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Topical Review

Evaluation and Management of Tolosa–Hunt Syndrome in Children: A Clinical Update

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ABSTRACT

BACKGROUND: Tolosa–Hunt syndrome is a painful ophthalmoplegia caused by an inflammatory process of unknown etiology in the region of the cavernous sinus, orbital apex, or superior orbital fissure. This disease is rare in the pediatric population. The objective of this study was to provide a clinical framework for the evaluation and treatment of children with this disorder. A systematic approach to the diagnosis of painful ophthalmoplegia in children is proposed. **METHODS:** We present a 15-year-old girl whose clinical presentation and neuroradiological findings support a diagnosis of Tolosa–Hunt syndrome as defined by the 2013 International Classification of Headache Disorders (Third Edition, ICHD-3 beta) diagnostic criteria. An exhaustive systematic literature search based on these criteria yielded 15 additional cases of Tolosa–Hunt syndrome in children. Clinical, demographic, and radiological features were retrospectively analyzed. The results and statistical analyses are reported. **RESULTS:** A total of 16 individuals were included in the final analysis. This review summarizes the current knowledge and recommendations for the diagnosis and management of pediatric Tolosa–Hunt syndrome. It highlights demographic, clinical, and radiological features of this disease in children and underscores areas of the literature where evidence is still lacking. **CONCLUSIONS:** Overall, Tolosa–Hunt syndrome seems to follow a similar course in children compared to adults. The diagnostic approach and treatment require specific considerations. New observations and possible features of pediatric Tolosa–Hunt syndrome are discussed. Further research is needed to optimize clinical detection and medical management of this disease.

Keywords: Tolosa–Hunt syndrome, painful ophthalmoplegia, headache, MRI, corticosteroids, childhood, pediatric

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Introduction

Painful ophthalmoplegia is a rare pathologic condition characterized by any combination of unilateral periorbital or hemicranial pain, ipsilateral oculomotor paralysis, and oculosympathetic dysfunction.[1-3] The differential diagnosis is extensive and includes neoplastic, infectious, vascular, and inflammatory causes.[3-6]

Tolosa–Hunt syndrome (THS) is a steroid-responsive painful ophthalmoplegia described in the 2013 International Classification of Headache Disorders (Third Edition, ICHD-3 beta) as unilateral orbital pain in association with paralysis of one or more of the third, fourth, and/or sixth cranial nerves.[7] The constellation of findings is due to extrinsic compression and secondary dysfunction of neurovascular structures within the cavernous sinus by a nonspecific inflammatory process.[3,8-12] Infrequently, when the area of inflammation extends into the orbital apex and/or superior orbital fissure, dysfunction of the optic, trigeminal, facial nerves and sympathetic innervation of the pupil can ensue.[3,13]

The clinical features of THS and the efficacy of steroid treatment were first described by Tolosa in 1954[14] and Hunt in 1961.[15] Smith and Taxdal later coined the term "Tolosa-Hunt syndrome" in 1966.[16] With an estimated yearly

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incidence of one case per million in the United States[6,17] and a mean age of onset of 38-41 ± 14-16 years,[3,13] THS is extremely rare in children.[8,18,19] The rarity of this syndrome contributes to the controversy that surrounds diagnostic approach and treatment strategies. The current lack of precise treatment guidelines can result in insufficient or extended therapy, which can lead to complications, unnecessary testing, and prolonged hospitalizations. Therefore the establishment of a clinical framework for the evaluation and management of THS is of essential importance.

There are no recent reviews of pediatric THS cases, particularly those that meet ICHD-3 beta criteria. We retrospectively analyze the clinical, demographic, and radiological features with a focus on the diagnosis and management of pediatric THS.

Patient Description

An otherwise healthy 15-year-old girl presented with a one-week history of severe left-sided headache, blurry vision, and ipsilateral painful ophthalmoplegia with horizontal diplopia on left gaze. The headache was periorbital and retro-orbital, nonradiating, and throbbing in nature. There was no previous history of headaches, trauma, rash, seizures, or recent illnesses. Family history was noncontributory.

Examination revealed impaired abduction of the left eye on lateral gaze consistent with sixth nerve palsy and an adduction deficit consistent with an additional third nerve involvement (Fig 1). Both pupils were 3 mm, round, and reactive to light. Fundoscopic examination was unremarkable. Facial sensation was intact, and there was no facial droop, ptosis, proptosis, or periorbital edema/erythema. The remainder of her examination was unremarkable.

Complete blood count with peripheral blood smear, serum electrolytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), angiotensin-converting enzyme, hemoglobin A_{1c}, thyroid panel, autoimmune antibodies (antinuclear antigen, antineutrophil cytoplasmic antibody), serum protein electrophoresis, and rheumatoid factor were all within normal limits. *Borrelia burgdorferi* serology, myasthenia gravis panel, HLA-B27, and neuromyelitis optica—immunoglobulin G were negative. A lumbar puncture was performed and showed a normal opening pressure. Cerebrospinal fluid (CSF) cell count was nornal. No oligoclonal bands were detected.

Her initial magnetic resonance imaging (MRI) scan with contrast showed no intracranial abnormalities on day one of admission. On day three, her ocular pain and headache spontaneously resolved. However, an MRI evaluation repeated to evaluate her persistent ophthalmoplegia showed abnormal enhancement of the posterior left cavernous sinus (Fig 2). Stenosis of the left cavernous internal carotid artery (ICA) was also noted and confirmed by angiography.

Corticosteroid treatment was begun on day three of admission when the results of radiological imaging combined with her clinical presentation raised our suspicion for a diagnosis of THS. She received 1 g prednisolone intravenously daily for two days and discharged on a tapering dose of oral prednisone for a total of eight days of treatment based on recommendations by the inpatient neurology service. Three months after discharge, another MRI showed a significantly smaller area of enhancement in the posterior left cavernous with marked improvement of left cavernous ICA stenosis. Although she continued to experience intermittent diplopia, her symptoms improved and gradually resolved over the course of a few weeks without further treatment. No additional follow-up studies were available.

Methods

A bibliographical search of PubMed for all studies published to date using the search terms “Tolosa-Hunt” and “pediatric,” as well as “Tolosa-Hunt” and “children” revealed 13 and 56 articles, respectively. Each article was read independently and systematically reviewed to identify additional cases in the reference list. Only pediatric case reports and single cases from larger case series that met current ICHD-3 beta criteria for THS were considered for inclusion in the study. Exclusion criteria included the following: (1) lack of precise diagnostic information, (2) unavailability of publication, and (3) single cases that were part of larger studies from which individual patient information could not be abstracted. Of all identified cases, only 15 qualified for a diagnosis of THS according to ICHD-3 beta (Table 1) and were included in the study.[1,8,19-30] Our 15-year-old patient, who also met these criteria, was included in the final analysis. A total of 16 cases were included.

From each of the cases, we abstracted the following information when available: (1) age, (2) sex, (3) symptom location (bilateral/unilateral), (4) cranial nerve involvement, (5) time interval between the onset of pain and ophthalmoplegia, (6) associated symptoms (i.e., nausea, vomiting, recent illnesses, family history of migraine headaches), (7) MRI findings, (8) response to steroid treatment, (9) corticosteroid dosing

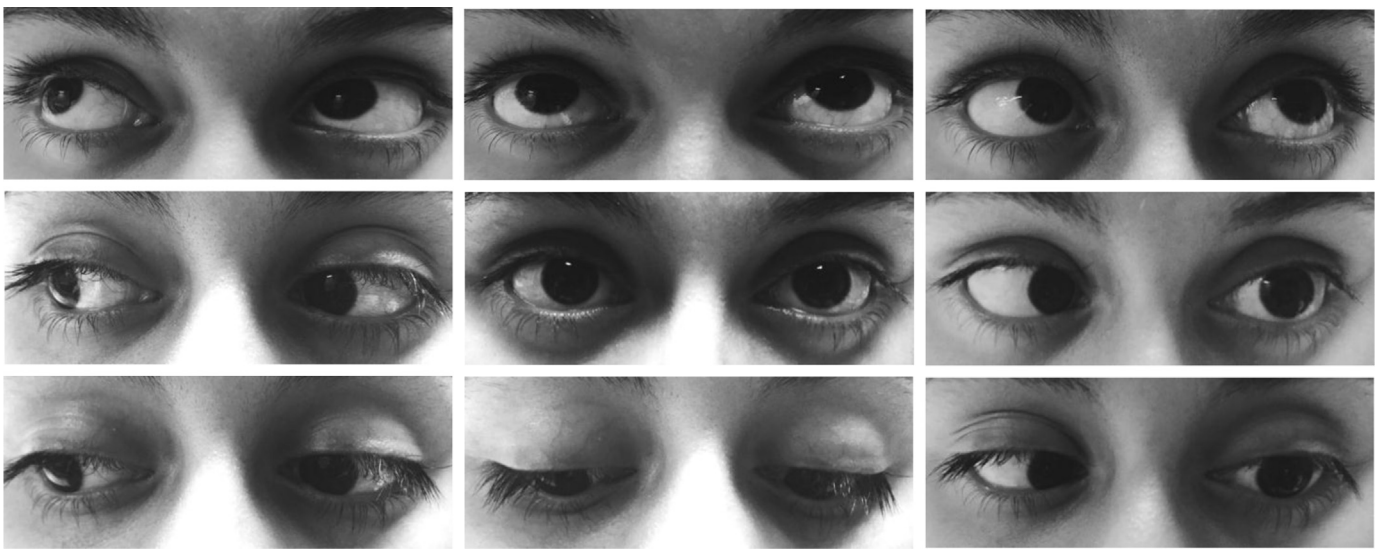

FIGURE 1.
Neuro-ophthalmologic examination; a nine-gaze photograph panel showing left-eye abduction limitation on left gaze and adduction deficit on right gaze suggestive of left sixth- and third-nerve palsy, respectively.