Thyroid Eye Disease

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Objectives

- To review the pathophysiology behind Thyroid Eye Disease
- To review current medical and surgical management of Thyroid Eye Disease

Financial Disclosures

- No conflicts of interest to disclose

Pre-Test

- The primary target within the orbit of cross reacting T-lymphocytes that lead to Grave's Ophthalmopathy is:
  - Optic nerve glial cells
  - Orbital fibroblasts
  - Conjunctival goblet cells
  - Corneal endothelial cells
- In surgical management of Grave's related strabismus, the ideal management is
  - Single eye surgery
  - Muscle resection type surgery
  - Muscle recessions, preferably with adjustable sutures
  - Avoidance of adjustable surgery

Thyroid Orbitopathy

- The most common specific inflammatory condition of the orbit
- Most common cause of unilateral and bilateral proptosis

Thyroid Orbitopathy

- Most common in women (6:1)
- Bimodal presentation 40-44 and 60-64
- Median age 43
- Genetic factors - 20-60% of patients have a positive family history.
- Smokers 7 times more likely to develop TED
- May precede, coincide or follow systemic manifestations of thyroid disease.

Thyroid Orbitopathy

- 90% Graves' hyperthyroidism
- 1% primary hypothyroidism
- 3% Hashimoto thyroiditis
- 6% euthyroid

Thyroid Orbitopathty

- Patients w/o history of abnormal thyroid function or regulation at diagnosis of TED risk of developing thyroid disease:
  - 25% within 1 year
  - 50% within 5 years.
- 30% of patients with autoimmune hyperthyroidism have or will develop TED

Thyroid Orbitopathy

- Usually a self limited disease
  - 6 months to 5 years
- Manifestations:
  - Congestion/Inflammation 90%
  - Eyelid retraction 90%
  - Proptosis 60%
  - Myopathy 40%
  - Compressive ON 5%
  - Corneal damage <1%
  - All findings, 5%

Pathophysiology

- Orbital changes caused by various processes
  - Inflammation & edema
  - Fibrosis
  - Fat proliferation

Pathophysiology

- Autoimmune reaction
- Cell and antibody-mediated reaction against TSH receptors
- Cloning of the TSH receptor allowed assessment of TSH-R in extrathyroidal tissues,
  - low abundance of TSH-R in cultured orbital fibroblasts and in normal orbital-adipose tissues.
  - elevated TSH-R in orbital tissues in TED patients, highest in those w/ active disease
- Elevated levels of anti–TSH-R antibodies in TED patients
- This and association b/w TED and Graves' hyperthyroidism support TSH-R as primary autoantigen in TED

Pathophysiology

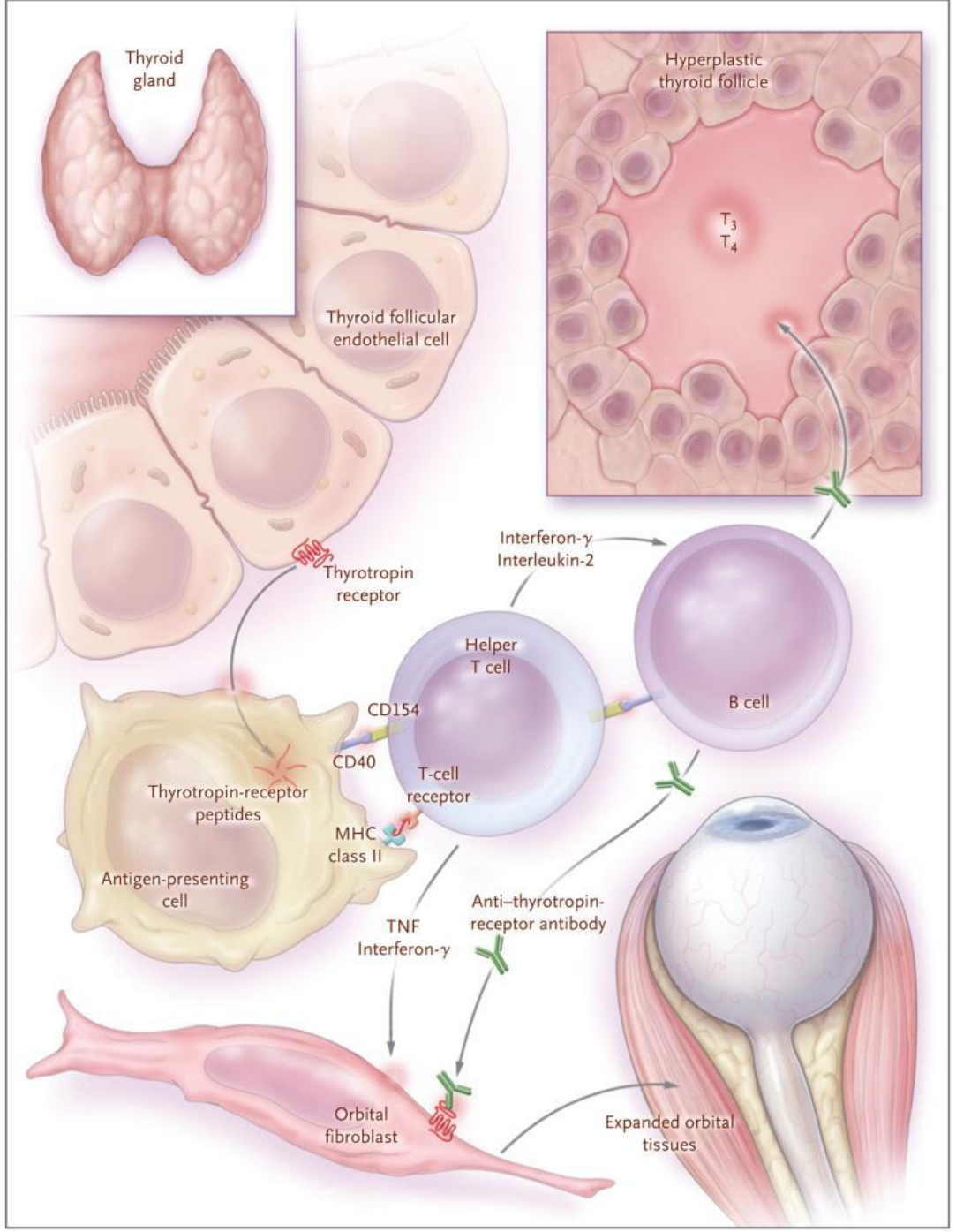
- T-cells react against thyroid follicular cells with common antigenic epitopes with orbital tissue
  - Causes active inflammatory phase
- **Orbital fibroblasts are the target of T-cell lymphocytes.**
  - CD40-receptor + (also found on B cells)
- T-Cells CD154 →CD40-R→pro-inflammatory cytokine production by orbital fibroblasts
  - IL 6, IL-8, PGE2
  - Incr. Hyaluronan and GAG synthesis
- T- cells secrete leukoregulin and interferon-γ
    - increased synthesis of hyaluronan and PGE2 by orbital fibroblasts
- IL-1 and interferon-γ, and IgG from patients with Graves' disease stimulates orbital fibroblasts to express adhesion molecules that promote direct interaction between target cells and inflammatory cells.

Pathophysiology

- Type I insulin-like growth factor receptor (IGF-IR) is another autoantigen in TED
- TED patient's orbital fibroblasts express higher than normal levels of IGF-IR
- Serum from patients w/ Graves' disease stimulates orbital fibroblasts from patients with TED
  - **effect inhibited by monoclonal Ab that blocks IGF-IR**
  - Suggests that signaling through IGF-IR mediates the process

Pathophysiology

- Antigen independent auto-inflammatory response
  - Cytokines and chemokines directly activate cell mediated response
  - Monocytes, NK and granulocytes involved



Bahn, RS. Grave's Ophthalmopathy. N Engl J Med 2010;362:726-38.

Pathophysiology

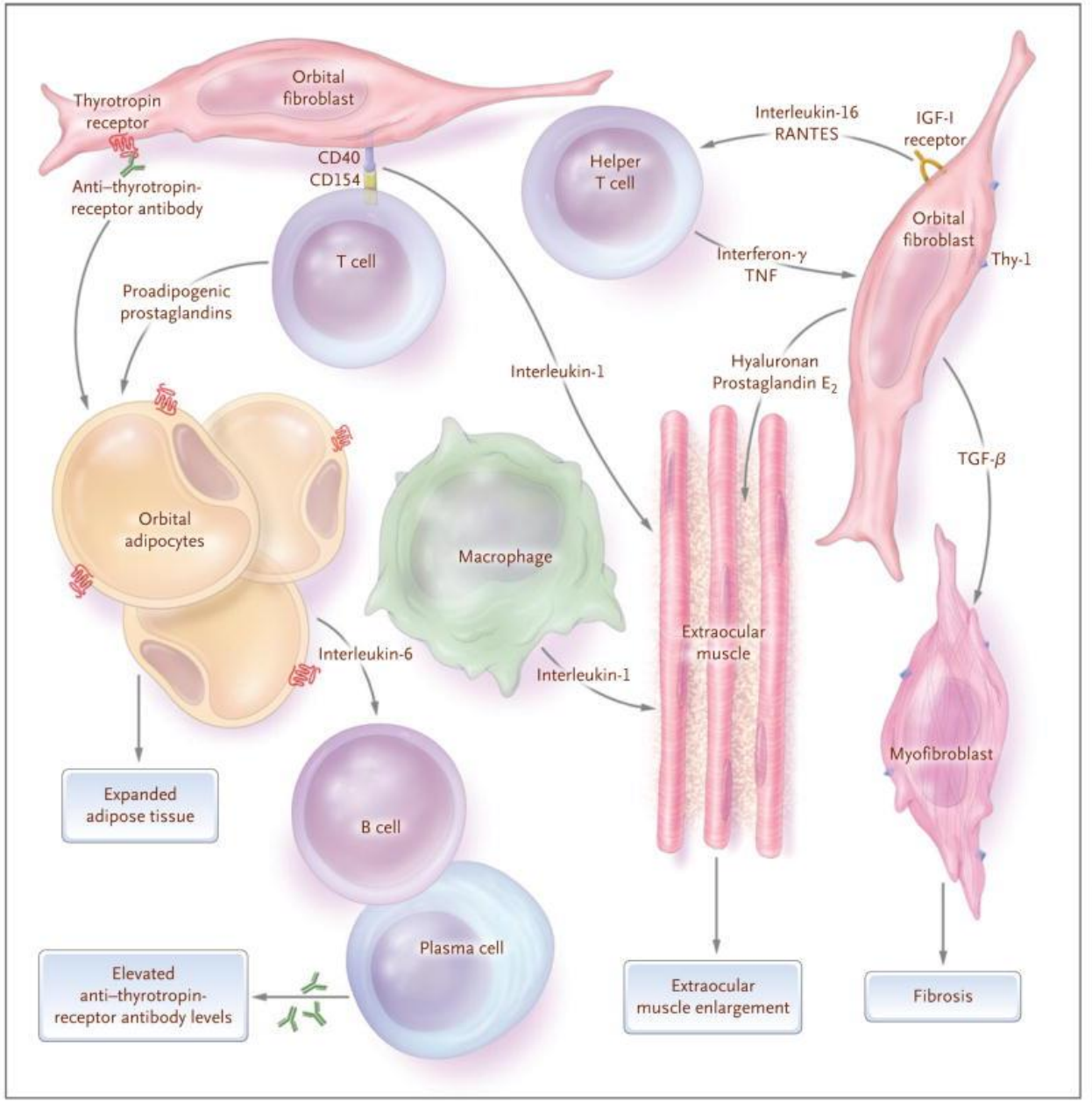
- Increased orbital fat is evident in TED
- Adipogenesis activated by transcriptional regulators→peroxisome-proliferator–activated receptor γ (PPAR-γ)
- Adipogenic genes for PPAR-γ, IL-6, adiponectin, and leptin may be overexpressed in TED
  - PPAR-γ agonists stimulate adipogenesis and expression of TSH receptor in cultured orbital preadipocytes.
- **Proptosis has been noted in patients w & w/o TED, after tx of type 2 DM with PPAR-γ agonists of the thiazolidinedione type.**
  - Thiazolidinedione induced thyroid associated orbitopathy Lee, S, Tsirbas, A. Goldberg, R, et al. BMC Ophthalmol 2007; 7: 8.

Pathophysiology

- Naturally occurring PPAR-γ ligands may stimulate adipogenesis in TED patients
  - COX-2 upregulated in the orbit of TED patients->
  - T cells produce prostaglandins and induce adipogenesis(PPAR-γ ligand)
- TSH can stimulate adipogenesis in mouse embryonic stem cells
  - Activation of TSH-R may initiates new fat-cell development.
- Orbital fibroblasts transfected with a TSH-R activating construct
  - **early adipocyte differentiation occurred**
  - hyaluronan production was stimulated
  - Suggests that TSH-R binding by anti– TSH-R ab in the orbit contribute to development of TED

Pathophysiology

- Cell-surface marker Thy-1 (CD90) is overexpressed in orbital tissues in TED
  - Thy-1 + fibroblasts are capable of producing of PGE2, IL-8, hyaluronan
  - **Thy-1 + fibroblasts differentiate into myofibroblasts that can mediate inflammation, repair, and fibrosis when stimulated by TGF-β**
  - **Fibroblasts w/in EOMs are almost exclusively Thy-1+**
  - **About ½ fibroblasts in adipose tissue are Thy-1 neg and are capable of differentiation into mature fat cells.**
  - **Proportions of Thy-1+ to Thy-1− fibroblasts and their exposure to TGF-β could explain why some fat proliferation vs fibrosis predominates in some patients**


Thyrotropin receptor
Orbital fibroblast
Anti–thyrotropin-receptor antibody
CD40
CD154
T cell
Proadipogenic prostaglandins
Helper T cell
Interleukin-16
RANTES
IGF-I receptor
Orbital fibroblast
Thy-1
Interferon-γ
TNF
Interleukin-1
Hyaluronan
Prostaglandin E_2
TGF-β
Orbital adipocytes
Macrophage
Interleukin-6
Interleukin-1
Extraocular muscle
Myofibroblast
Expanded adipose tissue
B cell
Plasma cell
Elevated anti–thyrotropin-receptor antibody levels
Extraocular muscle enlargement
Fibrosis

M.D.A

- 1st seen 10/01/2015
- Dx w hyperthyroidsm 1 year prior, s/p RIA
- On tx. w Synthroid
- Hx of R.A., on plaquenil
- 1 year ago bilateral redness, tx w lubricants primary OPH
- Progressive changes over 1 year

M.D.A

- VA 20/25 OU, normal IOP
- Exophthalmos w 24mm OD, 23 mm OS
- MRD1 7mm OU, (normal 4-5mm)
- Limited superior ductions, limited abduction OD, Left hypertropia worst in rt gaze sugg of RIR enlargement
- Conjunctival chemosis
- No marcus gunn pupil, normal fundus exam

TED Diagnosis

- 2 of the following 3 signs present:
  - Concurrent or recently treated immune-related thyroid dysfunction (1 or more of the following):
    - Graves hyperthyroidism
    - Hashimoto thyroiditis
    - Presence of circulating thyroid antibodies
      - TSH-receptor (TSH-R) antibodies,
      - thyroid-binding inhibitory immunoglobulins (TBII),
      - thyroid-stimulating immunoglobulins (TSI),
      - antimicrosomal antibody
  - Typical orbital signs (1 or more of the following):
    - Unilateral or bilateral eyelid retraction with (w or w/o lagophthalmos)
    - Unilateral or bilateral proptosis (compared to old photos)
    - Restrictive strabismus in a typical pattern
    - Compressive optic neuropathy
    - Fluctuating eyelid edema/erythema
    - Chemosis/caruncular edema
  - Radiographic evidence of TED—unilateral/bilateral fusiform enlargement of 1 or more of the following :
    - Inferior rectus muscle
    - Medial rectus muscle
    - Superior rectus/levator complex
    - Lateral rectus muscle

M.D.A.

- Assesment: TED w strabismus, eyelid retraction and proptosis
- Active inflammatory stage
- Tx alternatives discussed
  - Indomethacin, FML, lubrication
  - Orbit CT scan
  - Visual field testing

Classification

- Several scales available
  - Clinical activity score (CAS)
  - NOSPECS
  - EUGOGO
  - VISA
- Useful for studies, general guide
- Difficult to use in clinic

CAS

- 10 item list—1 point for presence of ea. item
  - Pain
    - Spontaneous orbital pain in the last 4 weeks
    - Gaze evoked orbital pain in the last 4 weeks
  - Redness
    - Eyelid erythema
    - Conjunctival injection considered to be due to active TED
  - Swelling
    - Eyelid swelling that is considered to be due to active TED
    - Chemosis
    - Inflammation of caruncle or plica semilunaris
    - Increase of ≥ 2 mm in proptosis over 1-3 months
  - Impaired function
    - Decrease in monoocular motility in any one direction of ≥ 8 degrees over 1-3 months
    - Decrease in visual acuity equivalent to 1 Snellen line over 1-3 months
- TED considered"active" if:
  - CAS≥ 3
- Helps predict benefit of immunosuppressive therapy

NOSPECS

- Disease Severity Scale
- Based on presenting features:
  - Class 0: **N**o signs or symptoms
  - Class 1: **O**nly signs (upper lid retraction and stare, +/- lid lag)
  - Class 2: **S**oft tissue involvement (edema of conjunctiva and lids, conjunctival injection)
  - Class 3: **P**roptosis
  - Class 4: **E**xtraocular muscle involvement (usually with diplopia)
  - Class 5: **C**orneal involvement (primarily lagophthalmos)
  - Class 6: **S**ight loss (due to optic nerve involvement)

EUGOGO

- Disease Severity Scale
- TED severity can be classified by the following measurements:
  - Presence of an RAPD
  - Record lid retraction
    - MRD 1 (note superior scleral show)
    - MRD 2 (note inferior scleral show)
    - Presence of temporal flare is present
  - Hertel exophthalmometer with intercanthal distance
  - Risk of cornea ulceration
    - Lagophthalmos
    - Bell's Phenomenon

EUGOGO

- Alternative classification scheme
- grades TED as:
  - Mild
    - Mild impact on daily life
    - Insufficient to justify immunosuppressive/surgical treatment
    - One or more of the following :
      - Minor lid retraction (< 2 mm)
      - Mild soft tissue involvement
      - Exophthalmos < 3 mm above normal for race and gender (~18 mm for Asians, 20 mm for Caucasians, and 22 mm for African Americans)
      - Transient or no diplopia
      - Corneal exposure responsive to lubricants

EUGOGO

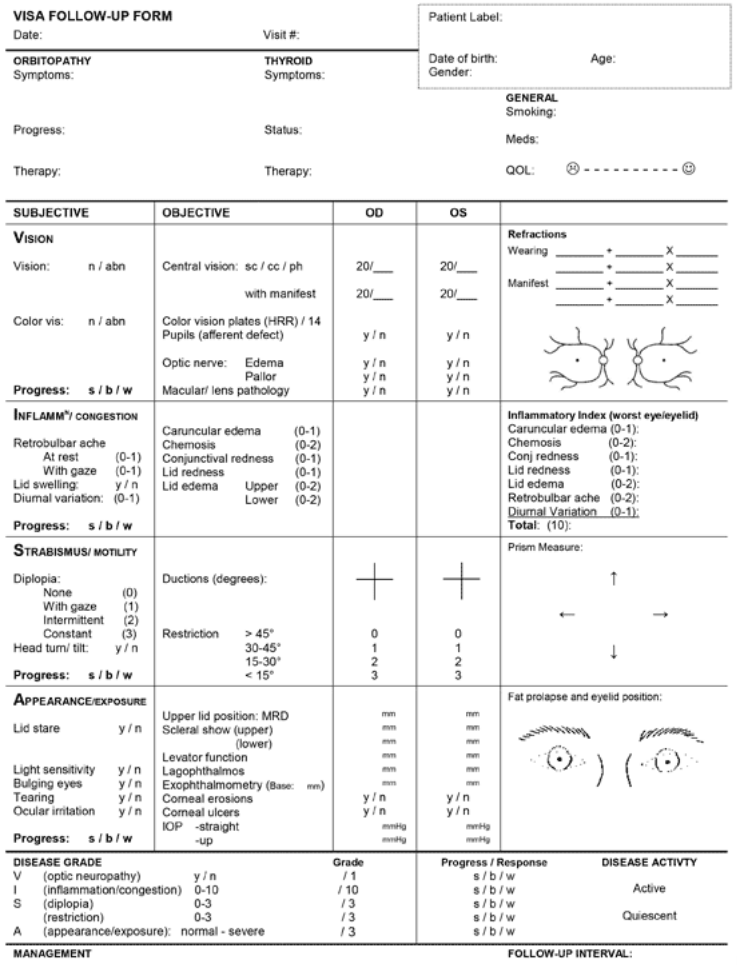
- Moderate-to-severe
  - Non-sight-threatening but sufficient impact on life to justify immunosuppression or surgical intervention
  - One or more of the following:
    - Lid retraction ≥ 2 mm
    - Moderate or severe soft tissue involvement
    - Exophthalmos ≥ 3mm above normal for race and gender
    - Transient or constant diplopia
- Sight-threatening
  - TED patients with resultant optic neuropathy
  - corneal breakdown
  - Warrants immediate intervention

TABLE 5. European Group on Graves'orbitopathy (EUGOGO)[36] recommends the following classification of patients with GO

Sight-threatening GO	Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown. This category warrants immediate intervention.
Moderate-to-severe GO	These patients usually have any one or more of the following: lid retraction >2 mm, moderate or severe soft tissue involvement, exophthalmos >3 mm above normal for race and gender, inconstant, or constant diplopia.
Mild GO	These patients usually have only one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, transient or no diplopia, and corneal exposure responsive to lubricants.

VISA

- Vision, Inflammation, Strabismus, Appearance



VISA FOLLOW-UP FORM

Date: Visit #:

Patient Label:

Date of birth: Age:
Gender:

ORBITOPATHY
Symptoms:

Progress:

Therapy:

THYROID
Symptoms:

Status:

Therapy:

GENERAL
Smoking:

Meds:

QOL: ☹ - - - - - - - - - - ☺

SUBJECTIVE	OBJECTIVE	OD	OS	
VISION				**Refractions**
Vision: n / abn	Central vision: sc / cc / ph	20/___	20/___	Wearing _____ + _____ X _____
	with manifest	20/___	20/___	_____ + _____ X _____
				Manifest _____ + _____ X _____
Color vis: n / abn	Color vision plates (HRR) / 14			_____ + _____ X _____
	Pupils (afferent defect)	y / n	y / n	
	Optic nerve: Edema	y / n	y / n	
	Pallor	y / n	y / n	
Progress: s / b / w	Macular/ lens pathology	y / n	y / n	
INFLAMM°/ CONGESTION				**Inflammatory Index (worst eye/eyelid)**
	Caruncular edema (0-1)			Caruncular edema (0-1):
Retrobulbar ache	Chemosis (0-2)			Chemosis (0-2):
At rest (0-1)	Conjunctival redness (0-1)			Conj redness (0-1):
With gaze (0-1)	Lid redness (0-1)			Lid redness (0-1):
Lid swelling: y / n	Lid edema Upper (0-2)			Lid edema (0-2):
Diurnal variation: (0-1)	Lower (0-2)			Retrobulbar ache (0-2):
				Diurnal Variation (0-1):
Progress: s / b / w				**Total**: (10):
STRABISMUS/ MOTILITY				Prism Measure:
Diplopia:	Ductions (degrees):	+	+	↑
None (0)				← →
With gaze (1)				↓
Intermittent (2)				
Constant (3)	Restriction > 45°	0	0	
Head turn/ tilt: y / n	30-45°	1	1	
	15-30°	2	2	
Progress: s / b / w	< 15°	3	3	
APPEARANCE/EXPOSURE				Fat prolapse and eyelid position:
	Upper lid position: MRD	mm	mm	
Lid stare y / n	Scleral show (upper)	mm	mm	
	(lower)	mm	mm	
	Levator function	mm	mm	
Light sensitivity y / n	Lagophthalmos	mm	mm	
Bulging eyes y / n	Exophthalmometry (Base: mm)	mm	mm	
Tearing y / n	Corneal erosions	y / n	y / n	
Ocular irritation y / n	Corneal ulcers	y / n	y / n	
	IOP -straight	mmHg	mmHg	
Progress: s / b / w	-up	mmHg	mmHg	

DISEASE GRADE		Grade	Progress / Response	DISEASE ACTIVTY
V (optic neuropathy)	y / n	/ 1	s / b / w	
I (inflammation/congestion)	0-10	/ 10	s / b / w	Active
S (diplopia)	0-3	/ 3	s / b / w	
(restriction)	0-3	/ 3	s / b / w	Quiescent
A (appearance/exposure):	normal - severe	/ 3	s / b / w	

MANAGEMENT **FOLLOW-UP INTERVAL:**

M.D.A.

- F/U 1 month later
- + marcus gunn pupil noted
- CT scan showed R-IR and R-MR enlargement, tight orbital apex
- Add to prior assessment compressive optic neuropathy

Central 30-2, Prueba de umbral

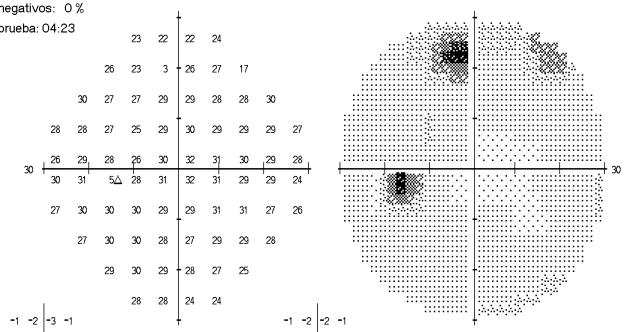
Monitor de fijación: Mancha ciega
Objetivo de fijación: Central
Pérdidas de fijación: 1/12
Errores falsos positivos: 0 %
Errores falsos negativos: 0 %
Duración de la prueba: 04:23

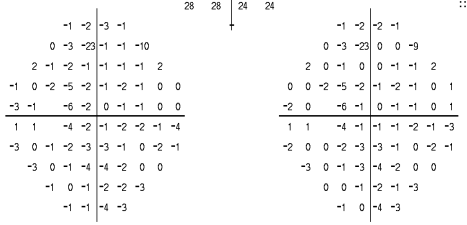
Estímulo: III, Blanco
Fondo: 31.5 ASB
Estrategia: SITA-Fast

Diámetro de pupila:
Agudeza visual:
RX: +3.25 DS DC X

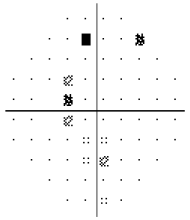
Fecha: 10-06-2015
Hora: 11:18 AM
Edad: 61

Foveal: 36 dB

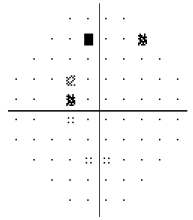




Desviación total



Desviación del modelo



PHG
Caso dudoso

VFI 98%

DM -1.77 dB P < 10%
DSM 2.99 dB P < 5%

:: < 5%
▒ < 2%
▓ < 1%
■ < 0.5%

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AVE JESUS T. PINERO NO.1250
SAN JUAN, PR 00922-0431
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Central 30-2, Prueba de umbral

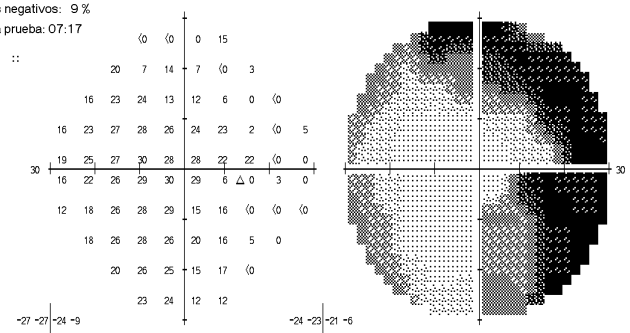
Monitor de fijación: Mancha ciega
Objetivo de fijación: Central
Pérdidas de fijación: 1/16
Errores falsos positivos: 1 %
Errores falsos negativos: 9 %
Duración de la prueba: 07:17

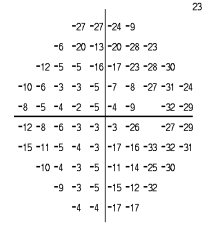
Estímulo: III, Blanco
Fondo: 31.5 ASB
Estrategia: SITA-Fast

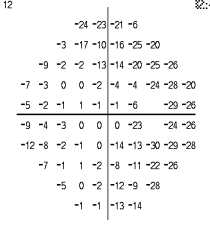
Diámetro de pupila:
Agudeza visual:
RX: +3.25 DS DC X

Fecha: 10-06-2015
Hora: 11:08 AM
Edad: 61

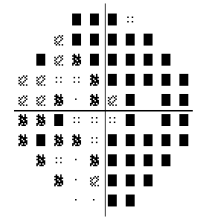
Foveal: 32 dB ::



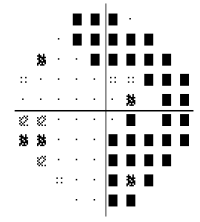




Desviación total



Desviación del modelo



PHG
Fuera de límites normales

VFI 74%

DM -11.92 dB P < 0.5%
DSM 10.66 dB P < 0.5%

:: < 5%
▒ < 2%
▓ < 1%
■ < 0.5%

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Management

- Goals:
  - Preserve vision
  - Avoid keratopathy
  - Correct diplopia
  - Improve lid function and appearance
- TED
  - Self limited, lasts 1-3 years
  - Acute phase – more responsive to medical tx
  - Chronic, quiescent phase – usually surgical tx
- Early tx important in decreasing disease severity

- Mild to moderate TED (~75%) supportive symptom management:
  - Ocular lubrication
  - Topical cyclosporine
  - Lifestyle modifications:
    - Smoking cessation
    - Sodium restriction to reduce water retention and tissue edema
    - Sleeping with the head of the bed elevated to decrease orbital edema
    - Sunglasses to decrease photophobia and feelings of dryness
  - Oral NSAIDs for periocular pain
  - Diplopia management:
    - Prisms
    - Strabismus surgery when stable
  - Selenium, was shown to benefit European patients with mild, non-inflammatory orbitopathy

Table 4-4 Management of Thyroid Eye Disease

- **Mild disease**
  - Observation
  - Patient education/lifestyle changes
    - Smoking cessation
    - Salt restriction
    - Elevation of head of bed
    - Wearing sunglasses
  - Ocular surface lubrication
- **Moderate disease**
  - Topical cyclosporine
  - Eyelid taping at night
  - Moisture goggles/chambers
  - Prism glasses or selective ocular patching
  - Moderate-dose oral steroid therapy
- **Severe disease**
  - High-dose oral steroid therapy or intravenous steroid therapy
  - Surgical orbital decompression (followed by strabismus surgery and/or eyelid surgery)
  - Periocular radiotherapy
- **Refractory disease**
  - Steroid-sparing immunomodulators (rituximab, others)

- Smoking cessation is a key part of treatment
  - Increases severity of disease
  - Decreases the effectiveness of treatment methods
  - Cyanide, (in cigarette smoke) converted in the body to thiocyanate, an anti-thyroid agent
    - inhibits iodine uptake
    - increases iodine excretion
    - inhibits thyroid hormone synthesis
- Smokers 2X as likely to develop Graves' disease when compared to nonsmokers.
- Patients with Graves' disease who smoke 7.7 X more likely to develop TED than nonsmokers.
- Smoking reduces the effectiveness of TED treatments such as corticosteroids and RAI.
  - "*Impact on smoking on the response to treatment of Thyroid Associated Ophthalmopathy*". Eckstein,A. Br J Ophthalmol 2003; 87:773-776

- Surgical management
- Approximately 20% of patients will undergo some type of surgery:
  - 13% eyelid surgery
  - 9% strabismus surgery
  - 7% orbital decompression
- Surgery is not advised until euthyroid
- TED should be stable for at least 6-9 months.
    - Unless compressive optic neuropathy or corneal exposure present
- In order to prevent repeat surgery following recovery from subsequent procedures, surgery for TED occurs in the following order, whenever possible
    - Orbital decompression
    - Strabismus surgery
    - Eyelid surgery

"The four Stages of Surgical Rehabilitation of the Patient with Dysthyroid Ophthalmopathy". Schoor,N., Seiff,S.Ophthalmol 93:476-483,1986

- Orbital decompression
- Extraocular muscle surgery
- Eyelid margin repositioning
- Blepharoplasty

Compressive Optic Neuropathy

- 6% TED patients affected
- Optic nerve compressed by EOM bellies at orbital apex
  - Inflammation and congestion at the orbital apex compresses the optic nerve and its blood supply
  - Expansion and congestion of orbital tissues can lead to optic nerve stretching
- May be present without significant proptosis
- Loss of vision
  - Visual field affected
  - Impaired pupillary responses (Marcus-Gunn sign)
  - Decreased color vision
  - Optic nerve edema may be present

Compressive Optic Neuropathy

- Management:
  - Steroids: First line of tx
    - Oral 80-100 mg, tapering 10 mg/week x 12 weeks
    - IV route: weekly for 12 weeks
  - Radiation:
    - concurrent with steroids
    - 2000 cGy divided in 10 sessions
  - Orbital Decompression: definitive tx

M.D.A.

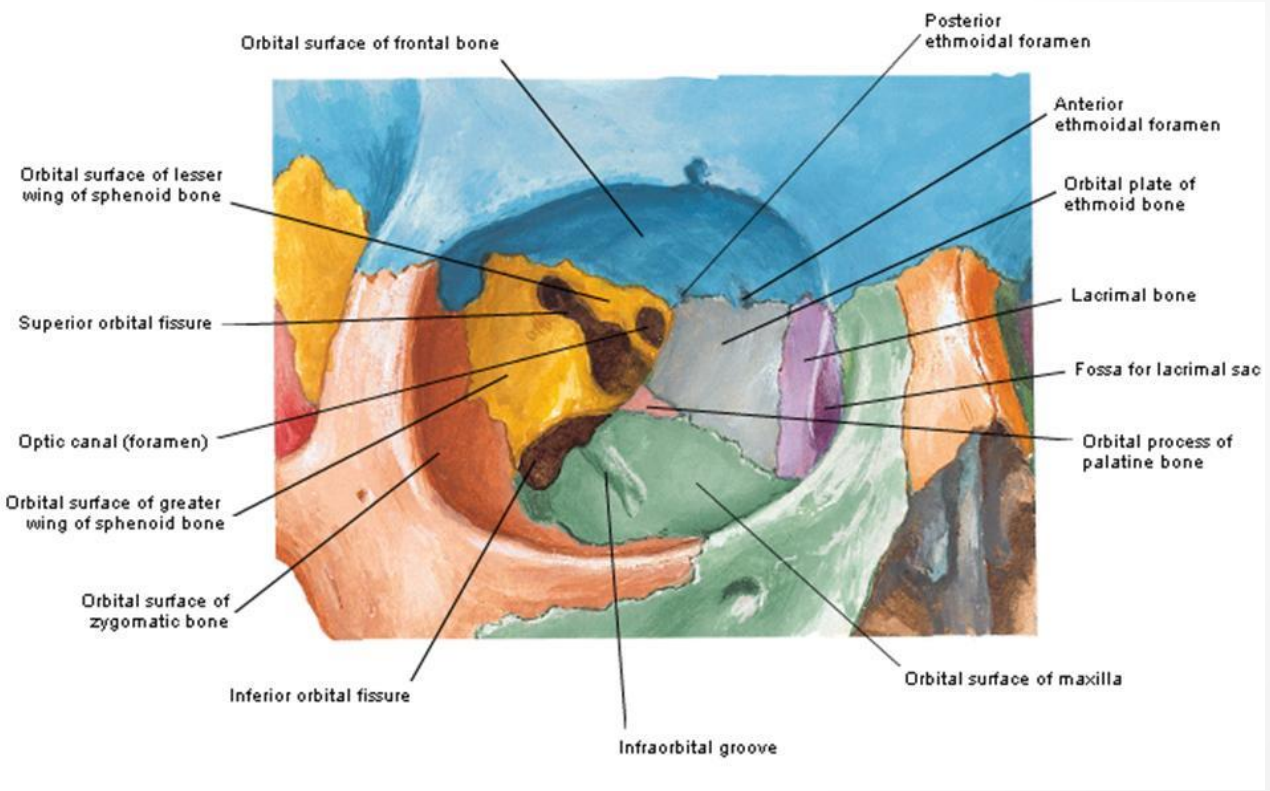
- Started on oral prednisone
- Coordinated w ENT for combined medial/floor decompression
- Decompression OD done 12/01/2015
- Post op strabismus worsened (expected)
- Tapered down prednisone
- Post op exoph: 20 mm OD, 22 OS
- Pt desired no more surgery
  - Referred for poss strabismus sx

Orbital Decompression

- Does not decrease inflammation
- Increases orbital volume to accommodate fluid, edematous tissue
- If proptosis not significant pt should be aware of eventual enophthalmos

Orbit Decompression

- Individualize
- 1, 2, 3, 4 walls
- Fat excision

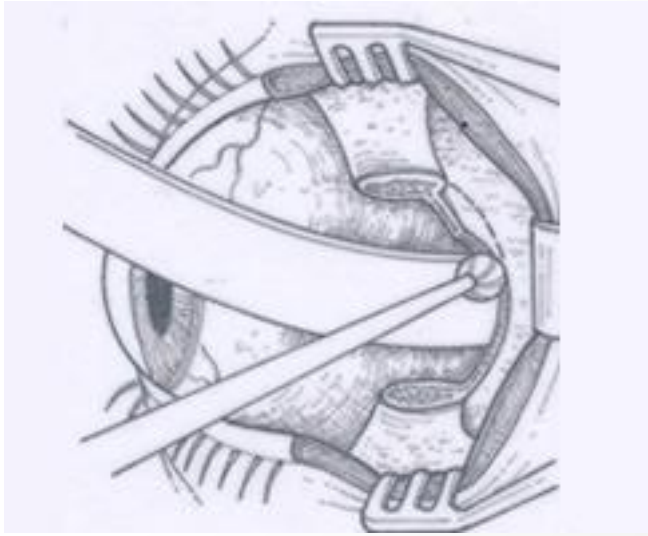


Medial Wall

- Endoscopic
  - Better posterior removal, ON compresssion
  - Cannot reach anteriorly, floor
- Transcaruncular:
  - Better anterior exposure, may be extended inferiorly for inferior decompression
- Lynch (transcutaneous)
  - Best exposure, more scarring

Lateral Wall

- Combined with medial wall decompression
- bone can be removed, burred down or advanced
- May reach sphenoid bone, B/W superior and inferior orbital fissure

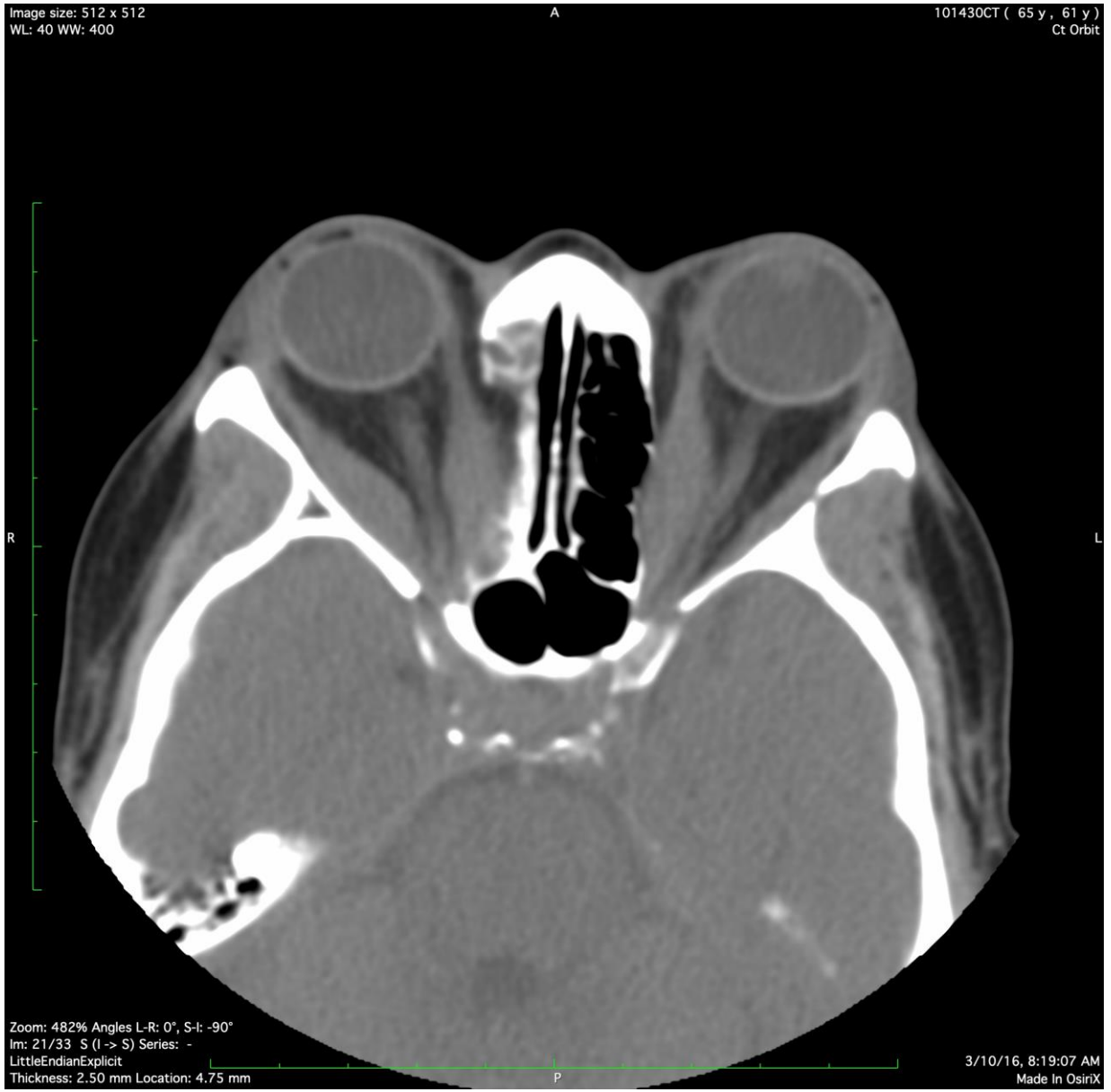


Inferior wall

- Greatest potential to induce diplopia
- May be combined with medial wall decompression
- Transcutaneous, transconjunctival or transmaxillary approach

Roof Decompression

- Largely discontinued
- Needs neurosurgeon
- Pulsation, CSF leaks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Ct Orbit
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Im: 21/33 S (I -> S) Series: -
LittleEndianExplicit
Thickness: 2.50 mm Location: 4.75 mm
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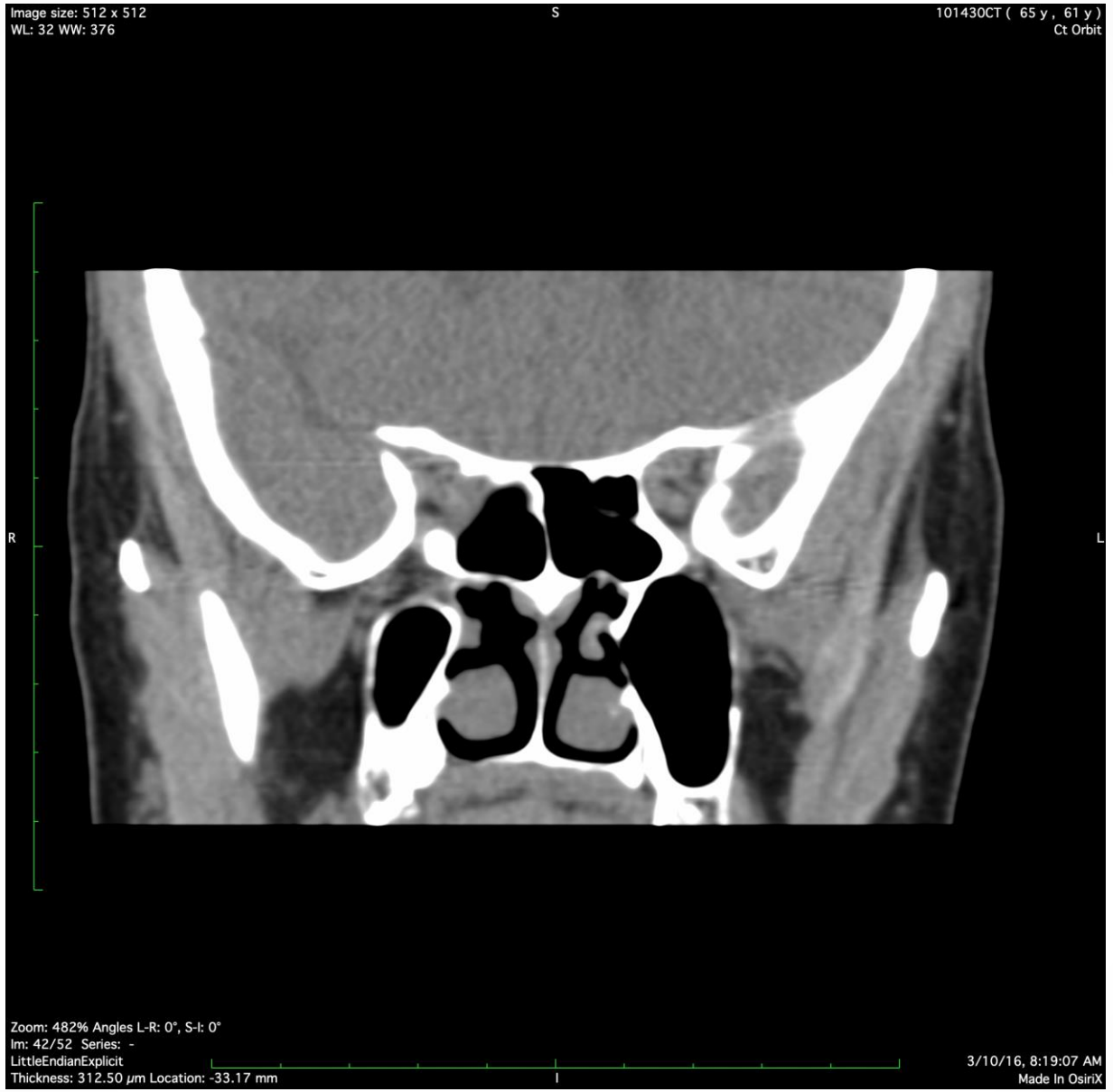
Made In OsiriX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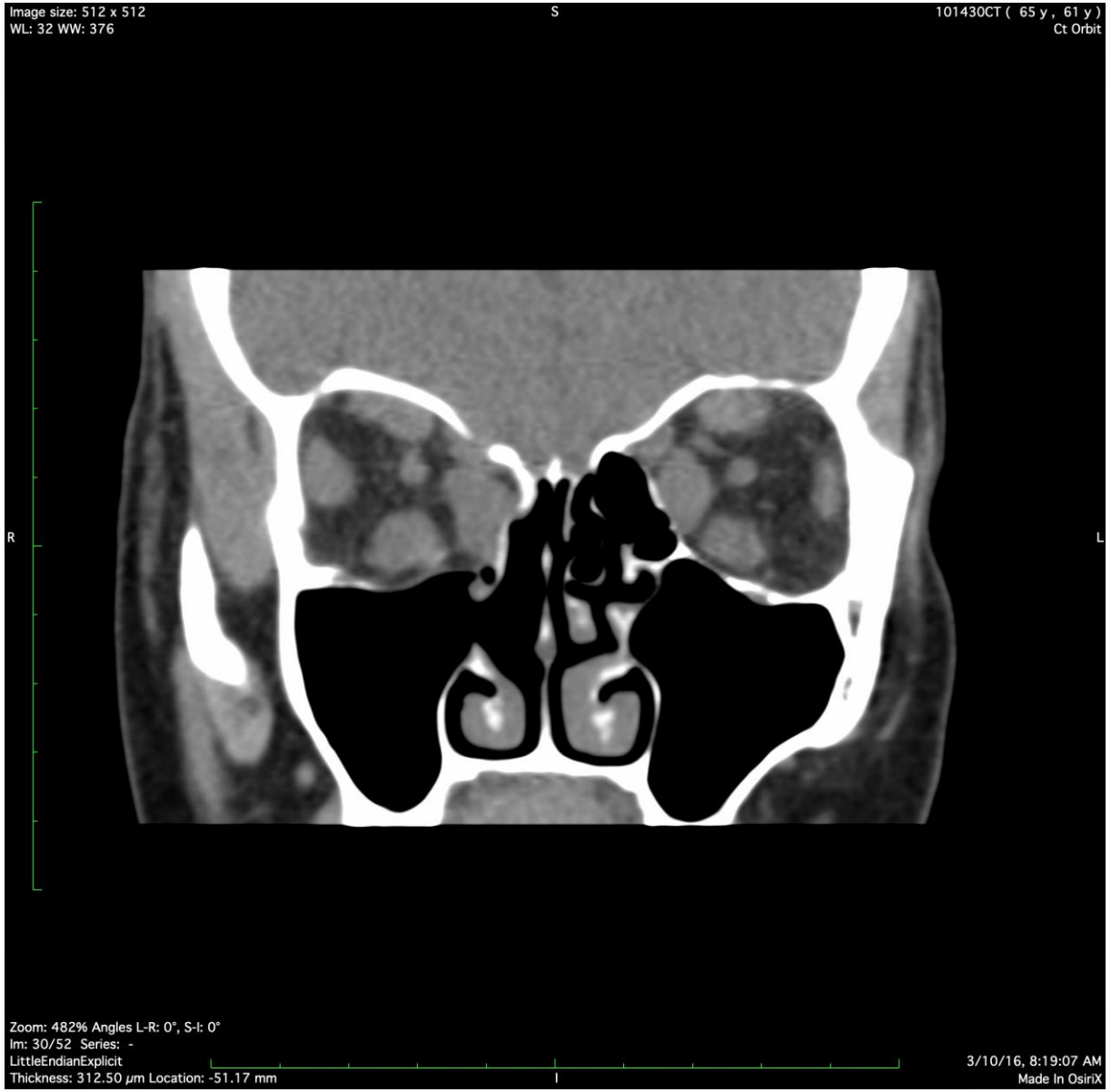
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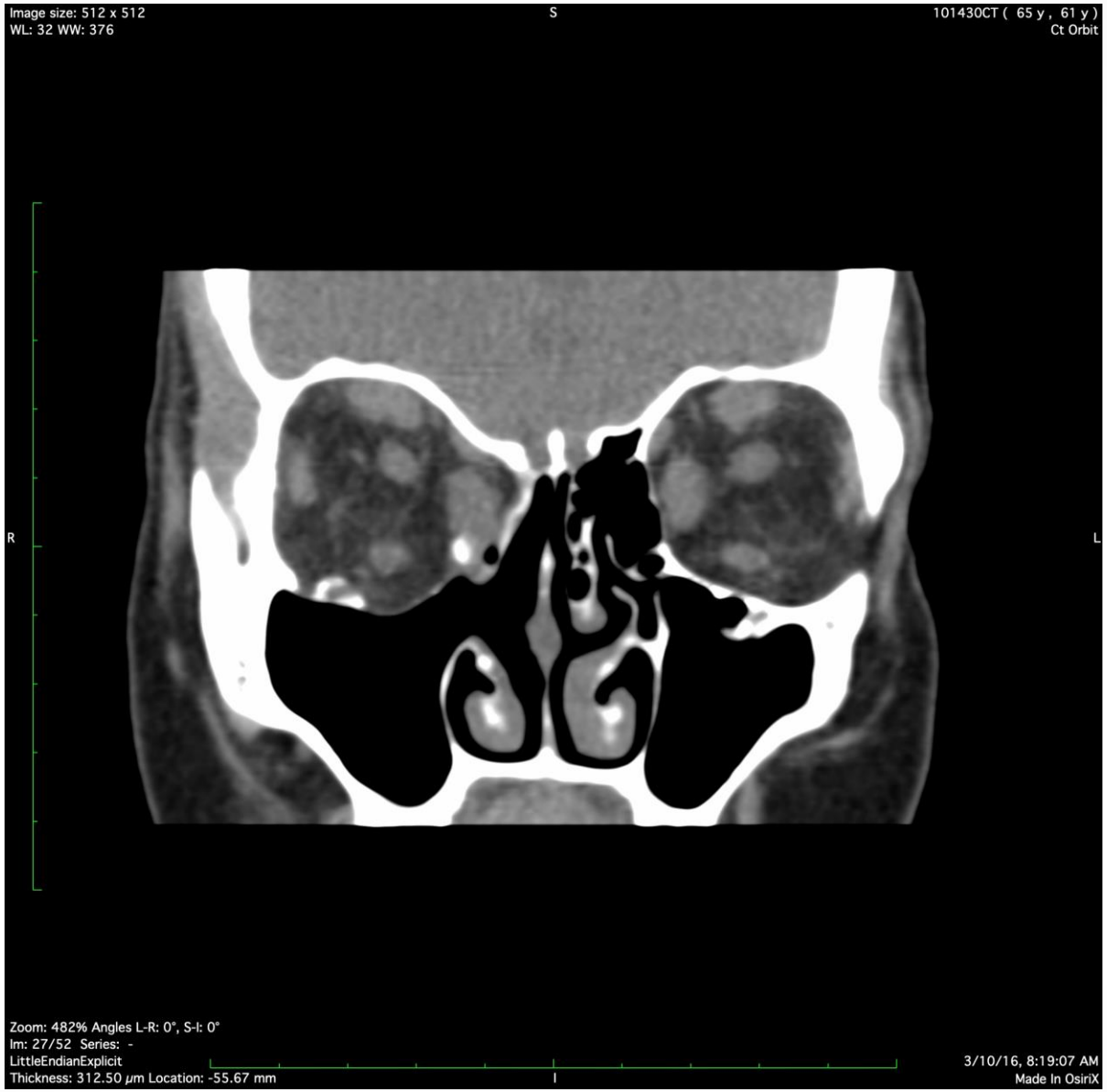
Image size: 512 x 512
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101430CT (65 y , 61 y)
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Zoom: 482% Angles L-R: 0°, S-I: 0°
Im: 27/52 Series: -
LittleEndianExplicit
Thickness: 312.50 μm Location: -55.67 mm
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Made In OsiriX

M.D.A

- Returns 1/8/16 c/o pain left eye
- Proptosis OS increased
- Bilateral limitation in abduction
- Assessed still active TED, now w contralateral involvement
- Re-started pred
  - Discussed radiotx, IV SM boluses, rituximab
- On f/u better, new CT scan ordered
- Orbit OS worse (but no Optic neuropathy).
- Tapered pred, scheduled 2nd eye sx

Exophthalmos

- 2nd most common TED sign (60%)
- Measurable (exophthalmometer)
- Exposure keratopathy
- Perceived deformity

Proptosis

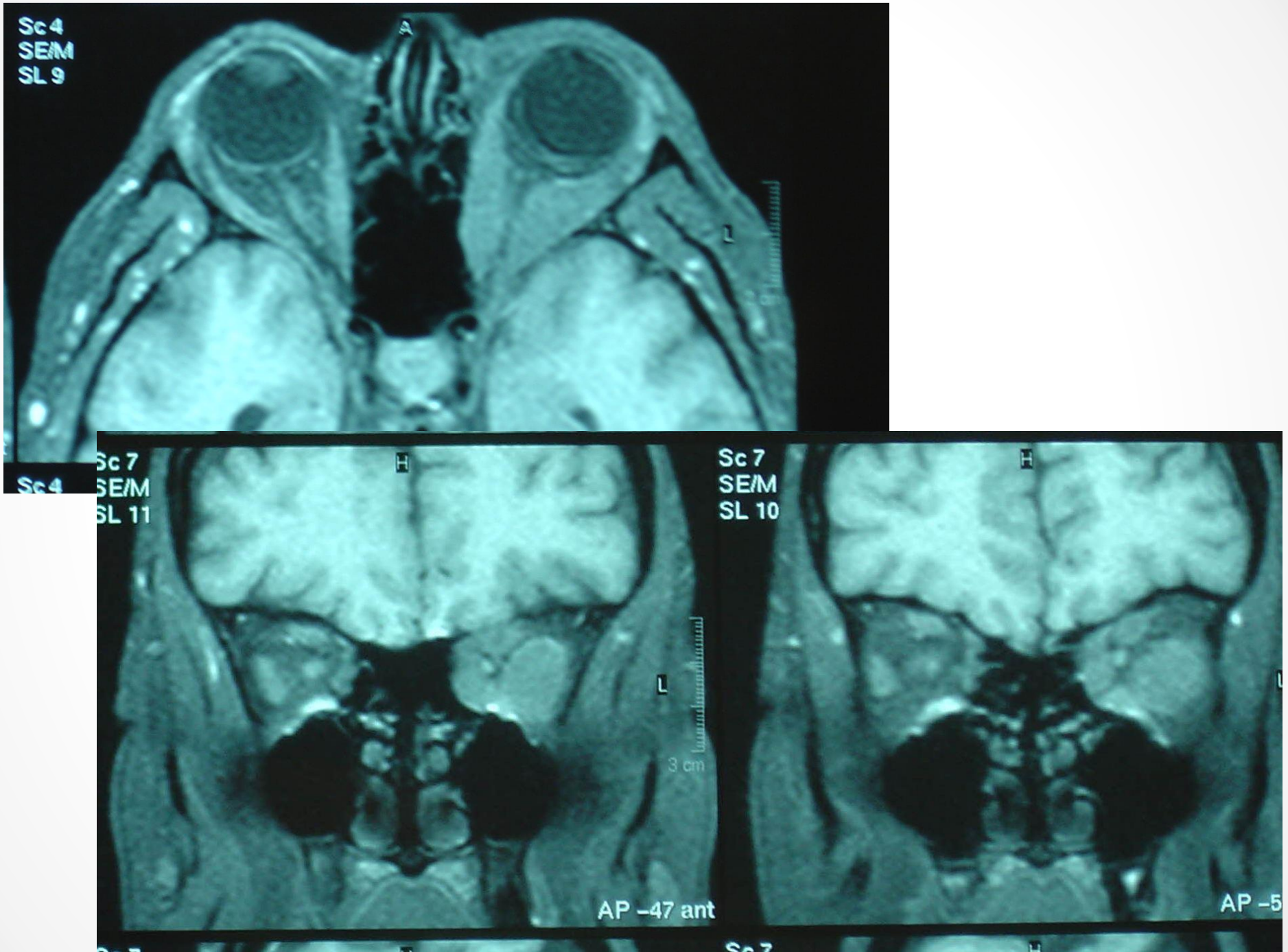
- May be axial, non-axial or asymmetric
- Mild: lubricants, retraction repair
- Severe cases, **keratopathy**: decompression

M.D.A.

- Underwent 2-wall decompression OS 6/14/16
- Exophthalmometry 19/21
- Significant dysmotility
- Referred for strabismus surgery

Strabismus

- 40% of TED patients
- I'MSLO
- Restricitive forced ductions
- Pain (ache)
- Characteristic imaging findings
  - Tendon sparing EOM enlargement
- Inflammation of EOM's
  - Fibrosis
  - Inelasticty
  - Restriction


Sc 4
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Sc 7
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SL 11
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3 cm
AP –47 ant
Sc 7
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SL 10
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AP –5

Extraocular Motility

- Management:
  - 1/3 cases respond to high dose prednisone, if in congestive phase
  - Radiation limited benefit
    - Neither useful in chronic cases
  - May try prisms
  - Strabismus Sx
    - Recessions (avoid resections)
    - Adjustable sutures

Strabismus

- Most TED patients with diplopia due to strabismus can be managed with prism glasses
- Indications for strabismus surgery
  - Diplopia in primary gaze or with reading.
  - Abnormal head positioning
  - Cosmesis

Strabismus

- Surgery
  - Delayed until disease stability has been demonstrated.
  - Recession of the affected muscles is recommended
  - Adjustable sutures are preferred
  - Diplopia is frequently improved post-operatively, but normal ocular motility is infrequently achieved
- Extraocular muscle recession can worsen proptosis
- Extraocular muscle recession can affect eyelid position upper and lower eyelid position
  - Strabismus surgery should come before corrective eyelid procedures.
- Botulinum toxin
  - Poor surgical candidates that cannot be treated with prisms may benefit.
  - Can be unreliable

MDA

- 1/12/17 f/u post strabismus surgery—pt happy
- Eyelid reconstruction started
  - 3/7/17 right eyelid retraction repair (with blepharoplasty)
  - 5/16/17 left eyelid retraction repair (with blepharoplasty)
  - 2/6/18 re-op right eyelid (Alloderm graft)

Eyelid Retraction

- Most common sign of TED (90%)
  - ↑ sympathetic tone
  - Contraction (fibrosis) levator palpebrae
  - Proptosis
  - Lacrimal gland scarring
- Dalrymple's sign
- Lagopthalmos
- Temporal flare

Eyelid Retraction

- Very common
- Sometimes improves with time
- Lid lag
- Lagophthalmos

Eyelid Retraction

- Treatment
  - Non-surgical
    - Injection of hyaluronic acid gel fillers
    - Botulinum toxin
  - Surgical
    - Eyelid weights
    - Incision and/or recession of one or more of the eyelid retractors
    - Full-thickness blepharotomy
    - Insertion of spacer material to lengthen the eyelid
  - Eyelid contouring

Corneal Exposure

- Risk factors:
  - Proptosis
  - eyelid retraction
  - Lagophthalmos
  - neurotrophic cornea
  - poor Bell's reflex.
- Prolonged corneal exposure ⟹corneal drying, ⟹ decreased vision, risk of ulceration, perforation

Corneal Exposure

- Non-emergent treatment
  - Environmental modifications (e.g. avoid direct wind, sunglasses etc)
  - Tear substitutes
  - Increasing tear production (cyclosporine, loteprednol, flurometholone)
  - Decreasing tear evaporation
    - Increasing oil content of tears
      - Omega-3 fatty acids
      - Warm compresses
    - Surgically decreasing corneal exposure
      - Lid retraction repair
      - Orbital decompression
      - Lid tarsorrhaphy
  - Decreasing tear outflow (punctal plugs or cautery)

Corneal Exposure

- Emergent treatment:
  - A bandage contact lens (BCL) or scleral contact lens with topical antibiotic ointment
  - A temporary tarsorrhaphy may be indicated
- Definitive treatment is to eliminate the cause of the exposure:
  - Orbital decompression
  - Eyelid retraction repair

Acute Congestive Phase

- Periorbital edema
- Conjunctival chemosis
  - Decreased venous drainage
  - Increased orbital pressure

Orbital Congestion

- Most irritating to patients
  - Tearing, FB sensation, light sensitivity
  - Conjunctival injection, chemosis
- Mild: reassurance, lubrication, NSAIDs
- Moderate: Steroids; ? Oral vs IV
- Severe: Steroids, Radiation, Immunosuppression, Orbital Decompression

Steroids

- Oral: prolonged treatment necessary, usually several months.
  - 1.0-1.5 mg /kg
  - Premature taper leads to recurrence
  - 60% effective
  - Side effects
- IV:
  - Better tolerated, more effective (~ 70%).
  - Treatment regime: 12 weeks
    - 6 weeks – 500 mg once weekly
    - 6 weeks – 250 mg once weekly
  - IV decreases the need for additional medical therapy.
- Ca++, vitamin D, and a proton pump inhibitor
- Monitor serum electrolytes, blood glucose, liver function tests (LFTs), and blood pressure.
- Doses exceeding 8 g (cumulative) are at risk for hepatic toxicity, electrolyte disturbances, and cardiac arrhythmias

Radiation

- Works only in the acute congestive phase
- Contraindicated in diabetics (retinopathy)
- 1500-2000 cGy divided over 10d

Radiation

- Mechanisms of action
  - Decreased lymphocytic response
  - Limits adipocyte differentiation and fatty hypertrophy
    - More effective in patients < 40 years old who have more orbital fat hypertrophy.
  - Radiation induces death of tissue-bound monocytes.
    - Radiation decreases the immune response at the orbit
      - Reduced inflammation of ocular surface and eyelids in ~ 60% of patients
- No effect on proptosis or eyelid retraction.
- Can be used to treat:
  - Compressive optic neuropathy
  - Ocular surface and periorbital tissue inflammation
  - Orbital congestion
  - Strabismus and ocular motility deficits
- Treatment regimen and effects
  - 2000 cGy, divided over 10 treatment sessions, during a 2-week time course
  - A maximum effect at 6 months post-treatment
  - Treatment is associated with a transient exacerbation of periorbital edema, conjunctival injection, and chemosis
  - May need concurrent steroids to decrease inflammation

Radiation

- Results can be irregular
  - Effectiveness 20% to 90%
  - The most convincing evidence for benefit is found in the treatment of restrictive vertical strabismus.
  - Phase at which it is given
  - Side effects
- A review concluded that combined corticosteroids + ORT better anti-inflammatory effect, than treatment with either alone

Radiation

- Contraindications
  - Patients with underlying microvascular retinopathy (DM/HTN)
    - increased incidence of radiation retinopathy (1-2%).
  - Increased risk of cataracts.
  - Theoretical concern for tumorigenesis

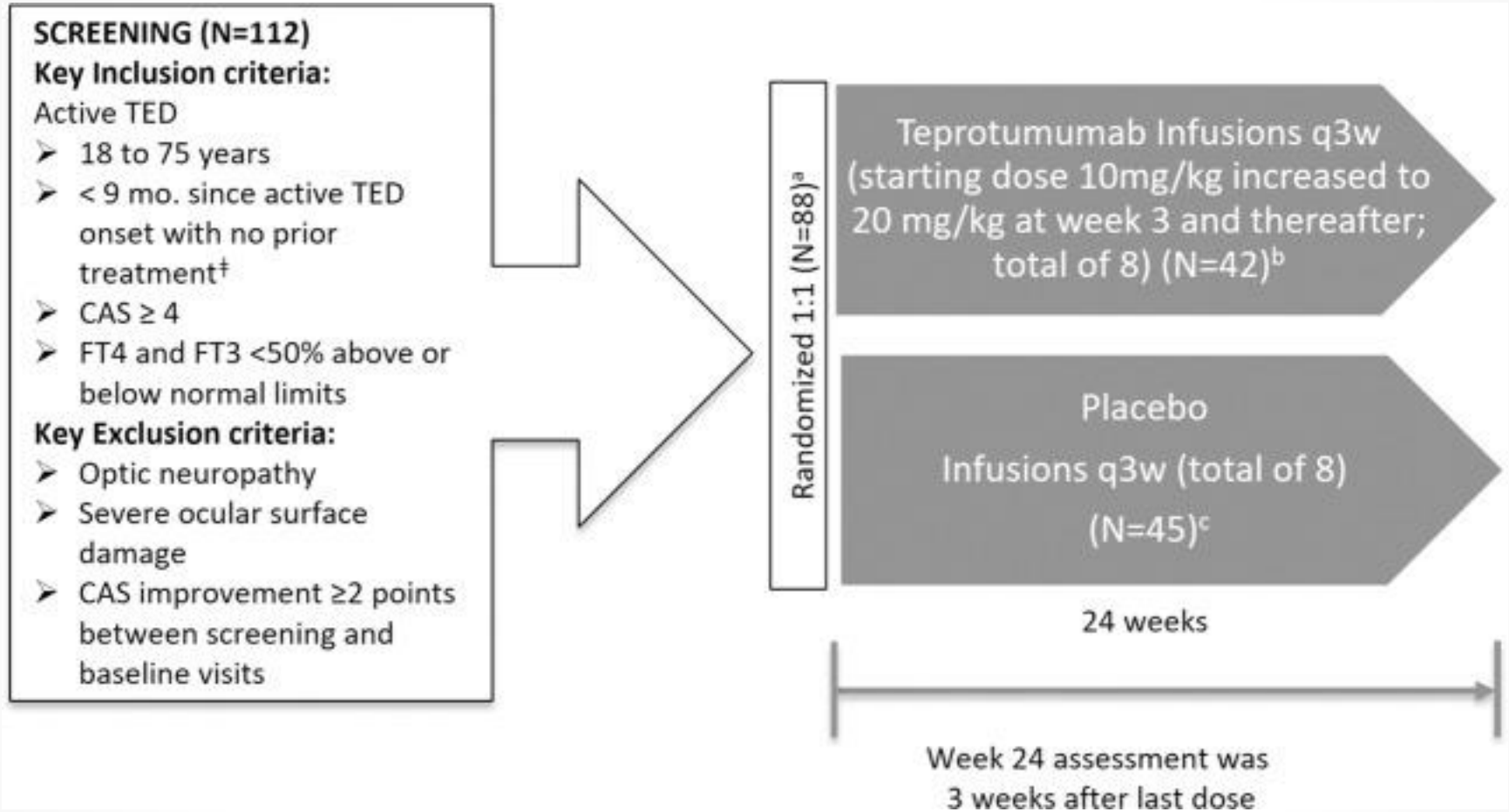
Rituximab

- Rituxan is a CD20-directed cytolytic antibody indicated for the treatment of patients with:
  - Non-Hodgkin's Lymphoma (NHL)/Chronic Lymphocytic Leukemia (CLL)
  - Rheumatoid Arthritis (RA)
- Targets CD-20 on B-cells ⇒ B-cell depletion in the thyroid gland ⇒ decreased TSI production.
- A study showed TED patients with CAS ≥ 4 that received rituximab (1000 mg, IV, twice over a two week interval) **showed an average decrease in CAS that ranged from 2.3 to 4.7, with a median decrease ranging from 2.5 to 4.5.**
  - Rituximab for thyroid eye disease.Silkiss RZ, et al. Ophthal Plast Reconstr Surg. 2010 Sep-Oct;26(5):310-4.
- The overall efficacy of rituximab therapy is complicated by the variable presentations and course of TED

- Infusion Reactions :
  - Rituxan administration can result in serious, including fatal infusion reactions.
  - Deaths within 24 hours of Rituxan infusion have occurred.
  - Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Carefully monitor patients during infusions.
  - Also risk of Progressive Multifocal Leukoencephalopathy

Teprotumumab

- Human monoclonal antibody (Graves' Disease IgG – GD-IgG) against the IGF-1-R
- Ongoing trials for treatment of patients with active, moderate to severe TED.
- IGF-1-R has mitogenic and anti-apoptotic functions.
- GD-IgG interacts directly with IGF-1-R.
- IGF-1-R is upregulated in TED.
- Anti-IGF-1-R therapy may interfere with this abnormal signaling pathway present in TED
- Phase 3 clinical trials



Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for thyroid-associated ophthalmopathy. New Engl J Med. 2017;376:1748–61.

Proptosis graded response at week 24
High response: a reduction ≥ 3 mm from baseline
Response: a reduction of 2 to < 3 mm from baseline
Low response: a of 1 to < 2 mm from baseline
No response: a reduction in proptosis < 1 mm

	Placebo ($N = 45$)		Teprotumumab ($N = 42$)	
	No. of subjects	%	No. of subjects	%
High response	4	8.90%	23	54.80%
Response	5	11.10%	7	16.70%
Low response	8	17.80%	8	19.00%
No response	22	48.90%	0	0.00%
Missing	6	13.30%	4	9.50%
Total	45	100.00%	42	100.00%

Selenium

- Shown to exert significant benefits in patients with mild, non-inflammatory orbitopathy.
- Benefits from selenium supplementation (100 µg twice daily) in Europe where the soil was selenium deficient.
- Unknown if this benefits other populations

Azathioprine

- This is a chemotherapeutic agent that inhibits DNA synthesis.
- Combined Immunosuppression and Radiotherapy in TED (CIRTED) trial
- Patients previously treated with oral prednisolone. No added benefit found from tx w radiotx, Aza, or combination

Methotrexate

- Studies have suggested it may be effective as a steroid sparing agent
- Improved CAS
- Succesful prednisone weaning
- Studies not blinded, not controlled, no comparison to prednisone

Mycophenolate Mofetil

- In a randomized study (MMF vs Steroids) the MMF group showed a better response percentage (92.5% vs 70.5 %)
- Greater improvement in diplopia and proptosis
- No disease re-activation

Tocilizumab

- Recombinant humanized monoclonal antibody against IL-6 R
- Used for RA, GCA
- Improved CAS, no relapses after infusion
- Improved proptosis and improved diplopia
- Not compared to steroids

Etanercept

- TNF receptor blocker
  - RA, JRA, psoriatic arthritis, ank. spondylitis
- Improved CAS
- Recurrence after tx cessation

Infliximab

- Case reports of response in steroid and surgery resistant cases

Cyclosporin

- Cyclosporin
  - less efficacious than prednisone for single drug therapy, but additive effect when used together
  - maximum daily dose 5 mg/kg
  - modify if creatinine level increase by 30%
  - side effects include hypertension, increase hepatic enzyme levels, renal insufficiency, gum hypertrophy

Somatostatin Analogues

- suppresses insulin like growth factor in extraocular muscles and fat cells
- inhibit fibroblast activity thus reducing the secretion of GAG
- good in patients with mild orbitopathy - soft tissue inflammation and symptomatic relief, but not in reducing muscle size.

"*Double Blind ,placebo controlled trial of Octreotide long acting repeatable in Thyroid Associated Ophthalmopathy*". Dickinson AJ. J Clin Endocrinol Metab 2004 89(12):5910-5

Cytokine Antagonists

- Pentoxifyliline- immunomodulatory effect on cytokine production.
- Inhibit GAG secretion by orbital fibroblasts.

"*Beneficial effect of Thyroid Associated Ophthalmopathy:a pilot study*". Balazs C. J Clin Endocrinol Metab 1997;82:1999-2002

Antioxidants

- Prospective, non randomized, comparative.
- 11 patients Mild – mod severe opththalmopathy., 11 placebo.
- Allopurinol 300mg daily and Nicotinamide 300mg. Daily
- 82% treated with antioxidants improved, 27% in control group.
- Soft tissue inflammation responded more tro treatment.

"*Antioxidant agents in the treatment of Graves Ophthalmopathy*."
Bouzas, E. AJO 2000;129:618-622

"Efficacy and Safety of Immunosuppressive Agents for Thyroid Eye Disease"
Diego Strianese, M.D., Ph.D.
Ophthal Plast Reconstr Surg, Vol. 34, No. 4S, 2018

- Recommendations
  - Steroids remains 1st line
  - Radiotx, 2nd line, can be combined w steroids
    - May reduce need for Sx or improve outcomes
  - MTX/MM can act as a SSA
  - Rituximab
    - Steroid resistant patients
    - Response may decrease w longer disease duration
    - Possible risk of inducing compressive optic neuropathy
  - Other biologicals may also have a role in disease suppression

TAO and RAI

- In some studies, RAI has been demonstrated to worsen TED (15-30%)
  - release of TSH-R antigens, incite enhanced immune response.
  - Hypothyroidism after RAI treatment may exacerbate TED via stimulation of TSH-R.
- Risk factors:
  - Hyperthyroid patients with severe, active TED
  - elevated T_3 levels
  - Smokers
- Concurrent tx with oral corticosteroids may ameliorate.
  - may be a reasonable strategy for high-risk patients,
  - may not indicated for the average patient.
- Patients with severe TED (rapidly progressive + congestion, + compressive optic neuropathy) may, as an alternative to RAI, benefit from thyroidectomy,

2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism
Eur Thyroid J. 2018 Aug; 7(4): 167–186.

- RAI causes progression or de novo occurrence (15-30%)of TED specially in:
  - smokers
  - Patients with preexisting and recent-onset TED
  - late correction of post-RAI hypothyroidism
  - high TSH-R-Ab levels
- In patients at risk of RAI-induced TED progression, oral low-dose steroid prophylaxis is effective, as shown in clinical trials and meta analyses
- Steroid prophylaxis can be avoided in patients with:
  - absent or inactive GO if other risk factors for RAI-associated progression of GO are absent
- Thyroidectomy does not seem to impact the natural history of GO
  - Alternative for pts w active TED

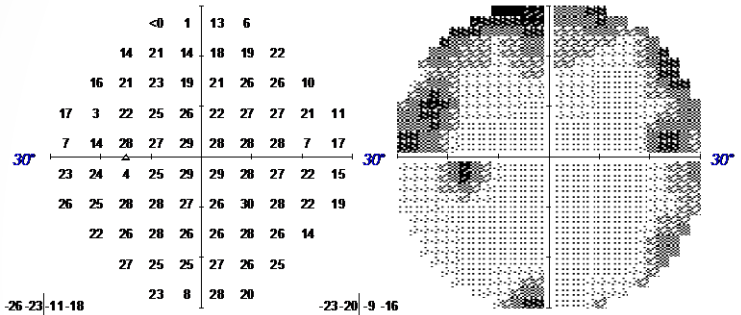
2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism
Eur Thyroid J. 2018 Aug; 7(4): 167–186.

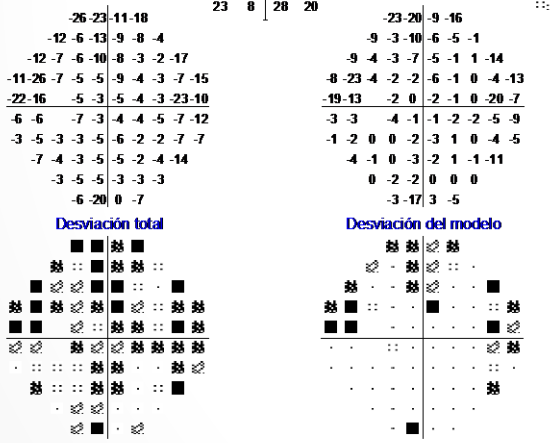
Degree of severity and activity of GO	ATD	RAI	Tx
Mild and inactive	Yes	Yes[1]	Yes
Mild and active	Yes[2]	Yes[3]	Yes
Moderate-to-severe and inactive	Yes	Yes[1]	Yes
Moderate-to-severe and active	Yes	No	No
Sight threatening	Yes	No	No

1. Steroid Prophylaxis in select cases
2. Selenium supplementation x 6 mos
3. Steroid prophylaxis 0.3/0.5mg/kg x 3 mos

OS Análisis de campo único — Central 30-2 Prueba de umbral

Monitor de fijación:	Mirada/Mancha ciega	Estímulo:	III, Blanco	Fecha:	14-feb-2019
Objetivo de fijación:	Central	Fondo:	31,5 asb	Hora:	9:04
Pérdidas de fijación:	0/15	Estrategia:	SITA Fast	Edad:	64
Errores falsos pos.:	0%	Diámetro de pupila:	4,2 mm *		
Errores falsos neg.:	24%	Agudeza visual:			
Duración:	05:42	Rx:	+3,25 DS		
Foveal:	33 dB				





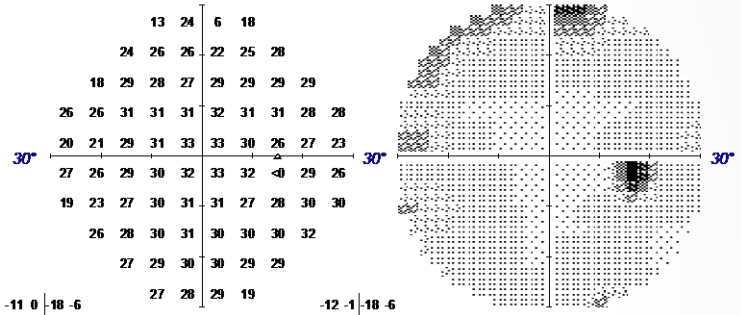
PHG: Fuera de límites normales

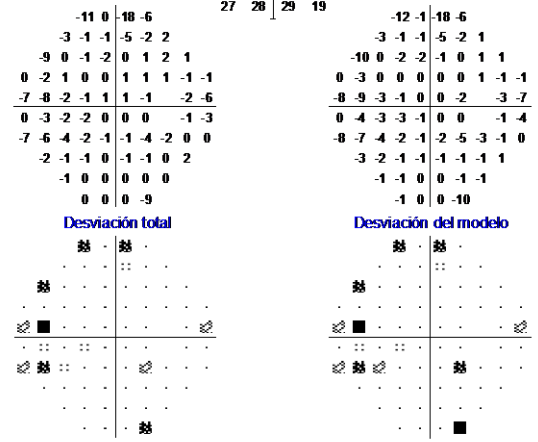
VFI: 92%
MD30-2: -6,60 dB P < 0,5%
PSD30-2: 5,84 dB P < 0,5%

:: P < 5%
P < 2%
P < 1%
P < 0,5%

OD Análisis de campo único — Central 30-2 Prueba de umbral

Monitor de fijación:	Mirada/Mancha ciega	Estímulo:	III, Blanco	Fecha:	14-feb-2019
Objetivo de fijación:	Central	Fondo:	31,5 asb	Hora:	8:59
Pérdidas de fijación:	4/12 XX	Estrategia:	SITA Fast	Edad:	64
Errores falsos pos.:	0%	Diámetro de pupila:	4,3 mm *		
Errores falsos neg.:	9%	Agudeza visual:			
Duración:	04:12	Rx:	+3,25 DS		
Foveal:	38 dB				





PHG: Dentro de límites normales

VFI: 98%
MD30-2: -1,34 dB
PSD30-2: 2,95 dB P < 5%

*** Fiabilidad de la prueba baja ***

:: P < 5%
P < 2%
P < 1%
P < 0.5%

Conclusions

- TED can be disfiguring
- Many patients are emotionally and psychologically affected due to their changes
- Education, reassurance, empathy are integral components of patient care.
- Traditionally, supportive care has been advocated unless severe complications present
- Earlier medical tx in the active phase may decrease necessity or complexity of surgery
- In the future steroid sparing agents may play a more central role in management

Post Test

- The primary target within the orbit of cross reacting T-lymphocytes that lead to Grave's Ophthalmopathy is:
  - Optic nerve glial cells
  - Orbital fibroblasts
  - Conjunctival goblet cells
  - Corneal endothelial cells
- In surgical management of Grave's related strabismus, the ideal management is
  - Single eye surgery
  - Muscle resection type surgery
  - Muscle recessions, preferably with adjustable sutures
  - Avoidance of adjustable surgery

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