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Graves' Ophthalmopathy – What Is It?

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Graves' disease is a frequent eye structure disorder. In 1835 Robert Graves described three patients, who had bulging eyes (exophthalmos) associated with thyroid gland enlargement (diffuse goiter), overactive thyroid gland (hyperthyroidism) and swelling of the skin covering the shins (pretibial myxedema). A parallel report was published by Carl Von Basedow in 1840. Since then in English literature this complex of conditions is named for Robert Graves, while in German speaking countries it is referred as Van Basedow's disease. It is remarkable that there is no general agreement as to what the disease should be called. Numerous labels including Graves' ophthalmopathy, Graves' eye disease, endocrine ophthalmopathy, immune exophthalmos, etc. have been advocated. In our clinic we suggest that "dysthyroid orbitopathy" constitutes a better and more accurate term to describe the disease.

Dysthyroid orbitopathy (D-O) usually occurs at the same time as Graves' thyroid disease (diffuse goiter with hyperthyroidism). Approximately 80% of patients with D-O are or were hyperthyroid; 10% were initially hypothyroid; while the remaining 10% appear to not have any deviations of normal thyroid hormone levels or are euthyroid. Even though we cannot always establish a relationship in some patients between the orbital pathology and thyroid pathology, future technology could lead to a more consistent association of thyroid and orbital inflammation.

D-O is an inflammation, presumably an autoimmune disorder that affects parts of the eye (the orbital structures), primarily the muscles that move the eyeball and, to a much lesser degree, the orbital fat. Patients with D-O exhibit a combination of symptoms and signs produced by the orbital inflammation. These may include red eyes (vascular congestion), double vision (extraocular muscles dysfunction), bulging eyes (proptosis) or visual loss (optic neuropathy).

The principal symptoms of D-O can be clearly understood from the changes involved. Enlargement of the orbital tissues gives rise to a difference between the bony orbital volume (the hard, stable structure) and its contents (now enlarged and engored) and explains the presence of proptosis and/or raised intraorbital pressure. Eyelid and red, swelling eyes (conjunctival swelling and conjunctival injection) are reflections of congestion of the veins and protrusion of orbital fat through the orbital septum. Severe lid retraction is the result of tightening of the fibers in the muscle that raises the eyelids (levator palpebral muscle). Bulging eyes (proptosis) in combination with lid retraction causes increased corneal exposure may lead to keratitis or corneal ulcer. This is manifested by tearing, general eye discomfort and blurred

vision. Eye pain is related to severe stages of corneal involvement or to the inflammatory process as such, and is one of the first symptoms to disappear after treatment. Double vision (diplopia) is very common in D-O and results from restricted eye movements. Restriction of eye movement occurs as a result of a build up of scar-like tissue (fibrosis) within various eye muscles (extraocular muscles) in a characteristically uneven (asymmetric) fashion. Pressure on the optic nerve (optic neuropathy) is seen in patients with extremely enlarged eye muscles (extraocular muscles) which squeeze the optic nerve deep within the eye socket. This complication is characterized by diminished visual sharpness (acuity), loss of peripheral vision (visual field defects) and reduced color vision.

Most investigators agree that D-O is often self-limiting. It progresses through a course of periodic flare-ups (exacerbations) until it "burns itself out" and finally returns to normal (spontaneous remission) within a period between three months and five years. However, sometimes treatment is required to prevent permanent damage. No single plan of treatment is best for all patients with D-O. Patients with only minor eye signs such as stare and lid-lag or sensitivity to light (photophobia) and excessive tearing (epiphora) are best treated with artificial tears or lubrication ointments to prevent or cure injury on the cornea surface (exposure keratitis). More serious symptoms need more extensive measures. In these cases the patient and the physician must carefully consider the advantages as well as the side effects while reaching the desired result.

Corticosteroids are widely used in the treatment of dysthyroid orbitopathy to suppress the inflammatory symptoms and to reduce orbital swelling, especially in patients with optic neuropathy. These drugs are thought to be effective in the early stages of the disease before a build up of scar tissue (extensive fibrosis) has occurred, but their precise mechanism of action is not fully understood. Systemic prednisone, taken orally in doses up to 80 mg a day, has proven to be effective in two out of every three patients with dysthyroid orbitopathy. Drawbacks of systemic steroid treatment include frequently occurring side effects, such as high blood pressure, insomnia, weight gain, depression, relapses of eye symptoms after discontinuation and incomplete reversal of the disease in some cases.

Like systemic prednisone, orbital supervoltage radiotherapy has been reported to be effective in some patients with active Graves' eye disease. A good response has been seen in patients with no previous treatment. Improvement is also noted in patients who had previously responded to systemic steroids. Some patients, who did not improve with corticosteroids, had a positive response with this treatment. Radiotherapy combined with corticosteroids appears to be even more effective. According to some authors, patients with a short history of ophthalmopathy generally show a better response than those with more long-term ocular changes. With modern irradiation techniques few complications are seen. However, radiotherapy in patients with coexisting diabetic retinopathy may be discouraged because of the potential risk of aggravating that condition or causing retinal damage.

Surgery has a definite place in the treatment of dysthyroid orbitopathy. With the exception of progressive optic neuropathy not responding to conservative treatment, surgery is usually postponed until the active phase of the disease has resolved. Most orbital surgeons agree that the operations should be

performed in a certain sequence: orbital decompression, if required, first, then correction of double vision and finally eyelid surgery. If these rules are not adhered to, the good results of a prior operation may be lost either by the recurrence of the disease or by the effect of a later procedure. Orbital decompression, for instance, may influence the ocular motility and change the lid aperture. Adjustment (recession) of the inferior rectus muscle may alter upper and lower lid retraction.

For each kind of surgery applied in D-O there are a great number of procedures. Not every patient will have the same benefits from a certain technique. Therefore, surgery must be tailored to the special needs of the individual patient.

Surgical decompression of the orbit in D-O is indicated when vision is threatened due to pressure on the optic nerve and after the failure of conservative treatment. The main purpose of this operation is to make more room for the swollen muscles by removing some of the bone around the eye. Since the first description of an orbital decompression in D-O by Dollinger in 1911, several alternative surgical techniques have been advocated, including one-, two-, three- and four-wall decompression. This procedure is best performed by a skilled and experienced neuro-ophthalmic orbital surgical team that uses an individualized approach in each case.

Orbital decompression is frequently complicated by worsening of pre-existing doublevision (extraocular motility dysfunction), regardless of the method. This must be treated by additional surgery after an appropriate length of time to allow for the elimination of the surgical swelling and stabilization of the myopathy.

Ocular motility imbalance resulting in double vision (diplopia) or neck problems (torticollis) that results from the way the patient holds his or her head to compensate is frequently found in patients with D-O. Criteria for corrective surgery is double vision in the front gaze that has been present and has not changed for at least six months. Success after surgery is defined as single vision in primary and reading positions. Long term satisfactory results of extraocular muscle surgery in patients with stable D-O can be achieved in almost 90% of the cases. A few require repeated surgery.

Lower lid retraction can also accompany bulging eyes (proptosis). This occurs frequently after adjustment of the inferior rectus muscle and is sometimes worsened by orbital decompression. One method for correction of lower lid retraction is to place a graft from the upper lid into the lower lid.

Another surgical procedure is eyelid lengthening for upper lid retraction, with or without removal of excess skin or fat (dermatochalasis).

All the operations on eye muscles and eyelids are done as outpatient procedures. 0nly orbital decompression requires inpatient surgery.

D-O has become a major research focus of an increasing number of clinicians and scientists worldwide. The idea that a multidisciplinary and coordinated approach to all facets of the disease is needed has been gaining ground. While significant progress has been achieved in recent years, we are only at the beginning of a new era in pursuit of fresh and rewarding answers to many old but pertinent questions.

- What is the cause of D-O?
- How and why is this disorder related to the thyroid gland and autoimmune thyroid disease?

- To what extent and by what methods should patients be investigated?
- What is the treatment of choice for the various manifestation of the disease?

Most workers in this field think that D-O is an autoimmune disease in which white blood cells react to the eye muscles by making specific antibodies. The antibodies found in patients with D-O may also be reactive to the thyroid gland. Antibodies are products of immune cells that recognize and combine with specific proteins, which most often leads to the removal of such proteins from the body. This is the way that the body fights infections. However, antibodies directed toward self proteins can cause autoimmune disease. Antibodies reacting with self proteins are found to some extent in all individuals, but they become especially active in D-O. Why this occurs is not understood. Both genetic and environmental factors may be involved. Currently many regulatory pathways of the immune system are being clarified. Once the mechanism of D-O development is understood the disease may become more easily treatable.

A major goal of our research program is to understand the mechanisms involved in the development and progression of the disease, so that more specifically directed therapies may be applied for its prevention and relief. Based on our unique observations, we have identified special peripheral blood tests that reflect immunological disturbances that appear to be linked with D-O. We are now gathering data to link these disturbances with the various stages of the disease. We hope that the evaluation of these blood tests will allow us to follow the patients more closely through the course of the disease and treatment and to prevent any undesirable increase in its severity.

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