated IgG antibody. Positive SARS-CoV2 PCR 3 weeks after her initial diagnosis is not uncommon and is thought to be due to persistent viral shedding.13 In addition, the diagnosis of THS is further supported by its prompt response to high dose systemic corticosteroids within days of initiation.3,14 Our patient showed quick clinical and radiographic resolution of her painful ophthalmoplegia and right upper eyelid ptosis following IV methylprednisolone. There was persistent narrowing of her right ICA on follow up neuroimaging. Although ICA narrowing associated with THS typically resolves with corticosteroids,15 the time frame between administration and response is variable.16

Our patient was found to have chronic non-obstructive sinusitis and was originally diagnosed with acute sinusitis via a telemedicine visit prior to admission. The misdiagnosis of THS as acute sinusitis has been previously reported.17 Given our patients underlying sinus disease, prior antibiotic exposure, and radiographic inflammation beyond the cavernous sinus, her clinical picture may have represented an independent infection or another etiology unrelated to her COVID-19 infection. However, as outlined above, her painful ophthalmoplegia, extensive negative work-up, radiographic findings, and prompt resolution to high-dose corticosteroids in the setting of SARS-CoV2 positivity is highly suggestive of THS secondary to COVID-19 infection.

Conclusion
We report the first case of THS after COVID-19 infection. THS is a rare, idiopathic, inflammatory disorder of the cavernous sinus and/or superior orbital fissure that presents with painful ophthalmoplegia. Although a diagnosis of exclusion, IHS diagnostic criteria are highly sensitive and MRI imaging can be helpful. The neuro-ophthalmic manifestations of COVID-19 are broad and should include THS. Further research on the etiology of THS and infectious, as well as autoimmune, associations are needed.

Clinical implications
- COVID-19 infection or vaccination may be an important factor for developing Tolosa-Hunt syndrome

Author contributions
All authors have read and approved the manuscript before submission. T.E., J.J., E.L.C., K. B.D., J.E.A.W., M.D.S. drafting/revising of the manuscript for content, including medical writing.

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Informed consent
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