Case Report

Disappearing diplopia - An unusual presentation of Tolosa-Hunt syndrome: A case report

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Abstract

Tolosa-Hunt syndrome (THS) is a rare benign treatable cause of painful ophthalmoplegia with frequent VI, III, IV cranial nerve (CN) involvement. Optic and trigeminal nerve involvement is rare but described. The disease is characterized by severe preceding or concomitant headache and remarkable response to steroids. Although labelled benign residual neurology is not uncommon in THS.

We present a case of THS in a middle-aged Sri Lankan male who presented initially with vertical diplopia and normal contrast enhanced CT scan, treated as for idiopathic IV nerve palsy. A month henceforth he developed severe episodic headache with autonomic symptoms, right sided ptosis and progressive visual impairment with improved diplopia, normal fundoscopy, inflammatory and infective markers and autoimmune profile. MRI brain showed enhancing lesion of cavernous sinus extending to orbital apex consistent with THS. He showed dramatic improvement with steroids with complete resolution of neurology at the end of 4 weeks.

THS should be considered in a patient presenting with disappearing painful diplopia. Headache may mimic primary headache syndromes and may not precede ophthalmoplegia. Imaging may be initially normal. MRI is mandatory for diagnosis as histology is not always feasible. Steroid responsiveness can be diagnostic if more sinister differentials are ruled out.

Keywords: Tolosa-Hunt syndrome, Painful ophthalmoplegia, Vertical diplopia, Steroid-responsive, Visual loss

Funding: None
Competing interest: None
Received: 02.04.2023 **Accepted revised version:** 23.08.2023 **Published:** 31.12.2023

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Cite this article as: Nasim F *et al,* Disappearing Diplopia; An unusual presentation of Tolosa-Hunt syndrome; a case report. Anuradhapura Medical Journal 2023; 17 (3): 58-63, DOI: http://doi.org/10.4038/amj.v17i3.7764

Introduction

Tolosa-Hunt syndrome (THS) is a rare idiopathic inflammatory granulomatous disease characterized by unilateral painful ophthalmoplegia. The disease involves the cavernous sinus and may even extend to the superior orbital fissure and orbital apex[1–3]. The disease is listed as a rare entity in National Organization for Rare Disorders with an incidence of 1-2 cases per million [1,3,4].

Patients can present with unilateral retro-orbital pain with ipsilateral ocular palsy. They may have sensory impairment of face along the distribution of ophthalmic or infrequently maxillary division of trigeminal nerve.

Visual impairment although sparce can still occur and can range from mild reduction of visual acuity to blindness. Optic disc is usually normal. Nevertheless, disc edema and pallor has been reported in a setting of optic neuritis [3,5]. A similar presentation to THS can be seen with lesions in the cavernous sinus such as intra-cavernous aneurysms, parasellar meningiomas, cavernous sinus thrombosis and invasive base of the skull tumors. Similarly, conditions causing granulomatous inflammation such as tuberculosis, syphilis and sarcoidosis are also part of the differentials [2]. THS has also been reported in association with fungal infections such as actinomyces [2].

Diagnosis is largely one of exclusion. Diagnostic criteria are described in international Classification of Headache Disorders (ICHD 3-beta), that includes granulomatous inflammation of cavernous sinus, superior orbital fissure or orbital apex demonstrated by MRI or biopsy, paresis of one or more of third, fourth or sixth nerve, associated headache and exclusion of other causes. Steroid responsiveness is remarkable and may aid in a diagnosis [1].

We report a case of painful diplopia with unilateral headache suggestive of primary headache syndrome that later progressed to visual impairment with resolving diplopia. Brain imaging was initially normal but was later consistent with THS. The remarkable recovery with steroids reinforced the diagnosis.

Case report

A 48-year-old teacher from a village in central province of Sri Lanka presented to our unit with painful binocular vertical diplopia worsening towards left downward gaze with right sided ptosis. There was no diurnal variation of the drooping or diplopia. The patient did not complain of red, gritty eyes or discharges. He had no proptosis, chemosis or facial paraesthesia at the time but complained of recurrent throbbing retro-orbital pain radiating to temporal scalp worsening with eye movements. One episode lasted nearly 15-20 seconds and responded to paracetamol. On examination he had right sided partial ptosis with equally reactive pupils but no demonstrable ophthalmoplegia. Contrast CT brain was normal other than for bilateral maxillary sinus thickening. His EMG was not suggestive of myasthenia gravis, blood sugar, inflammatory markers, and other biochemical markers were normal. A clinical diagnosis of idiopathic trochlear neuropathy was made. Patient was discharged with advice on fusion exercises and treatment for sinusitis and planned for review.

In the subsequent two months he developed a severe headache and retro-orbital pain associated with autonomic symptoms of rhinorrhoea, nasal congestion and right sided red eye that occurred in clusters. There was gradual right sided visual blurring with an improvement of diplopia during the next six weeks. Patient did not complain of floaters flashes or any positive visual symptoms but noticed right sided forehead numbness within the same period. The headache was suggestive of a trigeminal autonomic cephalgia (TAC) thus an indomethacin trial was implemented without success.

At the second consultation two months after, the patient did not complain of fever, joint symptoms, rash, or sinus symptoms. Neither did he complaint of early morning headache that exacerbated on cough or straining. He did not have any other focal neurology. There was no aura, jaw claudication, limb girdle pain or stiffness. No personal or family history of diabetes or other neurological disease recorded.

Examination revealed right sided partial ptosis (Figure 1) and reduced visual acuity with perception of light and movement alone. Right sided relative afferent pupillary defect was detected. Visual fields were constricted on the right with a lower quadrant predominant central scotoma. Sensory loss over the right V1 distribution was noted. Neurological examination was otherwise unremarkable. Slit lamp examination and intraocular pressures were normal.

His basic investigations including full blood count, renal and liver profile, electrolytes with serum calcium and phosphate were normal. Inflammatory markers including ESR, CRP and procalcitonin were not significantly elevated. Lab values of blood tests are illustrated in table 1. Chest Xray was unremarkable.

CSF showed WBC 7/cumm (Lymphocytes 100%), RBC: 8/cum, protein 33.70mg/dl and CSF sugar 4.5mmol/L (Blood sugar: 5.5mmol/L) with normal CSF pressure. CSF for TB and fungal studies proved negative. EMG showed no evidence of neuromuscular disorder. ANCAs and ANA were negative. CXR was normal with normal ACE levels. Ultrasound abdomen did not show any organomegaly, lymphadenopathy or intraabdominal masses.

Table 1: Summary of laboratory investigations

Test	Result	Reference
Complete blood count		
Leucocyte count	$6.53\times10^3/\mu L$	$4\text{-}10\times10^3/\mu L$
Hemoglobin	12.5g/dL	11-16g/dL
Platelet count	$202\times10^3/\mu L$	150-450×103/µL
MCV(meancorpucular volume	89.5fl	80-100 fl
Differential WBC count		
Neutrophils	$3.64\times 10^3/\mu L$	150-250×103/µL
Lymphocytes	2.45×10^3 / µL	0.8-4 × 103/µL
Eosinophils	$0.08\times 10^3/\mu L$	0.02-0.5× 103/µL
Inflammatory markers		
ESR (erythrocyte sedementation rate)	35mm/1st hour	10mm/1st hour
CRP (c-reactive protein)	15mg/L	<10mg/L
Serum creatinine	69.9µmol/L	53-97µmol/l
Serum sodium	141mmol/L	135-147mmol/L
Serum pottasium	4mmol/L	3.5-5.2 mEq/L
AST (aspartate transaminase)	17.9U/L	<31U/L
ALT (alanine transaminase)	13 U/L	<34U/L
ALP (alkaline phosphatase)	77.5U/L	30-120U/L
GGT (gamma-glutamyl transferase)	43.1U/L	<32U/L
Total Bilirubin	9.22µmol/L	5-19µmol/L
Total protein	6.6g/dL	6.6-8.3g/dL
Albumin	4g/dL	3.5-5.3g/dL
Serum Calcium	2.2mmol/L	2.10-2.55 mmol/L
Serum Phosphate	1.09mmol/L	0.81-1.45mmol/L

Contrast CT at second admission detected a small soft tissue density contrast enhancing lesion at the right sided orbital apex, adjacent to the optic canal with thickening of the intra-canalicular segment of the optic nerve (Figure 2).

MRI brain revealed Inflammatory /infective lesion involving the right cavernous sinus, superior orbital fissure, orbital apex, and the optic nerve compatible with THS. Lacrimal glands were normal and there was no hypo or hyperintense lesions or meningeal thickening noted (Figure 3).

It was challenging to rule out a possible fungal infection or granulomatous inflammation as expertise for orbital biopsy was unavailable at our facility. The use of steroids would be therapeutic for THS, while being detrimental for fungal infection. Nevertheless, a decision for a steroid trial was taken after much contemplation.

The diagnosis of THS was made with clinical features and compatible MRI. Confirmation was ascertained with rapid and drastic improvement in symptoms with steroids (oral prednisolone 60mg/d).

Patient's headache disappeared within a day. His vision improved drastically which initially manifested as reappearance of diplopia. His vision gradually normalized and diplopia improved in four weeks. The steroids were tapered over 8 weeks with no recurrence of symptoms.

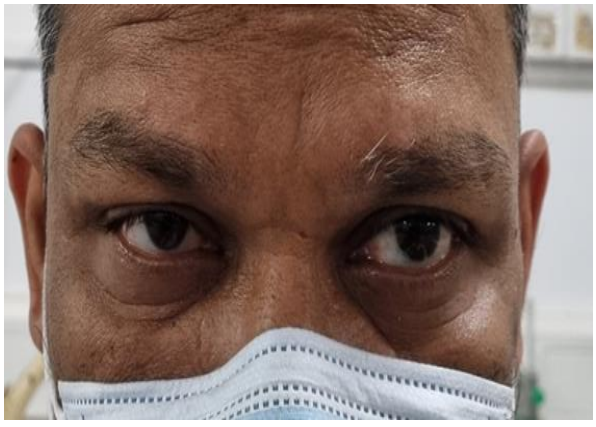

Figure 1: Right sided subtle partial ptosis.

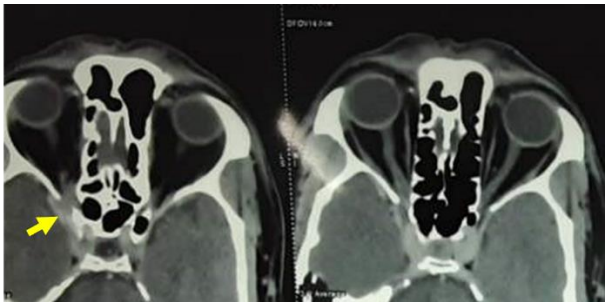

Figure 2: Contrast CT brain showing evidence of contrast enhancing soft tissue density lesion in orbital apex shown by arrow.

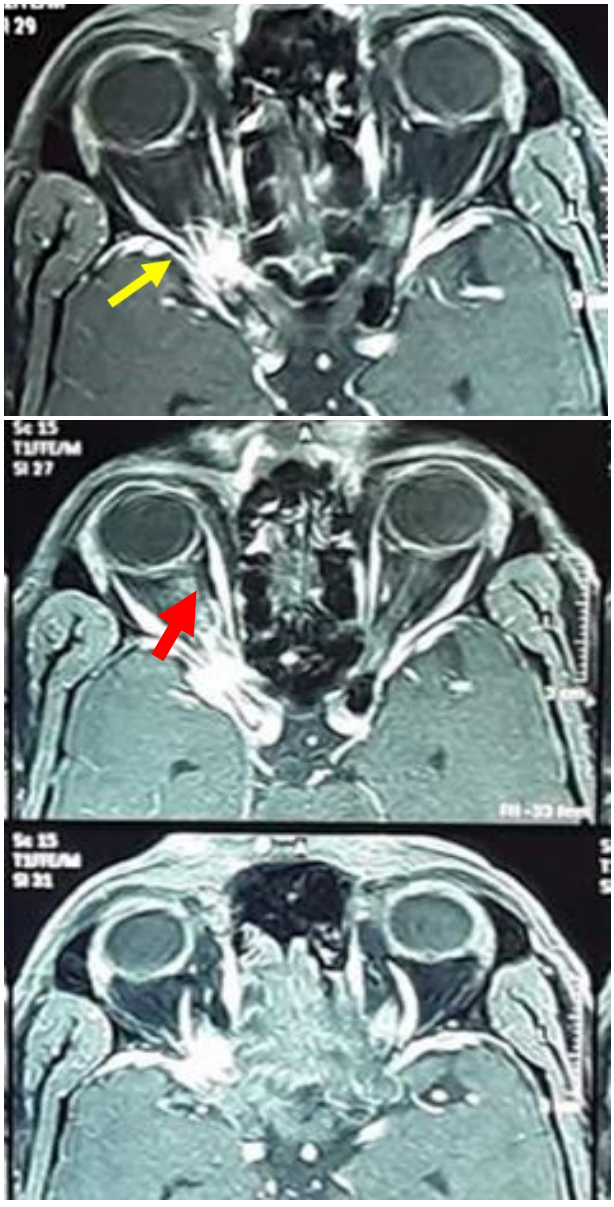

Figure 3: MRI brain: Yellow arrow indicating asymmetrical contrast enhancement on right sided anterior cavernous sinus extending into the anterior orbital apex and superior orbital fissure. Note the ill-defined enhancement of retro-orbital fat shown with the red arrow. Intracanalicular segment of optic nerve is thickened and enhancing.

Discussion

This case is a representation of THS, first presenting with isolated trochlear nerve palsy with minimal ophthalmoplegia. Involvement of optic nerve which in itself rare, was perceived as disappearance of diplopia that occurred later with a unilateral headache that resembled a primary headache syndrome. The case is a demonstration of atypical late onset headache and negative imaging early in the course of the disease in a patient with THS. With previous imaging features of sinusitis, exclusion of a fungal infections was thought to be necessary, nevertheless orbital biopsy was not feasible and a decision on steroids were taken with positive responsiveness that reinforced the diagnosis.

THS was first described by Tolosa in 1954 in a patient with recurrent painful ophthalmoplegia involving cranial nerves (CN) III, IV, VI and V1. Years later in 1961 Hunt et al described a similar presentation in six more individuals[1,2].The syndrome was named Tolosa Hunt syndrome since 1966[1]. The case presentation seems to vary. While some studies have demonstrated frequent involvement of the III (78-91%) cranial nerve a study done by Kim et al. 2021 demonstrated a more frequent involvement of the VI cranial nerve (72.73%) whilst cranial nerves III and IV were at 45.45% each[3]. Optic and trigeminal involvement were very infrequent in this study. Nevertheless, these numbers do not seem to be universal, with diverse epidemiological data from numerous studies[3]. Our patient had IV CN nerve involvement at the initial presentation, with very subtle ophthalmoplegia not obvious on examination. The unilateral headache which was considered insignificant at the time was attributed to sinusitis demonstrated in CT. This headache was unbearable by the time he presented next along with new onset visual loss of right eye. Interestingly his diplopia improved with worsening visual impairment. Fundoscopy being normal, presentation was like that of retrobulbar optic neuritis where the patient and physician both see nothing.

Optic nerve involvement in THS is uncommon[5,6]. This is an indication of orbital apex involvement. There

have been cases of permanent visual impairment despite the benign nature of the disease [3,5].

Our patient's initial contrast CT being normal, he was discharged with a diagnosis of idiopathic IV nerve palsy. Although Gadolinium enhanced contrast MRI is the imaging modality of choice [1,6], it is considered less specific in the context of THS [1]. We are unable to say if an MRI would have shown evidence of inflammation if done at first presentation. However, at second presentation both MRI and CT scans were positive with MRI showing characteristic features of THS. Typically, MRI in THS shows thickening of CS which is isointense on T1, Iso or hypointense on T2 with contrast enhancement[7]. Abnormally enlarged and enhanced CS with extension into the superior orbital fissure and the apex may also be seen[5,7]. Although not commonly recommended, a paper by Kwan E et al, 1987 describes the use of high-resolution CT (HRCT) in the diagnosis of THS [8]. Similarly, the role of CT has been described in other papers, but the recommendation is to proceed to MRI in case of negative CT[5]. HRCT may lack sensitivity to soft tissue changes with superimposed beam hardening and bone streak artifacts compared to MRI (5) but may still show soft tissue changes in the area of CS/SOF. Thus, is useful in a resource poor setting such as ours, especially when MRI may take time. Cases with negative MRI are also described in literature [8]. As such our case is a demonstration of possible negative imaging especially in [3]the early course of the disease.

Our patient's headache was not intractable until a month after the onset of diplopia. This is unusual for a case of THS where the headache precedes or occurs concomitantly with ophthalmoplegia[3]. Furthermore, our initial impression of the headache was of a primary headache syndrome such as TAC (Trigeminal autonomic cephalgia), paroxysmal hemicrania or cluster headache which led to a trial of indomethacin without benefit. The headache of THS is described in literature as intense, severe, boring, lancinating or stabbing, usually periorbital later extending to retro-orbital frontal and temporal regions [5]. There have been cases where THS had been treated as for sinusitis or cluster headache[4].

As the patient's initial CT was suggestive of sinusitis the exclusion of fungal sinusitis was necessary prior to the commencement of steroids. His inflammatory markers were normal and was otherwise hemodynamically stable. His did not have any evidence of immunosuppression. Following negative fungal studies in CSF, the option of orbital apex biopsy was contemplated. Due to the complex nature of the procedure and the unavailability of this high-risk procedure at our facility and the possibility of fungal granulomatous inflammation being remote, it was justifiable to start a steroid trial to confirm diagnosis. The patient did not deteriorate and the rapid recovery with steroids was instrumental in making a definitive diagnosis.

Biopsy in the context of THS although useful is rarely recommended in literature[5]. Rapid resolution of symptoms within 1-3 days of steroid administration can also be used in the diagnosis [1,2]. We were unable perform biopsy in our patient, but this has been the case in many reported cases [9]. In case of a fungal infection steroids could be detrimental and a biopsy may be beneficial.

Headache resolution is usually very rapid in THS, typically within 48 to 72 hours, although ophthalmoplegia may take longer to resolve on average close to 26 days [4,10]. Our patient's headache resolved within 12 hours and visual impairment started improving within the same time. His diplopia returned within 12 hours and completely resolved within 4 weeks.

THS is considered a benign disease with considerable morbidity. Before the era of steroid therapy spontaneous remission was also known to occur[5]. Residual CN palsies are seen infrequently. Steroids may have a place in altering the natural course of the disease, although conclusive evidence of the exact effect is unavailable [5]. Some cases have used intravenous methyl prednisolone in patients whereas others have preferred oral high dose steroids[9]. We commenced our patient on oral prednisolone and the patient achieved complete clinical resolution. Follow up of these patients is important as neoplasms can have a positive response to steroids initially but may recur subsequently[5,6]

Conclusion

THS can present as diplopia without ophthalmoplegia. Although uncommon visual impairment due to optic nerve involvement is a sinister symptom that can manifest as disappearance of diplopia. Headache may mimic primary headache syndromes with autonomic symptoms and may not always be present at outset. Imaging may be normal at the onset of symptoms thus cause further confusion with primary headache syndromes, as such may be repeated if clinically implicated. Biopsy can be diagnostic but not freely available as such is not always recommended. Steroid

responsiveness can be used to establish a diagnosis after ruling out possible disease mimics.

Declarations

-Consent for publication: Written informed consent was taken from the patient for publication of this case report.

-Availability of data and material: Data generated during this study are included in this published article. All the data are available in the repository of National hospital Kandy,

-Competing interests: The authors declare that they have no competing interests

-Funding: This study was self-funded by the investigators, no external organization or institution was involved in the study

-Authors' contributions: All authors read and approved the final manuscript.

-Acknowledgements: We express our gratitude to the patient who kindly gave consent for publication of this case report

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