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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.

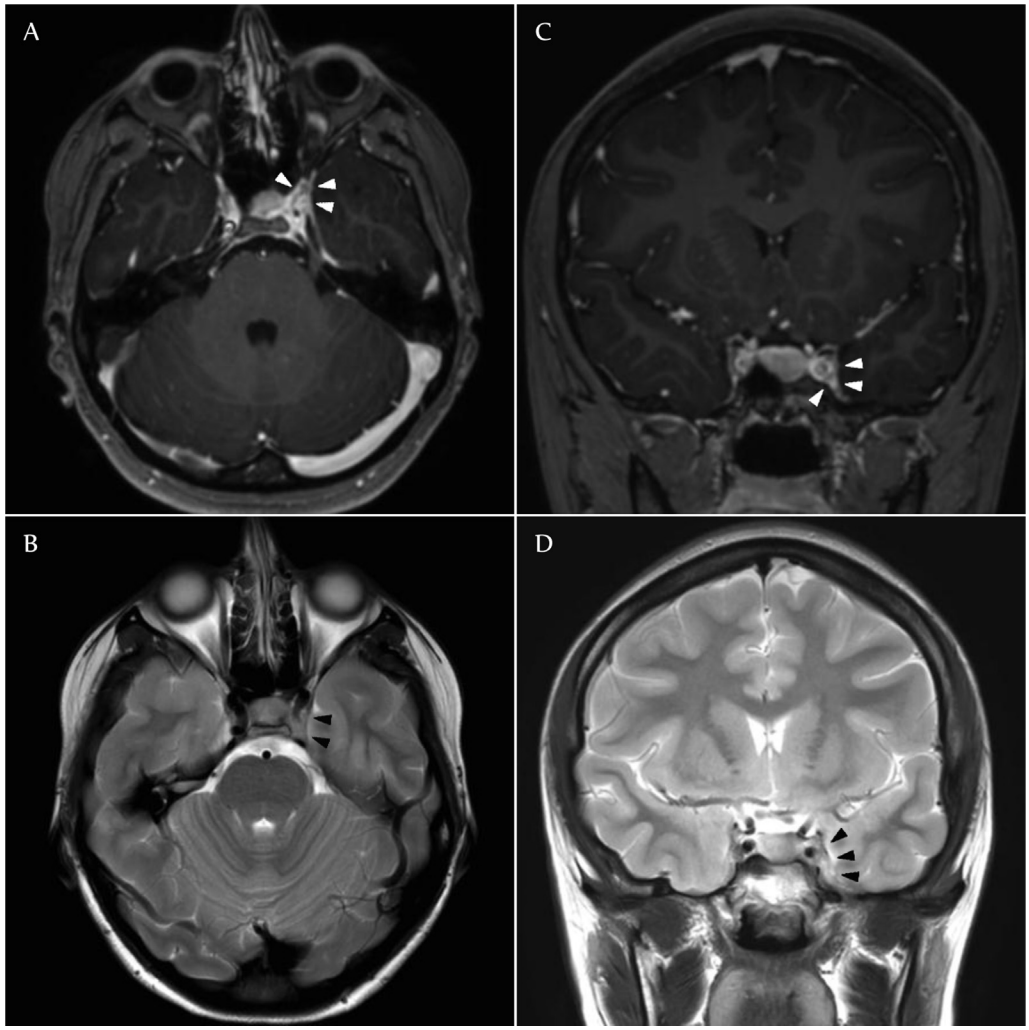

FIGURE 2.
Magnetic resonance imaging of the brain showing an enhancing space-occupying lesion within the left cavernous sinus (arrowheads): (A) Postgadolinium T1-weighted and (B) T2-weighted axial views; (C) postgadolinium T1-weighted and (D) T2-weighted coronal views.

used, (10) time interval between initiation of therapy and symptom resolution/normalization of MRI findings, (11) diagnostic testing results, and (12) time of follow-up MRI studies.

Corticosteroid treatments included prednisone, prednisolone, methylprednisolone, and dexamethasone given orally or intravenously. To facilitate comparison among patients, we converted the initial dose of steroids used

TABLE 1.
The 2013 ICHD-3 Beta Diagnostic Criteria for 13.7 Tolosa-Hunt Syndrome

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 IIIrd, IVth and/or VIth cranial nerves
C. Evidence of causation demonstrated by both of the following:
   1. Headache has preceded paresis of the IIIrd, IVth and/or VIth nerves by $\leq$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.

Comments: Some reported cases of 13.7 *Tolosa-Hunt syndrome* have had additional involvement of the Vth nerve (commonly the first division) or optic, VIIth or VIIIth nerves. Sympathetic innervation of the pupil is occasionally affected. The syndrome has been caused by granulomatous material in the cavernous sinus, superior orbital fissure or orbit in some biopsied cases.
Careful follow-up is required to exclude other causes of painful ophthalmoplegia such as tumors, vasculitis, basal meningitis, sarcoid or diabetes mellitus.
Pain and paresis of 13.7 *Tolosa-Hunt syndrome Tolosa-Hunt syndrome* resolve when it is treated adequately with corticosteroids.

Abbreviations:
ICHD-3 beta = International Classification of Headache Disorders, Third Edition (beta)
MRI = Magnetic resonance imaging

into the equivalent of prednisone, by noting that 5 mg prednisone is equivalent to 5 mg prednisolone, 4 mg methylprednisolone, and 0.75 mg dexamethasone.[31] Patients initially treated with corticosteroid doses equivalent to less than 0.5 mg/kg/day of prednisone were divided into a "low-dose" steroid group, 0.6 to 1.9 mg/kg/day prednisone into an "intermediate-dose" group, and more than 2 mg/kg/day prednisone into a "high-dose" steroid group.

The outcome features in each subject were resolution of orbital pain and of cranial nerve paralysis either within or after 72 hours after the initiation of steroid therapy. We also noted the number of recurrences, if any, among the three subgroups. Considering all subjects together, the possible relationship between steroid dose (low, intermediate, or high) and the outcome variables (pain and/or ophthalmoplegia resolution and recurrence) was evaluated by means of the chi-square and Fisher-Freeman-Halton test. The *P* value was set at 0.05.

Results

Clinical and demographic features

We reviewed and retrospectively analyzed 15 published examples of THS in children that fulfilled 2013 ICHD-3 beta diagnostic criteria (Table 1). With the addition of the patient from our center, a total of 16 cases were studied. Demographic and clinical features are summarized in Table 2.

The median age of onset of THS in children was 11 years (interquartile range, four to nine years); 60% of the patients were female and 40% were male. Symptoms were unilateral in 94% of patients and bilateral in the remaining 6%. The third cranial nerve was involved most frequently (81%), followed by the sixth (56%), fourth (13%), and fifth cranial nerves (7%). Facial nerve dysfunction was reported once (6%). One third of the patients reported multiple ($\geq$2) cranial nerve palsies and two thirds also had oculosympathetic dysfunction. Among those with multiple cranial nerve involvement, the third and sixth cranial nerves were simultaneously affected in five and the third and fourth in one patient.

The average time between the onset of orbital pain and the development of ophthalmoparesis was 6 $\pm$ 5 days (median, 4 days; interquartile range, 2 to 9). The pain lasted 3 $\pm$ 2 days on average, whereas the oculomotor dysfunction tended to last longer, ranging from three days to three months when treated and up to six months without treatment.

Associated symptoms included nausea in 21% of patients and a history of recent/chronic infection in 23%. No family history of migraine headaches was reported, and no persistent neurological deficits were observed in any of these individuals.

Diagnostic evaluation

Results of a complete blood count, ESR, and CRP were available in eight of 16 patients. These were normal in all but one patient, whose ESR and CRP were slightly elevated.[29] When reported, electrolytes, coagulation studies, hemoglobin A_{1c}, antinuclear antibody, angiotensin-converting enzyme, antimitochondrial antibody, thyroid panel, antineutrophil cytoplasmic antibody, and *Borrelia* serology were all normal (data not shown). A lumbar puncture was performed in 38% of patients. Opening pressure, CSF cell count, protein, glucose, electrophoresis, and microbiologic cultures (bacterial, fungal, and viral) were normal in all instances.

Neuroradiological findings

All included patients underwent contrast-enhanced cranial MRI. Abnormal enhancement of the affected cavernous sinus was detected in 75%. Bilateral intracavernous enhancement was reported once.[28] In the remaining 25% with a normal MRI on initial evaluation, follow-up MRI performed within four days to five months after the initial study showed contrast enhancement of the cavernous sinus in all cases. Complete normalization of MRI findings was reported within 3 $\pm$ 1 months of treatment on average. Narrowing of the cavernous ICA was detected in 44% of patients either by MRI, angiography, or both.

Treatment and outcome

Fifteen patients were treated with corticosteroids (94%). Spontaneous resolution of symptoms precluded the need for therapy in the remaining case.[1] Among those who received treatment, 73% experienced complete resolution of ocular pain within 72 hours, 20% were pain free within one week, and the remaining 7% experienced pain for up to two weeks. In regard to the oculomotor paralysis, one third of the patients were symptom free within 72 hours and the remaining two thirds fully recovered within 4 $\pm$ 1 weeks.

The three diagnostic subgroups (high-, intermediate-, and low-dose groups) did not differ in most of the variables analyzed. No significant differences were found between dosing and response to therapy (pain or palsy relief either before or after 72 hours). The only exception was recurrence, which was significantly more likely among patients in the low-dose group (Table 3). No recurrences were reported among patients in the high-dose group (χ^2 = 9.5, Fisher-Freeman-Halton test P = 0.03).

Discussion

Clinical and demographic features

This retrospective study of 16 patients suggests that in children with THS tend to follow a similar course to that of adults. Pediatric THS has no gender predilection. Affected individuals generally report a "boring" or "stabbing" retroorbital pain that is typically preceded by the ophthalmoplegia by several days, but ophthalmoplegia can begin simultaneously with the pain or even precede it. As with adults, the third cranial nerve is most frequently involved, followed by the sixth, fourth, and fifth cranial nerves.[2,5,7,10] Symptoms are typically unilateral, but bilateral presentations can also occur. Although pupillary sympathetic dysfunction has been reported in about 30% of patients,[32,33] its frequency was much higher among children in this study (67%).

Diagnostic evaluation

Diagnosis is based upon clinical presentation in conjunction with radiological findings.[8] The differential diagnosis is extensive and includes neoplastic, vascular, traumatic, or infectious etiologies (Table 4) that must be excluded by appropriate investigations (Table 5).[9,12,34-37]

TABLE 2.
Summary of Pediatric Cases of Tolosa–Hunt Syndrome

Authors	Age	Sex	CN Involved	Other Symptoms	MRI	Steroid Dose Used*	Outcome	Treatment Duration	Follow-up MRI
del Toro et al.[1]	10	M	III	Ptosis, dilated pupil	CS + ICA	Not treated	Pain resolved within 3 days, ophthalmoplegia within 10 days.	NA	1 Month normal
Yeung et al.[8]	9	M	III	Ptosis, dilated pupil, nausea	CS + ICA	Low dose for 2 weeks (failed), then high dose	Pain resolved immediately, ophthalmoplegia improved within 4 days of high dose	8 Weeks of high dose	2 Months improved, 2 years normal
Pienczk-Reclawowicz et al.[19]	14	M	III, IV, VI	None	CS + ICA	Intermediate dose	Pain resolved within 3 days, ophthalmoplegia within 2 weeks.	8 Days	6 Months normal
Koul et al.[20]	—	—	VI	None	CS + ICA	Intermediate dose	Pain resolved within 3 days, ophthalmoplegia within 3 weeks	Unspecified	6 Weeks normal
Benzohra et al.[21]	4	F	VI	None	CS + ICA	High dose	Pain resolved immediately, ophthalmoplegia unspecified	2 Months	2 Months normal
Cerisola et al.[22]	11	M	III, VI, VII	Ptosis	CS + ICA	Intermediate dose	Pain resolved within 2 weeks, ophthalmoplegia within 1 month	8 Weeks, multiple trials due to recurrence	20 Months later improved
Jain et al.[23]	9	M	VI	None	CS	Unspecified	Pain resolved immediately, ophthalmoplegia within 6 weeks	Unspecified	7 Weeks normal
Jain et al.[23]	18	F	III, VI	None	CS + MC	Unspecified	Pain resolved immediately, ophthalmoplegia within 6 weeks	Unspecified	9 Weeks normal
Kang et al.[24]	7	M	III	Ptosis, dilated pupil	CS	Low dose, then intermediate dose	Pain resolved immediately, ophthalmoplegia unspecified, recurred during tapering	Unspecified	1 Month normal
Kim et al.[25]	11	F	III	Abdominal pain, diarrhea	CS	Intermediate dose	Pain resolved within 1 week, ophthalmoplegia within 3 weeks	Unspecified, taper started at 3 weeks	3 Months normal
Kóbor et al.[26]	12	F	VI	None	CS	Unspecified dose	Patient had no pain, ophthalmoplegia resolved within 6 months	Discontinued after 1 week for "inefficacy"	6 Months improved, 1 year normal
Maji et al.[27]	12	F	III	Ptosis, dilated pupil	CS + ICA + OA	Unspecified dose	Pain resolved within 2 days, ophthalmoplegia within 1 month	Unspecified	Unspecified, but normal at follow-up
Nezu et al.[28]	12	F	III, VI	None	CS (bilateral)	Intermediate dose	Pain and ophthalmoplegia resolved within 3 days but recurred after treatment discontinuation	1 Month, then 10 months	3 Years normal
Slattery et al.[29]	17	F	VI	None	CS + MC + PA	High dose	Pain resolved within 1 week, ophthalmoplegia within 2 weeks	8 Weeks	2 Months normal
Zanus et al.[30]	8	F	III, IV	Ptosis, abdominal pain, diarrhea, vomiting	CS	Intermediate dose	Pain resolved within 3 days, ophthalmoplegia within 2 weeks	8 Days	6 Months normal
Present case	15	F	III, VI	None	CS + ICA	High dose	Pain resolved before treatment, ophthalmoplegia improved after 2 weeks but still present at 2-month follow-up	8 Days	2 Months improved

Abbreviations:
CN = Cranial nerve
CS = Cavernous sinus
ICA = Internal carotid artery
MC = Meckel's cave

* Corticosteroid doses are defined as: "low" dose ≤0.5 mg/kg/day, "intermediate" dose = 0.6 to 1.9 mg/kg/day, and "high" dose ≥2 mg/kg/day of prednisone or their equivalent.

TABLE 3.
Relationship Between Effectiveness of Steroid Treatment Dose on Pain and Recurrence

P value of Fisher-Freeman-Halton Test	Corticosteroid Dose			χ^2
	Low	Intermediate	High	
Response to steroids				
Pain relief ≤72 h	1	5	2	1.5
Pain relief ≥72 h	1	1	2	$P = 0.14$
Palsy relief ≤72 h	0	1	0	1.1
Palsy relief ≥72 h	2	5	4	$P = 0.50$
Recurrence				
Yes	2	1	0	9.5
No	0	5	3	***P* = 0.03**

The *P* value in bold was set at 0.05.
"Low" dose refers to less than 0.5 mg/kg/day of prednisone or its equivalent, "intermediate" dose to 0.6 to 1.9 mg/kg/day prednisone or its equivalent, and "high" dose to more than 2 mg/kg/day.

The initial evaluation consists of a thorough examination and history, routine laboratory studies, and contrast-enhanced cranial MRI. In THS, the results of routine laboratory investigations are typically normal, with the exception of ESR and CRP which may be elevated.[29] When the MRI is normal or demonstrates changes consistent with cavernous sinus inflammation, CSF studies should be performed to exclude other possible causes of orbital inflammation, including central nervous system disease.[4]

Specific serologic studies such as antinuclear antibody and anti-dsDNA (lupus), angiotensin-converting enzyme (sarcoidosis), antineutrophil cytoplasmic antibody (Wegener granulomatosis), hemoglobin A_{1c} (diabetic ophthalmoplegia), *Borrelia burgdorferi* serology (Lyme disease), and HIV testing are recommended if the initial evaluation is unremarkable.[10,38] Surgical biopsy is rarely performed, and we suggest that this may not be warranted in many cases if careful observation and appropriate follow-up neuroimaging is performed. A systematic diagnostic approach to the child with painful ophthalmoplegia is proposed in Fig 3.

TABLE 4.
Differential Diagnosis of Painful Ophthalmoplegia

1. Infection
   - Bacterial (sinusitis, cellulitis, mastoiditis)
   - Viral (Herpes zoster, cytomegalovirus)
   - Fungal (mucormycosis)
   - Mycobacterial (tuberculosis)
2. Malignancy
   - Primary intracranial tumors
     - Chondroma
     - Meningioma
     - Neurofibroma
     - Pituitary adenoma
   - Local or distant metastases
     - Lymphoma
3. Trauma
4. Vascular
   - Carotid dissection
   - Cavernous thrombosis or fistula
   - Intracavernous carotid aneurysm
   - Wegener granulomatosis
5. Other
   - Diabetic ophthalmoplegia
   - Ophthalmoplegic migraine
   - Orbital pseudotumor
   - Sarcoidosis
   - Multiple sclerosis
   - Neuromyelitis optica
   - Tolosa–Hunt syndrome

TABLE 5.
Diagnostic Evaluation of Tolosa–Hunt Syndrome

1. Routine laboratory testing*
   - Complete blood count
   - Erythrocyte sedimentation rate
   - C-reactive protein
   - Glucose, hemoglobin A_{1c}
   - Electrolytes
   - Liver function tests
2. Serologic testing
   - Angiotensin-converting enzyme
   - Antinuclear antibody
   - Anti-dsDNA
   - Antimitochondrial antibody
   - Antineutrophil cytoplasmic antibody
   - *Borrelia burgdorferi* serology
   - HIV testing
3. Cerebrospinal fluid studies*
   - Cell count and differential
   - Cultures (bacterial, fungal, viral)
   - Glucose
   - Oligoclonal bands
   - Opening pressure
   - Protein
4. Neuroimaging
   - Cerebral angiography
   - Contrast-enhanced magnetic resonance imaging*
5. Biopsy (rarely performed)

* Represents testing that should always be performed in the initial evaluation.

Neuroradiological findings

Contrast MRI enhancement of the affected cavernous sinus that is isointense on T1 and isointense or hypointense on T2 is a typical finding in THS.[6] However, other conditions such as lymphoma, sarcoidosis, and meningioma can have similar findings, and the clinician must keep these in mind when interpreting MRI results.[2,5,39,40] Infrequently, the MRI can be normal in patients with THS.[9,12,33,38,41-43] In this study, MRI demonstrated cavernous sinus enhancement in all patients whose initial MRI was normal. Based on this observation, we suggest that it may be possible that visible lesions on MRI may take some time to develop and therefore a normal MRI should not preclude a diagnosis of THS. When the initial MRI is normal and the clinical suspicion remains high for this syndrome, repeated MRI evaluation is advisable.

In addition to cavernous contrast MRI enhancement, focal ICA narrowing can be seen in some cases (44% in this study).[2,10,44] Rarely, these changes may only be detectable on angiography despite a normal MRI.[44] Although this finding is not pathognomonic of THS and the diagnostic role of angiography in THS has not been established, angiographic findings may offer valuable diagnostic information in some cases, particularly when the MRI is normal.

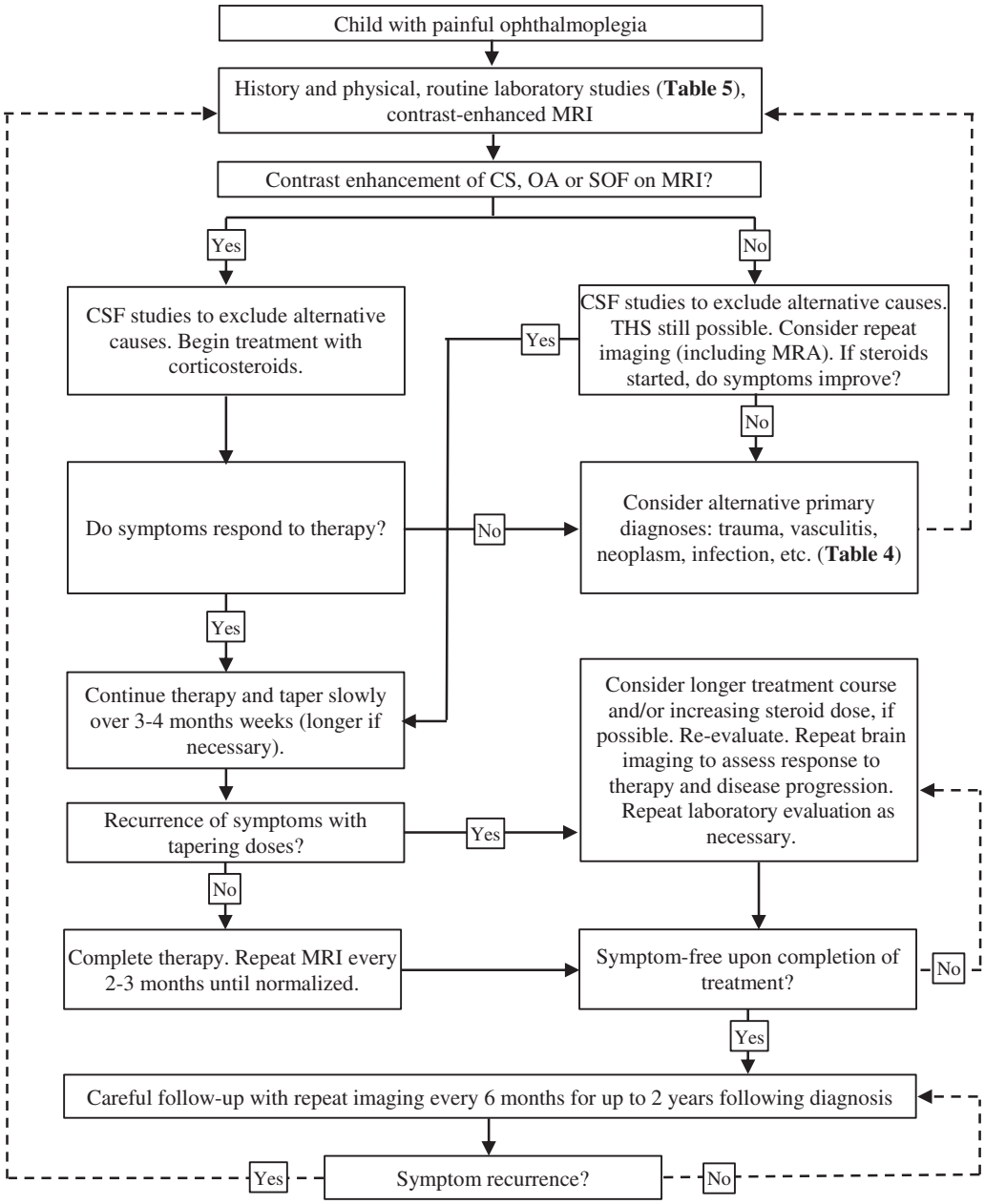

FIGURE 3.
Proposed diagnostic approach to painful ophthalmoplegia in children with suspected Tolosa–Hunt syndrome (THS). CNS, central nervous system; CS, cavernous sinus; CSF, cerebrospinal fluid; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; OA, orbital apex; SOF, superior orbital fissure.

Treatment and outcome

Significant orbital pain reduction after treatment with corticosteroids is a characteristic feature of THS.[13] The ophthalmoparesis typically resolves within weeks to months after the initiation of treatment, but spontaneous resolution can occur when untreated.[3,12,13,16,38,45] Neurological deficits may rarely persist.

In this study, the orbital pain resolved within 3 ± 2 days after the initiation of treatment. Resolution of cranial nerve palsies occurred later within 4 ± 1 weeks. Because recovery times of up to ten months have been previously reported,[13] the relatively fast response to therapy among patients in this series compared to the general population may lend support to previous claims that younger patients may show a better response to treatment and have a faster recovery compared to older patients.[13] Future studies are needed to confirm this possibility.

Relapses can occur in up to one half of reported cases of THS (19% in this study) in intervals of months to years and can be ipsilateral, contralateral, or bilateral.[18,28,38,46-48]

In this study, patients in the low-dose (<0.5 mL/kg/day of prednisone or the equivalent) steroid group had a higher recurrence rate compared to those in the intermediate- and

high-dose groups. Across all patients, corticosteroids were given for 3 ± 2 months on average, ranging from one week to two years. Regardless of dosing, shorter treatment courses (less than one month) and faster tapers (within one to two weeks) were also associated with higher recurrence rates and longer recovery times associated with longer treatment courses.

Based on these observations, a reasonable approach to therapy is initial treatment with intermediate-to-high dose steroids (~1 mg/kg/day) tapered slowly over three to four months or longer in cases of recurrence. The resolution of ocular pain is a good indicator that a slow taper can be initiated.[12,21,40]

If symptoms do not respond promptly to steroids or if their efficacy is lost after an initial response, more aggressive testing with repeated imaging, serologic evaluation, and lumbar puncture is recommended as these may be manifestations of an acute process necessitating proper evaluation and treatment.[24] In these cases, cerebral angiography can be considered.

Second-line treatments include focal radiotherapy,[49] methotrexate,[48] and infliximab,[50] but their clinical usefulness in children has not been established.

Follow-up

THS is generally a benign process with a relatively good prognosis for complete recovery. In this study, normalization of MRI findings occurred within 3 ± 1 months of treatment with one study reporting complete normalization of findings after two years. These observations support previous recommendations for follow-up MRI studies every three to six months after the initial diagnosis for up to two years to assess therapy response, follow disease progression, and consider alternative diagnoses in cases of nonresolution.[9,10,38]

Future directions

Painful ophthalmoplegia is caused by a large number of processes that exert a mass effect on the cavernous sinus, including infection. Although cytomegalovirus-related cavernous sinus inflammation has been reported,[37] the notion that infectious disease could represent a cause of THS has not been explored. In the patients we analyzed, painful ophthalmoplegia after infection was reported in three instances.[25,29,30] Another individual developed bacterial meningitis during treatment for THS.[24] Future studies are needed to understand the possible role of infection in the pathogenesis of this disease.

The 1988 International Headache Society diagnostic criteria for THS[51] were substantially revised in 2004[52] and in 2013.[7] In our opinion, ICHD criteria could benefit from further clarification in future revisions. Specific consideration can be given to extending the importance of follow-up MRI studies in patients whose initial MRI evaluation is normal, given that visible lesions on MRI may take some time to develop. Future revisions may also consider that THS symptoms are not strictly unilateral and that recurrences may be bilateral or contralateral.[6,8,28,46] Furthermore, the ocular pain does not always precede the development of ophthalmoplegia by ≤2 weeks, and it can occur simultaneously with it or precede it in some cases.

Limitations

The retrospective nature of this analysis significantly restricted our ability to gather specific data. Some studies provided limited details regarding recurrence, follow-up study results, specific corticosteroid dose, and treatment duration, which may have impacted our results. Strict application of current ICHD-3 beta diagnostic criteria could have led to the exclusion of true cases of pediatric THS, and the small sample size may not have been sufficient for adequate analysis and may not be an accurate representation of the entire population. The possible confounding role of disease severity and the effects of the drugs and doses used to treat each of the patients in our study may have also introduced bias by indication. Despite these limitations, our results are an important first step in understanding the pathophysiology, diagnosis, and management of THS in children and can serve as a guide for the design of future studies.

Conclusion

THS follows a similar course in children and adults. Although MRI plays a major role in the diagnosis of this disease, a normal MRI on initial evaluation does not preclude a diagnosis of THS. Appropriate follow-up imaging (including magnetic resonance angiography) can help establish the diagnosis in these individuals. Low-dose corticosteroids and short treatment courses may be insufficient to effectively manage the symptoms of THS and to help prevent future recurrences. A systematic diagnostic approach to the child with painful ophthalmoplegia is proposed. Painful ophthalmoplegia can signify a serious neurological emergency that requires extensive evaluation to elucidate potentially serious etiologies. A key to avoiding unnecessary testing and prolonged hospitalizations is prompt recognition of symptoms and timely initiation of treatment.

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