

# Thyroid Associated Ophthalmopathy:

Review of Pathophysiology, Clinical Manifestations and Imaging

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# Introduction

1. Graves' disease is a common autoimmune disorder of the thyroid.
2. The etiology is not known but is likely multifactorial, involving susceptibility genes and environmental triggers.
3. **Antibodies bind to the Thyroid-Stimulating Hormone receptor (TSHr)** in follicular cells and overstimulate thyroid hormone production, resulting in **hyperthyroidism**
4. Involvement of the eyes, known as **thyroid-associated ophthalmopathy**, occurs in **25-50%** patients with Graves' disease.
5. **5-7% of patients with TAO suffer from severe orbital disease**, leading to progressive proptosis, extraocular muscle (EOM) dysfunction and optic neuropathy.
6. Imaging of the orbits is typically used to exclude other causes of proptosis and to determine the presence of subclinical EOM enlargement and orbital apex compression.

# Epidemiology

1. Incidence ranges from 1:2000 to 1:5000
2. TAO is the most common cause of exophthalmos
3. Age: most commonly 30-50 years, but may affect any age
4. Females are 3-6 times more commonly affected than males



**Figure 2. Exophthalmos.** Adult woman with TAO exhibiting bilateral proptosis and lid retraction (a). Same patient 3 months later with inflammation, chemosis, eyelid swelling and increased proptosis (b). Images borrowed from the American Academy of Ophthalmopathy.



**Figure 3. EOM fibrosis.** Adult male with proptosis, eyelid retraction and hypotropia secondary to inferior and medial rectus muscle fibrosis. Images borrowed from the American Academy of Ophthalmopathy.

# Pathophysiology

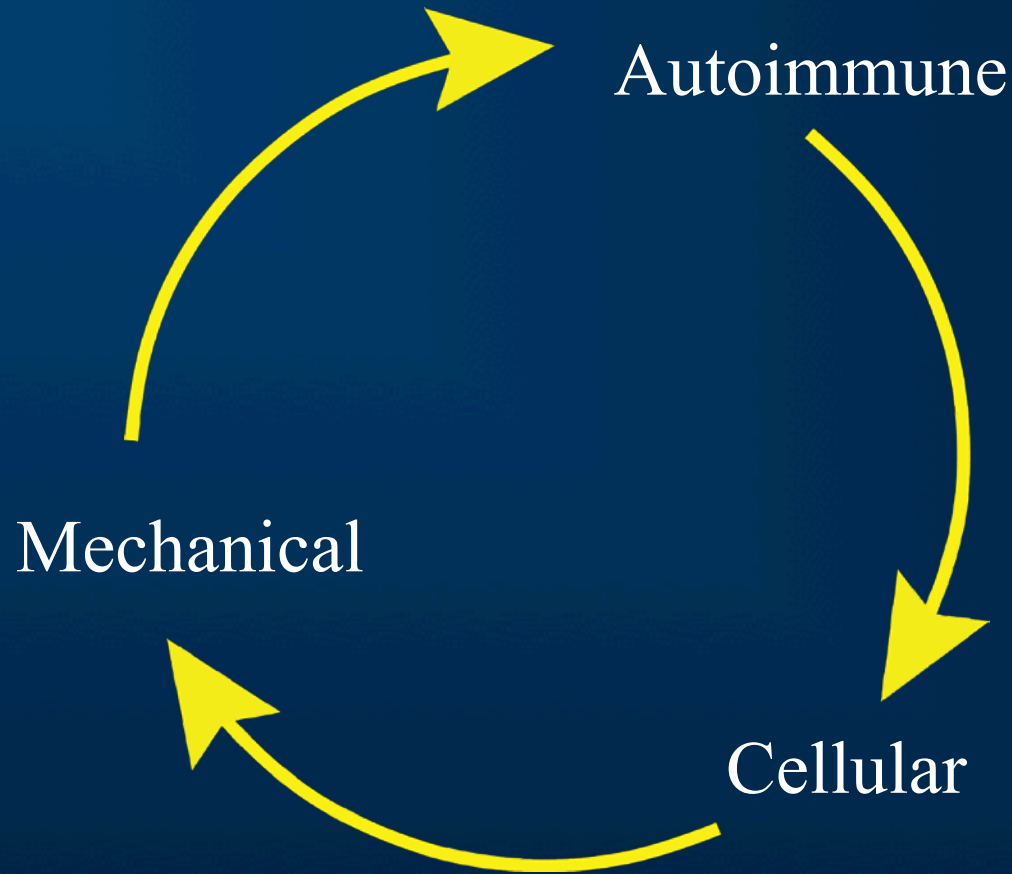


Figure 1. Pathophysiology. Positive feedback loop involving autoimmune, cellular and mechanical processes

# Risk factors for progressive TAO

1. Male gender
2. Age > 50yrs
3. Cigarette smoking.
4. Onset of symptoms in < 3 months
5. Diabetes
6. Uncontrolled hyperthyroidism
7. Pretibial myxedema
8. Elevated cholesterol
9. Peripheral vascular disease

TAO results in an overall increase in EOM and/or adipose tissue, involving a positive feedback loop:

## 1. Autoimmune

- a. TSHr mRNA and proteins have been found in orbital adipose and connective tissue
- b. TAO may result from T- or B-cell mediated autoimmune process against antigenic peptide fragments of TSHr.
- c. Autoimmune response results in local inflammation, recruitment of leukocytes (predominantly T-cells) and production of *cytokines*.



TAO results in an overall increase in EOM and/or adipose tissue, involving a positive feedback loop:

## 2. Cellular

- a. *Cytokines* stimulate fibroblasts to produce **glycosaminoglycans**, in which concentrations are elevated within adipose and EOM tissue.
- b. Different types of fibroblast populations, which vary from patient to patient, may explain why some patients exhibit predominantly EOM enlargement while others demonstrate retrobulbar fatty proliferation.
- c. Chronic inflammation results in EOM fibrosis.

TAO results in an overall increase in EOM and/or adipose tissue, involving a positive feedback loop:

### 3. Mechanical

- a. Increased volume of orbital adipose and/or EOM leads to elevated intraorbital pressure and proptosis
- b. Elevated intraorbital pressures further reduce lymphatic and venous drainage, leading to accumulation of local cytokines and aggravation of local inflammation

# Clinical Manifestations

## 1. Hyperthyroidism

- a. Nervousness/irritability, fatigue, palpitations, heat intolerance, weight loss, atrial fibrillation

# Clinical Manifestations

## 2. Manifestations of Graves disease

- a. Diffuse goiter, TAO, localized dermopathy, lymphoid hyperplasia, thyroid

# Clinical Manifestations

## 3. TAO

- a. Common signs: **eyelid retraction** and **periorbital edema**
- b. Other: feeling of grittiness, retrobulbar pain / pressure, chemosis, scleral injection, **exophthalmos** (up to 33%), **EOM dysfunction / diplopia** (5-10%), keratitis, optic neuropathy/visual loss (rare).
- c. Clinical exam findings: decreased visual acuity, afferent pupillary defect, visual field defects, diminished color or brightness perception.

# Clinical Manifestations

4. Laboratory evaluation of hyperthyroidism
  - a. **Depressed thyrotropin (TSH)** confirmed with **elevated** serum free **thyroxine (T4)**
  - b. If T4 is normal, then triiodothyronine (T3) may be slightly elevated, indicating early disease.

# Clinical Manifestations

5. Abnormal thyroid function tests (indicating hyperthyroidism) with clinical findings of Graves disease are diagnostic

# Clinical Manifestations

6. Measurement of TSHr antibodies may be performed if diagnosis remains uncertain.
  - a. TSH binding inhibitory activity assay (TBII): positive in 70-90% of patients
  - b. Second generation TBII assays are up to 99% sensitive



# Imaging Findings

## Ultrasonography

Non-invasive, economical and accessible modality, which may demonstrate:

1. Enlarged EOM on gray scale imaging
2. Enlarged superior ophthalmic vein
3. Increased arterial flow.
4. Internal irregularity and medium-high reflectivity on A-scan imaging

# Imaging Findings

## Computed Tomography

1. Not necessary with majority of patients with typical clinical and laboratory manifestations

# Imaging Findings

## Computed Tomography

### 2. Indications

- a. Non-axial or unilateral exophthalmos, requiring exclusion of other etiologies of proptosis
- b. Atypical ocular motility disturbance and diplopia
- c. Clinical findings of optic neuropathy – evaluate for orbital apex compression
- d. Pre-operative assessment prior to orbital decompression

# Imaging Findings

## Computed Tomography

### 3. EOM enlargement

- a. Average EOM measurements: inferior 4.8 mm, medial 4.2 mm, superior 4.6 mm, lateral 3.3 mm
- b. EOM enlargement secondary to acute inflammatory and chronic fibrofatty changes, with **sparing of tendons**
- c. Most commonly bilateral and enlargement of all EOM, but may also be unilateral (30%) and isolated to one EOM.
- d. Initial description of TAO by Enzmann et al. [1979] found that medial and inferior rectus muscles were most frequently and disproportionately involved compared to other EOM groups
- e. On contrary, Nugent et al. [1990] and Feldon et al. [1985] reported proportional enlargement of all EOM
  - TAO is 1.5 times normal EOM size in patients with TAO and 2 times normal EOM size in patients with optic neuropathy [Nugent 1990]
- f. Clinically apparent ocular motility dysfunction correlated with significantly increased mean muscle diameters [Nugent 1990].

# Imaging Findings

## Computed Tomography

### 4. Exophthalmos

- a. Globe protrusion more than 21 mm anterior to interzygomatic line on axial CT scans at level of lens.
- b. More commonly secondary to EOM enlargement than increased retrobulbar fat.

# Imaging Findings

## Computed Tomography

### 5. Apical Crowding

- a. Most typical cases of optic neuropathy can be diagnosed clinically.
- b. Indication for CT: patients who cannot adequately perform tests; optic neuropathy is symmetric or complicated by concomitant ocular abnormalities
- c. Grade 1: 0-25% effacement of perineural fat; Grade 2: 25-50%, Grade 3: >50%
- d. Majority of patients (2/3) with optic neuropathy demonstrated Grade 3 [Barrett 1988].
- e. *Diagnosis of optic neuropathy should not be made in absence of clinical exam findings of optic neuropathy.*

# Imaging Findings

## Computed Tomography

### 6. Superior Ophthalmic Vein (SOV)

- a. Dilation secondary to compression of SOV drainage at orbital apex by enlarged EOM
- b. Significant increase in SOV diameter (approx  $2.4 \text{ mm} \pm 1.1 \text{ mm}$ ) on axial CT in patients with optic neuropathy compared to patients with no optic neuropathy [Nugent 1990]

# Imaging Findings

## Computed Tomography

### 7. Optic Nerve Sheath Complex

- a. Significant increase in diameter of retrobulbar optic nerve sheath on axial CT in patients with optic neuropathy
- b. Secondary to cerebrospinal fluid accumulation within subdural space
- c. Differential: optic neuritis, elevated intracranial pressure, orbital pseudotumor, optic nerve tumors



# Imaging Findings

## Computed Tomography

### 8. Lacrimal Gland

- a. Gland enlargement and displacement of more than 50 percent anterior to frontozygomatic process in patients with optic neuropathy [Nugent 1990]



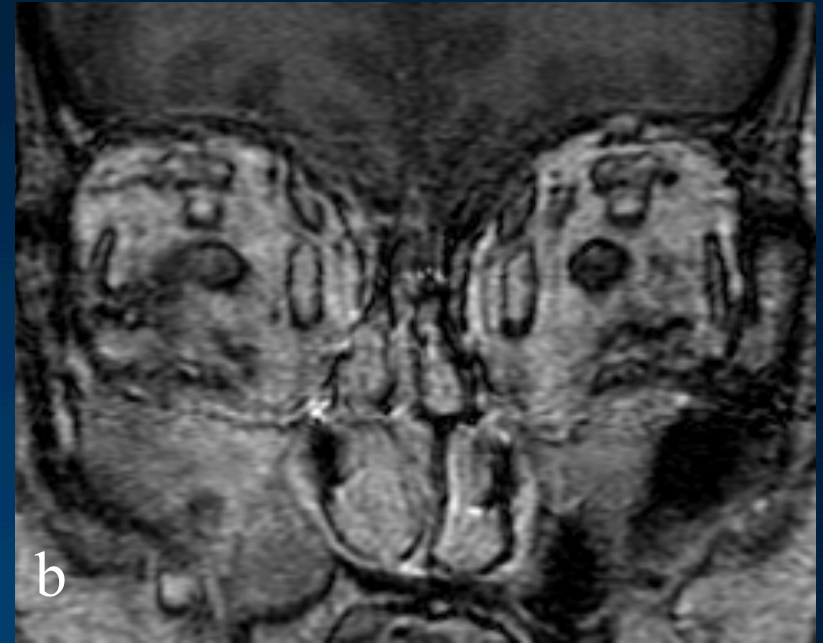
**Figure 4. EOM.** Coronal reconstruction from a CT of the orbits demonstrating enlargement of the inferior and medial EOM.



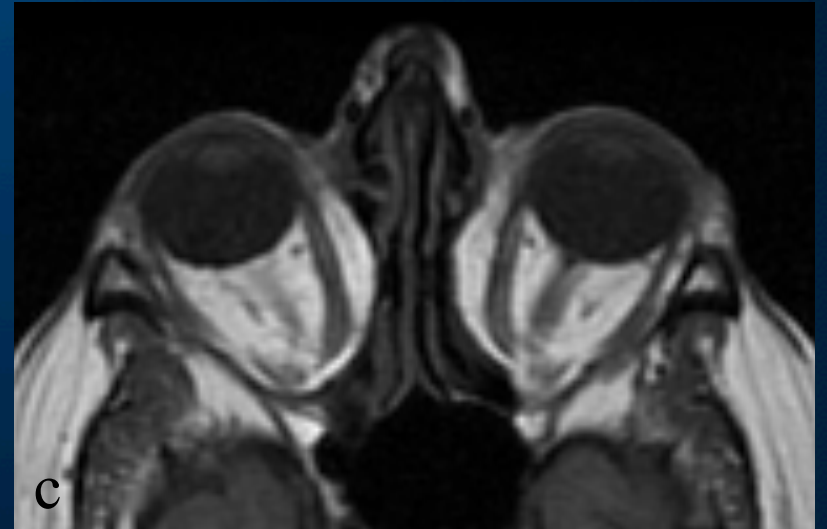
**Figure 5. EOM.** Coronal CT reconstruction exhibiting enlargement of the superior, medial, inferior and left lateral EOM.

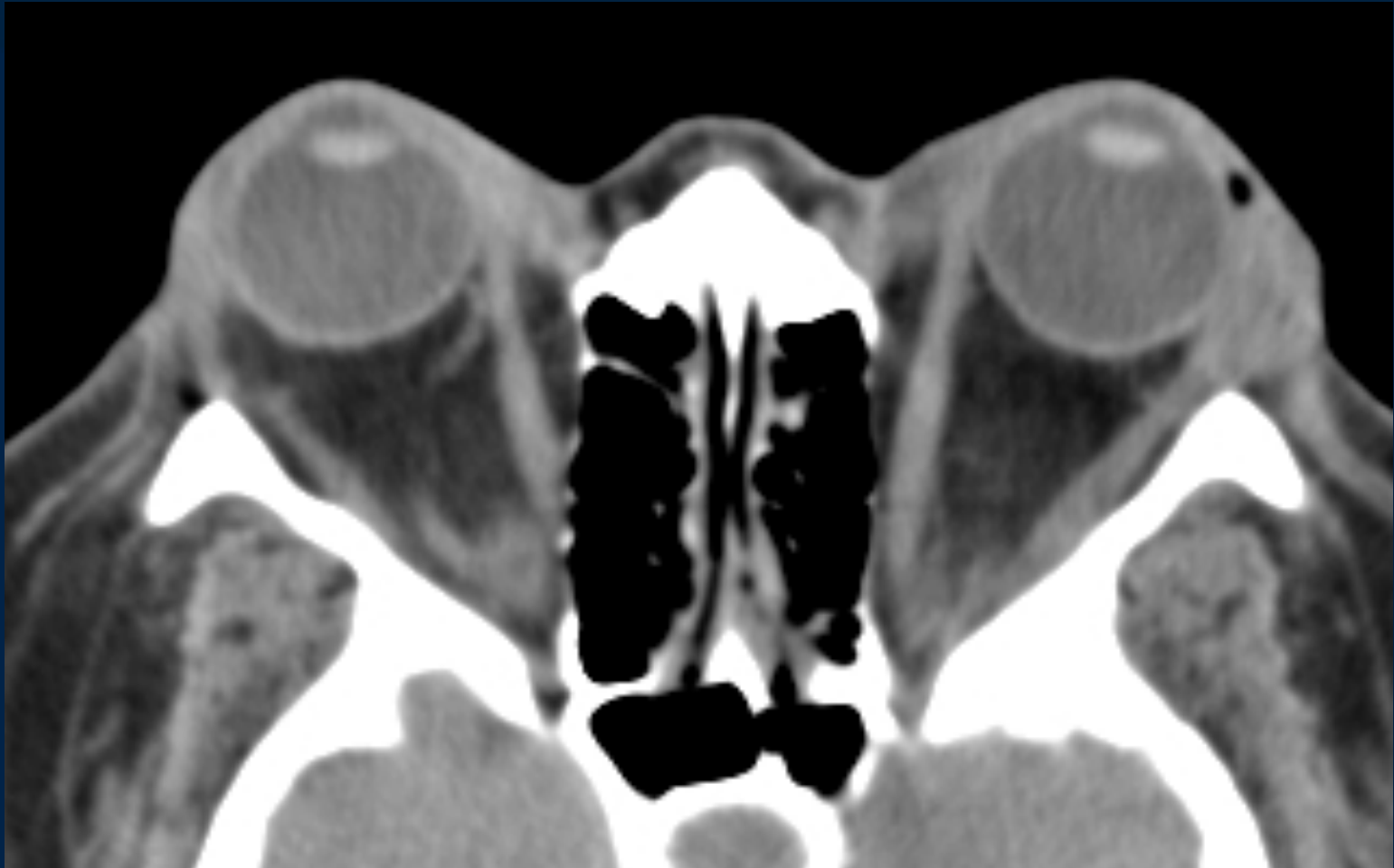


**Figure 6. Diffuse EOM enlargement.** Coronal (a) and sagittal reconstructions from a CT of the orbits demonstrating diffuse enlargement of all EOM's. Note sparing of perineural fat.

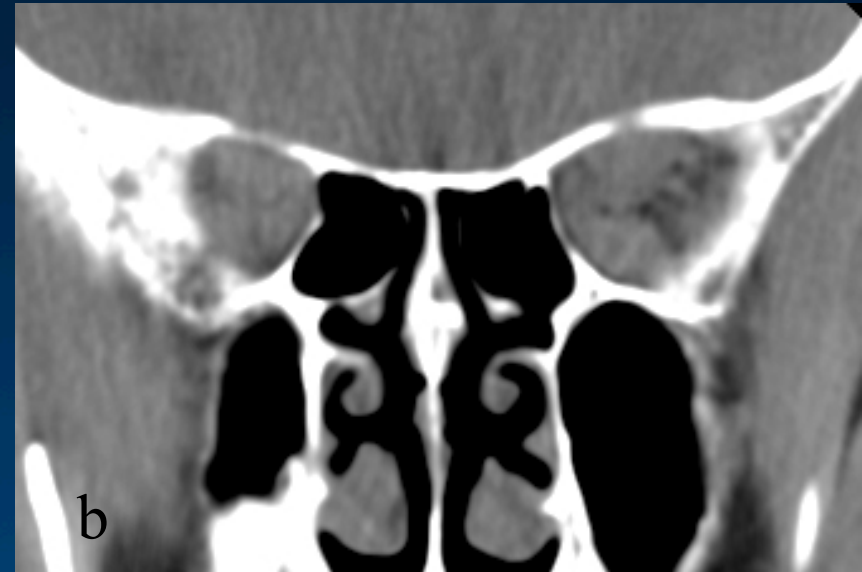


**Figure 7. Increased retroorbital fat.** Coronal reconstruction (a) from a CT of the orbits demonstrating increased retroorbital fat resulting in exophthalmos. Coronal (b) and axial (c) T1-weighted images from an MR of the same patient also revealing increased retroorbital fat.





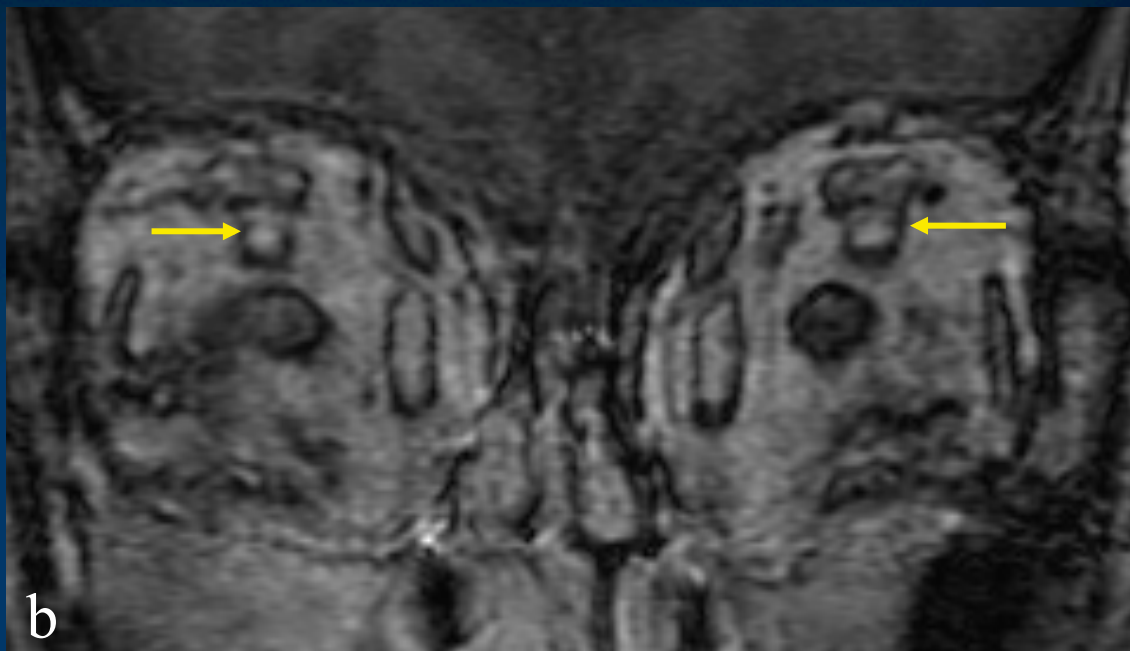
**Figure 8. Exophthalmos.** Axial CT reveals globe protrusion more than 21 mm anterior to the interzygomatic line.



## Figure 9. Apical crowding.

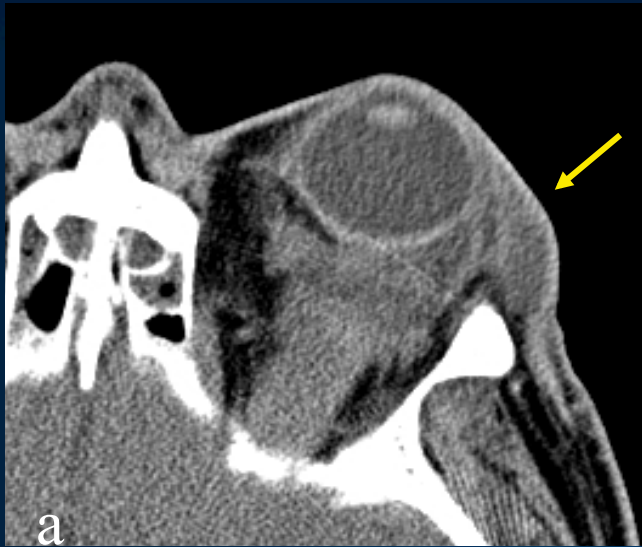
Coronal reconstructions (a and b) from a CT of the orbits demonstrates diffuse EOM enlargement at the apex with partial loss (25-50%) of perineural fat planes. Tc-99m thyroid scan (c) of the same patient with Graves revealing diffuse increased uptake in an enlarged gland. 24 hr I-123 thyroid uptake was 84%.





**Figure 10. Superior ophthalmic vein dilation.** Mild dilation of the superior ophthalmic vein bilaterally (*arrows*) on axial T1-weighted (**a**) and post-contrast coronal SPGR (**b**) images.





**Figure 11. Lacrimal gland enlargement.** CT of the orbits reveals mildly edematous left lacrimal gland (*arrow*) on axial image (a), infiltration of the retro-orbital fat secondary to inflammatory changes on axial (b) and coronal reconstruction images (c), and dilated right superior ophthalmic vein (*dashed arrow*) on sagittal reconstruction (d).

# Imaging Findings

## Magnetic Resonance Imaging

1. MR can help differentiate between active and inactive states of inflammation

# Imaging Findings

## Magnetic Resonance Imaging

2. Normal EOM demonstrate
  - a. Low signal on T1-weighted
  - b. Intermediate signal on T2-weighted
  - c. Intense enhancement on post-contrast fat suppressed T1-weighted images secondary to extensive capillary network.

# Imaging Findings

## Magnetic Resonance Imaging

3. Active inflammation results in edematous changes of the EOM:
  - a. Enlarged EOM
  - b. **Increased T2-weighted signal**
  - c. May show decreased contrast enhancement (suggesting impaired microcirculation)

# Imaging Findings

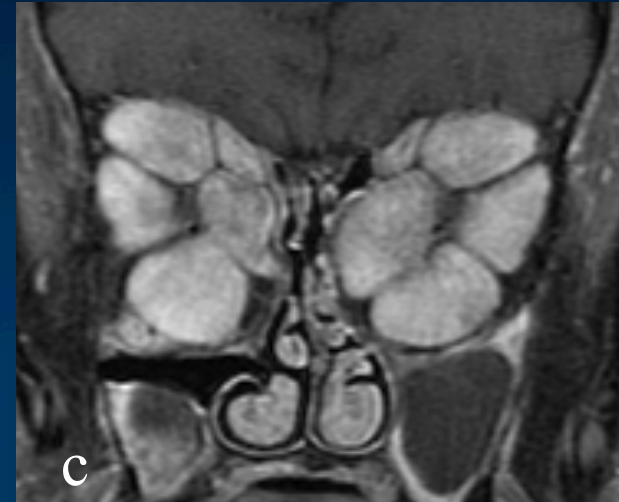
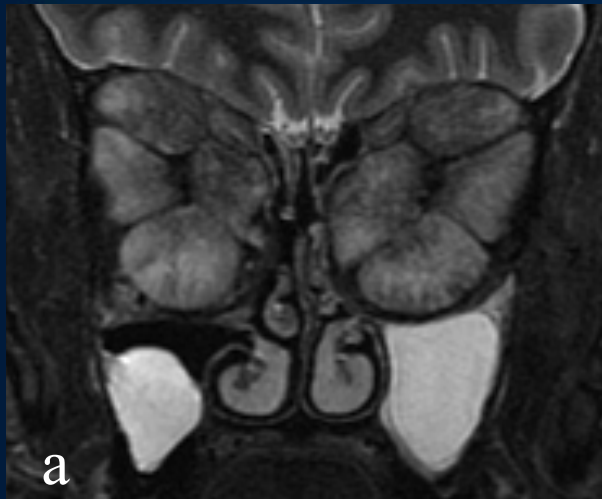
## Magnetic Resonance Imaging

4. **Chronic fibrotic changes:** normal or decreased size of EOM and **decreased signal on all sequences.**

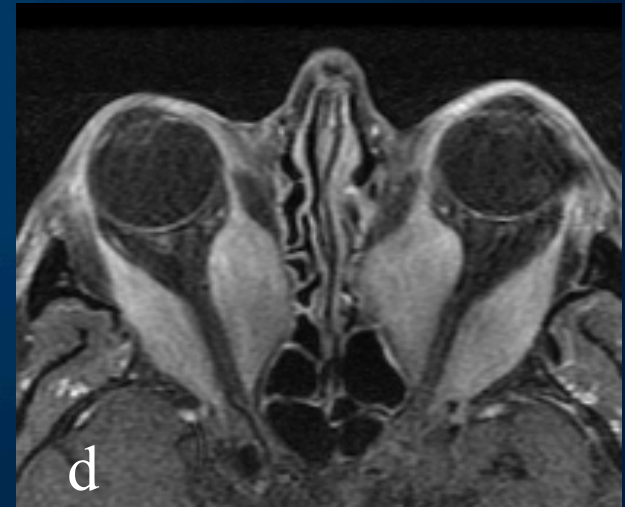
# Imaging Findings

## Magnetic Resonance Imaging

5. Foci of increased T1- and T2-weighted images represent fatty degeneration of muscles.



**Figure 12. Active inflammation of EOM.** MR of the orbits demonstrate diffuse EOM enlargement and increased signal on coronal inversion recovery (a), decreased signal on coronal T1-weighted (b), and homogeneous enhancement on post-contrast coronal (c) and axial (d) T1-weighted images.

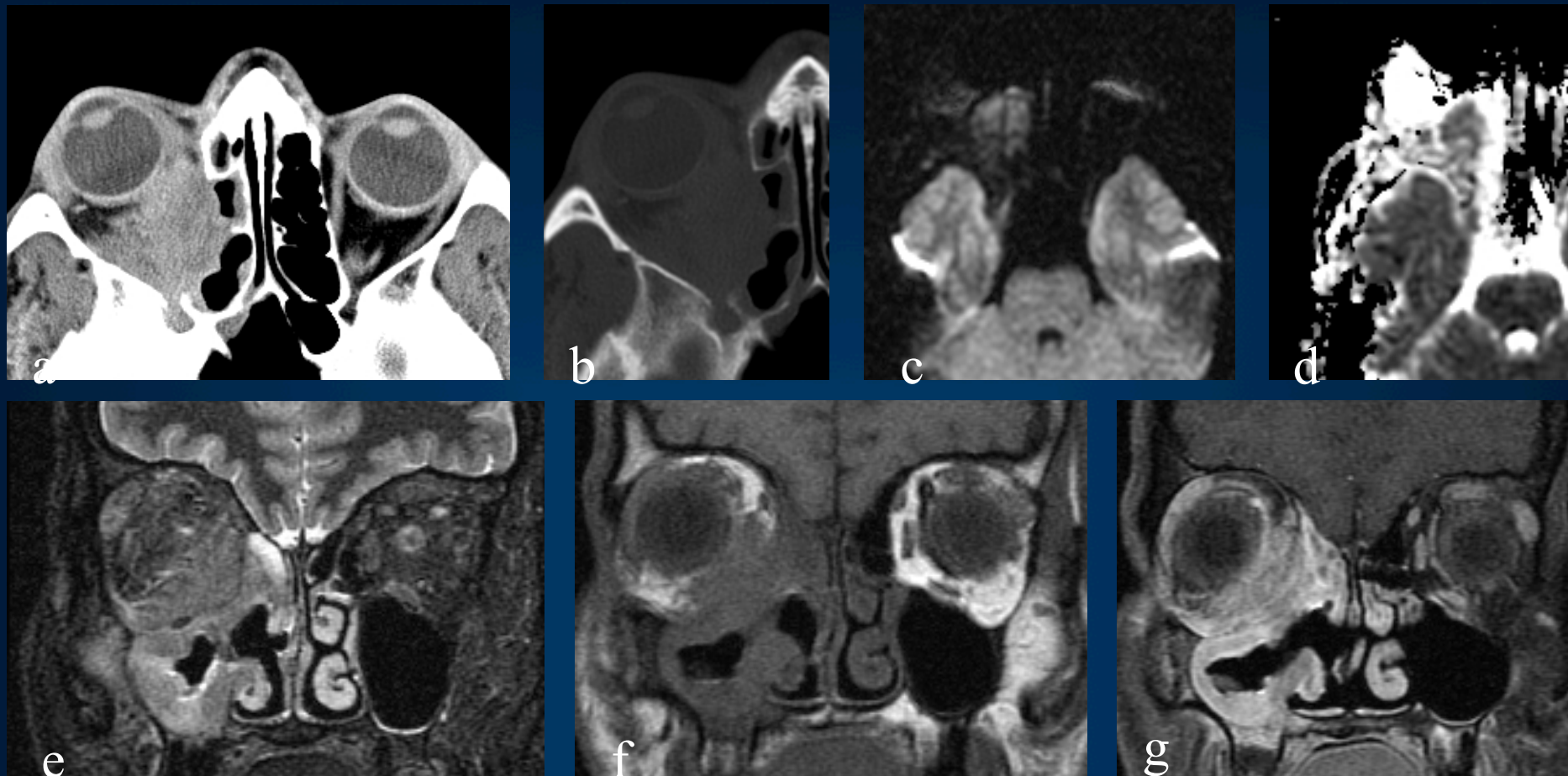


# Differential Diagnosis

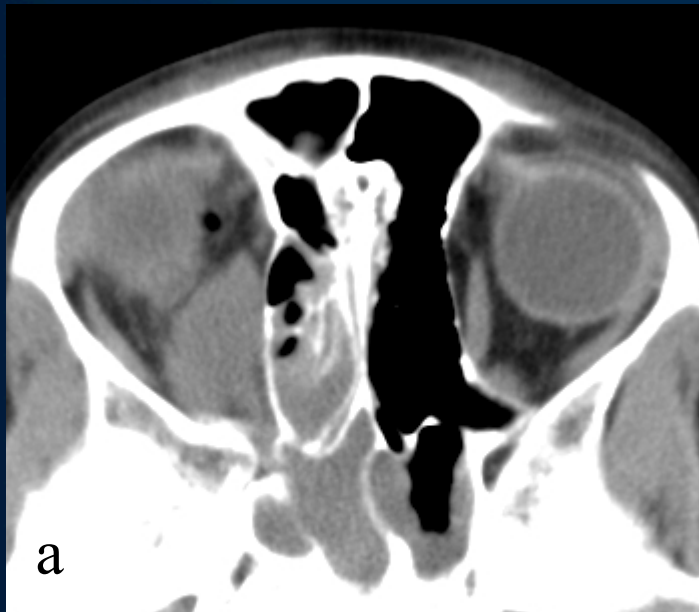
## 1. Inflammatory pseudotumor

- a. Common cause of unilateral proptosis
- b. Pathology: Idiopathic inflammatory process involving B/T-cells and myofibroblastic spindle cells
- c. Clinical manifestations: orbital pain over several months, exophthalmos, uveal and scleral thickening, diplopia, ptosis, reduced ocular motility, chemosis, decreased vision in severe cases
- d. CT: Moderately enhancing mass with associated fat infiltration/edema, bony erosion, remodeling, sclerosis and frank destruction Tendon involvement with EOM inflammation.
- e. MR: May present with lacrimal gland enlargement, diffuse thickening along ocular wall or optic nerve, ill-defined infiltration within orbit, or uniform unilateral enlargement of one or more EOM.
  - Iso- to hypointense on T1-weighted images
  - Hypointense on T2-weighted sequences
  - Variable enhancement on post-contrast T1-weighted images.





**Figure 13. Inflammatory pseudotumor.** Contrast enhanced axial CT image of the orbit in soft tissue (a) and bone windows (b) demonstrate ill-defined enhancing retroorbital mass eroding into the right ethmoid air cells. MR orbits reveals restricted diffusion of the retroorbital mass on DWI (c) and ADC map (d), heterogeneous increased signal on coronal T2-weighted (e), isointense signal on T1-weighted (f), and heterogeneous enhancement on post-contrast T1-weighted (g) images.



**Figure 14. Inflammatory pseudotumor.** CT of the orbits reveal a right retroorbital intraconal mass extending into the right maxillary sinus with bony destruction on axial (a) and coronal recons in bone window (b) and post-contrast (c) images.

# Differential Diagnosis

## 2. Myositis

- a. Denotes inflammation limited to the EOM
- b. Etiology: idiopathic (related pathologically to pseudotumor without presence of inflammatory mass), infectious or autoimmune etiologies
- c. Clinical manifestations: acute orbital pain, diplopia, proptosis, eyelid swelling, conjunctival injection
- d. Imaging
  - Unilateral or bilateral, single or multiple muscle involvement
  - Enlarged edematous muscles (increased T2-weighted signal)
  - May involve tendon insertion onto globe

# Differential Diagnosis

## 3. Lymphoproliferative malignancies

- a. Uncommon site of involvement, representing 1-5 % of all patients
- b. Pathology: Typically **Non-Hodgkin's** lymphoma
- c. Clinical manifestations: gradual onset painless swelling of the eye or low-grade proptosis, blurred vision or floaters
- d. Imaging:
  - Focal (lacrimal gland) or diffuse
  - **Commonly posterior segment of the eye** but can occur anywhere within orbit
  - CT: Iso to slightly hyperdense, typically moderate diffuse enhancement
  - MR: Iso to slightly hyperintense on T1- and T2-weighted sequences, mild to marked homogeneous enhancement

# Differential Diagnosis

## 4. Metastases

- a. Uncommon cause of unilateral exophthalmos
- b. Pathology: Most commonly **breast** followed by **lung**; other primary sites include choroid, GI, prostate, transitional cell, melanoma
- c. Clinical manifestations: Diplopia and eye lid swelling, visual loss, orbital pain and proptosis
- d. Imaging: Invasive mass more commonly involving the retroorbital fat and bone than EOM with heterogeneous enhancement
- e. Median survival is slightly over 1 year.

# Differential Diagnosis

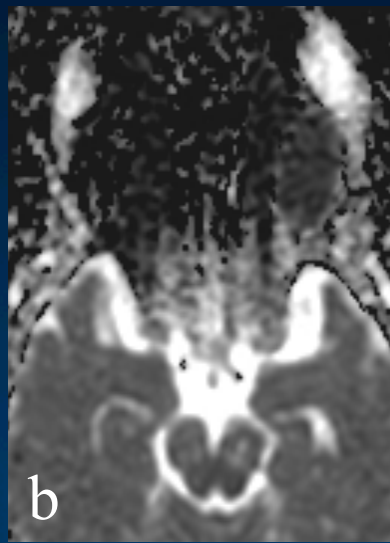
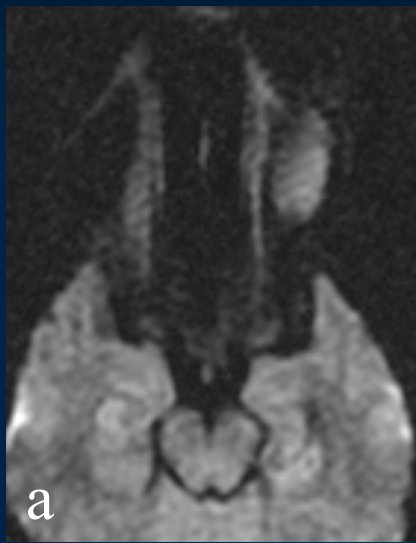
## 5. Sarcoid

- a. **Ophthalmologic involvement is common** among patients with sarcoid (20-25%)
- b. Pathology: Non-caseating granulomas
- c. Clinical manifestations: **Anterior uveitis**, lacrimal gland enlargement, proptosis, eyelid swelling, visual changes
- d. Imaging
  - Ga-67: non-specific uptake which may help confirm diagnosis
  - CT: enlarged lacrimal gland and EOM (uncommon), thickening of optic nerve or uveal sclera, abnormal enhancement of optic nerve
  - MR:
    - i. Enlarged lacrimal gland with isointense signal on T1-weighted, hypointense signal on T2-weighted and homogenous enhancement
    - ii. EOM enlargement with significantly decreased signal on T2-weighted images.

# Differential Diagnosis

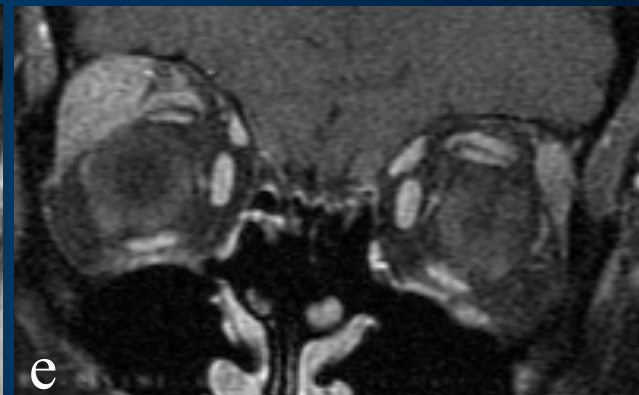
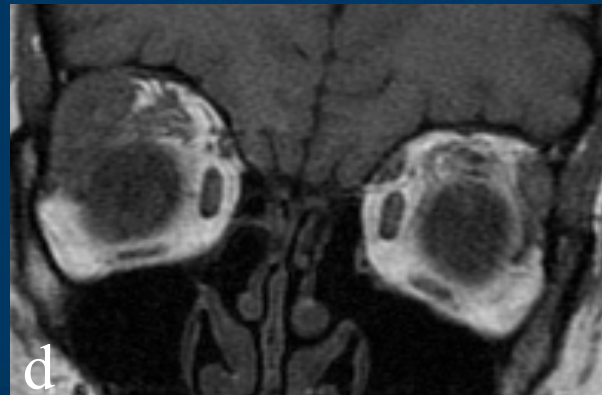
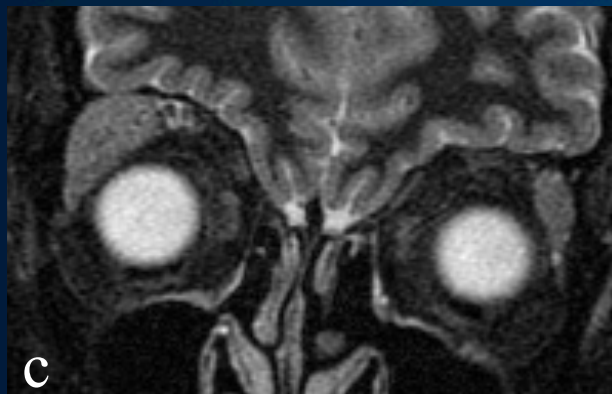
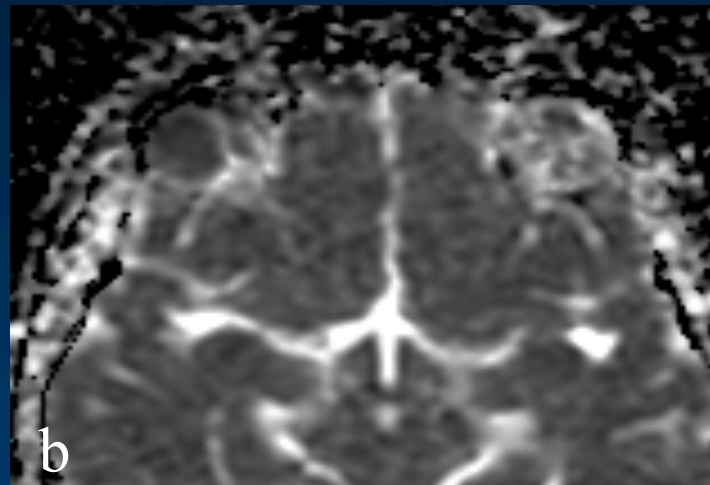
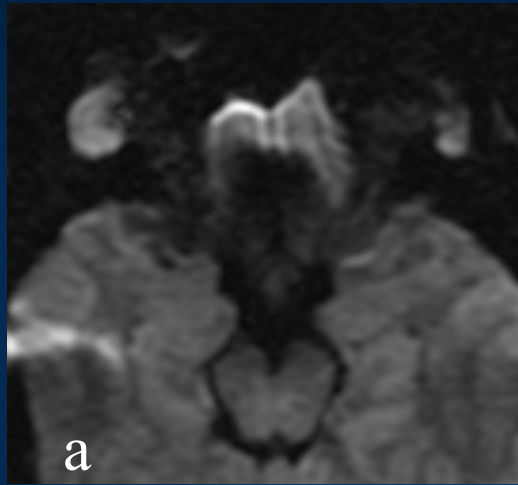
## 6. Carotid cavernous sinus fistula

- a. Etiology: Traumatic or spontaneous
- b. Pathology: Abnormal fistulous connection between carotid artery and cavernous sinus with anterior venous drainage
- b. Clinical Manifestations: Unilateral proptosis, orbital pain
- c. Imaging: dilated SOV, engorged orbit and EOM
- d. SOV may thrombose

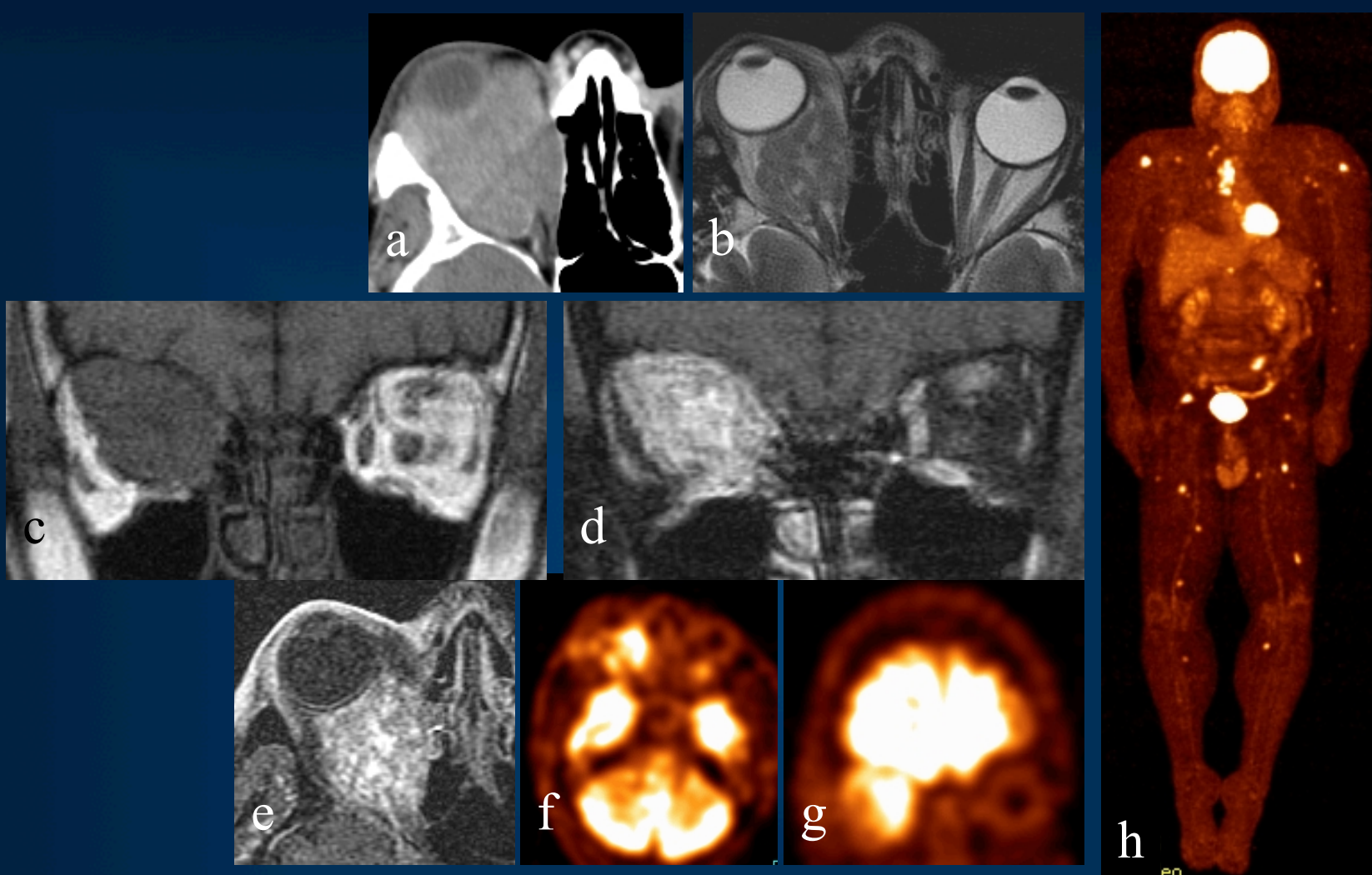


**Figure 15. Lymphoma.** MR of the orbits demonstrates a lobulated retroorbital intraconal mass which exhibits restricted diffusion on DWI (a) and ADC map (b), isointense signal on axial T2-weighted (c), sagittal T1-weighted (d) and no enhancement on post-contrast T1-weighted (e) images.





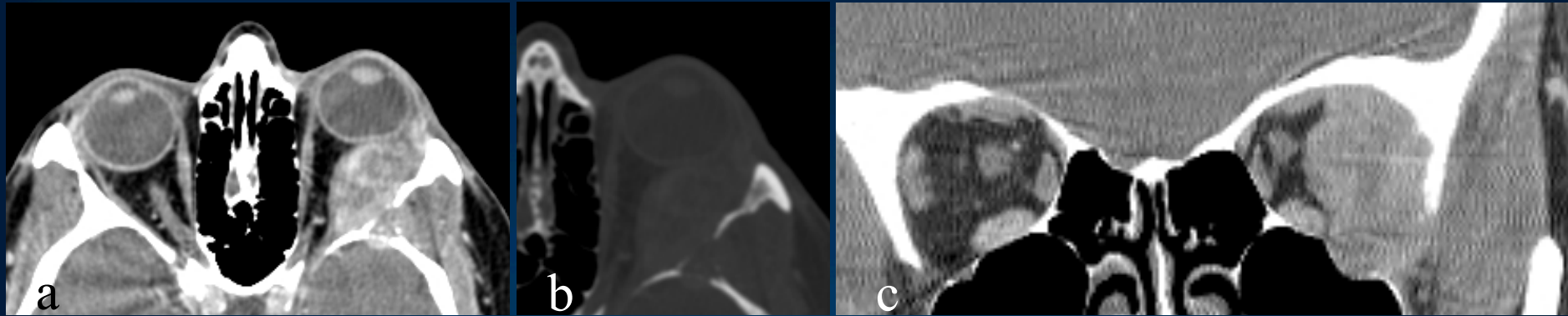
**Figure 16. Lymphoma.** MR of the orbits reveals enlargement of the right lacrimal gland, which exhibits restricted diffusion on DWI (a) and ADC map (b), mildly increased signal on coronal T2-weighted, isointense signal on T1-weighted and homogeneous enhancement on post-contrast T1-weighted (e) images.



**Figure 17. Metastatic melanoma.** Right retroorbital intraconal mass that demonstrates heterogeneous high attenuation on non-enhanced axial CT (a), isointense signal on axial T2-weighted (b) and coronal T1-weighted images (c), heterogeneous enhancement on post-contrast coronal (d) and axial (e) T1-weighted images, and hypermetabolic activity on axial (f) and coronal (g) on F-18 FDG PET images (max SUV 8.2). **Note** diffuse metastasis on whole-body F-18 FDG MPR image (h).



**Figure 18.** Metastatic squamous cell carcinoma. Contrast-enhanced axial CT reveals invasive right extraconal mass extending beyond the lateral wall of the orbit.



**Figure 19. Metastatic adenocarcinoma.** Invasive left extraconal mass extending beyond the lateral wall and floor of the orbit with destructive changes involving the greater sphenoid bone. Contrast-enhanced axial CT in soft tissue (a) and bone windows (b), and two coronal reconstructions (c and d).



# Summary

1. TAO is a common manifestation of Graves disease
2. TAO results from an increase in adipose/EOM volume, involving a positive feedback loop of autoimmune, cellular and mechanical processes.
3. CT findings include EOM enlargement, increased retroorbital fat, proptosis, apical crowding, SOV dilation, optic nerve sheath dilation and lacrimal gland enlargement
4. MR can also detect EOM edema and chronic fibrosis.
5. Differential includes pseudotumor, lymphoma, sarcoid and myositis.

# Take Home Points

- TAO is the most common cause of exophthalmos
- Imaging is not typically needed
- Common indications include asymmetric proptosis and optic nerve dysfunction
- MR can determine presence of active inflammation
- Diagnosis of optic neuropathy should be made in the presence of clinical findings.

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