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A CASE OF PROBABLE TOLOSA-HUNT SYNDROME CO-OCCURRED WITH COVID-19 INFECTION

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Abstract

Introduction*: The novel coronavirus 2019 (COVID-19) pandemic started in Wuhan city, China in December 2019 and now the infection has a high prevalence worldwide and the pandemic is still ongoing. Symptomatic patients with COVID-19 typically complain of fever and respiratory, as well as gastrointestinal symptoms. It is known that human coronaviruses and particularly severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) are neuroinvasive and neurotropic. There is growing evidence of various neurological complications and manifestations of COVID-19 infection. Neurological symptoms may range from mild, non-specific presentations such as headache to severe complications both in the central or peripheral nervous system. Even rare neurological disorders can occur during or after this infection.*

Case presentation: *We report a case of a 65-year-old female with COVID-19 infection, who also developed left ophthalmoparesis with two cranial nerve palsies, which further was concluded to be a probable Tolosa-Hunt syndrome, an association not yet been described in the literature. The decision was made to treat with glucocorticosteroids, followed by dramatic relief of pain (which also speaks in favor of the diagnosis).*

Conclusion *This report describes an interesting case of probable Tolosa-Hunt syndrome, a rare peripheral nervous system involvement syndrome, co-occurred with COVID-19 infection. Whether this was just a co-occurrence or the inflammation was triggered by a SARS-CoV-2 infection, is still a question to be discussed. The possible causal link between these two conditions may help to understand both conditions better.*

Keywords: *COVID-19, neurologic complication, Tolosa-Hunt syndrome.*

Introduction

By January 26, 2021, the novel coronavirus disease 2019 (COVID-19) pandemic had caused 99 363 697 confirmed cases and 2 135 959 deaths worldwide. It is much more than was caused by severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) in 2013: 8273 cases, 775 deaths, and 1139 cases, 431 deaths, respectively. [*Li Z. et al, 2020*].

According to National Center for Disease Control and Prevention by January 26, 2021, there are 166 232 confirmed cases of COVID-19 and 3052 deaths in Armenia.

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Symptomatic patients with COVID-19 typically complain of fever and respiratory symptoms, including dry cough and dyspnea. Also, gastrointestinal symptoms, such as diarrhea, may occur. There is increasing evidence of neurological manifestations and complications of COVID-19 [*Ahmad I. et al., 2020, Montalvan V. et al., 2020*]. Peripheral nerve involvement was reported in COVID-19 infection, mostly as acute polyneuropathy [*Mao L. et al., 2020*].

Nervous system involvement can be reported as non-specific complications of systemic disease, effects of direct viral infection (transsynaptic spread or via blood-brain barrier), and inflammation of nervous system and vasculature (para- or postinfectious). [*Ellul MA et al., 2020, Zubair A et al., 2020*]. This report describes an interesting case of

unilateral painful ophthalmoplegia, probable Tolosa-Hunt syndrome, a rare disorder, co-occurred with COVID-19 infection.

Tolosa- Hunt syndrome (THS) is recognized by the National Organisation for Rare Disorders (NORD) as one of the rare disorders. [*Kostrzewski MS 2006*]. According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), it is a syndrome of painful ophthalmoplegia: unilateral headache, combined with ipsilateral paresis of one or more of the III, IV, and VI cranial nerves (Table 1) [*Olesen J. 2018*].

Oculosympathetic paralysis, sensory loss in the distribution of the ophthalmic and occasionally the maxillary division of the trigeminal nerve. Various combinations of the cranial nerve involvement may occur. The exact cause of THS is not known, but it is thought to be associated with autoimmune inflammation (usually granulomatous) of the cavernous sinus and/or superior orbital fissure [*Kline LB et al., 2001; Amrutkar C et al., 2020*].

Table 1.

Diagnostic criteria for Tolosa-Hunt syndrome, according to International Classification of Headache Disorders [*Olesen J.,2018*]

A.	Unilateral orbital or periorbital headache fulfilling criterion C
B.	1. Granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by MRI or biopsy AND 2. Paresis of one or more of the ipsilateral 3rd, 4th, and/or 6th cranial nerves
C.	Evidence of causation demonstrated by both of the following: 1. Headache is ipsilateral to the granulomatous inflammation 2. Headache has preceded paresis of the 3rd, 4th, and/or 6th nerves by <2 weeks, or developed with it
D.	Not better accounted for by another ICHD-3 diagnosis

Case Report

A 65-year-old female with a history of arterial hypertension, hypothyroidism, and type 2 diabetes mellitus was brought to the emergency department with complaints of eight-day fever, generalized weakness, myalgias, and shortness of breath. She was treated initially with azithromycin and non-steroidal anti-inflammatory drugs.

During physical examination in the emergency department her vital signs were as follows: blood pressure - 130/80 *mm Hg*, body temperature 37.2°*C*, and oxygen saturation - 70%.

On admission, she had chest computed tomography (CT) with a diagnosis of bilateral interstitial polysegmental pneumonia (with about 60% affected surface). Nasopharyngeal swab for 2019-nCoV viral ribonucleic acid RNA was positive. She was admitted to the National Center for Infectious Diseases. Routine blood examinations included a complete blood count, coagulation profile, and serum biochemical tests (including renal and liver function, glucose, and electrolytes). Briefly, the patient's plasma samples were analyzed with a chemiluminescent immunoassay based on the ACCENT 200 Clinical Biochemistry Analyser (PZ Cormay S.A., Poland): deviations from normal values are listed in Table 2.

Table 2.

Blood test deviations from normal values.

Parameters	Tolosa-Hunt syndrome	Normal range
Platelet count (x $10^9/L$)	821	150 – 400
White blood cells (x $10^9/L$))	16.79	3.5 – 10.0
Neutrophils (x $10^9/L$))	14.7	1.6 – 7.0
Lymphocytes (x $10^9/L$))	0.77	1.0 – 3.0
Fibrinogen (*ng/dL*)	544.0	200 – 400.0
Ferritin (*ng/mL*)	463.5	13.0 – 350.0
Glucose (*ng/mL*)	15.0	4.0 – 6.1

On the 5th day of hospitalization, she suddenly started to complain of severe left-sided headaches. Suddenly, 4-5 days later after, headache onset, she developed left-sided ptosis and was examined by a neurologist.

Neurologic examination revealed intact mental status: she was awake, alert, oriented to self, date, and place. There were no meningeal signs. Cranial nerve

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

examination showed that right eye movements were completely normal, but there was left eye ptosis, and when the eyelid is elevated, severe vertical diplopia appeared. Left eye adduction and downward movements were partially preserved (probably due to intact trochlear nerve function). Left eye abduction and upward movements were absent. The left pupil was dilated, while the light reflex was weak. She also mentioned hypesthesia in the left frontal (supraorbital) region. Her face was otherwise symmetrical, and swallowing and speech were normal. No motor and coordination deficits were seen. Her sensation was intact to pinprick.

Head CT did not reveal any significant findings in brain tissue and cavernous sinus, and the radiological conclusion was pansinusitis.

The final neurological conclusion was probable Tolosa-Hunt syndrome (THS). THS is treated usually with a short course of glucocorticosteroids, and fast relief of pain in the first 24-48 hours after glucocorticoid administration aided the diagnosis. So the decision was made to treat with methylprednisolone, 48 mg per day. Her headaches dramatically disappeared in one day, and after 3 days the patient was discharged. In a week following the discharge from the hospital, there was mild symptom improvement.

Discussion

It is known that human coronaviruses are neuroinvasive and neurotropic [*Desforges M. et al., 2020*]. Multiple neurologic manifestations have been reported in patients with COVID-19 including altered mental status, ischemic stroke, and Guillian-Barre syndrome [*Ellul MA et al., 2020, Varatharaj A et al., 2020*].

Our case report does not fit all diagnostic criteria for Tolosa-Hunt syndrome described in the International Headache Society classification [*Olesen J., 2018*], mainly because it was technically impossible to do brain MRI or biopsy to verify the presence of granulomatous inflammation of the cavernous sinus. But we would like to mention that Tolosa-Hunt syndrome cases were described also with normal MRI [*Abdelghany M et al.*, 2015*]*. Also, we could not obtain the results for autoinflammatory markers, such as anti-neutrophil cytoplasmic antibodies (ANCA), anti-double stranded DNA (Anti-dsDNA) antibodies, anti-smith antibody (anti-Sm antibodies), Lyme disease panel, and treponemal antibody test.

However, considering severe unilateral headache, palsies of two relevant cranial nerves (oculomotor and abducens nerves), and the ophthalmic branch of the trigeminal nerve on the same side, developed few days after headache onset, and dramatic response of pain to glucocorticoid treatment, we speculate that it could be Tolosa-Hunt syndrome. As such, a question arose on whether the COVID-19 infection and THS were causally related, or this was just a co-occurrence. Although it is not possible to answer this question, we think the inflammatory pathogenesis proposed for THS could be triggered by the viral infection. If so, we may further support the viral/autoimmune mechanisms possibly underlying THS. Moreover, the occurrence of THS with COVID-19 may shed light on the mechanisms of COVID-19 neuroinvasion.

Conclusion

COVID-19 infection is characterized by primary involvement of the respiratory system. However, there is a growing evidence of common neurological manifestations and complications of COVID-19. Thus, descriptions of such new associations are important. We report the first case of probable Tolosa-Hunt syndrome described in the patient with SARS CoV-2 infection. The possible causal link between the two conditions may help in the understanding of both diseases. It is also important to collect data about various central and peripheral nervous system involvement syndromes to assess the whole range of short and long term neurological complications in COVID-19 infection.

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