# Tolosa-Hunt syndrome after chikungunya infection

## Síndrome de Tolosa-Hunt após infecção por chikungunya

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## ABSTRACT

This case report aimed to describe the Tolosa-Hunt syndrome in a patient infected with chikungunya and highlight the relevance of considering chikungunya as a possible cause of the Tolosa-Hunt syndrome, especially in endemic or epidemic infection sites. A 63-year-old female patient diagnosed with chikungunya 2 months earlier was being followed up by a general practitioner. She had painful ophthalmoplegia associated with eyelid ptosis in the left eye (LE) for 1 month. Intraocular pressure (IOP) of 20 and 26 mmHg. Patient was prescribed 1 drop of Timolol maleate 0.5% every 12 hours and prednisone 60mg/day for 14 days. Two weeks later, the painful ophthalmoplegia resolved and the eyelid ptosis improved. Computed tomography (CT) scan of the skull and orbits revealed left orbital proptosis with thickening of the lateral and superior rectus muscle and the muscle belly at its tendinous insertion, erythrocyte sedimentation value (ESV) 42, and positive serology for IgG and IgM antibodies to chikungunya was positive. Treatment was then changed to prednisone 40mg/day for seven days, decreasing every seven days, and timolol maleate was discontinued. This case highlights the necessity of including chikungunya as a possible cause of Tolosa-Hunt Syndrome (THS) in endemic or epidemic infection sites, guaranteeing an early diagnosis and appropriate treatment.

## RESUMO

O objetivo deste relato foi descrever a ocorrência da síndrome de Tolosa-Hunt em uma paciente após infecção por chikungunya. Este relato de caso visa destacar a importância de considerar a chikungunya como uma possível causa de síndrome de Tolosa-Hunt, especialmente em locais de infecção endêmica ou epidêmica. Paciente do sexo feminino, 63 anos, diagnosticada com chikungunya há 2 meses, apresentou oftalmoplegia dolorosa associada a ptose palpebral em olho esquerdo após 1 mês. A pressão intraocular era de 20 e 26 mmHg. A paciente recebeu timolol 0,5% 1 gota a cada 12 horas e prednisona 60 mg/dia por 14 dias. Após 2 semanas, houve resolução da oftalmoplegia dolorosa e melhora da ptose palpebral. Tomografia computadorizada de crânio e órbitas revelou proptose orbital à esquerda com espessamento de músculos e VHS 42. Sorologia foi positiva para chikungunya. O tratamento foi ajustado para prednisona 40 mg/dia, diminuindo semanalmente, e suspensão do timolol. Este caso destaca a necessidade de incluir a chikungunya como uma possível causa de síndrome de Tolosa-Hunt em áreas de infecção endêmica ou epidêmica, garantindo um diagnóstico precoce e tratamento adequado.

## INTRODUCTION

Chikungunya is caused by an RNA virus belonging to the Alphavirus genus of the Togaviridae family. The disease is transmitted to humans by female *Aedes aegypti* and *Aedes albopictus* mosquitoes infected by the chikungunya virus (CHIKV). The incubation time can last from 4 to 8 days,[1] and the acute phase of the disease begins with the abrupt onset of fever, headache, fatigue, gastrointestinal symptoms, rash, myalgia, and severe arthralgia.[2] Ophthalmologic manifestations from conjunctivitis to optic neuritis can occur during any phase of the disease, with photophobia and retro-orbital pain being frequently observed during the acute phase. In addition, neurological complications such as meningoencephalitis have been reported, as well as other neurological manifestations such as neuropathy and focal neurological deficit.[3,4]

In Brazil, chikungunya is a crucial topic for public health. Between January and May 2021, the Ministry of Health recorded 36,242 probable cases of chikungunya, with the southeast region having the second highest incidence with 20 cases per 100,000 inhabitants.[5] Painful ophthalmoplegia syndrome consists of periorbital or hemicranial pain, combined with ipsilateral ocular motor nerve palsies, oculosympathetic paralysis, and sensory loss in the distribution of the ophthalmic division. Various combinations of these cranial nerve palsies can occur, localizing the pathological process in the cavernous sinus/superior orbital fissure region.[6] Tolosa-Hunt syndrome (THS) is a rare disease whose etiopathogenesis is unknown[7] but four main causes are speculated: trauma, neoplasm, aneurysm, and inflammation.[4] Currently, its diagnosis is based on the criteria outlined by the International Headache Society 2004 (IHS-2004).[6]

This case report aimed to describe a rare syndrome manifestation in a patient with chikungunya; thus, this report serves as a warning to health professionals to ensure early diagnosis and adequate treatment, especially in regions where the disease is endemic (CAAE: 58999022.1.0000.5509).

## CASE REPORT

A 63-year-old female homemaker presented with a complaint of painful ophthalmoplegia associated with eyelid ptosis in the left eye (LE) for 1 month. The patient was diagnosed with chikungunya 2 months before presentation and was being treated and monitored by a general practitioner. Personal history included systemic arterial hypertension and insulin-dependent type 2 diabetes mellitus. Biomicroscopy of the right eye (RE) without alterations and LE with total eyelid ptosis (Figure 1), proptosis, and chemosis was 1+/4+. Extrinsic eye movement presented a total limitation of elevation and partial limitation of abduction of LE.

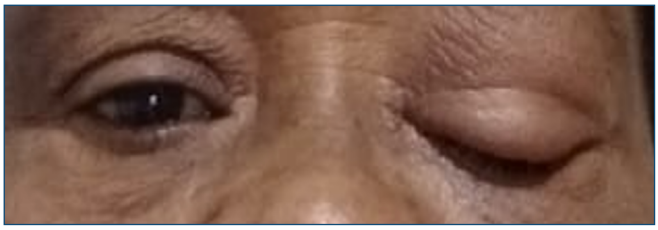

**Figure 1.** Total eyelid ptosis in the left eye.

The neurological test showed a relative afferent pupillary defect in the LE. Intraocular pressure (IOP) of 20 and 26 mmHg was noted.

Retinal mapping revealed no change in both eyes. We prescribed one drop of 0.5% timolol maleate every 12 hours and prednisone 60 mg/day for 14 days. Reassessment after 3 days of using the medication showed significant improvement in pain and partial improvement in ptosis; 2 weeks later, resolution of painful ophthalmoplegia and improvement of eyelid ptosis were observed. No change occurred in RE, and relative afferent pupillary defect was missing in LE. The IOP dropped to 15 and 18 mmHg. The following imaging and laboratory tests were performed: computed tomography (CT) of the skull and orbits with contrast showed left orbital proptosis, infiltrative tissue with soft tissue attenuation in the left orbital apex, obliteration of intraoral fat and extension to the superior orbital fissure, and optic nerves with shape, topography, thickness, and anatomical contours within the normal range (Figure 2).

Magnetic resonance imaging of the skull and orbits with contrast showed tissue with slight hyposignal on T1-weighted images occupying the left orbital apex, with obliteration of intraoral fat, and extending to the superior orbital fissure and cavernous sinus, involving the left optic nerve in the orbital apex and part of its canalicular portion and without other alterations (Figure 3).

Erythrocyte sedimentation value 42, C-reactive protein 4, and positive serology for IgG and IgM antibodies to chikungunya were noted. Complete blood count, coagulation test, glycated hemoglobin, fasting glucose, thyroid function, anti-HIV, FTA-ABS, VDRL, ANA, and serology for dengue were within the normal range. Treatment was then changed to prednisone 40 mg/day for 7 days, with subsequent regression every 7 days to 20 mg/day and then 10 mg/day, and timolol maleate was discontinued.

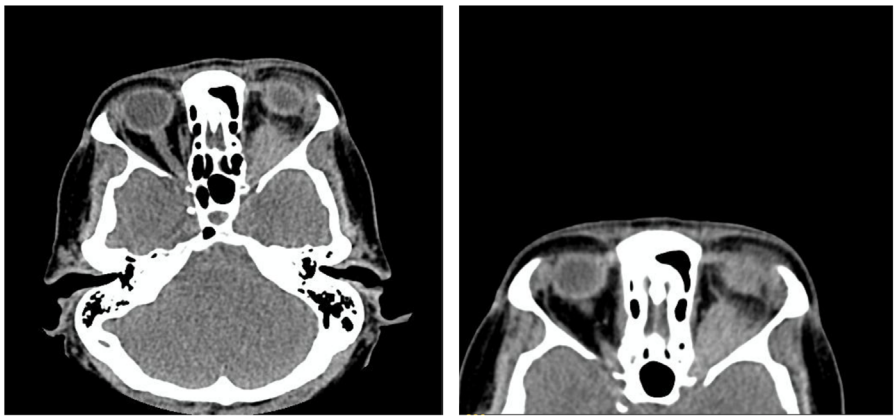

**Figure 2.** Contrast-enhanced computed tomography of the skull and orbits showing left orbital proptosis, infiltrative tissue with soft tissue attenuation in the left orbital apex, with obliteration of intraconal fat and extension to the superior orbital fissure.

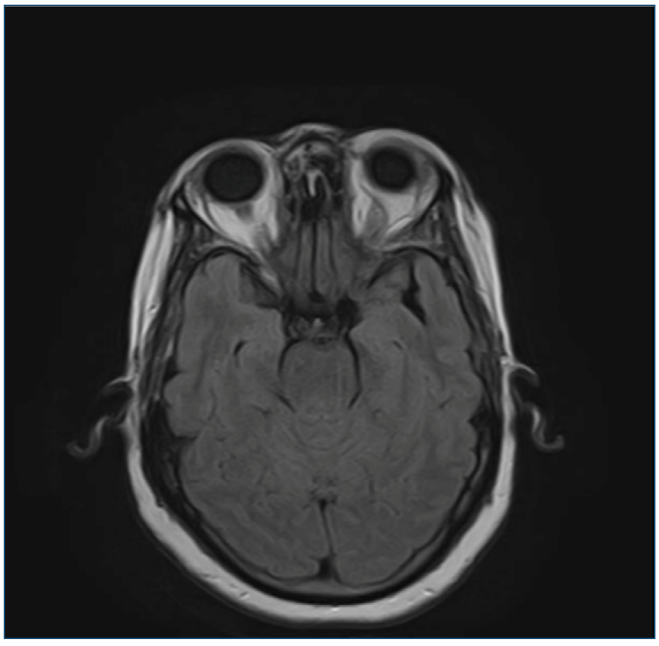

**Figure 3.** Contrast-enhanced magnetic resonance image of the skull and orbits showing tissue with slight hyposignal on T1-weighted images occupying the left orbital apex.

The patient had no eyelid ptosis and IOP was within the normal range after 1 week. New CT images of the skull and orbits showed no changes.

## DISCUSSION

There has been an emergence of CHIKV infection in the Americas since 2013[6], and Brazil has several epidemic regions and significant mortality rates, such as, for example, in the state of São Paulo.[5] Although the exact mechanism of eye involvement after chikungunya infection is not fully understood, the simultaneous occurrence of systemic and ocular diseases indicates the possibility of direct viral involvement.

CHIKV antigens were detected in the corneal stroma, sclera, and iris-ciliary bodies, which supports the hypothesis that these sites are directly affected, causing episcleritis, retinitis, panuveitis, and optic neuritis.[8,9] However, the etiology of THS remains unknown. There is no information available on what triggers the inflammatory process in the cavernous sinus/superior orbital fissure region, which is considered idiopathic orbital inflammation, and a diagnosis of exclusion that requires an evaluation to rule out a tumor, vascular causes, or other forms of inflammation[4] (Chart 1). Currently, its diagnosis is based on the 2004 IHS criteria,[6] which was used to confirm an episode of unilateral orbital pain that persists for a week without treatment, paresis of one or more cranial nerves (compulsorily of the third, fourth and/or cranial nerves) or sixth), and paresis coinciding with the onset of pain, pain, and paresis improving within 72 hours when adequately treated with steroids in the current case. These and other causes have been excluded.

**Chart 1.** Differential diagnosis for Tolosa-Hunt Syndrome

| Category | Conditions/details |
|---|---|
| Trauma | - |
| Vascular | Intracavernous carotid artery aneurysm; posterior cerebral artery aneurysm; carotid-cavernous fistula; carotid-cavernous thrombosis |
| Neoplasm | Primary intracranial tumor; pituitary adenoma; meningioma; craniopharyngioma; sarcoma; neurofibroma; Gasserian ganglion neuroma; Neurofibroma; lymphoma leukemia; primary cranial tumor: chordoma, chondroma, giant cell tumor; metastasis: nasopharyngeal tumor cylindroma; adamantinoma; squamous cell carcinoma; myeloma |
| Others | Bacterial sinusitis, mucocele, periostitis viral; Herpes zoster fungal; mucormycosis spirochetal; syphilis mycobacterial; tuberculosis sarcoidosis Wegener's granulomatosis; eosinophilic granuloma; diabetic ophthalmoplegia; giant cell arteritis; ophthalmoplegic migraine |

In this report, the temporal association between the primary symptoms, ocular manifestations, positive IgM serology, and exclusion of etiologies that could justify this

ophthalmological clinical picture indicated the diagnosis of THS associated with chikungunya. Although this association is rare, treatment for THS with corticosteroids has been described as it was documented by Hunt 40 years ago. Since then, there has been little new information about optimal dosage, treatment duration, or alternative forms of therapy.[7,10] Because they have been used successfully, corticosteroids were chosen and should preferably be started as soon as possible after diagnosis to improve the patients' symptoms. Treatment with oral prednisone proved to be effective and satisfactory for the patient in this study.

Considering the aforementioned statistical data, it becomes clear that health professionals need to maintain vigilance when evaluating patients diagnosed with chikungunya, even after the acute phase of the infection. This vigilance is crucial to identifying ocular abnormalities that may result from CHIKV infection, as timely recognition and treatment are essential to avoid delays in the management of these manifestations.

The pathophysiology of THS provides insight into its mechanisms, especially in the post-vaccination scenario. THS is primarily characterized by idiopathic granulomatous inflammation affecting the cavernous sinus and superior orbital fissure region. This inflammation involves cranial nerves, leading to symptoms such as painful ophthalmoplegia. While the exact etiology remains unclear, hypotheses suggest that an autoimmune mechanism may play a role. After vaccination, it is postulated that immune system activation could contribute to this inflammatory process. Components of the vaccine might trigger cross-reactive immune responses or heighten cytokine production, fostering a pro-inflammatory environment. Additionally, the activation of autoreactive T lymphocytes could potentially target orbital tissues, exacerbating inflammation in predisposed individuals.

This report highlights a rare temporal association between chikungunya and THS, yet it also underscores the broader need for vigilance in contexts such as post-vaccination. Recognizing early signs and understanding the multifactorial etiology of THS, including possible immunological triggers, can significantly impact patient outcomes. Spreading awareness among health professionals about such correlations ensures timely diagnosis and effective management, ultimately advancing care standards for individuals at risk of THS and similar conditions.

## AUTHORS' CONTRIBUTION

Jade Pinto de Queiroz Guerra and Celso Busnelo Moreno contributed to the patient's care and to the collection of clinical data and images for the case. João Marcelo Cecílio Ribeiro contributed to the analysis and interpretation of the manuscript content. Guilherme Novoa Colombo Barboza contributed to the study design. Marcello Novoa Colombo Barboza contributed to data interpretation and critical review of the content. Priscilla Fernandes Nogueira contributed to the study design, data acquisition, and critical review of the content. All authors approved the final version of the manuscript and are responsible for all its aspects, including ensuring its accuracy and integrity.

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