Pediatric Neurology 99 (2019) 60–63

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observation

Tolosa-Hunt Syndrome: Clinical Manifestations in Children

Maria Tsirigotaki, MD [a], George Ntoulios, MD [b], Michail Lioumpas, MD [c], Spyridon Voutoufianakis, MD, PhD [d], Pelagia Vorgia, MD, PhD [e, *]

[a] Neonatal Intensive Care Unit, University Hospital, Heraklion, Crete, Greece
[b] Department of Pediatrics, Venizelion General Hospital, Heraklion, Crete, Greece
[c] Neonatal Intensive Care Unit, Makarios Hospital, Nicosia, Cyprus
[d] Ano Viannos Health Center, Crete, Greece
[e] Pediatric Department, University Hospital Of Heraklion, Medical School, University of Crete, Heraklion, Crete, Greece

ARTICLE INFO

Article history:
Received 30 June 2018
Accepted 12 February 2019
Available online 20 February 2019

Keywords:
Tolosa-Hunt syndrome
Pediatric
Painful ophthalmoplegia
Tolosa-Hunt syndrome seventh nerve paresis

ABSTRACT

Background: Tolosa-Hunt syndrome (THS) is a rare condition in children characterized by painful ophthalmoplegia caused by inflammation of unknown etiology in the cavernous sinus, superior orbital fissure, or orbital apex. Our main purpose was to report two pediatric cases of THS, a typical one and another extremely rare one preceded by facial palsy.
Methods: Both cases were diagnosed with THS based on the 2013 International Classification of Headache Disorders (ICHD-3 beta) criteria. A literature review was also performed concerning epidemiology, clinical and imaging features, diagnostic criteria, treatment, and outcome of THS with a focus on children.
Results: The first patient was a 14-year-old boy who presented with third nerve palsy, four weeks after the diagnosis and treatment of peripheral seventh nerve palsy and the second patient was a 10-year-old girl who presented with a five-day history left-sided ptosis, periorbital pain, and diplopia.
Conclusions: THS is a rare condition in pediatric population that requires an extensive evaluation before the final diagnosis is made. Seventh nerve palsy preceding the diagnosis of THS is particularly rare in children. This patient represents only the second reported example of seventh nerve involvement in a child with THS.

Introduction

Tolosa-Hunt syndrome (THS) was first described by Tolosa (1954) and Hunt (1961) and has an estimated annual incidence of one case per million in adults in United States.[1] There are only case reports of THS in children. A recent review increased the pediatric Tolosa-Hunt cases to only 16.[2] We present two additional pediatric patients.

THS is characterized by painful ophthalmoplegia due to inflammation in the cavernous sinus, superior orbital fissure, or orbital apex. This syndrome can be associated with paresis of one or more of the third, fourth, or sixth cranial nerves. Of note, seventh nerve involvement in THS has been described in adults but is not common in children.[3] Sympathetic innervation of the pupil is occasionally affected. Ophthalmoparesis coincides or follows the orbital pain that resolves within 72 hours after the administration of corticosteroids. THS is caused by granulomatous material in the cavernous sinus, superior orbital fissure, or orbit in some biopsied cases. Its etiology remains unknown but extensive evaluation and follow-up are required to exclude other causes of painful ophthalmoplegia, such as infection, tumor, vascular abnormalities, and autoinflammatory disorders.[4]

Diagnosis is based on specific criteria that were defined in 1988 and were revised in 2004 and 2013 by the International Classification of Headache Disorders (ICHD-3 beta)[5] (Table 1). Although computed tomography (CT) and magnetic resonance imaging (MRI) findings are not pathognomonic, they contribute to the diagnosis and follow-up of THS.[4]

MRI of the brain and orbits is the preferred neuroimaging method. Thickening of the cavernous sinus, superior orbital fissure,

Conflict of interest and source of funding statement: The authors declare no conflict of interest or financial disclosures concerning the materials or methods used in this study or the findings specified in this article.

* Communications should be addressed to: Dr. Vorgia; Pediatric Department; University Hospital of Heraklion; Medical School; University of Crete; Heraklion, Crete 71500, Greece.
E-mail address: vorgia.p@uoc.gr (P. Vorgia).

https://doi.org/10.1016/j.pediatrneurol.2019.02.013
0887-8994/

TABLE 1.
Revised ICHD-3 Criteria for the Diagnosis of Tolosa-Hunt Syndrome

Diagnostic Criteria
A. Unilateral headache fulfilling criterion C
B. Both of the following:
1. Granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, demonstrated by MRI or biopsy
2. Paresis of one or more of the ipsilateral third, fourth, and/or sixth cranial nerves
C. Evidence of causation demonstrated by both of the following:
1. Headache has preceded paresis of the third, fourth, and/or sixth cranial nerves by ≤2 weeks, or developed with it
2. Headache is localized around the ipsilateral brow and eye
D. Not better accounted for by another ICHD-3 diagnosis

Abbreviations:
ICHD = International Classification of Headache Disorders
MRI = Magnetic resonance imaging

or orbital apex with strong enhancement after gadolinium administration is common.

Treatment with glucocorticosteroids is recommended in THS although controversy exists regarding dosage, route, and length of administration.[4] Evidence in children is scarce and based only in information derived from case reports or series.[5] Alternative treatments include immunosuppressants, usually not required, given the typical steroid responsiveness of THS.[1,2] THS rarely leaves neurological sequelae although relapses are common in up to 40% of patients.[2] Close clinical and radiological follow-up is required.

The only pediatric patient with THS preceded by seventh nerve palsy was described by Cerisola et al.[3] in 2011. We report the rare occurrence of THS preceded by peripheral seventh nerve palsy in a 14-year-old boy in association with paresis of the third cranial nerve that developed over the course of eight weeks along with a 10-year-old girl with typical manifestations of THS.

Patient 1

This 14-year-old boy presented with acute intermittent, throbbing headache at the left temporal region with poor response to common analgesics. Neurological examination, cerebrospinal fluid study, and fundoscopy were normal. An MRI of the brain and the orbits performed few days later was also normal. Over the course of four weeks, he developed left upper and lower facial paralysis with mouth drooping and inability to close the left eyelid. The findings were consistent with peripheral seventh nerve palsy and he was treated with oral prednisolone and valaciclovir for seven days with gradual complete recovery. Eight weeks later, he was readmitted with diplopia, left exotropia, downward and outward left eye deviation, and ptosis of the left eyelid consistent with third cranial nerve palsy, which was also associated with left periorbital pain and vomiting. Fundoscopy and the rest of his examination were

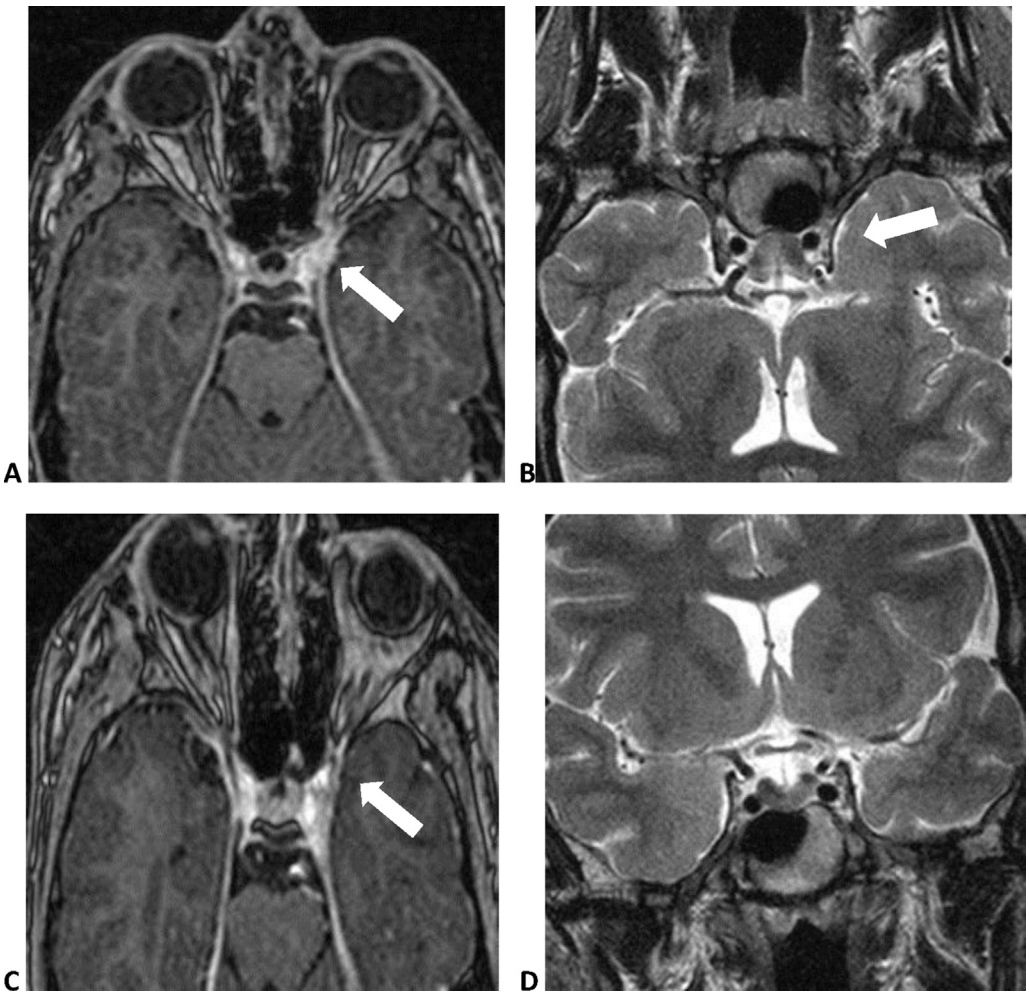

FIGURE. MRI axial imaging of a 14-year-old boy with left orbital pain, ptosis, diplopia, and third nerve palsy, four weeks after the diagnosis and treatment of ipsilateral seventh nerve palsy. MRI axial imaging without (A) and with (B) enhancement demonstrates granulomatous inflammation of the left cavernous sinus homogeneously enhancing after contrast administration. MRI findings normalized completely one month later (C, D). MRI, magnetic resonance imaging.

TABLE 2.
Differential Diagnosis of Painful Ophthalmoplegia in Patients 1 and 2

Differential Diagnosis	Investigations	Patient 1	Patient 2
1. Infection	Serology testing for HSV1, HSV2, syphilis, toxoplasma, rubella, EBV, CMV, and Borrelia burgdoferi, mycoplasma	Negative	Negative
	Tuberculin skin test	Negative	Negative
	Cerebrospinal fluid polymerase chain reaction analysis for EBV, CMV, HSV1, HSV2, and VZV	Negative	Negative
2. Malignancy	Excluded by CT and MRI findings, no relapse after 3 years of follow-up Cerebrospinal cytology normal		
3. Trauma	No relevant history, excluded by CT and MRI findings		
4. Vascular cause	CT and MRI findings negative for vascular cause		
5. Others Diabetic ophthalmoplegia Ophthalmoplegic migraine Orbital pseudotumor Sarcoidosis Multiple sclerosis* Neuromyelitis optica*	Angiotensin converting enzyme, hemoglobin A1C, thyroid panel, autoimmune antibodies (antinuclear antigen, anti-neutrophil cytoplasmic antibody, anti-dsDNA), C3, C4, serum protein electrophoresis, and rheumatoid factor Cerebrospinal fluid cytology and electrophoresis	Within normal range Normal	Within normal range Normal
6. THS Multiple sclerosis* Neuromyelitis optica*	2013 ICHD-3 beta criteria fulfilled for diagnosis, MRI findings consistent with THS Aquaporin 4 antibodies: note done MOG antibodies: not done MRI findings: not suggestive for multiple sclerosis or neuromyelitis optica		

Abbreviations:
CT = Computed tomography
ICHD = International Classification of Headache Disorders
MOG = Myelin oligodendrocyte glycoprotein
MRI = Magnetic resonance imaging
THS = Tolosa-Hunt syndrome
* Aquaporin 4 and Myeline Oligodendrocyte Glycoprotein antibodies were not done because cerebral MRI findings were not suggestive for Multiple Sclerosis or Neuromyelitis Optica.

normal. A cranial CT was performed and repeated MRI revealed soft tissue in the left cavernous sinus with increased contrast enhancement after gadolinium administration (Fig). Narrowing of the cavernous portion of the internal carotid artery was not observed. Having excluded other causes of painful ophthalmoplegia (Table 2), a diagnosis of THS was made based on the ICHD-3 beta diagnostic criteria. A lumbar puncture was performed with normal findings and cytology. Cerebrospinal fluid polymerase chain reaction analysis for Epstein Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus 1 (HSV1), herpes simplex virus 2 (HSV2), and varicella zoster virus (VZV) was negative. Serology, especially for Lyme disease, was also negative.

Oral methylprednisolone was administered (1 mg/kg/day) for seven days, then tapered over a three month interval. Complete resolution of pain was observed within 72 hours. He also received antibiotics awaiting culture and serology results. His ophthalmoplegia regressed gradually and his MRI findings had almost resolved four weeks after treatment. Subsequently, the patient underwent close clinical and imaging follow-up with no relapse during a three-year interval.

Patient 2

This 10-year-old girl presented with a five-day history of periorbital headache, acute diplopia, and left ptosis. Twenty-four hours before admission a slight asymmetry of eye fissures was noted with a slight left ptosis. An evidently dilated left pupil was noticed with sluggish response to light, vertical diplopia, and adduction deficit, all findings consistent with third nerve palsy. Cranial CT was normal and laboratory investigations excluded possible causes of painful ophthalmoplegia (Table 2). An MRI of the brain and the orbits revealed tissue in the left cavernous sinus with increased contrast enhancement after gadolinium administration. She was diagnosed with THS because she completely fulfilled the revised ICHD-3 beta criteria for the diagnosis in terms of clinical and neuroimaging findings.[5] A lumbar puncture was performed with normal findings and cytology. Cerebrospinal fluid polymerase chain reaction analysis for EBV, CMV, HSV1, HSV2, and VZV was negative. Serology was also negative.

The patient was treated with IV methylprednisolone (1 mg/kg/day) for 14 days, then tapered over one month. Her symptoms resolved within 72 hours. Repeated MRIs in one, three and six months later, were normal.

Discussion

THS in children is a rare cause of painful ophthalmoplegia that is caused by nonspecific inflammation of the cavernous sinus or superior orbital fissure of unknown etiology. The revision of the diagnostic criteria by the ICHD in 2013 has aided the clinical diagnosis[5]; however, the data regarding the disease course and management remain scarce, thus reporting new cases is very important. In a recent systematic review by Pérez and Evangelista,[2] only 16 cases of pediatric THS were identified. We present here two additional pediatric patients with THS. The first case is particularly rare among THS cases, because seventh nerve involvement has only been described in one child.[3] Apart from the third, fourth, and sixth cranial nerves that are typically involved in THS because of their proximity with the cavernous sinus, involvement of other nerves is rare and probably supports the suspicion that THS is part of a multiple nerve inflammation syndrome. Taking into account common relapses and corticosteroid responsiveness of THS, an autoimmune underlying mechanism affecting cranial nerves could be a possible cause although a specific biomarker has not been found yet. Seventh nerve palsy preceding the diagnosis of THS has been described in adults but is very rare in children.[3] In 2011, Cerisola et al.[3] reported an 11-year-old boy with involvement of the left cavernous sinus, five months after peripheral seventh nerve palsy. The child was treated with low dose corticosteroids and developed multiple relapses that responded to repeat courses of oral steroids. Normalization of imaging was not initially achieved despite the clinical response to treatment. Our patient fulfilled the ICHD-3 beta

criteria for diagnosis of THS syndrome, including three episodes of unilateral orbital pain, paresis of the third cranial nerve, and demonstration of soft tissue by MRI after exclusion of other causes. The paresis coincided with the onset of pain, which resolved within 72 hours after starting methylprednisolone treatment. After initiation of corticosteroids, signs regressed within few weeks with almost complete MRI normalization one month later. In contrast to the Cerisola et al. patient,[3] our patient was relapse-free at a three-year follow-up with no neurological sequelae.

Our second patient was a 10-year-old girl who presented with unilateral third nerve palsy associated with ipsilateral periorbital pain and the presence of inflammatory tissue in the left cavernous sinus with strong contrast enhancement. The age of this girl's symptom onset is in accordance with a median age 11 years that has been previously reported.[2] The third cranial nerve is the most frequently involved nerve in THS, encountered in more than 80% of THS cases.[2,4] The symptoms were unilateral in 95% of reported cases.[1] Twenty-four hours before admission, she had only a slight asymmetry of eye fissures. Neuroimaging studies revealed soft tissue of the left cavernous sinus whereas the right one appeared normal, as described in 75% of all reported cases.[2] Narrowing of the cavernous internal carotid artery has been described in 44% of all reported cases, but was not detected in either of our cases.[2,4]

Treatment of THS remains controversial.[2,4] Corticosteroids are the cornerstone of therapy; however, few data are available concerning the most effective course, route of administration, optimal dose, and length of treatment for children with THS. Alternative therapies are usually not required given the typical steroid responsiveness. In our first patient, administration of oral methylprednisolone at a dose of 1 mg/kg/day for seven days and gradual tapering over three months proved effective. The second patient was treated with intravenous methylprednisolone at a dose of 1 mg/kg/day for 14 days, then tapered slowly over one month and the symptoms resolved within 72 hours. Neither patient has experienced a relapse during more than three years of clinical and MRI follow-up. More studies are required to establish the optimal corticosteroid course for the treatment of children with THS and further follow-up. THS is rare in children and should be considered among causes of painful ophthalmoplegia among pediatric population. Reporting of new cases is of paramount importance in providing more data regarding the course of the disease and the treatment outcomes of this entity. Our first patient is only the second child to experience seventh nerve involvement due to THS.

References

1. Amrutkar C, Burton EV. Tolosa-Hunt syndrome. StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2018.
2. Pérez CA, Evangelista M. Evaluation and management of Tolosa-Hunt syndrome in children: a clinical update. Pediatr Neurol. 2016;62:18–26.
3. Cerisola A, González G, Scavone C. Tolosa-Hunt syndrome preceded by facial palsy in a child. Pediatr Neurol. 2011;44:61–64.
4. Benzohra DE, Damry N, Delpierre I, et al. Tolosa-Hunt syndrome in children. JBR-BTR. 2011;94:290–292.
5. Hao R, He Y, Zhang H, et al. The evaluation of ICHD-3 beta diagnostic criteria for Tolosa–Hunt syndrome: a study of 22 cases of Tolosa–Hunt syndrome. Neurol Sci. 2015;36:899–905.