

Unilateral orbital pain, ptosis and binocular diplopia in three patients: case reports and review

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Abstract

This report aimed to evaluate the clinical presentation, diagnosis and management of 3 Chinese patients with Tolosa-Hunt syndrome by reviewing a non-comparative, retrospective case series. Three patients (age range, 31-60 years) with Tolosa-Hunt syndrome seen at Caritas Medical Centre, Hong Kong from January 2012 to May 2014 are reported. They presented with symptoms of unilateral orbital pain, ptosis and binocular diplopia, and subsequently developed various presentations including facial hypoesthesia, facial weakness, proptosis, and pupil-involving third, fourth, fifth, sixth or seventh nerve palsies. All patients responded to systemic steroid therapy while one developed relapse when oral steroid therapy was tapered. Tolosa-Hunt syndrome is a rare clinical condition in Chinese with various presentations. Clinical suspicion with comprehensive patient evaluation is essential to establish the correct diagnosis. Treatment should be individualized and tapered according to clinical response.

more cranial nerves (usually the third, fourth or sixth cranial nerve). The efficacy of oral steroid treatment has been reported.⁷ Tolosa-Hunt syndrome is a relatively uncommon condition and should be differentiated from thyroid eye disease, infection, malignancy and surgical causes of painful ophthalmoplegia.⁸⁻¹⁰

We report on 3 patients with Tolosa-Hunt syndrome who presented to the Caritas Medical Centre, Hong Kong from January 2012 to June 2014. All patients presented with ophthalmoplegia that improved following administration of oral steroid although 1 patient experienced disease relapse while tapering off his steroids.

Case reports

Case 1

A 49-year-old woman with good past health presented in May 2014 with a 3-month history of episodic right-sided orbital pain, ptosis and binocular diplopia. On clinical examination, her vital signs were stable. Best-corrected visual acuity of the right eye was 6/12 and that of the left eye was 6/7.5. There was anisocoria and the right pupil was mid-dilated but responsive to light. Left pupillary reaction was normal. There was no relative afferent pupillary defect. She had a right-sided ptosis (**Figure 1a**) and impairment of elevation, depression and abduction, consistent with a third and sixth cranial nerve palsy. No facial or motor loss was noted in the distribution of the trigeminal nerve. Hertel's exophthalmometer reading revealed no proptosis. Intraocular pressure was normal in both eyes and fundoscopic examination was also normal.

Blood workup including complete blood count, liver and renal function tests, thyroid function test, C-reactive protein

Key words: Ophthalmoplegia; Tolosa-Hunt syndrome

Introduction

Tolosa-Hunt syndrome is a disease that results from a cryptogenic granulomatous lesion within the cavernous sinus or superior oblique fissure of the orbit.¹⁻⁶ It has been documented as episodic orbital pain with paralysis of 1 or

and venereal disease research laboratory (VDRL) test were normal. The patient was referred for an urgent non-contrast computed tomography (CT) of the brain and no significant abnormality was detected. Magnetic resonance imaging (MRI) of the brain and orbit with contrast showed an enhancing lesion at the right cavernous sinus causing lateral and superior bulging of the right cavernous sinus wall extending to the ophthalmic fissure and orbital apex (**Figure 1b**). Magnetic resonance angiogram (MRA) showed an absence of stenosis or aneurysm in the Circle of Willis.

The patient was treated with oral steroids and showed significant relief of orbital pain within 72 hours. The patient was prescribed oral prednisolone 60 mg daily (1 mg oral prednisolone per kg body weight). The dose of oral steroid was gradually tapered (60 mg for 1 week, 50 mg for 1 week, 40 mg for 1 week, 30 mg for 1 week, 25 mg for 1 week, 20 mg for 3 weeks and 15 mg for 2 weeks, followed by a maintenance dose of 10 mg). The patient had no systemic side-effects from oral steroids. The treatment duration was 6 months in total. MRI of the brain and orbit with contrast performed 4 months after steroid treatment revealed a reduction in size of the infiltrative lesion in the right cavernous sinus (**Figure 1c**). The visual acuity of the right eye improved to 6/6. There was also complete resolution of the ophthalmoplegia and ptosis (**Figure 1d**). There was no relapse of the disease 6 months after stopping oral steroids.

Case 2

A 31-year-old man was evaluated for left-sided orbital pain, left eye partial ptosis, left facial hypoesthesia and weakness for 3 weeks in March 2014. His medical history was unremarkable. Visual acuity was 6/6 for both eyes. Both pupils were equal, round and reactive to light, and intraocular pressure was normal. Extraocular movement revealed impairment of left eye abduction and adduction. Fundus examination was normal. There was no proptosis on Hertel's exophthalmometer examination. He had hypoesthesia in the ophthalmic and maxillary distributions of the left trigeminal nerve. There was weakness in both the left upper and lower face. Clinical findings were consistent with partial left third, fifth (first and second branch), sixth and lower motor neuron seventh cranial nerve palsy.

Complete blood count, liver and renal function tests, thyroid-stimulating hormone, glucose, erythrocyte sedimentation rate, rheumatoid factor, antinuclear antigen, anti-acetylcholine receptor antibodies and VDRL test results were normal. A non-contrast CT brain and orbit showed enlargement of the left cavernous sinus, left superior ophthalmic vein and left sphenoid sinus. MRA confirmed no abnormal high-flow signal over the left cavernous sinus or left ophthalmic vein. MRI brain and orbit with contrast showed an extensive enhancing soft tissue infiltration at the left parasellar region with involvement of the left cavernous sinus (**Figure 2a**). The left parasellar infiltration extended laterally along the anterior aspect of the petrous apex with involvement of the left geniculate ganglion and distal left internal auditory canal. This could have accounted for the facial nerve palsy. It also

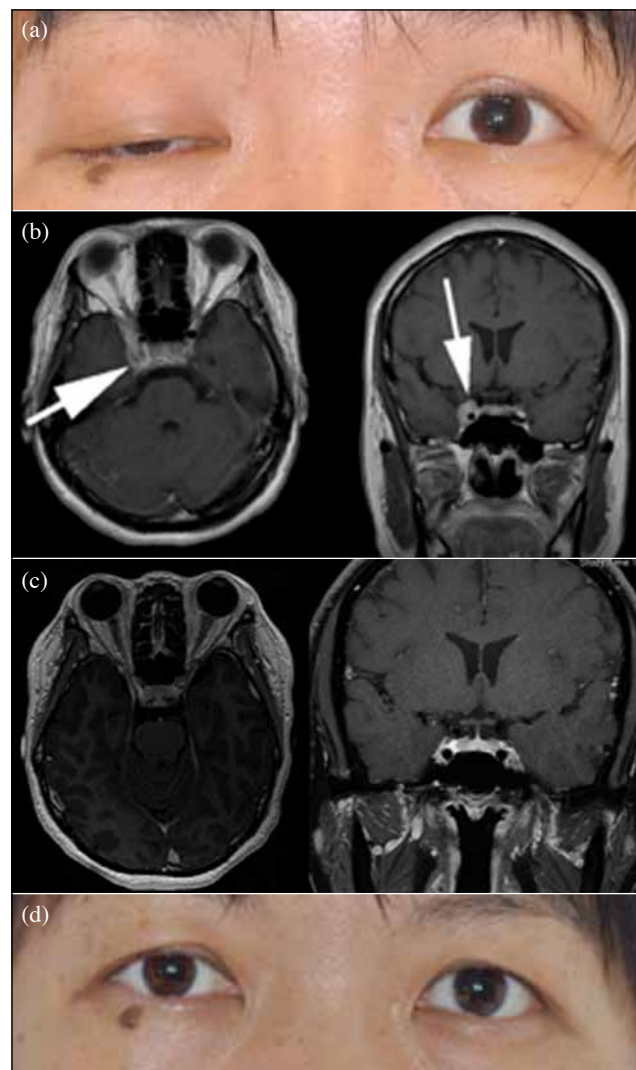


Figure 1. Patient 1: (a) Clinical photo at initial presentation. Magnetic resonance imaging of the brain and orbit with contrast showing (b) an enhancing lesion at the right cavernous sinus (arrows) and (c) the right cavernous sinus infiltrative lesion has decreased in size after oral steroid treatment. (d) Clinical photo taken after oral steroid treatment for 6 months.

extended posteriorly along the left-sided tentorial edge and inferiorly down to the left foramen ovale.

The patient was prescribed oral prednisolone, with a gradual tapered dose (60 mg daily for 1 week, 50 mg daily for 1 week, 40 mg for 2 weeks, 30 mg for 2 weeks, 20 mg for 2 weeks and then 10 mg for 16 weeks). The duration of steroid treatment was 6 months. There were no systemic side-effects from oral steroid therapy. A subsequent contrast MRI performed 2 months after the initial MRI showed no focal brain lesion and the previous left parasellar mass was no longer present, compatible with resolution of the inflammation (**Figure 2b**). The diplopia and numbness over of the distribution of the first branch of the trigeminal nerve had resolved with mild ptosis over the left side. Follow-up at 6 months after stopping oral steroids showed no recurrence of symptoms.

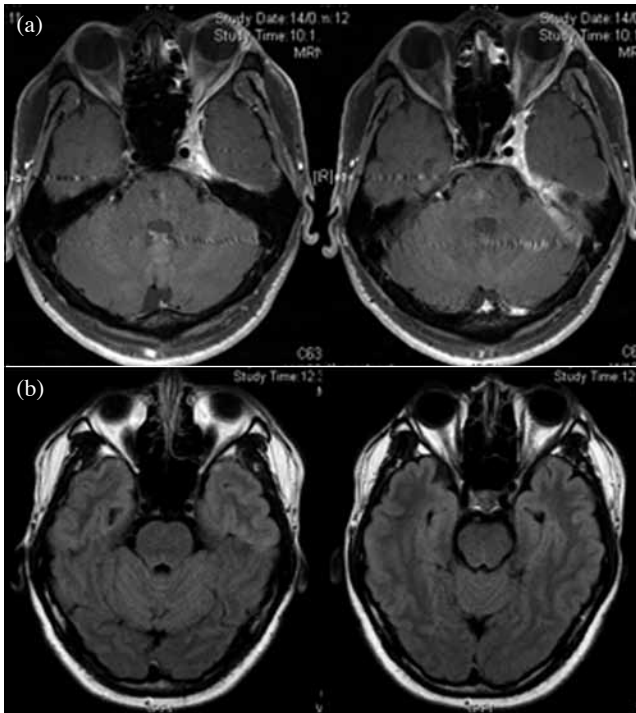


Figure 2. Patient 2: Magnetic resonance imaging of the brain and orbit with contrast showing (a) extensive soft tissue infiltration at the left parasellar region with involvement of left cavernous sinus, and (b) after treatment, absence of the previous parasellar mass, compatible with resolution of inflammation.

Case 3

A 60-year-old man presented with a 2-week history of right orbital pain, ptosis and binocular diplopia in January 2012. He had a history of systemic hypertension and obstructive sleep apnea. On clinical examination, his vital signs were stable. Best-corrected visual acuity of both eyes was 6/8.5. External examination revealed right proptosis measuring 20 mm and 17 mm over the right and left eye, respectively with the Hertel’s exophthalmometer. Both pupils were equal with no anisocoria and reactive to light. No relative afferent pupillary defect was detected. Ophthalmological examination revealed limited extraocular movement in all gazes over the right eye, Parks-Bielschowsky 3-step test was positive, compatible with a partial third, fourth and sixth cranial nerve palsy. Intraocular pressure was normal in both eyes as was fundoscopic examination with no optic disc edema or pallor.

Laboratory evaluation including complete blood count, liver and renal function tests, thyroid-stimulating hormone, glucose, erythrocyte sedimentation rate, anti-acetylcholine receptor antibodies, rheumatoid factor, antinuclear antigen, and VDRL test were unremarkable. CT brain and orbit with contrast showed abnormal contrast enhancing soft tissue thickening at the anterior aspect of the right cavernous sinus extending to the right superior orbital fissure and orbital apex. MRI brain with contrast demonstrated an enhancing lesion at the medial aspect of the right temporal fossa immediately anterior to the right cavernous sinus (**Figure**

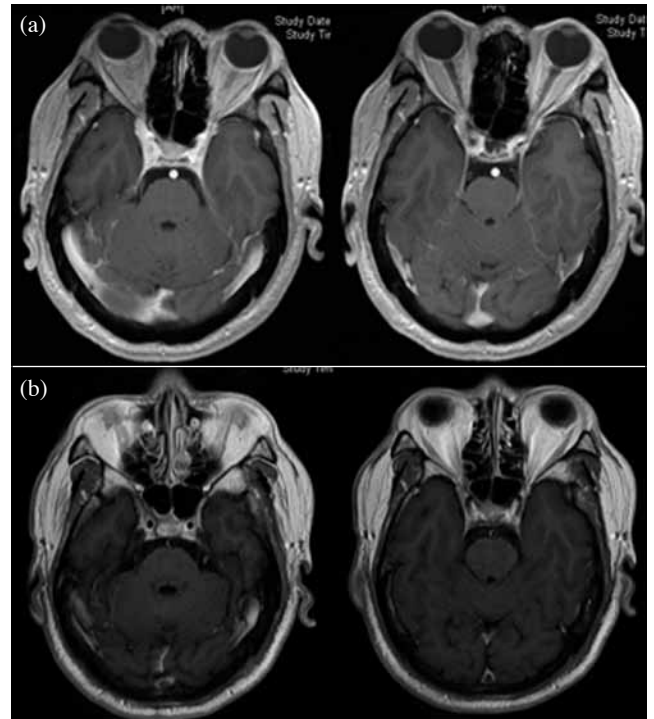


Figure 3. Patient 3: Magnetic resonance imaging of the brain and orbit with contrast demonstrating (a) an enhancing lesion in the medial aspect of the right temporal fossa immediately anterior to the right cavernous sinus, and (b) a mild increase in soft tissue at the right orbital apex and right cavernous sinus 6 months after initial presentation.

3a). The lesion was abutting the right optic nerve at the orbital apex. The clinical and radiological features were compatible with Tolosa-Hunt syndrome. MRA of the Circle of Willis showed no significant stenosis or aneurysm.

The patient was prescribed oral steroids (prednisolone 60 mg for 2 weeks, 50 mg for 1 week, 40 mg for 1 week, 20 mg for 1 week, 10 mg for 1 week, and then 8.5 mg as maintenance dose). Six weeks after treatment, the ptosis resolved completely with only mild residual proptosis and mild limitation of right eye elevation.

Six months after initial presentation while the patient was still on a maintenance prednisolone dose of 8.5 mg daily, there was a relapse. The patient presented with right-sided complete sixth nerve palsy. Repeat MRI of brain and contrast showed mild increase in soft tissue noted at the right orbital apex and right cavernous sinus (**Figure 3b**). The lesion was radiologically less active as suggested by T2 and post-contrast images. He was treated as a relapse of Tolosa-Hunt syndrome and oral prednisolone dose was increased to 40 mg daily. Steroids were continued for a further 22 months and slowly tapered (40 mg for 4 weeks, 30 mg for 2 weeks, 25 mg for 2 weeks, 20 mg for 2 weeks, 15 mg for 3 weeks, 12.5 mg for 6 weeks, 10 mg for 6 weeks, 7.5 mg for 8 weeks, 5 mg for 8 weeks, 4 mg for 8 weeks, 3 mg for 8 weeks, 2 mg for 16 weeks and 1 mg for 16 weeks). The patient experienced no systemic side-effects from the oral steroids. The ophthalmoplegia and ptosis resolved at the end

of treatment. He continues to be monitored and showed no relapse at his last clinical visit, 12 months after stopping the oral steroids.

Discussion

Tolosa-Hunt syndrome is inflammation within the cavernous sinus and was first described by Hunt et al in 1961.² The diagnostic criteria of Tolosa-Hunt syndrome are summarized in **Table 1**; all criteria shall be fulfilled before a diagnosis is made.^{11,12} Tolosa-Hunt syndrome is usually unilateral with no predisposition for the right or left cavernous sinus and is bilateral in 4.1% to 5.0% of cases.^{13,14} The diagnosis of Tolosa-Hunt syndrome is made after exclusion of other pathologies. Many clinical conditions can mimic Tolosa-Hunt syndrome, including neoplasm, infections or vascular conditions such as aneurysms. In our case series, the diagnosis was based on clinical presentation, radiological imaging and laboratory investigations to exclude pathologies with similar presentations. The etiology of Tolosa-Hunt syndrome is not well understood and a literature search failed to find any known systemic associations. Smith and Taxdal¹⁵ described the use of oral steroids as a diagnostic trial, suggesting that inflammation within the cavernous sinus was the probable cause.

The demographic distribution of Tolosa-Hunt ranges from 3 to 80 years of age with males and females equally affected.¹⁶ The median age of our patients was 49 years (range, 31-60 years). All 3 patients presented with unilateral orbital pain, ptosis and binocular diplopia. All had neurological

symptoms and signs. The clinical findings and treatment outcome in our 3 patients are summarized in **Table 2**. Frequently, involvement of cranial nerves may be with one nerve or a combination. Palsies of the third, fourth, fifth (first and second divisions) or sixth cranial nerves are typical. The facial nerve does not run through the cavernous sinus region but is reported to be involved in Tolosa-Hunt syndrome.¹⁴ Involvement of the facial nerve, however, has not been clearly demonstrated in neuroimaging of most cases.¹⁴ One case of Tolosa-Hunt syndrome with facial nerve palsy has been reported in the literature with simultaneous enhancement of the cavernous sinus and facial nerve on contrast-enhanced MRI.¹⁷ It was suggested that localized inflammation arising distant from the cavernous sinus via a systemic route was more likely than direct extension of the inflammatory process.¹⁸ In contrast, our second patient with facial nerve involvement had MRI scans performed that confirmed extension of soft tissue swelling along the anterior aspect of the petrous apex with involvement of lateral geniculate ganglion, which anatomically explains the facial nerve palsy.

Proptosis may be noted in 20% of patients with Tolosa-Hunt syndrome.¹⁶ One of our patients had proptosis at initial presentation. The pupil is involved in about one quarter of Tolosa-Hunt syndrome cases.¹⁹ Involvement of the parasympathetic constrictor fibers of the third cranial nerve and the sympathetic dilator fibers in the pericarotid plexus may be the contributing cause.⁷ The lesion of Tolosa-Hunt syndrome is usually located at the lateral wall of the cavernous sinus.²⁰ This explains the presence of pupil-involving third

1	One or more episodes of unilateral orbital pain persisting for weeks if untreated
2	Paresis of one or more of the third, fourth and/or sixth cranial nerves and/or demonstration of granulomas by magnetic resonance imaging or biopsy
3	Paresis coincides with the onset of pain or follows it within 2 weeks
4	Pain and paresis resolve within 72 hours when treated adequately with corticosteroids
5	Other causes have been excluded by appropriate investigations

	Patient No.		
	1	2	3
Clinical findings			
Sex	F	M	M
Age (years)	49	31	60
Laterality	Right	Left	Right
Presenting visual acuity	6/12	6/6	6/8.5
Symptoms	Orbital pain, ptosis, diplopia	Orbital ptosis, ptosis, facial hypoesthesia, weakness	Orbital pain, ptosis, diplopia
Cranial nerve involvement	3rd, 6th	Partial 3rd, 4th, 5th (1st and 2nd branch), 6th, LMN 7th	Partial 3rd, 4th, 6th
Pupil involved	Yes	No	No
Proptosis	No	No	Yes
Treatment/outcome			
Response to steroid	Yes	Yes	Yes
Relapse	No	No	Yes
Duration of treatment (months)	6	6	28
Visual acuity (after treatment)	6/6	6/6	6/8.5

Abbreviation: LMN = lower motor neuron.

nerve palsy in some patients, as in our last case.

Intracranial aneurysms arise from the intracavernous carotid, posterior communicating or basilar artery, and may also present as orbital pain and ophthalmoplegia. As no clinical features are pathognomonic for Tolosa-Hunt syndrome, MRI and MRA play an important role in establishing the diagnosis. MRA is very sensitive for the detection of aneurysms larger than 5 mm.²¹ The 3 patients in our series showed corresponding enhancing lesions within the orbital apex on contrast MRI brain but all had normal MRA. Our findings are consistent with literature reports of neuroimaging in Tolosa-Hunt syndrome that classically shows an intermediate signal on T1-weighted MRI imaging that enhances with contrast.^{3,6,22,23} In addition to diagnosis, MRI is also useful to monitor progression of the disease and to document the reduction in size of the inflammation following oral corticosteroid therapy.²⁴ In our case series, repeated MRI scans in 2 patients showed a reduction in lesion size.

Treatment includes oral steroids in most cases. Tolosa-Hunt syndrome usually responds promptly to steroid therapy within 48 hours,⁷ although spontaneous resolution without treatment may occur within 8 weeks.²⁰ Regular follow-up

is essential even for patients who show a clinical response to steroids as the disease may follow an unpredictable clinical course. Some patients can have steroids tapered off without recurrence. Others can have flare up of the disease when steroids are tapered or can have late recurrence.²⁰ Our last patient demonstrated an initial response to steroid therapy but had a relapse after tapering of steroids. A long and slow tapering was adopted to prevent further relapse of his disease. It is essential for the treatment regimen to be individualized and titrated according to clinical response.

Although Tolosa-Hunt syndrome is not a common ophthalmological disease, its presentation can be quite debilitating for patients although the response to systemic steroid treatment is often rewarding. Thus, a high index of clinical suspicion, appropriate imaging and laboratory investigations are essential to making the correct diagnosis and starting treatment promptly.

Declaration

The authors declare no financial or proprietary interests and patient consent was obtained for the use of clinical photographs for the purpose of research publication.

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