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# TOLOSA-HUNT SYNDROME AS A PRESENTATION OF SJÖGREN'S-ASSOCIATED VASCULITIS

Jack Vella, Nicola Dingli, Paul John Cassar, Maria Bonello

Mater Dei Hospital, Msida, Malta

**Corresponding author's e-mail:** jack.vella@gov.mt

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## ABSTRACT

Tolosa-Hunt syndrome is a clinical quadrad consisting of unilateral headache, ipsilateral cranial nerve palsy, granulomatous inflammation on imaging or biopsy and no other headache syndrome to explain the diagnosis. It may be secondary to systemic inflammatory disease, and clinicians should aggressively search for underlying causative pathology.

A 73-year-old patient presented with this quadrad, in whom workup identified a systemic large-vessel vasculitis secondary to Sjögren's disease. The patient was treated with rituximab and steroids, with considerable improvements in both her orbital pathology and vasculitis.

The quadrad of Tolosa-Hunt syndrome should prompt investigation for systemic autoimmune and inflammatory disease rather than being assumed to be idiopathic.

## KEYWORDS

Tolosa-Hunt syndrome, Sjögren's disease, vasculitis, ophthalmoplegia, cranial neuropathy

## LEARNING POINTS

- 'Tolosa-Hunt syndrome' is a descriptive term for an idiopathic presentation; it does not establish aetiology. Secondary causes should be considered and thoroughly worked up.
- The workup should extend beyond local orbital pathology to systemic autoimmune and inflammatory disorders, including potentially serious vasculitis.
- Sjögren's-associated vasculitis may produce neurological manifestations resembling polyarteritis nodosa; rheumatology input and treatment of the underlying vasculitis may improve the neurological syndrome.

## INTRODUCTION

Tolosa-Hunt syndrome is a clinical quadrad defined in the International Headache Classification as:

- Unilateral retro-orbital headache;
- Ipsilateral cranial nerve III, IV or VI palsy;
- Granulomatous infiltration of the orbit on imaging or histology biopsy;
- Not better accounted for by another ICDH-3 diagnosis[1,2].

The term is used somewhat inconsistently in clinical

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contexts. It is sometimes used descriptively in any case of painful ophthalmoplegia, which fits the above quadrad, and other times used specifically to refer to idiopathic cases. The name is controversial, as some believe that it is misleading as a diagnostic label which makes no inference as to the underlying disorder, and failing to investigate fully could cause one to miss significant underlying pathology[2,3]. It is suggested that the term remains purely descriptive and agree with the notion that the name is non-diagnostic. The prefix 'idiopathic' should be added in cases where the aetiology is unknown.

## CASE DESCRIPTION

A 73-year-old woman, previously healthy, presented to the emergency department with a two-day history of double vision, and left-sided headache and mild photophobia. She reported no neck stiffness, fever, sensorimotor disturbance, involuntary movements, speech disturbance or decline in visual acuity. She was otherwise well in the weeks prior to presentation. Her medical history was only significant for recurrent sinusitis, and she was on no regular medications or supplements. She was a non-smoker who did not consume alcohol.

On examination, she was haemodynamically stable and afebrile. She was alert and oriented and had no visible rashes or meningism. There was no abnormality in limb power, tone, reflexes or coordination. Gait was normal. Cranial nerve examination revealed diplopia, which was worst on left lateral gaze, with slight limitation of abduction of the left eye. There were no fatigable muscle groups.

Her blood results revealed normal thyroid function tests, lipid profile and HbA1c *(Table 1)*. The C-reactive protein and erythrocyte sedimentation rate results were both slightly elevated; she underwent a non-contrast computed tomography (CT) brain scan, which was unremarkable.

| Investigation | Result | Reference range |
|---|---|---|
| Haemoglobin (g/dl) | 13.6 | 12–15.5 |
| White cell count (×10$^9$/l) | 8.04 | 4.3–11.4 |
| Platelets (×10$^9$/l) | 391 | 132–349 |
| C-reactive protein (mg/l) | 14.5 | 0–5 |
| Erythrocyte sedimentation rate (mm) | 58 | 33–37 |
| Creatine kinase (U/l) | 33 | 26–192 |
| Urea (mmol/l) | 3.6 | 1.7–8.3 |
| Creatinine (µmol/l) | 65 | 45–84 |
| Serum protein electrophoresis | Monoclonal band detected (5.7%), IgG lambda | - |
| Free light chain ratio | 0.425 | 0.31–1.56 |
| Vitamin B12 (pmol/l) | 216 | 156–672 |
| HbA1c (%) | 5.85 | 4.7–6.4 |
| Free thyroxine (pmol/l) | 17.40 | 11.9–20.3 |
| Thyroid stimulating hormone (µIU/ml) | 1.696 | 0.3–3 |

**Table 1.** *Serum results available at first presentation.*

| Investigation | Result | Reference range |
|---|---|---|
| CSF colour | Colourless | - |
| CSF turbidity | Clear | - |
| CSF coagulum | Absent | - |
| CSF erythrocytes (×10$^{12}$/l) | 0.000 | - |
| CSF nucleated cell count (×10$^9$/l) | 0.003 | - |
| CSF polymorphonuclears (×10$^9$/l) | 0.001 | - |
| CSF lymphocytes/mononuclear (×10$^9$/l) | 0.002 | - |
| CSF other cells (×10$^9$/l) | 0.00 | - |
| CSF protein (mg/l) | 667 | 150–450 |
| CSF glucose (mmol/l) | 0.425 | 0.31–1.56 |
| CSF immunoglobulin G (mg/l) | 216 | 156–672 |
| CSF viral polymerase chain reaction (enterovirus, HSV, mumps, varicella zoster) | 5.85 | 4.7–6.4 |
| CSF bacterial polymerase chain reaction *(N. meningitidis, H. influenzae, S. pneumoniae)* | 17.40 | 11.9–20.3 |
| CSF microscopy, culture and sensitivity, and Gram stain | 1.696 | 0.3–3 |
| CSF cytology | | |

**Table 2.** *Results of cerebrospinal fluid (CSF) analysis.*

The initial workup and suspected diagnosis focused on a vascular mononeuropathy, such as an ischaemic process affecting cranial nerve VI or its nucleus in the left medulla. Aspirin 75 mg daily was prescribed, and she was admitted to hospital for further investigation. The lack of vascular risk factors, subacute onset and headache, were atypical for a vascular insult. Non-arteritic neuropathies were also considered including demyelination, and inflammatory mononeuropathy as in vasculitis. The differential also included a non-localised pressure effect after a raised intracranial pressure, or an orbital process such as infiltration, cavernous sinus thrombosis and orbital myositis. A CT venogram, an magnetic resonance imaging (MRI) orbits and an MRI angiography were performed; these were unremarkable. Optical coherence tomography and fundoscopy were also normal. The patient was discharged home with a plan for early follow-up with the results of a connective tissue and autoimmune panel. However, she presented again to hospital one week later with worsening diplopia, now in all directions of gaze, and retro-orbital pain. Her ocular examination revealed left-sided partial ptosis, as well as complete failure of all left-sided extraocular movements including adduction, abduction, upgaze and downgaze. The clinical picture now reflected a subacute, progressive, unilateral and complete ophthalmoplegia. The

differential diagnosis was now focused on an inflammatory or infiltrative process affecting the orbits. This included diagnoses such as sarcoidosis, orbital myositis, cavernous sinus thrombosis and idiopathic Tolosa-Hunt syndrome.

A lumbar puncture was performed, which showed mildly raised cerebrospinal fluid protein *(Table 2)*, and the MRI was repeated with orbital sequences. The MRI appearances had evolved considerably; now an area of increased isointense T1-signal uptake in the left cavernous sinus and left-sided retro-orbital fat stranding was appreciable *(Fig. 1)*.

At this time, the patient's autoimmune and connective tissue disorder screen was issued *(Table 3)*. This showed a markedly elevated total extractable nuclear antigen (54.1 U/ml, reference 0–19 U/ml), which was subtyped to show an elevated anti-SSA antibody (ratio 3.5, reference 0–1) profile. Anti-nuclear antibody was positive (>1/1000) with a homogeneous anti-nuclear factor pattern.

We then sought rheumatology input and took a targeted history. The patient reported a 10-year history of dry eyes and dry mouth, for which she had previously undergone allergy testing. She had no genital dryness or skin rashes, arthralgias or purpura.

She was started on prednisolone at a dose of 1 mg/kg/day. Shortly after starting steroids she underwent a whole-body positron emission tomography computed tomography (PET-CT), which showed avid tracer uptake in the thoracic aorta and medium sized vessels, consistent with a large/medium vessel vasculitis. A lip biopsy was also performed, which showed mononuclear cell infiltration, periductal fibrosis and acinar atrophy, consistent with chronic sialadenitis and Sjögren's disease. In view of the extensive large-vessel involvement on PET-CT, she was subsequently started on six-monthly infusions of rituximab.

A temporal artery biopsy was performed, which showed no evidence of arteritis. An ultrasound of her parotid glands showed mild enlargement and hypervascularity. High-resolution CT of the chest performed immediately after her first rituximab dose demonstrated interstitial lung disease with a non-specific interstitial pneumonia pattern.

Her restricted eye movements and partial ptosis both improved in the first six weeks after starting prednisolone,

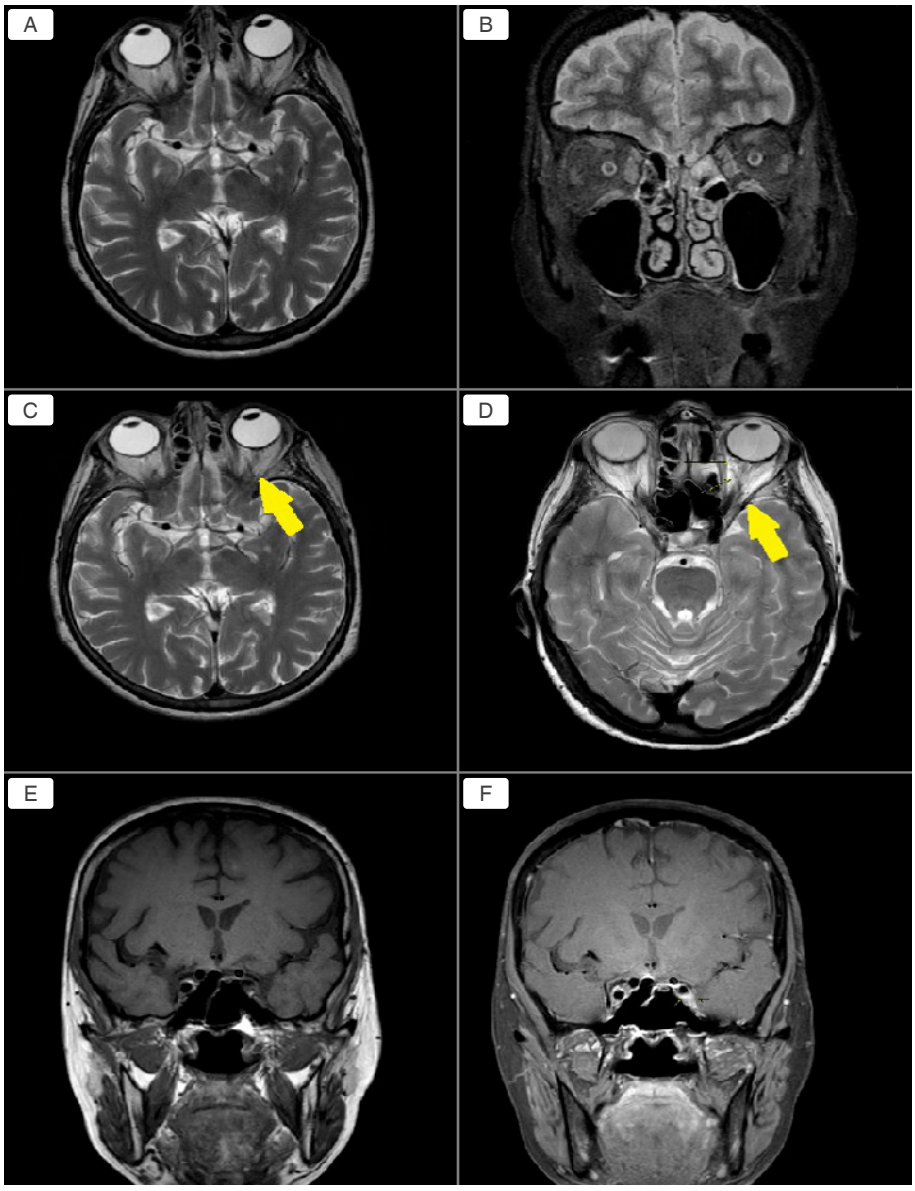



***Figure 1.*** *MRI scan of the brain at two points in the clinical history. A) T1-weighted non-contrast MRI of the brain in axial view, at initial presentation. Normal appearance of the orbit and cavernous sinus; B) A coronal view of the same T1 scan; C) A T2 weighted MRI with contrast, taken two weeks later, after worsening of diplopia and retro-orbital headache. There is subtle asymmetry of the cavernous sinuses (arrow), D) with increased isointense T1 signal in the left cavernous sinus with increased contrast uptake (arrow). Left retro-orbital fat stranding is also notable. D) A coronal view of the same T1 weighted MRI with contrast, F) demonstrating increased contrast uptake.*

| Investigation | Result | Reference range |
|---|---|---|
| Anti-nuclear antibody (ANA) | Positive, 1:1,000 titre | - |
| Anti-double stranded DNA (IU/ml) | <10 | 0–100 |
| Rheumatoid factor IgM (IU/ml) | 10 | 0–15.9 |
| Anti-neutrophil cytoplasmic antibody (ANCA) – anti-MPO antibody (U/ml) | <2 | 0–20 |
| ANCA – anti-PR3 antibody (U/ml) | <2 | 0–20 |
| Total extractable nuclear antigen (U/ml) | 54.1 | 0–19 |
| Anti-SSA (Ro) antibody (Ab) | 3.5 | 0.1–1 |
| Anti-DFS70 Ab, anti-mitochondrial M2 Ab, anti-ribosomal P protein, anti-histone Ab, anti-nucleosome Ab. Anti-proliferating cell nuclear Ab, anti-centromere protein B, anti-jo-1 Ab, anti-Scl-70 Ab (anti-topoisomerase I), anti-SSB Ab (La), anti-Ro52 Ab. Anti-Sm (Smith) Ab, anti-RNP Ab | Negative | - |
| Angiotensin converting enzyme (U/l) | 49.80 | 13.3–63.9 |
| Syphilis serology | Negative | - |
| HIV serology | Negative | - |
| Epstein-Barr virus polymerase chain reaction | Negative | - |
| Cytomegalovirus polymerase chain reaction | Negative | - |

***Table 3.*** *Results of autoimmune and connective tissue disorder panel from serum.*

but the headaches persisted and did not change in severity. Her symptoms flared up in the weeks after starting rituximab, while she was on a tapering prednisolone regime, requiring readmission to hospital and reintroduction of prednisolone at a 1 mg/kg/day regime. In the months since initiating rituximab, her headaches became less frequent, and both the partial ptosis and diplopia improved; she was successfully tapered down to a 0.1 mg/kg/day dosage. The interstitial lung disease cleared from imaging two months after starting treatment.

One year on, she had no residual ptosis or clinically apparent cranial nerve palsy and was planned to continue six-monthly rituximab for control of her large-vessel vasculitis.

## DISCUSSION

Tolosa-Hunt has been reported with other systemic and autoimmune inflammatory disorders such as systemic lupus erythematosus and Wegener's granulomatosis) but has not been reported in association with Sjögren's disease. Sjögren's disease notoriously presents with exocrine gland dysfunction, but extraglandular manifestations such as vasculitis are well reported. When present, vasculitis in Sjögren's disease is known to behave similarly to that in polyarteritis nodosa (PAN)[4,5], which has been demonstrated to present with ocular motility impairment[6,7].

The pathophysiology of orbital involvement in large-vessel vasculitis is unclear. There are several potential physiological explanations for the clinical presentation in this case. One possible explanation is that of inflammatory arteropathy of the microvasculature supplying the cranial nerves in the orbit, in a process akin to mononeuritis multiplex[8]. The reason why the cranial nerves affecting eye movements appear to be more selectively targeted by Sjögren's and PAN is yet to be clarified. Vasculitic arteropathy could also affect the extraocular muscles themselves, resulting in muscle ischaemia and oedema, a potential culprit for the appearances on MRI[8].

Another possible mechanism is that of ocular myositis secondary to the Sjögren's disease itself and unrelated to the vasculitic element. Orbital myositis has been demonstrated in the context of primary Sjögren's disease[9]. Although the patient in this case had a normal serum creatinine kinase and muscle aldolase, the area affected was relatively focal, and possibly small enough to not cause a detectable rise in serum muscle enzymes. One case of Sjögren's disease presenting with a cranial nerve VI palsy and orbital inflammation, as here, was reported last year in the absence of any vasculitic process[10].

In this case, the combination of progressive painful ophthalmoplegia, evolving orbital MRI abnormalities, positive anti-SSA antibodies, chronic sicca symptoms, biopsy-proven chronic sialadenitis and PET-CT evidence of large/medium vessel vasculitis, supported Sjögren's-associated systemic inflammatory disease as the underlying pathology.

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