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SIGHT-THREATENING GRAVES' OPHTHALMOPATHY

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CLINICAL RECOGNITION

Ophthalmopathy may develop any time in the course of Graves' disease, or infrequently in association with primary thyroid failure or apparent Hashimoto's thyroiditis, and is infrequently accompanied by thyroid dermopathy. Graves' ophthalmopathy (GO) is usually mild to moderately severe, and about 75% of Graves' patients apparently have no ocular involvement. However, GO may be sight threatening in 1-2% of cases. The latter represent an emergency requiring immediate treatment. GO-related sight loss may be due to corneal breakdown or, more frequently to dysthyroid optic neuropathy (DON). Corneal involvement and/or DON require an **urgent referral** to specialists. As shown in Table 1, these risky conditions should be suspected in patients with unexplained reduction in visual acuity (blurred vision which does not clear with blinking or closing one eye), changes in the intensity or quality of colors, history of popping out of the eyeballs (globe subluxation), presence of corneal opacity, incomplete closure of the eyelids (lagophthalmos), if associated with poor Bell's phenomenon, spontaneous or gaze-evoked orbital pain, if associated with up-gaze restriction. DON may develop acutely (hours) or insidiously (weeks to months).

Table 1. Symptoms and Signs of Sight-Threatening Graves' Ophthalmopathy
Symptoms
Severe eye pain and scratchy sensation
Acute or subacute blurred vision not clearing with blinking (abnormalities of tear film) or closing one eye (abnormality in eye movements)
Deterioration in the quality or intensity of color vision
Episode(s) of globe subluxation (popping out eyes)
Signs
Corneal opacity
Lagophthalmos (incomplete eye closure) particularly if associated with visible cornea on attempted eye closure
Pale or swollen disc, choroidal folds at fundoscopy

PATHOPHYSIOLOGY

Graves' ophthalmopathy is an autoimmune disorder triggered by autoreactive T-lymphocytes recognizing antigen(s) shared by the thyroid and the orbit. Culprit antigens may be the TSH receptor and the IGF-1 receptor. After antigen recognition, a cascade of events is triggered leading to orbital fibroblast proliferation, preadipocyte fibroblast differentiation into adipocytes, secretion of a number of cytokines in turn stimulating fibroblast growth, infiltration of extraocular muscles, and

increased secretion of the hydrophilic glycosaminoglycans. These reactions eventually cause an expansion of the fibroadipose tissue, swelling and dysfunction of extraocular muscles, edema of orbital and periorbital tissues. These changes mechanically explain the most relevant clinical manifestations of the disease, such as exophthalmos, diplopia (double vision), and sight loss due to compression of the optic nerve.

DIAGNOSIS AND DIFFERENTIAL

The diagnosis of GO is usually easy in patients with Graves' disease and bilateral ocular involvement. It may be more difficult when it is not associated with thyroid dysfunction (euthyroid Graves' disease) or ocular involvement is asymmetrical or apparently unilateral. In these cases, other causes of exophthalmos and dysmotility must be ruled out. The latter include orbital tumors, vascular causes (e.g., arteriovenous fistulas), idiopathic myositis, and other inflammatory disorders.

Diagnostic Tests

Minor corneal abnormalities can be detected by slit lamp examination of the cornea which reveals punctate fluorescein staining. Severe corneal damage, usually occurring in patients with marked exophthalmos, is evident simply using a strong light. This shows a marked redness of the lower conjunctiva, a grey corneal opacity, or even a corneal abscess. The eyelids do not close over the cornea and the cornea is visible on attempted eye closure.

DON is due to optic nerve compression, most frequently occurring at the orbital apex (apical crowding), by the enlarged extraocular muscles, or to optic nerve stretching in the event of extreme exophthalmos. Although no single test is sufficient to establish or rule out DON, optic nerve involvement should be investigated by assessing best corrected visual acuity, color vision (e.g., using Ishihara charts), pupil responses by the swinging flashlight test for a relative afferent pupil defect, fundoscopy (optic disc pallor or swelling, choroidal folds), perimetry, or visual evoked potentials. Measurement of intraocular pressure (IOP), particularly in upward gaze, is useful to detect increases due to tightness of the inferior rectus muscle (Table 2). Orbital imaging (CT or MRI) are fundamental to show apical crowding and other features, such as intraorbital fat prolapsed and bony orbital angles, correlated with DON.

Table 2. Testing for Corneal Damage or Optic Neuropathy
Cornea
Direct visual examination
Slit lamp examination with corneal fluorescein staining
Optic Nerve
Best-corrected visual acuity
Color vision (Ishihara charts or others)
Pupil responses to swinging flashlight test (relative afferent papillary defect, RAPD)
Fundoscopy
Perimetry
Visual evoked potentials
Measurement of intraocular pressure (particularly in up-gaze)
Orbital imaging (CT or MRI)

THERAPY

Corneal Breakdown

Frequent (hourly) use of topical lubricants and antibiotics is warranted. If these and other measures, such as moisture chambers, are not sufficient to prevent corneal ulceration and perforation, temporary measures to improve eyelid closure are necessary. These include blepharroraphy, tarsorraphy, emergency gluing, amnion membranes, and botulinum toxin. After controlling the acute situation, permanent improvement of eyelid closure is mandatory (Table 3). Corneal grafting may be then necessary.

Table 3. Managing Corneal Breakdown or Optic Neuropathy
Corneal Breakdown
Intensive (hourly) topical lubricants and antibiotics
Moisture chambers
Temporary measures to improve eye closure: blepharroraphy, tarsorraphy, amnion membranes, botulinum toxin, emergency gluing
Optic neuropathy
First-line treatment: intravenous methylprednisolone (0.5-1 gram in slow 2-3-hour infusion) for 3 consecutive days to be repeated on the next week
Second-line treatment: orbital decompression, if response is absent or poor after two weeks

Optic neuropathy

DON must be treated aggressively. Intravenous glucocorticoids are the first-line treatment. Evidence of the best therapeutic regimen is missing. A commonly used protocol is based on the slow (2-3 hour) infusion of 0.5-1-gram methylprednisolone for three consecutive days. Gastric protection is required. Control of blood glucose and electrolytes is needed, as well as frequent measurement of blood pressure during and for a few hours after infusion. This treatment can be repeated during the next week. If, however, the response to treatment is poor or absent within two weeks or glucocorticoid treatment causes severe side effects, the patient should be promptly submitted for orbital decompression to prevent irreversible damage and sight loss (Table 3).

Treatment of ON (as well as of corneal breakdown) should be performed in specialized centers. New therapies using immune-suppression with agents such as rituximab or teprotumumab (antibody to IGF-1 receptor) are under investigation, but their role in the setting of sight-threatening Graves' ophthalmopathy is unsettled. In particular, rituximab cannot prevent the occurrence of DON and, therefore, should not be used in patients with impending or overt DON.

FOLLOW-UP

After the emergency treatment (medical and/or surgical), residual manifestations of Graves' ophthalmopathy should be treated, as appropriate. If the disease is still active, glucocorticoid treatment can be continued using either oral or intravenous glucocorticoids. It is recommended not to exceed a cumulative dose of 8 grams of intravenous methylprednisolone per cycle because of potential severe hepatotoxicity. If the ophthalmopathy is inactive, rehabilitative surgery (orbital decompression and/or squint surgery and/or eyelid surgery) is often necessary for cosmetic and/or

functional reasons.

All patients should be urged to refrain from smoking, because the latter is associated with more severe forms of GO and a decreased effectiveness of glucocorticoids (and orbital radiotherapy). The dilemma of the optimal long-term treatment for hyperthyroidism in patients with GO remains unsolved in the absence of sound evidence based on randomized clinical trials. Comparative benefits of anti-thyroid drugs, RAI, and surgery are described in the first reference below.

GUIDELINES

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