Medical Grand Round

- **Two patients presenting with Ophthalmoplegia**

- Dr K.M Lo
- Department of Medicine
- Alice Ho Nethersole Hospital

The first patient

- Madam G.C
- F/ 46 a Philippine domestic helper living in HK for 3 years.
- Non-smoker, non-drinker
- Presented with left side headache , left forehead pain and seeing double visions for 3 weeks.

History

- She had double vision worse on looking horizontally to the left side .
- The double vision persisted and had no variation with the time of the day.
- She had left-sided forehead and eye pain and numbness for 3 weeks
- The pain was persistent but not brought on by coughing , sneezing or straining and there was no associated nausea and vomiting .

History

- There was no associated symptoms such as flashes of light ,reddening of eyeball nor tearing.
- The headache described as accompanied pain over the eye ball.
- She had nasal blockage for 4 days before admission but no recurrent nasal bleeding / dizziness /ringing ears /deafness nor other ear symptoms .
- She denied drooling of saliva, swallowing difficulty or other limbs weakness.
- There was no recent head trauma

History

- There was no recent skin rashes, joint pain.
- She had no history of diabetes, hypertension
- She had no history of recent travelling and she was not on regular medication or herbs taken.

History

- 2 years ago, she had history of decrease visual acuity at her left eye and she consulted a private ophthalmologist.
- She was told to have inflammation of the nerve of the left eye with vision returned back to normal after medication.
- 6 months before admission , she had L eye pain and facial asymmetry. She was admitted to a regional hospital and she was told to have a nerve palsy and ?minor stroke. She was given a course of medication for 1 week and recovered completely .

Physical examination

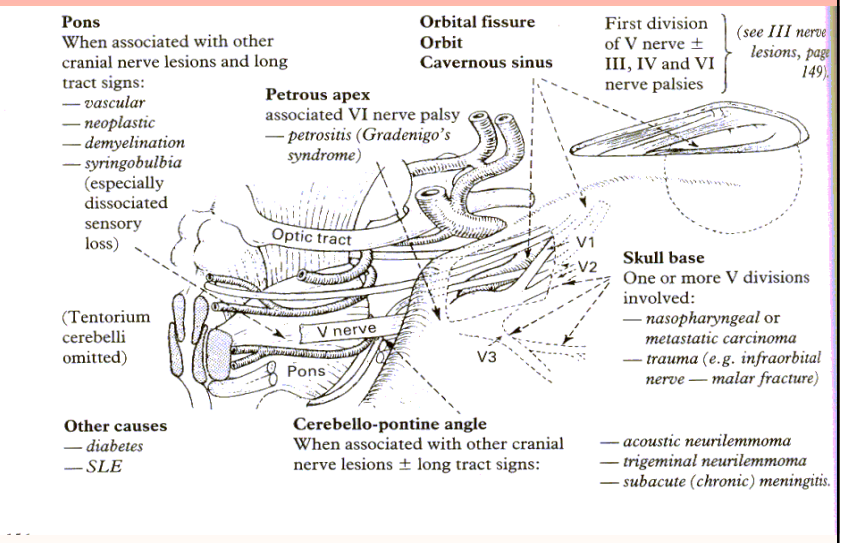
- L eye partial ptosis, horizontal diplopia (worse on looking at left side and upward)
- Impaired in sensory arm of the left cornea reflex.
- Decrease in the light touch sensation of the the L forehead confined to CN V 1st territory.
- Feature compatible with left III ,V (I st division), VI nerve involvement.
- No proptosis or enlarged thyroid.

Physical exam

- No facial nerve palsy and the other cranial nerves were intact
- Otoscopic examination , Rhinnes test and Weber test are normal.
- Fundi: normal findings
- Limb power and reflexes are normal

Provisional Diagnosis

- DDx:
- Lt Superior Orbital Fissure/ Orbital apex Syndrome
- Orbital pathology ? Secondary to inflammatory disease/ malignancy
- NPC
- multiple sclerosis
- myasthenia gravis



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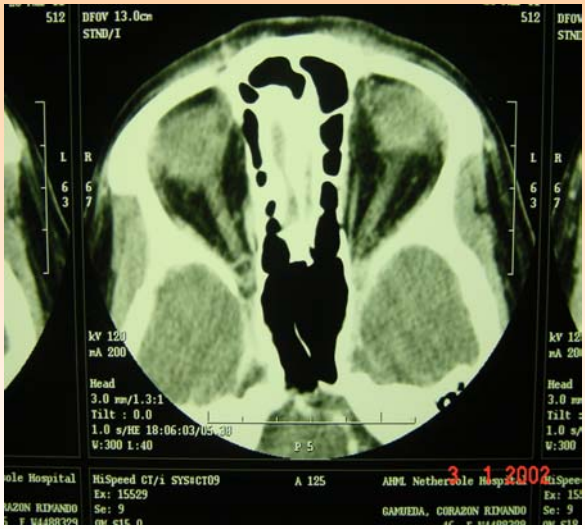
Investigation

- CBP :WBC 9.8, Hb 12.2, Plt 236
- ESR 60 mm/hr
- RFT : 137/ 3.7 / 3 / 51
- APTT/PT/INR normal
- spot glu : 5.3
- CXR - normal findings
- Urgent CT brain : no intracranial pathology detected.

Eye consultation

- Clinically feature of left partial CN III, VI and CN V1 nerve involvement
- urgent CT orbit /carvenous sinus was performed for clinical orbital apex/superior orbital fissure lesion .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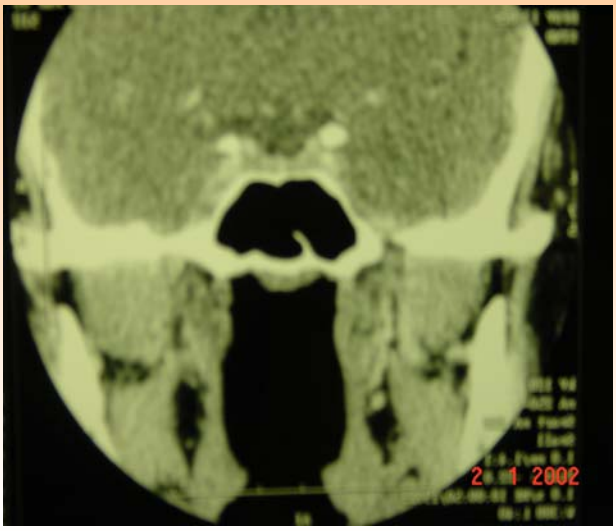
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CT findings

- CT Orbit:
- crowding in the left orbital apex with enlarged optic nerve / sheath and decrease in retrobulbar fats.
- no definite enhancing mass lesion seen and no bony lesion
- Normal opacification of cavernous sinus
- Conclusion : pseudotumor possible but other aetiology cannot be excluded.
- suggest MRI orbit.

Clinical progress

- DDx
- superior orbital fissure syndrome / orbital apex syndrome, Tolosa Hunt syndrome
- Myasthenia gravis
- NPC

Further progress

- Proceed to Tensilon test for MG in view of partial ptosis and V1 nerve palsy and test for anti-AChR Ab.
- Lumbar puncture for oligoclonal bands and infectious causes.
- Tensilon test and anti-AChR Ab -ve

LP findings

- clear & colourless
- RBC 2, WBC -ve
- TP 0.29, glu 3.4 (bl. Glu 5.3)
- no oligoclonal band
- Gram stain -ve
- Ink stain -ve
- AFB smear -ve
- no fungal element seen
- Culture : no growth

Further progress

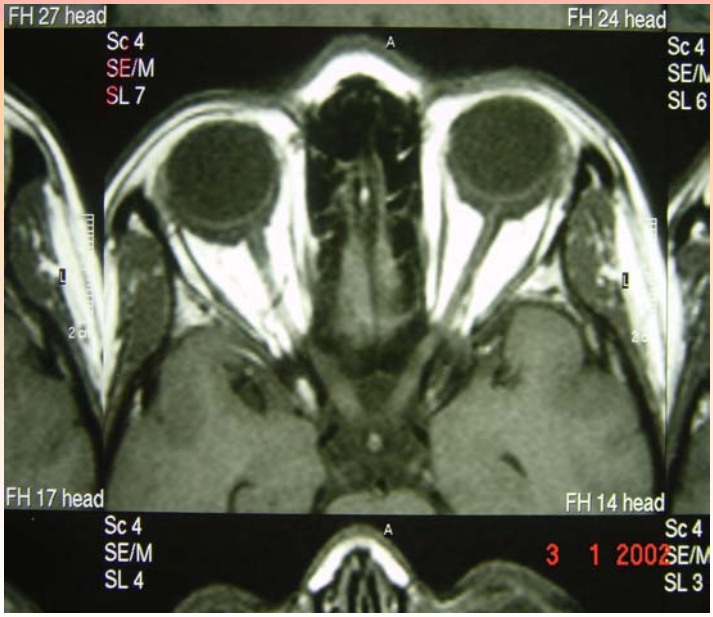
- Fiberoptic endoscopy of nasopharynx performed : no NP lesion identified.
- Further blood test:
- ANA 1:40 and ANCA -ve

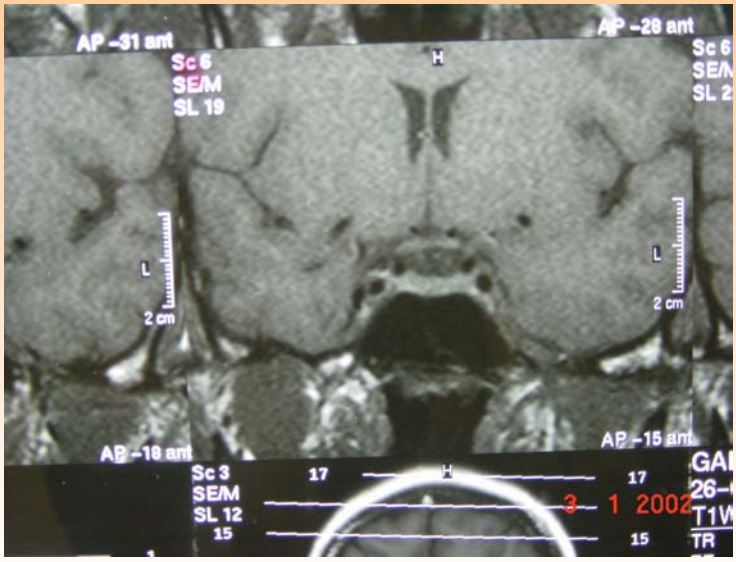
Treatment

- Prednisolone 80mg daily was given in liason with ophthalmologist with presumptive diagnosis of **Tolosa-Hunt Syndrome.**
- The symptoms improved 2 days after steroid given.

MRI Brain findings

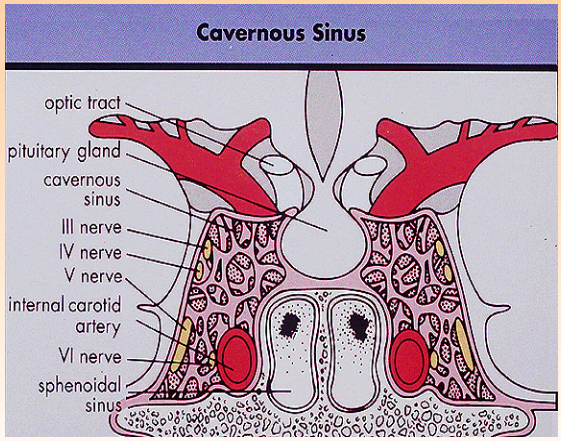
- MRI Brain and Orbit was performed 1 /52 after steroid given
- MRI brain and Orbit :
- no evidence of optic neuritis, retrobulbar or cavernous sinus abnormality.





Cavernous sinus syndrome

superior orbital fissure syndrome



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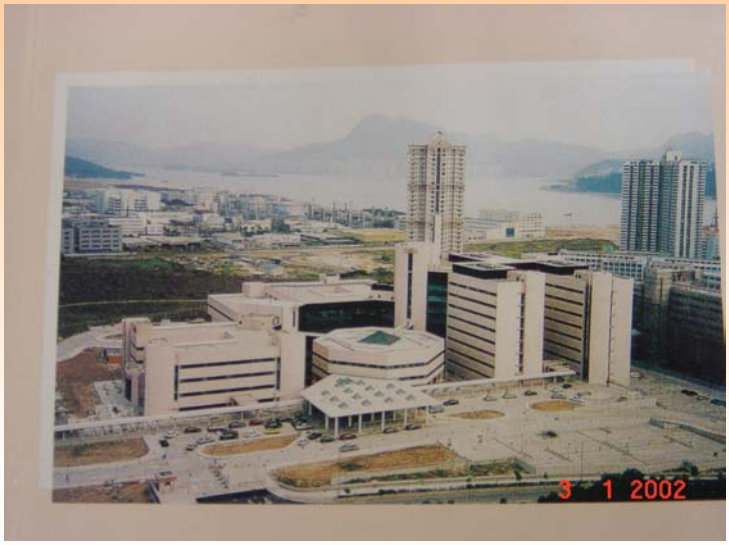
Progress

- The prednisolone was gradually tailed off in 6 weeks.
- She kept on improving in terms of headache, pain over the eyes as well as the diplopia after steroid therapy.
- There was no diplopia on follow up at 2 months and no neurological deficit was detected.

Tolosa-Hunt syndrome



Tolosa

- In 1954, Edvardo Tolosa of Barcelona described a 47-year-old male with signs and symptoms of severe retro-orbital and supraorbital pain, followed later by paralysis of the third, fourth, and sixth cranial nerves, and a diminished corneal reflex.
- The patient had had a similar episode 3 years previously, but had spontaneously recovered. Angiography showed a suggestive narrowing of the carotid siphon just distal to the cavernous sinus.

Tolosa

- The patient died 3 days after a negative intracranial exploration.
- At autopsy, ``The intracavernous portion of the carotid artery was wrapped in granulomatous tissue which did not obstruct the lumen of the sinus."
- The process had also invaded the adjacent cranial nerves.

Painful ophthalmoplegia of Hunt

- Hunt et al. (1961) reported six examples of the ``painful ophthalmoplegia'' syndrome and set forth the following criteria.
- **(1) Pain may precede the ophthalmoplegia by several days, or may not appear until some time later. The pain is not a throbbing, paroxysmal hemicrania but is a steady pain behind the eye and in the brow.**
- **(2) Neurologic involvement is not confined to the 3rd CN 3 , but may include the 4th and 6th CN as well as the first (and occasionally the second) division of the CN V. The optic nerve and the oculosympathetic fiber may be involved, resulting in diminished vision.**

Painful ophthalmoplegia of Hunt

- (3) The symptoms last for weeks or months.
- (4) Spontaneous remission occurs, sometimes with residual neurologic deficit.
- (5) Attacks recur at intervals of months or years.
- (6)Exhaustive studies, including angiography and surgical exploration, have produced no evidence of involvement of structures outside the cavernous sinus.

Painful ophthalmoplegia of Hunt

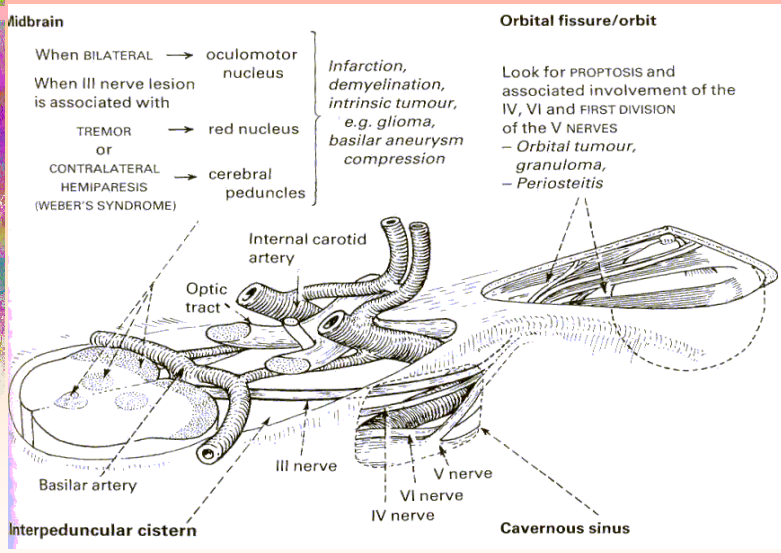
- Hunt et al. (1961), in a study, of the histologic material from Tolosa's (1954) case, noted that: ``The region where the carotid artery enters the cranial cavity by penetrating the outer wail of the cavernous sinus is the site of a low-grade, non-specific, inflammatory process.
- This process is characterized by proliferation of fibroblasts and by infiltration of the septa and wall of the sinus with lymphocytes and plasma cells. There is no necrosis, and no polymorphonuclear cells are present. No fibrinoid collagen degeneration is observed.

Painful ophthalmoplegia of Hunt

- The adventitia of the carotid artery, as well as the smaller vessels, is only incidentally infiltrated by the chronic inflammatory cells." Hunt et al. found no evidence for a primary arteritis. The granulomatous lesion had engulfed the abducens nerve and all small connecting branches of the carotid plexus and the ophthalmic division of the trigeminal nerve.
- Myelin sheaths were fully preserved, and no inflammatory changes were seen within the perineurium. He emphasized that the etiology of the syndrome was still unknown.

Superior orbital fissure syndrome

- Lakke (1962) published a review of the so-called superior orbital fissure syndrome and presented convincing evidence that many examples of this syndrome are **clinically indistinguishable from the inflammatory cavernous sinus syndrome of Tolosa or the ``painful ophthalmoplegia'' syndrome of Hunt.**
- Lakke described a 47-year-old man in Utrecht with violent right-sided, stabbing headache .This patient developed progressive paresis of all of his R 3rd nerve and depression of his right corneal reflex. His right pupil, though small, reacted normally to a direct light stimulus.



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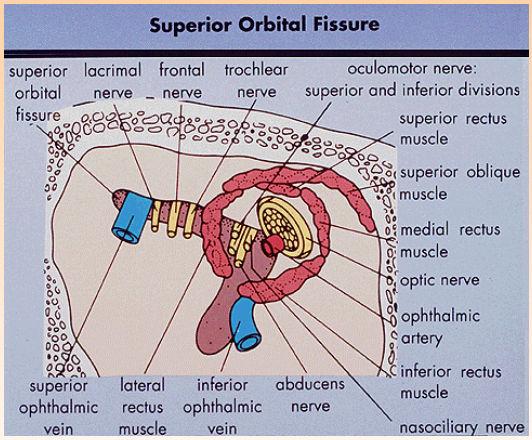
Superior orbital fissure



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Superior orbital fissure syndrome

- A neurosurgical exploration revealed a thin layer of grayish red granulation tissue on the lateral wall of the cavernous sinus and on the dura covering the lesser wing of the sphenoid. Histologic examination of a biopsy specimen showed inflammatory tissue containing PMN cells. The dura mater from the region of the superior orbital fissure was necrotic in some places and lined with granulation tissue. **The histologic diagnosis was pachymeningitis of undetermined etiology.**

Superior orbital fissure syndrome

- Granulomatous inflammation of the CS may produce a painful ophthalmoplegia, other lesions that involve structures within the SOF or CS may also produce painful ophthalmoplegia that is often responsive to systemic corticosteroid therapy.
- Thomas and Yoss (1970) found that neither the spectrum of symptoms and the clinical courses are similar disregard the underlying lesion, whether it is neoplastic, aneurysmal, or inflammatory. **These investigators found evidence of both spontaneous and steroid-induced remissions and stressed the need for complete neuroradiologic investigation in patients with the syndrome of painful ophthalmoplegia.**

Tolosa Hunt syndrome

- In 1966, Smith and Taxdall were the first to apply the eponym **"Tolosa-Hunt syndrome" to this entity.**
- They emphasised **the use of steroids as a diagnostic test."**
- The authors stated that "The administration of large doses of systemic steroids for 48 hours produces a dramatic response in painful ophthalmoplegia, which allows prompt differentiation of these cases."

Tolosa-Hunt syndrome

- While this may be true in the majority of cases, several points must be kept in mind.
- It has been emphasized, noninflammatory lesions causing painful ophthalmoplegia may appear to respond dramatically to systemic corticosteroids and that if a patient with a presumed Tolosa-Hunt syndrome *does not* respond to systemic administration of corticosteroids, the syndrome is almost certainly *not* inflammatory in nature however, the **reverse is not always true.**

Tolosa-Hunt syndrome

- It may takes days, weeks, or months to resolve ophthalmoplegia and may never resolve completely.
- Third, the availability of CT scan and MRI , as well as DSA allow the physician to perform a sensitive neuroradiologic evaluation of the cavernous sinus and orbital apex regions

Tolosa-Hunt syndrome

- In addition to tumors, aneurysms, and inflammatory lesions, vascular processes may produce painful ophthalmoplegia. Painful ophthalmoplegia has been described in patients with syphilis, giant cell (temporal) arteritis, diabetes mellitus rheumatoid arthritis and systemic lupus erythematosus

The criteria of the international Headache Society , 1988

- Episode(s) of unilateral orbital pain for an average of 8 weeks ,if untreated , with associated paresis of one or more of the CN 3,4,6 .
- CN paresis may coincide with the onset of pain or follow it with in a period of up to 2 weeks. And the pain must be relieved within 72 hr after the initiation of corticosteroid therapy .
- Other causative lesions must be excluded by neuroimaging.

- Journal of Neurology 1999, vol 246 issue 5 pp371-377

Tolosa-Hunt syndrome

- This syndrome is characterized by recurrent severe painful ophthalmoplegia and idiopathic granulomatous inflammation of the cavernous sinus and superior orbital fissure.
- "Tolosa-Hunt syndrome"is a rare syndrome accounted for only 2.9 percent of the cases of painful ophthalmoplegia.
- Published cases of the Tolosa-Hunt syndrome the peak incidence was between the fourth and sixth decades, with no sex predilection and rare neurologic or systemic findings.
- However, imaging studies must be done first to rule out other causes, such as intracranial hemorrhage, tumors, or cerebral aneurysms.

Tolosa-Hunt syndrome

- The painful ophthalmoplegia is localized to the cavernous sinus and orbital apex, and exhaustive hematologic, cerebrospinal fluid, and neuroradiographic studies reveal no cause.
- Some patients have a spontaneous remission, whereas others have a marked improvement after a limited course of steroids. Pathological examination is limited because of the surgical in accessibility of the cavernous sinus, and there have been only a few examinations at autopsy

Tolosa-Hunt syndrome

- Patients complain of pain, which is a defining symptom. The pain lasts an average of 8 weeks if untreated. Ocular motor cranial nerve palsies may coincide with the onset of pain or follow it within a period of up to 2 weeks
- It usually described as "intense", "severe", "boring", "lancinating", or "stabbing". It is periorbital in location, frequently extending into the retro-orbital, frontal, and temporal region

Tolosa-Hunt syndrome

- All three ocular motor cranial nerves may be involved, in various combinations. ent.
- At times**, optic nerve dysfunction has been reported with Tolosa-Hunt syndrome, indicating that the pathological process may involve the orbital apex**
- The optic disc may be normal, swollen, or pale in appearance, and visual decline may be minimal or lead to blindness. **Loss of acuity is variable and unpredictable, and, on occasion, may be permanent.**

Tolosa-Hunt syndrome

- Tolosa-Hunt syndrome follows an unpredictable course. Usually acute at onset, the patient's symptoms typically last from days to weeks.
- **Before the use of systemic corticosteroids there was clear evidence that spontaneous remissions occurred.** However,recurrences are common, taking place in about a half of reported patients, usually at an interval of months or years from the initial attack.

Tolosa-Hunt syndrome

- Although Tolosa-Hunt syndrome is a self limited illness, it does cause considerable morbidity. Infrequently, residual cranial nerve palsies persist.
- Although there is no conclusive evidence to show that steroids lessen the degree or duration of the ophthalmoplegia, there is dramatic reduction of pain, often within 24 hours.

Tolosa Hunt syndrome

- Radiologic abnormalities have been described in a number of cases of Tolosa-Hunt syndrome.
- Venography has been performed on several patients and often shows obstruction of the third portion of the ipsilateral superior ophthalmic vein as well as obstruction within the ipsilateral cavernous sinus. Some investigators have emphasized that venography may be abnormal when all other neuroradiologic tests are unremarkable

Tolosa Hunt syndrome

- Orbital venography often disclosed abnormalities in filling of the superior ophthalmic vein or cavernous sinus,but **these techniques are difficult and therefore not consistently performed.**
- Venographic abnormalities are not specific for Tolosa-Hunt syndrome, and may be found with space occupying lesions or other inflammatory processes in the orbit or parasellar region.

Tolosa Hunt syndrome

- Arteriographic findings in the Tolosa-Hunt syndrome include irregular narrowing, flattening, and displacement of the intracavernous portion of the internal carotid artery, at times suggesting a mass in this region) as well as hypervascularity with the suggestion of an orbital mass

Tolosa Hunt syndrome

- High resolution CT can also demonstrate soft tissue changes but is less sensitive than MRI. This is due to lack of sensitivity to soft tissue change with superimposed beam hardening and bone streak artifacts.
- Thus, **even if CT is normal, MRI must still be performed to appropriately evaluate the region of the cavernous sinus or superior orbital fissure.**

Tolosa Hunt syndrome

- **Contrast enhanced MRI with multiple views, particularly coronal sections, should be the initial diagnostic study performed.** Numerous reports have demonstrated an area of abnormal soft tissue in the region of the cavernous sinus in most, but not all, patients with Tolosa-Hunt syndrome
- Typically, the abnormality is consistent with an inflammatory process. In addition, there is enhancement of the abnormal area after intravenous injection of paramagnetic contrast. With corticosteroid therapy, the abnormal area decreases in volume and signal intensity in most reported cases.

Tolosa Hunt syndrome

- Some authorities would suggest that resolution of imaging abnormalities after a course of systemic corticosteroids should be considered "diagnostic" of Tolosa-Hunt syndrome.
- However, caution is advised when assessing the salutary effects of steroids, as improvement both clinically and radiologically may occur with other disease processes. "False positive" steroid responsiveness with a "remitting" course can be seen with both malignant processes (for example, lymphoma) as well as more benign disorders (for example, vasculitis).

Role of imaging

- Evolving diagnostic techniques, in particular the high-resolution neuroimaging of CT and MRI scanning, have revolutionized the imaging of orbital and intracranial disease.
- The neuroimaging can exclude large parasellar tumor masses, such as a pituitary adenoma, meningioma, and craniopharyngioma, or an invasive nasopharyngeal cancer.

A 73-Year-Old Man with Severe Facial Pain, Visual Loss, Decreased Ocular Motility, and an Orbital Mass

- A Parasellar lesion of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma, with infiltration of orbital muscle, soft tissue, and lacrimal gland presenting as Tolosa-Hunt syndrome.

- Peter Rubin, and Nancy L. Harris
- NEJM 1993 vol 328 p.266-275

Important entities to exclude

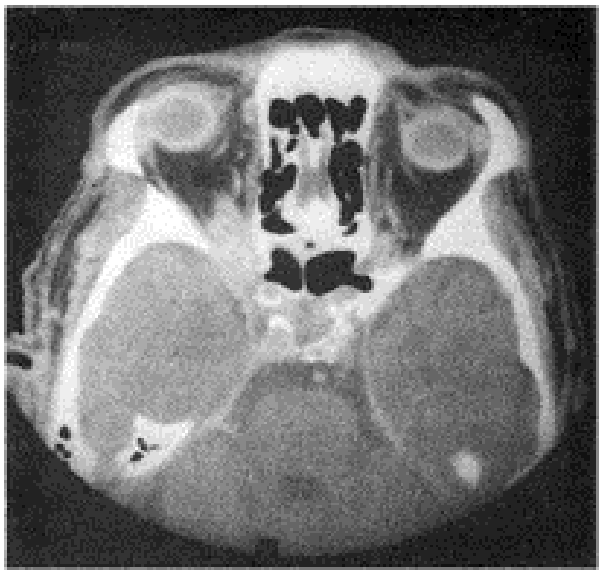
- Pituitary tumours or Parasellar tumors that suddenly expand into the cavernous sinus produce a syndrome of multiple ocular motor palsies associated with severe headache and visual failure (pituitary apoplexy).
- Giant internal carotid aneurysms within the cavernous sinus present with a slowly progressive painful ophthalmoplegia.

Diagnostic Category	Diagnostic Possibilities
Orbital	
Inflammatory, infectious	
Orbital cellulitis	Bacterial
	Adjacent sinusitis
	Penetrating trauma
	Septic embolus
	Viral
	Herpes zoster
	Fungal
	Mucor, aspergillus
Inflammatory, noninfectious	Thyroid-related orbitopathy
	Idiopathic (orbital pseudotumor)
Vascular	Orbital hemorrhage
	Arteriovenous malformation
Neoplasm at orbital apex	Primary
	Secondary extension of sinus or intracranial lesion
	Metastasis
Non-orbital	
Neoplastic	
Primary intracranial	Pituitary adenoma
	Meningioma
	Craniopharyngioma
Cranial	Chondroma
	Multiple myeloma
	Lymphoma
Secondary	Nasopharyngeal carcinoma
Metastatic	Breast adenocarcinoma
	Prostatic adenocarcinoma
	Lung carcinoma
Infectious	Bacterial, viral, fungal
Inflammatory	Tolosa–Hunt syndrome
	Herpes zoster
	Wegener's granulomatosis
	Temporal arteritis
	Sarcoidosis
Vascular	Aneurysm
	Carotid-cavernous fistula
	Dural-cavernous fistula
	Cavernous-sinus thrombosis
Traumatic	Fractures, hematoma
Other	Diabetic cranial polyneuropathy

*Broad diagnostic categories are shown, with a limited list of diagnostic possibilities.

- Differential diagnosis of the pain ophthalmoplegia
- NEJM vol 328 p.270

CT Scan with Contrast Enhancement through the Orbits, Revealing an Ill-Defined Mass in the Apex of the Right Orbit, with Extension into the Right Cavernous Sinus. NEJM vol 328 p.266-275



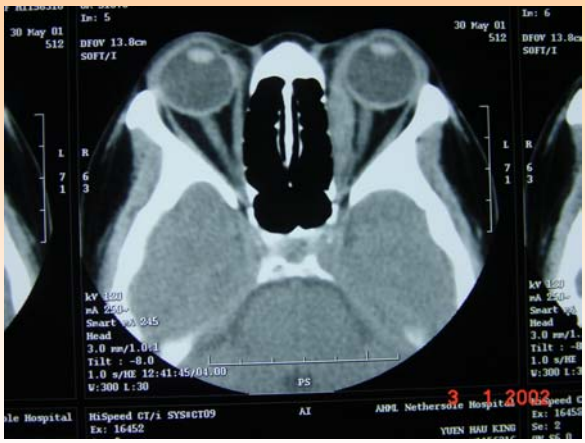
Patient 2 -- 41 year old lady with L CN VI palsy

- 41 year old lady who enjoys good past health without diabetes .
- She presented to us with chronic headache for 5 yrs and double vision on horizontal gaze towards the L side for 1 year
- She exhibits no fatiguability.
- She has no other ENT symptoms
- Physical exams : impaired horizontal gaze compatible with left CN VI palsy/ medial rectus lesion

Patient 2

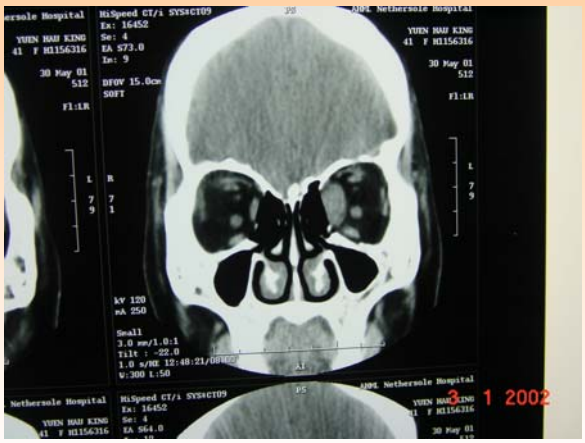
- Investigation showed
- Spot sugar normal
- Tensilon test -ve
- AChR-ab -ve

Patient 2



Patient 2

- CT orbit showed thickened medial rectus of the L side of spindle shape . Radiological Ddx chronic myositic pseudotumor and thyroid eye myopathy



- L medial rectus Bx was performed in view of abnormal CT findings
- Bx showed feature consistent with myositis scanty amount of perivascular and perimysial lymphocytic infiltrates were noted and these are highlighted by lymphocyte common antigen immunostaining ,no malignant infiltrates identified

Case2

- She was treated with oral prednisolone 15mg daily for 4 weeks.
- Subsequent follow up showed resolution of the double vision and neurological sign

Orbital lesions

- Orbital masses almost inevitably result in proptosis.
- Small tumours in the region of the optic nerve (e.g. sheath meningiomas) are likely to have produced substantial visual impairment and proptosis is slight .
- The ophthalmoplegia resulting from orbital masses reflects both nerve and muscle involvement.

Diagnostic Category	Diagnostic Possibilities
Orbital	
Inflammatory, infectious	
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	Penetrating trauma
	Septic embolus
	Viral
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	Meningioma
	Craniopharyngioma
Cranial	Chondroma
	Multiple myeloma
	Lymphoma
Secondary	Nasopharyngeal carcinoma
Metastatic	Breast adenocarcinoma
	Prostatic adenocarcinoma
	Lung carcinoma
Infectious	Bacterial, viral, fungal
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	Herpes zoster
	Wegener's granulomatosis
	Temporal arteritis
	Sarcoidosis
Vascular	Aneurysm
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Other	Diabetic cranial polyneuropathy

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Orbital lesion minic THS

- Differential diagnosis of the pain ophthalmoplegia
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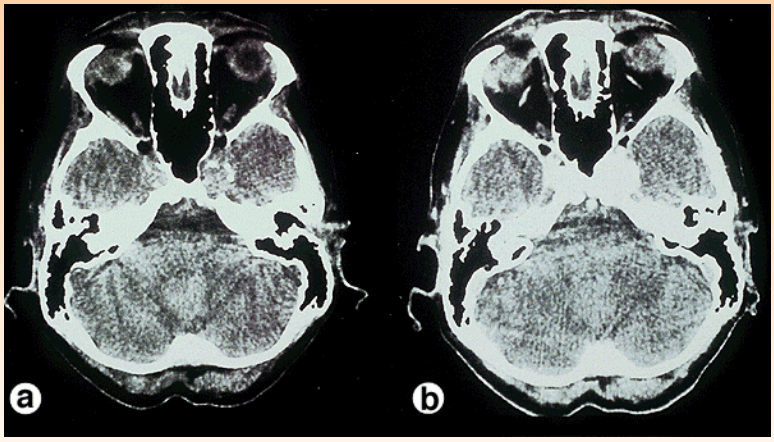
Cavernous anerysm



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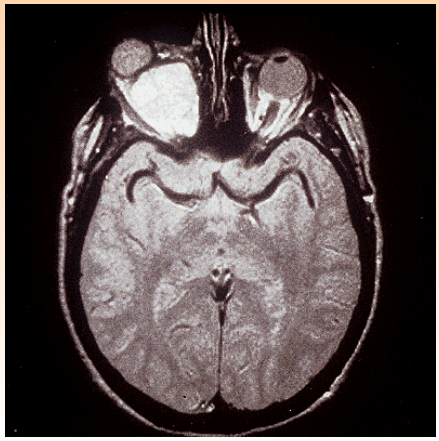
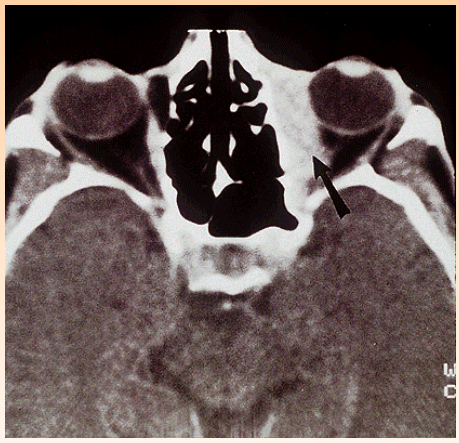
Orbital carvernous haemangioma



Orbital pseudo-tumor



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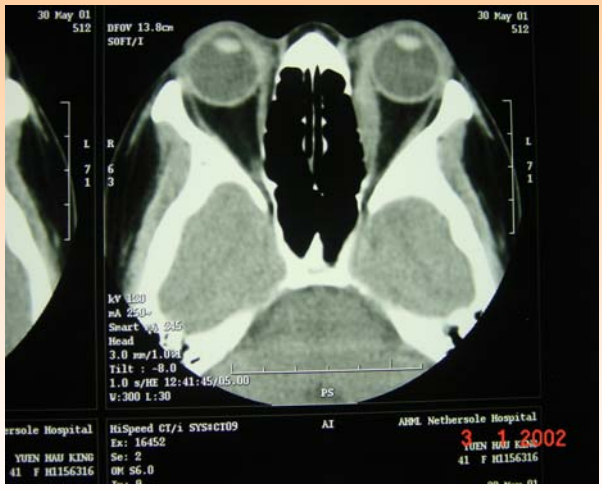
Our patient's CT orbit



Bring Home Message

- **THS should be alerted in a clinical settings of painful ophthalmoplegia together with lesions of the anterior cavernous sinus with involvement of the oculomotor, trochlear and abducens nerves, together with the first division of the trigeminal nerve occur .**
- **Although it is a granulomatous inflammatory lesion of unknown aetiology, potentially treatable pathological processes has to be excluded . These include meningioma, nasopharyngeal carcinoma, aneurysm and pituitary tumour.**
- **Prompt treament is required as it can proceed to blindness**
- **It is necessary to watch out for infective cause before considering steroid therapy**

Reference:

- L B Kline, WF Hoyt ,Nosological entities :The Tolosa-Hunt syndrome JNNP 2001;71;577-582
- Rubin and Harris:NEJM Vol 328 p.266-275
- Kelly and Wu : NEJM Vol 341 p.265-273
- Kenneth W. Lindsay: Neurology and Neurosurgery illustrated ELBS 2nd edition p.150-156
- G.David Perkin ; Clinical Neurology


Thank You