Thyroid Ophthalmopathy

Department of Ophthalmology

Acknowledgement

- UptoDate: Graves' orbitopathy: Diagnosis and Treatment.
- Cummings Otolaryngology. Girod, Douglas A.; Wemer, Richard D.; Larsen, Christopher G.. Published January 1, 2015. © 2015.
- Endocrinology : Adult and Paediatric. Burch, Henry B.; Bahn, Rebecca S.. Published January 1, 2016. © 2016.
- Some of the images used were taken from eyetext.net

Learning Objectives

- **At the end of this class the students shall be able to :**
- Understand the pathogenesis and clinical features of thyroid eye disease.
- Enumerate and elicit the common eye signs of thyroid ophthalmopathy.
- Have a basic understanding of principles of management of the disease.

Introduction

- Thyroid eye disease is an autoimmune disease producing symptoms related to inflammation, accumulation of fluid in the orbit and also to adipogenesis raising intra-orbital pressure.
- Synonyms
- Graves' ophthalmopathy/orbitopathy (GO)
- Thyroid eye disease (TED)
- Thyroid associated ophthalmopathy (TAO)
- Dysthyroid ophthalmopathy

Epidemiology

- Prevalence of thyroid ophthalmopathy = 0.4%

  Women > Men
- But severity greater in men
- Bimodal age distribution – Peak incidence in fourth and sixth decades of life
- May be exacerbated by stress and smoking
- Most common cause of exophthalmos
- >50% of cases with Graves' disease have eye involvement

Etiology

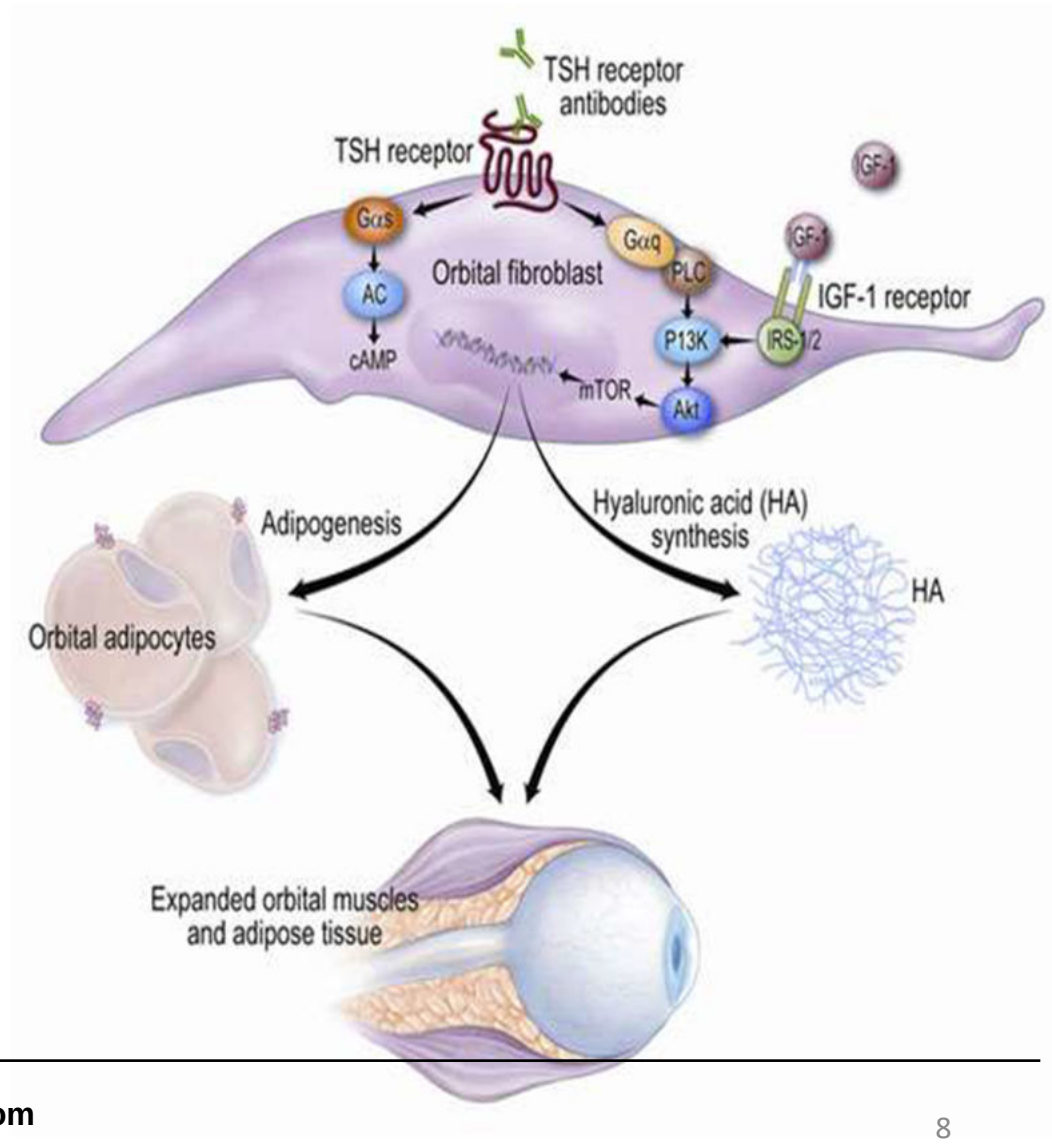
- Graves' hyperthyroidism (90%)
- Hypothyroid Hashimoto's thyroiditis
- Euthyroid subjects with no current or past evidence of thyroid hyper or hypofunction (so called euthyroid Graves' disease).
- In patients with Grave's disease, eye signs may precede, coincide with or follow the hyperthyroidism

Risk factors

- Smoking (strongest modifiable risk factor)
- Family history
- Monozygotic twins

Pathogenesis

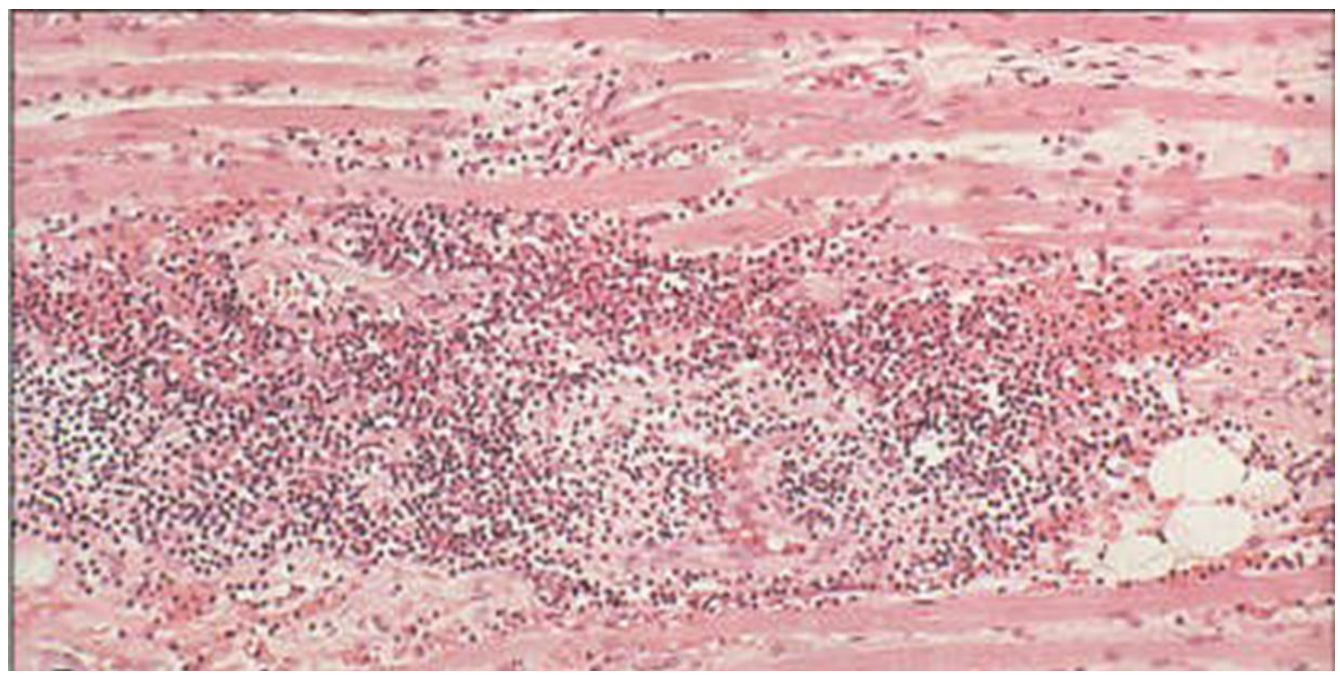
- Autoimmune process manifesting as:
  - Extraocular muscle myositis
  - T-cell inflammatory infiltrate
  - Fibroblast proliferation
  - Glycosaminoglycan overproduction
- Increase in soft tissue mass within bony orbit due to extraocular muscle enlargement, increased orbital fat and connective tissue
- Later in disease, inflammatory infiltrate replaced by widespread fibrosis
- "Inactive" phase occurs after 8months to 3years



pathogenesis

- Pleomorphic cellular infiltrate
- Increased secretion of GAG's
- Osmotic imbibition of water
- Muscular swelling upto 8 times
- Subsequent degeneration leading to fibrosis

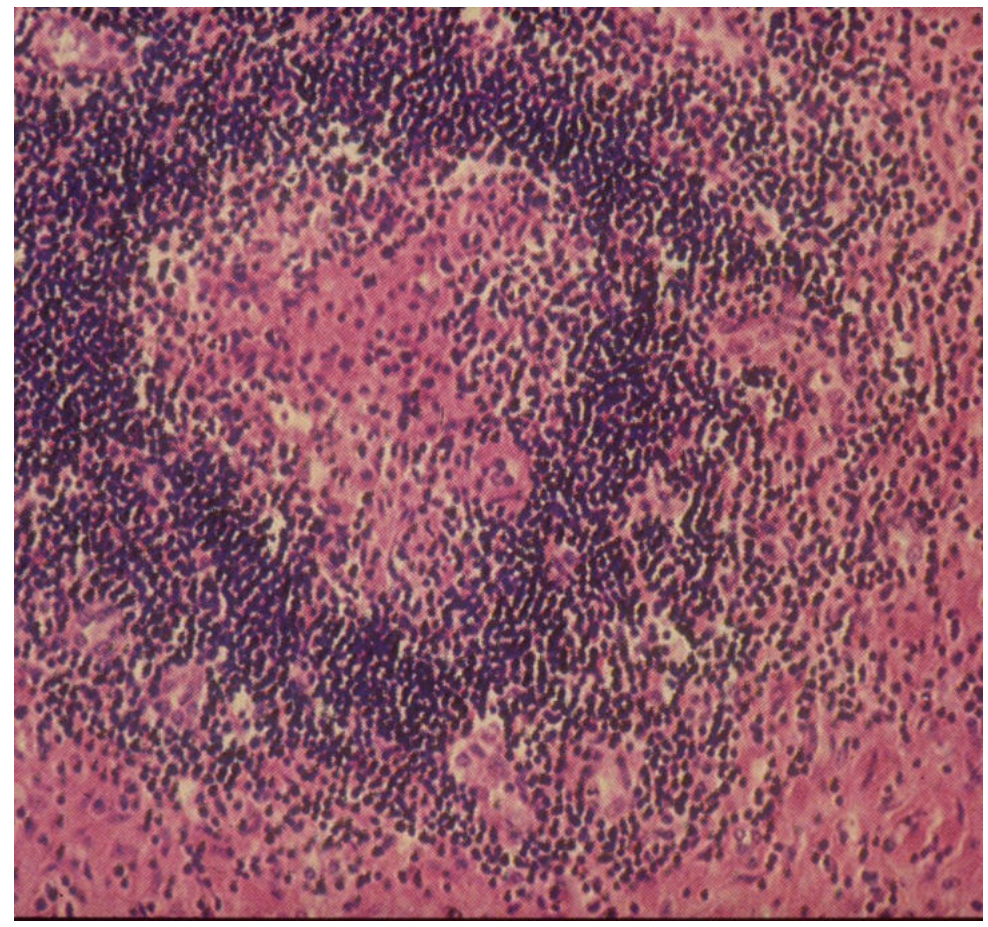
Histology



Fluid and inflammatory cells separate the muscle bundles of the extraocular muscles

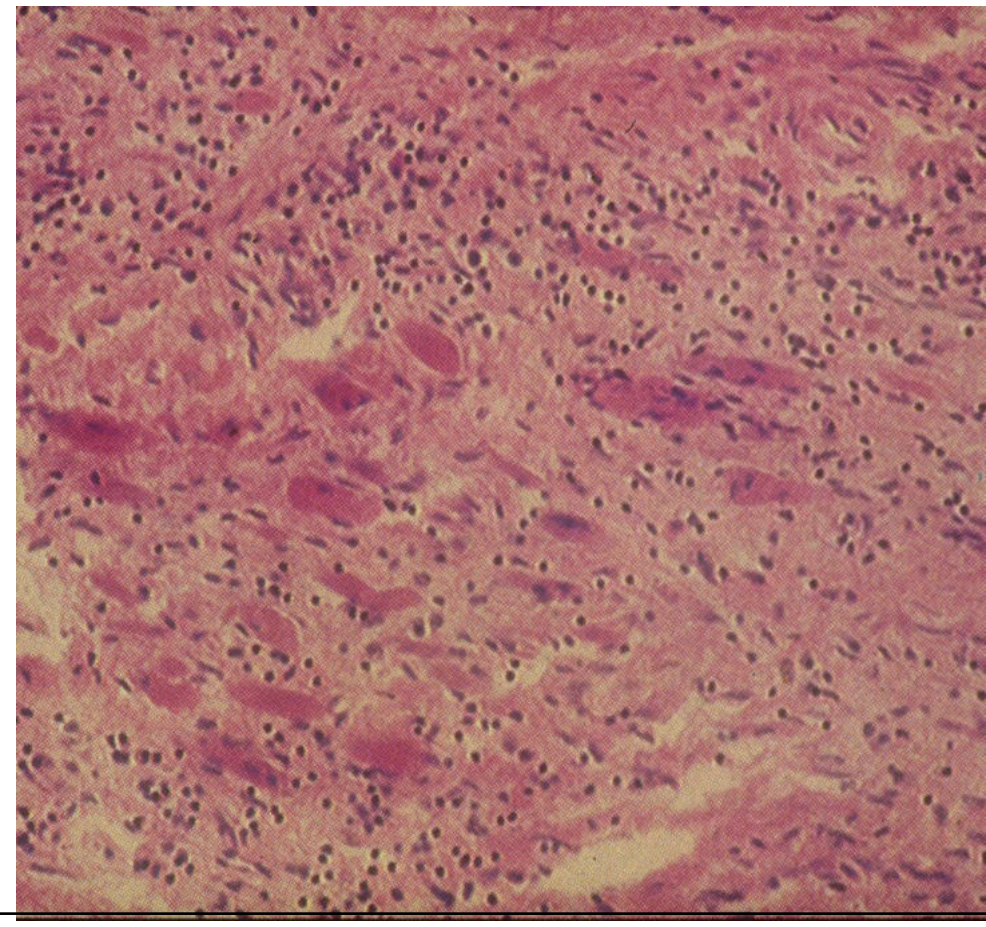
Histology

Lymphocytes, plasma cells, macrophages and mast cells infiltrate extraocular muscles, fat and connective tissue



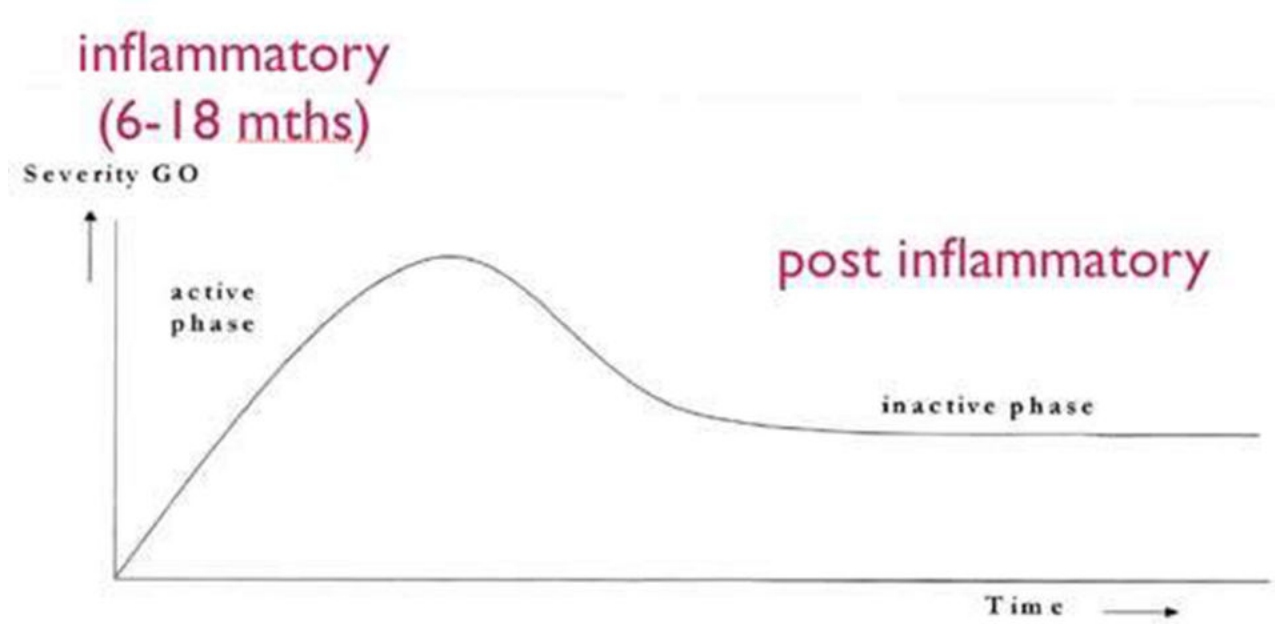
Histology

Degeneration of muscle fibres Leads to fibrosis of the involved muscle



Natural History of Thyroid Eye Disease

- Progressive phase lasting for up to 18 months
- Stable (inactive) phase



Course of disease

- **Inflammatory/active phase**

Fibrotic/inactive phase

Clinical course of orbital disease proceeds independently of thyroid gland dysfunction and treatment

Symptoms

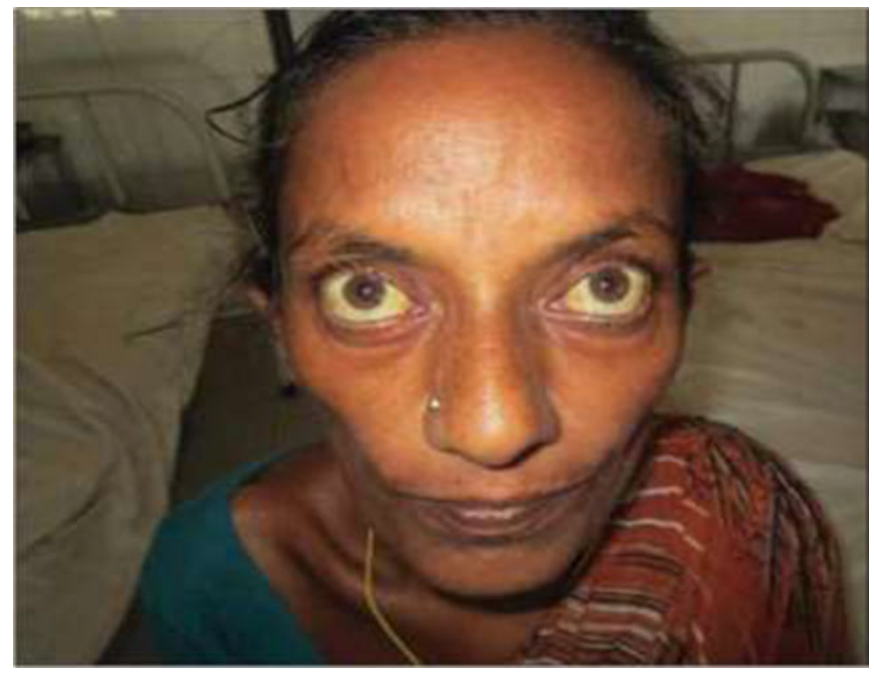
- Foreign body sensation
- Epiphora (tearing)
- Photophobia
- Bulging of eyes
- Puffiness of eye lids
- Diplopia
- Visual loss

Signs

- Eyelid Retraction
- Proptosis
- Restrictive Myopathy
- Soft Tissue Involvement
  --- Conjunctival hyperaemia, lid oedema and chemosis
- Optic Neuropathy

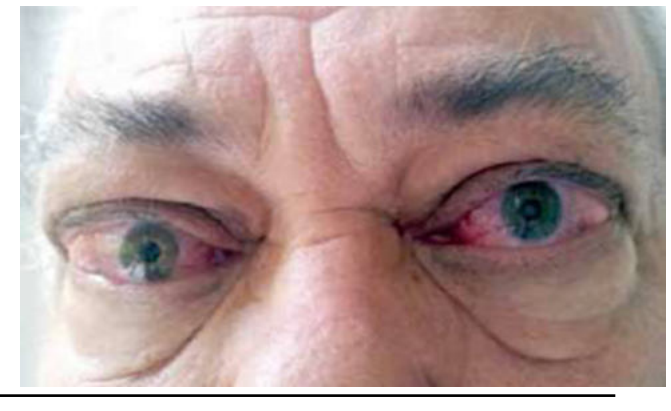
Clinical signs in TED

- **Facial signs**
- Joffroy's sign-absent creases in the forehead on superior gaze



Clinical eye lid signs in TED

- Kocher's sign- staring appearance
- Rosenbach's sign- tremors of eyelids
- Von graefe's sign- lid lag on downgaze
- Dalrymple's sign- lid retraction
- Stellwag's sign- incomplete & infrequent blinking
- Gifford's sign- difficulty in everting the upper lid
- Enroth 's sign- edema of lower lid
- Griffith's sign- lower lid lag on upgaze



Soft Tissue Inflammation

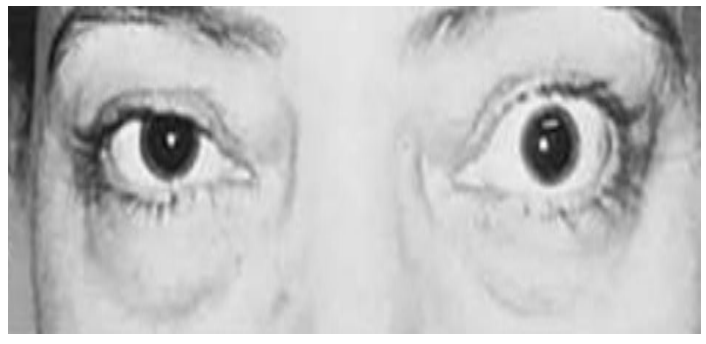
- Often the earliest sign.

  Consists of
- periorbital edema
- conjunctival hyperemia
- chemosis
- superior limbic keratoconjunctivitis

Eyelid retraction

- Also called Dalrymple's sign.
- Normally, upper eyelid- 2mm below limbus
- Lower eyelid-inferior limbus
- When retraction occurs, the sclera (white) can be seen

  Occurs due to :
- Increased sympathetic stimulation of Müller's muscle by thyroid hormone
- Overaction of the levator muscle contracting against a tight inferior rectus

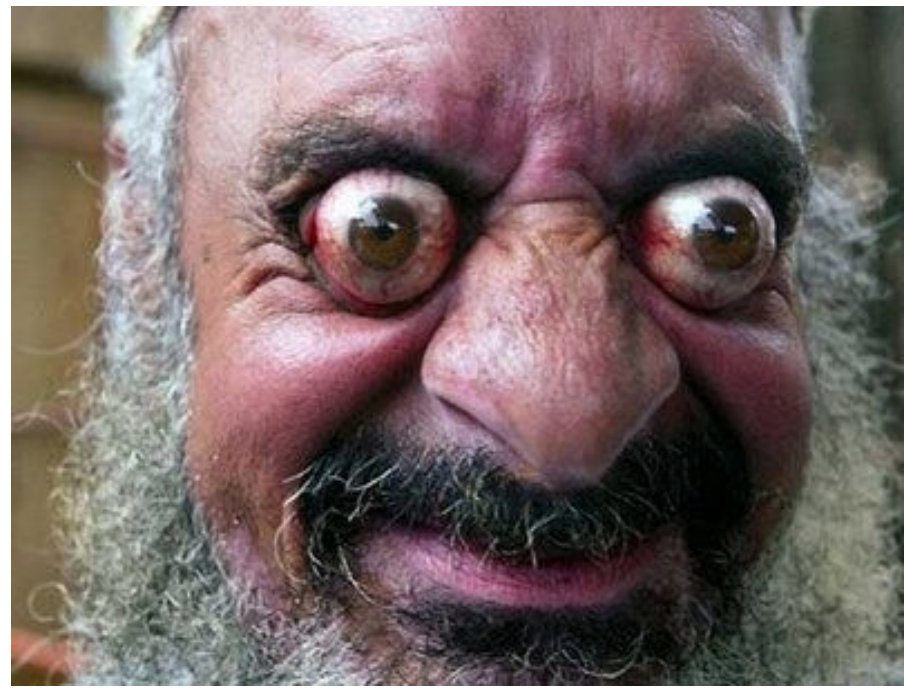


Proptosis

- Usually (90%) bilateral
- Thyroid eye disease is the most common cause of unilateral

  and bilateral proptosis in adults
- Axial
- Resulting from enlargement of the extraocular muscles and adipose

  tissue, as well as orbital fat
- Deposits and the infiltration of orbital tissues by GAGs and leukocytes



Proptosis

- It does not respond to hyperthyroidism treatment
- Is permanent in 70% of cases.
- Severe proptosis prevents adequate lid closure
- May lead to severe exposure keratopathy and corneal ulceration.

Restrictive Myopathy

- Eye movements are restricted due to oedema in extraocular muscles during infiltrative stage and subsequent fibrosis.
- Despite expansion of the extraocular muscles , the muscle fibres themselves are normal.
- IR>MR>SR>LR
- Pressure exerted by a fibrotic inferior rectus muscle on the globe may cause a spike in intraocular pressure during upgaze.

Dysthyroid Optic Neuropathy (DON)

Optic neuropathy as result of optic nerve compression ~~from enlargement of extraocular muscles~~

WERNER´S CLASSIFICATION - NOSPECS

- Class 0: **N**o signs or symptoms
- Class 1: **O**nly signs (lid retraction, stare ± lid lag)
- Class 2: **S**oft tissue involvement
- Class 3: **P**roptosis
- Class 4: **E**xtraocular muscle involvement
- Class 5: **C**orneal involvement
- Class 6: **S**ight loss (optic nerve involvement)

EUGOGO classification

- **Mild** : eyelid swelling , lid retraction, proptosis

- **Moderate-Severe** : Active disease (EOM dysfunction, diplopia , proptosis >25 mm)

- **Very severe** : Compressive Optic Neuropathy , Corneal exposure (needs emergent surgery)

VISA classification

- **V** (Vision) , **I** (inflammation), **S** (Strabismus) , **A** (Appearance)
- Vision/CON
- Inflammation/Congestion : based on documented change of inflammation rather than absolute value
- Strabismus/Motility : measuring ductions and alignments
- Appearance/Exposure
- Score of 5 or more —> Active disease or progression (Consider Steroids)

Differential Diagnosis

- Orbital tumors (primary or metastatic)
- Orbital pseudotumor
- Wegener’s granulomatosis
- Orbital infection
- Carotid-cavernous sinus fistula

Diagnosis

- **Characteristic eye findings**
- **Thyroid dysfunction**
- **Imaging**

Blood investigations

- Highly sensitive & specific -- **T4(thyroxine) + TSH or serum TSH**
- If eye findings associates with euthyroid Graves' disease –
- **Thyroid peroxidase antibody**
- **Antibody to thyroglobulin**

- Others
- **Free T4 index**
- **Thyroid-stimulating immunoglobulin**
- **Antithyroid antibodies**
- **Serum T3**

Radiological Evaluation

- Usually employed if cause of exophthalmos is unclear (ie. normal thyroid lab studies, or history/physical examination inconsistent with thyroid disease)

- Also to determine optic nerve involvement if not obvious by fundoscopic examination.

- Distinct sparing of muscle tendons in thyroid ophthalmopathy.

Radiological Evaluation

- CT scan is currently the imaging study of choice.
- MRI is sensitive for showing compression of the optic nerve.

- Neuroimaging usually reveals
- Thick muscle belly with tendon sparing
- Usually IR & MR
- Bilateral muscle enlargement is the norm
- Unilateral cases usually represent asymmetric involvement rather than normality of the less involved side

Axial and coronal C.T. scan in Thyroid eye disease

33

- Non-contrast enhanced coronal orbital CT scan most helpful to assess size of extraocular muscles.

A

B

Axial CT of orbits demonstrating medial rectus enlargement

Management

- **T** – Tobacco abstinence
- **E** – Euthyroidism
- **A** – Artificial tears
- **R** – Referral
- **S** – Self help groups

Medical Management of Hyperthyroidism

- Anti-thyroid drugs : thinoamides (PTU) , carbimazole , methimazole.
- Thionamides inhibit synthesis of thyroid hormones.
- Need 6-8 weeks to achieve euthyroid state
- Side effects of anti-thyroid drugs
  Skin rash , urticarial , arthralgia , fever

Treatment of mild Thyroid eye disease

Signs / Symptoms	Management Options
Peri-orbital oedema	Elevation head of the bed, anti-diuretics
Dryness, foreign body sensation	Artificial eye drops and ointment
Lagophthalmos	Nocturnal eye taping, eyes shield
Eyelid retraction	Topical Guanethidine or β-blockers eye drops
Diplopia	Prisms
Photophobia	Sunglasses

Symptomatic treatment

- Artificial tears
- Eye shades
- Raise head of bed at night
- Diplopia can be managed with prism glasses
- Eventually may require strabismus surgery
- Conserve useful vision
- Minimize amount of exposed cornea
- May require lid surgery
- Treat optic neuropathy

Selenium

- 200 microgram/day for 6 months
- For Mild disease

- Antioxidant effect
- Immunomodulatory effect : reduce thyroid autoantibodies
- Reduces severity of disease and improve quality of life

Corticosteroids

- Intravenous , Oral
- IV pulses are more effective and have less side effects
- IV dose (max 8 grams) : 500 mg weekly for 6 weeks and then 250 mg weekly for 6 weeks
- Relapse is common (20%)
- Steroid response is evident usually 2-4 weeks later
- Moderate to severe TED : 71% respond to IV steroid vs 51% with oral
- IV steroids for compressive Optic Neuropathy

Rituximab

- Chimeric mono-clonal antibody targets CD20
- CD20 is expressed on more than 95% of B cells and plasma cells
- RTX removes B cells and short-lived plasma cells
- RTX depletes 95% of mature B cells , blocks Ab production , and decreases inflammatory cytokine release
- For steroid-refractory disease
- Side effects : Allergic reaction (mild) PML (severe)

Orbital Radiation

- Mechanism : lymphocyte sterilization, destruction of tissue monocytes
- 20 Gy in 10 divided sessions over 2 weeks
- May have a role in patients with TED who have restricted ocular motility or active disease
- Some studies have shown benefit (controversial)
- More suited for patients > 35 years of age
- Contra-indicated in pre-existing retinopathy (diabetes , hypertensive)

Botulinum Toxin

- Neurotoxin , inhibits acetylcholine release
- For upper lid retraction (transconjunctival , transcutaneous route)
- Effect on Muller’s muscle and LPS
- Side effects of Botox : bruising , ptosis and diplopia

Orbital Decompression for TED

- Decompression usually in stable phase of disease.
- Indications
- compressive optic neuropathy
- severe exposure keratopathy
- Need to discuss goals of surgery with patients.
- Post-operative complications (diplopia, vision loss)
- Outcome is variable : degree of fibrosis , fat expansion , bone available, duration of optic neuropathy.
- Decompression —> Muscle Surgery —> Lid surgery

Strabismus Surgery for TED

- In the stable phase with stable alignments for 6 months
- Aim is single binocular vision in primary and reading position
- Typically involves release of the restricted muscle by recession rather than resection
- Conjunctival dissection is challenging
- Use of adjustable sutures is strongly recommended due to the variability in fibrosis, resulting in unpredictable results.
- Oblique surgery can increase area of single binocular vision

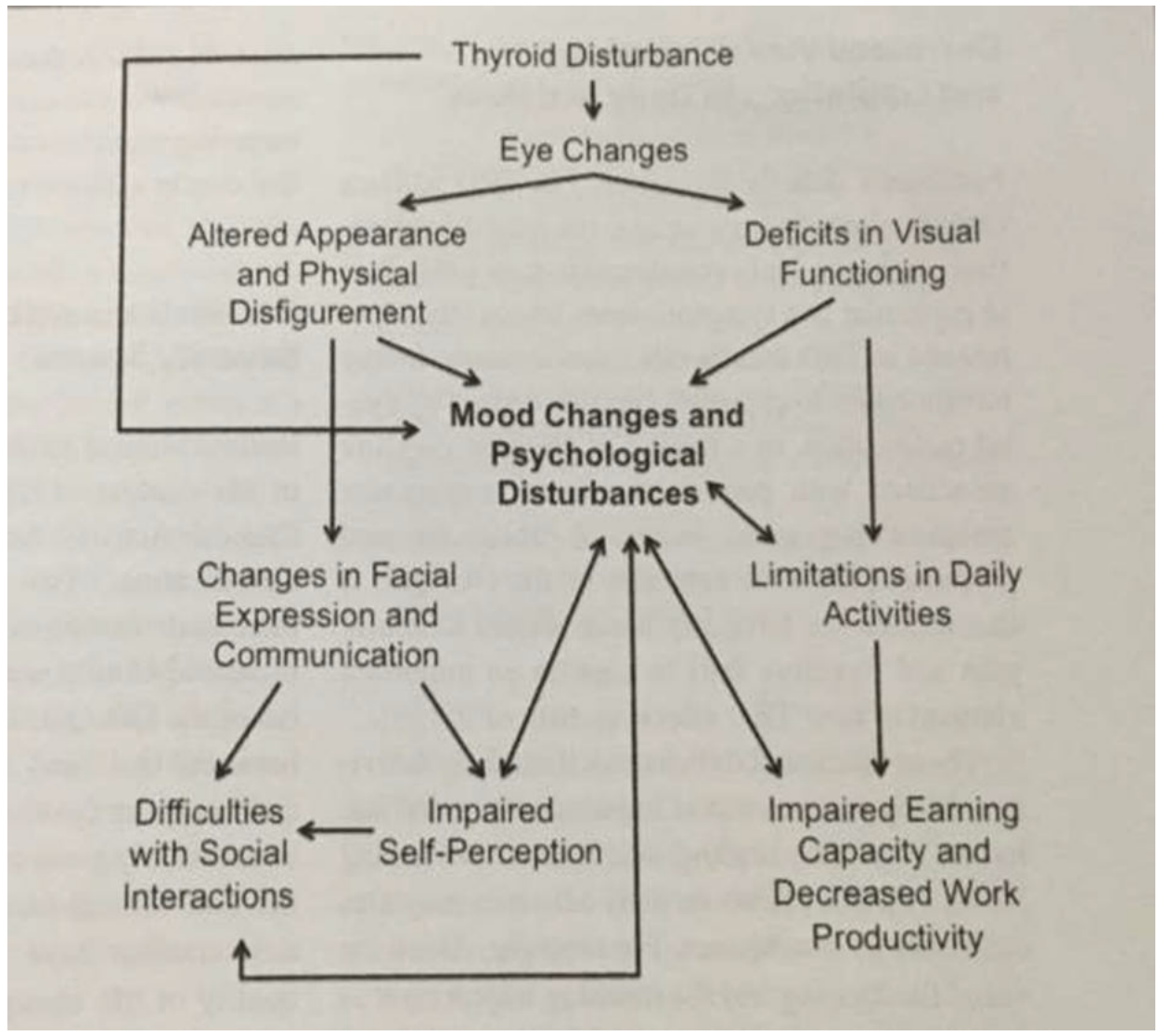
Eye lid surgery

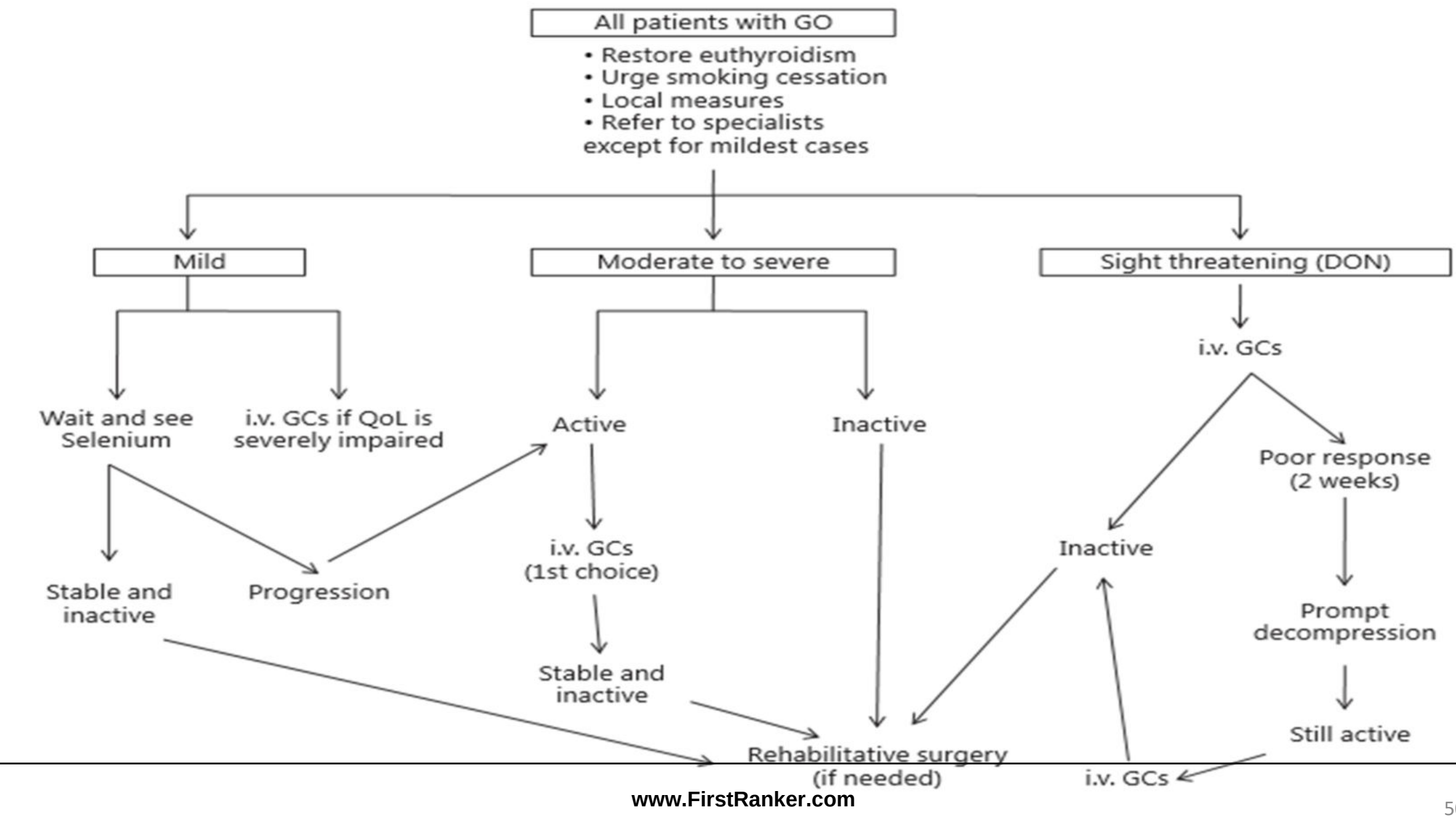
- The most common indication for lid surgery is upper lid retraction.
- Graded Muller's and levator aponeurosis weakening.
- Lower lid lengthening is indicated in lower lid retraction.

Psychological Impact of TED

- Disfigurement/altered facial appearance
- Misinterpretation as hostile or angry
- Almost 50% of TED suffer depression and/or anxiety
- 90% of TED have appearance concerns (young females)
- 44% have self-confidence issues
- Quality of life measures and questionnaires
- Multidisciplinary approach (psychiatric included)
- Support groups

Psychological Disturbances in TED





Conclusion

- Activation of thyrotropin receptor on orbital fibroblast by circulating autoantibodies plays a primary role in development of thyroid ophthalmopathy.
- Management is based on accurate assessment of both severity and activity of disease.
- Immunosuppressive therapy is reserved for patients with clinically active moderate to severe disease

Thank You