5 Things That Changed How I Manage Graves' Disease

I. **Below I highlight the 5 things that are not commonly know or are commonly misunderstood**
II. Graves' Orbitopathy
    a. Also goes by
        i. Thyroid Associated Ophthalmopathy (TAO)
        ii. Thyroid Eye Disease (TED)
        iii. Graves' Ophthalmopathy
        iv. Graves' Dysthyroid Ophthalmopathy
    b. Graves' Disease (GD) is an autoimmune disease that targets 3 tissues
        i. Orbit
            1. 30-50% of Graves' patients have apparent ophthalmopathy
        ii. Thyroid
            1. Thyroid and Orbit manifestations typically happen within 18 months of each other with Thyroid complications appearing first.
        iii. Skin
    c. Previous thinking was that GD damaged the thyroid gland which led to ophthalmic complications
    **d. Current knowledge states that GD is an autoimmune disease that can affect orbit, thyroid, and skin independently. It is not the thyroid directly leading to ocular damage. This is important to keep in mind as the clinician searches for comorbidities and determines treatment strategies.**
III. Ophthalmic Manifestations of Graves'
    a. Exophthalmos – always bilateral though often asymmetric
        i. Most common cause of exophthalmos is Graves' - 50%
    **b. Dry eye**
        **i. This is a frequent complaint**
        **ii. May be due to increased inflammation, specifically T-cell lymphocytes in lacrimal gland**
        **iii. Foreign body sensation, epiphora**
        **iv. If severe enough can lead to corneal complications (up to 5% of patients)**
    **c. Eye Pain/Pressure**
        **i. Can be at rest**
        **ii. Can be with temporal and/or downward eye movement**
    **d. Diplopia**
        **i. Swollen EOMs**
        **ii. Happens up to 25% of Graves' patients**
    **e. Eyelid retraction - from overactive sympathetic innervations to upper eyelid**
    **f. Redness of conjunctiva, caruncle, eyelid**
    **g. Rarely Optic Nerve Compression (only 3-5% of patients)**
        **i. Called Dysthyroid Optic Neuropathy (DON)**
        **ii. Leads to optic nerve edema and/or atrophy**

IV. Ethnic Differences in Ocular Manifestations
    a. Asian patients have less severe manifestations of orbital disease
        i. More likely to get DON due to shallower orbit and narrower apical configuration
        ii. More difficult to diagnose exophthalmos due to lid aperture shape and structure
        iii. Upper limit of normal exophthalmometry value is 18
    b. White
        i. May have more severe manifestations of orbital disease
        ii. Upper limit of normal exophthalmometry is 21
    c. Black
        i. Not much data on severity
        ii. More difficult to diagnose due to anatomy
        iii. Upper limit of normal exophthalmometry is 24
        iv.
V. NO SPECS classification of severity
    a. Not beneficial because:
        i. Assessing the grades are arbitrary and loosely defined
        ii. Does not allow for easy documentation of disease progression between visits
        iii. Rank order not consistent with how eye specialists examine their patients
        iv. Offers little insight into function or treatment of patients
VI. VISA classification of severity
    a. Vision/DON
    b. Inflammation/congestion
    c. Strabismus/motility restriction
    d. Appearance/exposure
    e. Rate from most important to treat to least important
    f. Better able to detect difference between exams
    g. More geared to treatment strategies
VII. Thyroid Manifestations
    a. Hyperthyroidism
        i. Majority of patients with GD get this ~80%
        ii. Nervousness
        iii. Heat Intolerance/Sweating
        iv. Tremor
        v. Increased appetite
        vi. Weight loss
        vii. Neuropsychological
            1. Often overlooked symptom of Graves'
            2. Depression
            3. Tension
            4. Anxiety
    **b. Hypothyroidism**

i. **Uncommon in GD – but up to 15%**
ii. Lethargic
iii. Low appetite
iv. Low sex drive
v. Weight gain
vi. Cold, clammy

c. **Euthyroid**
i. **Uncommon in GD ~ 5%**
ii. No thyroid symptoms

VIII. Skin Manifestations
a. Pre-tibial myxedema (increased collagen in skin of shin)
b. This is not common – up to 5% of patients

IX. Pathogenesis of Graves'
a. Inflammatory autoimmune disorder that affects thyroid, orbit, and skin
b. Body produces autoantibodies to thyrotropin stimulating hormone receptor (TSHR) which chronically stimulates synthesis.
i. Leads to abnormally high T3 and T4
ii. Negative feedback loop decreases thyrotropin stimulating hormone (TSH) which increases T3 and T4
c. Inflammation
i. CD4 and CD8 T cells, B cells, Plasma cells, Macrophages
d. Simultaneously affects orbit fat and muscle
i. Increase in
1. Fibroblasts, Myofibroblasts
2. Hyaluronic Acid
3. Increased Collagen
4. Adipogenesis from TSHR antibody attack
ii. Increase in Orbital Fat leads to increase in inflammation which exacerbates inflammation

X. Diagnosis
a. Appearance
i. Stare
ii. Eyelid retraction (in up to 90% of patients)
1. Measure distance from corneal light reflex to superior eyelid
2. Present if you notice upper eyelid at superior limbus or higher
iii. Caruncle injection and edema
iv. Eyelid edema and redness
b. Exophthalmos
i. Note ranges
c. Symptoms
i. Dry eye symptoms
ii. Ache at rest or with movement

iii. Diplopia

d. Imaging
    i. CT is best
        1. Allows volume measurement of
            a. Orbital fat
            b. Lacrimal gland
            c. Extraocular Muscles
    ii. MRI less helpful but better if need many images over time
**e. Labs**
    **i. Anti-thryoglobulin (TSI)**
    **ii. Anti-thyroid peroxidase**
    **iii. Anti-TSH receptor**
    **iv. T3 and T4 levels**
    **v. TSH levels**
    **vi. This is a more extensive evaluation than I learned. Would strongly encourage sending to endocrinologist, especially if patient has normal T3, T4, TSH (if that is all you are checking).**

XI. Treatment
a. Most patients stabilize over 6-18 months
b. Systemic Steroids
    i. Oral and/or Intravenous. Not to exceed 8g each course.
    ii. Stabilize inflammation
    iii. Prevent further orbital swelling
c. Most important treatment is to STABILIZE THYROID!
    i. Radioiodine, Thyroid Medication, and Thyroidectomy all aim to stabilize the thyroid
d. Radioiodine for hyperthyroidism
    i. Some studies show exacerbation of Graves' orbitopathy in up to 20% of patients
    ii. Need 6 week of low dose steroid to prevent this
e. Anti-thyroid medication
f. Thyroidectomy – never proven effective
g. Psychiatric Medication
    i. Quality of Life
h. Orbital Decompression
    i. Likely need strabismus surgery also due to diplopia
        1. As high as 64% after decompression
    ii. Need to be stable (inactive GO) for several months before surgery is practical
i. Topical Lubrication
    i. Treating exposure keratopathy
    ii. Treating symptoms
    iii. Most advise to lubricate aggressively
j. Selenium supplements may help if mild

k. Important to remember systemic implications and utilize team approach including
    i. Endocrinologist
    ii. Primary Care Physician
    iii. Ophthalmology (neuro, oculoplastics)
    iv. Mental Health

**XII. Smoking cessation!!**

- **i. Worsening of disease**
    1. **Increased free radicals lead to proliferation of fibroblasts and glycosaminoglycans**
- **ii. Helps prognosis for recovery**
- **iii. Non-smokers (or those who quit) do better with treatment**
    1. **61/65 (94%) of non smokers benefited from treatment**
    2. **58/85 (68%) of smokers benefited from treatment**
- **iv. This is one of the most important things to discuss with your patient. Will influence course of disease and treatment. Very Important!!**

XIII. The 5 things I learned

a. New and better understanding of pathogenesis of Graves' disease
b. Understanding possibility of Hypothyroidism or Euthyroidism with Graves'
c. Extent of ocular signs and symptoms
d. Laboratory investigation
e. Smoking cessation

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