

Ocular Changes and Approaches of Ophthalmopathy in Basedow – Graves- Parry- Flajani Disease

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ABSTRACT

Basedow-Graves disease is an autoimmune condition with multiple local and systemic aspects. Among these, oculoopathy has a major impact on patient’s life from both functional and esthetic point of view. Basedow-Graves oculoopathy requires an appropriate positive and differential diagnosis using clinical and imagistic approaches. Treatment is always required in moderate or severe forms and it begins with simple general points and continues with medical and surgical therapies. Current article stresses upon the most characteristic clinical signs of thyroidian ophthalmopathy and the required current therapeutic approaches.

Keywords: exophthalmic goitre, Basedow-Graves disease, thyroidian ophthalmopathy

INTRODUCTION

Grave’s disease is the most common cause of hyperthyroidism in young people, affecting mainly the female population with a female to male ratio of 5/1 to 8/1, associating diffuse goitre, ophthalmopathy and skin changes along with signs and symptoms of

hyperthyroidism (1). The disease has an autoimmune determination and it is induced by autoantibodies against TSH receptor which stimulate this receptor via intracellular signaling pathways resulting increased hormone synthesis and secretion (2). Currently there are 3 types of autoantibodies against TSH receptor accepted worldwide: TSI (Thyroid Stimulating Immunoglobulin) belonging to Ig G family and acting

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as LATS (Long Acting Thyroid Stimulant), TGI (Thyroid Growth Immunoglobulin) with implications in follicle development and enlargement and TBII (Thyrotropin Binding Inhibiting Immunoglobulin) which inhibits the natural binding between TSH and TSH receptor, but stimulating TSH receptor and thus the thyroid function (2). This hyperthyroidian status affects gradually patient`s life through general, cardiovascular, respiratory, neurologic, psychological, gastrointestinal, electrolyte, metabolic, ocular and reproductive changes (3).

The name of the condition comes from the two prominent authors who described main characteristics of the disease: Robert James Graves from Dublin and Carl Adolph von Basedow from Germany (4). There are also in use alternate names for the disease according to the names of other physicians with preoccupations in this field like March, Parsons, Flajani, Begbie, and others (5). It is mandatory to mention the fact that the first one to describe this disease was Caleb Hiller Parry in 1825, ten years before Graves and Basedow, but Grave was the first to identify the three major diagnostic signs: goiter, palpitations and exophthalmos (6). Among clinical aspects of the disease the ocular changes are difficult to manage and may severely compromise patient`s vision (7). Current article propose to describe these changes along with nowadays approaches of orbitopathy. □

EYE CHANGES

Graves` ophthalmopathy encompasses a whole spectrum of eyeball, orbit, eye muscle, fat, nervous and vascular changes due to orbit infiltration with plasma cells, lymphocytes and mucopolysaccharides, with spare of the inner eyeball (8). The external eyeball muscle are also involved in inflammatory and later fibrotic processes and as the disease progresses along with orbital oedema onset, the ocular changes became the most severe and irreducible component (7). Sympathetic nervous system plays a key role in these changes and consequently correcting the levels of thyroid hormones could help reduce the ocular signs (8).

About a quarter of patients with Graves disease suffer from clinically obvious ophthalmopathy but only 5% will develop a severe one although at closer inspection and imaging studies a larger amount of individuals will have obvious ophthalmopathy (9).

Patient`s look is fixed, blinking is rare, palpebral fissures are widened, eyelids movement are slowed, elements that characterize a "frightened face". Ophthalmoplegia could be present or absent as well (10). Superior eyelid folds is hyperpigmented (Jellinek`s sign), eyelids are animated by thin tremors when closed (Rosenbach`s sign) (9), the eyebrows are lost in the extreme third of eyelid (Hertoge`s sign) and in spite of the fact that retroocular infiltration pushes the eyeball forward exists the sensation that eyeballs are protruded because of upper eyelid retraction (Stellwag`s sign) (1). Superior retracted eyelid is moving difficultly and abruptly (Gifford`s sign) (10). Squint and lack of convergence of eyeball become obvious when patient stares at a close object (Moebius`s sign) and there is a dissinergism between eye ball`s and superior eyelid`s movement especially when patient is looking downward (von Graefe`s sign) and between eyeballs and frontal muscles movements when patient is looking upward (Kocher`s sign) (11). Abduction and rotation of eyeball is limited also (Jendrassik`s sign), iris is completely discovered by eyelids (Darlimple`s sign) and the eyeball movements are performed difficultly, abruptly and incompletely (movement`s cap phenomenon) (12). Internal eyeball muscle are also involved, so pupillary constriction at normal light is fast and exaggerated (Coweh`s sign) and mydriasis is obtained very quickly after instillation of soft adrenaline solution into conjunctiva sac (Loewi`s sign) (11). In order to insure some extra protection to the eyeball suffering from lagophthalmos drip secretion is increased (Willbrand- Saenger`s sign) (6). When eyeball moves extremely, horizontal nystagmus is seen (Saiton`s sign) and the eyelids, especially the upper one develop oedema (Enroth`s sign) but the last one seems to improve with treatment (1). In case of ophthalmoplegia, all voluntary eyeball motions are abolished but automatic and pupillary reactions are preserved (Ballett`s sign) (6). Ophthalmic fundus exam demonstrates abnormal intense pulsation of retina`s arteries (Beck`s sign) actually translating widening of sphignomanometric formula but the phenomenon can also be observed in other areas of the body (12). At the same time, intraocular pressure is elevated (Sattler`s sign). Around insertion areas of the four rectus muscles of the eyeball a vascular band network is noticed and this network joints the four insertion points (Topolanski`s sign) (11). Eyeball tends to remain laterally in extreme position (Suker`s sign) and while patient

successively executes abduction and adduction movements there exist the impression of a brutal fast movement of the eyeball (Wilder’s sign) (12). In some cases congestive oculopathy is present and is characterized by chemosis, conjunctivitis, periorbital oedema, corneal ulcers, optic nerve atrophy and optic neuritis (6). Inferior eyelid might be hyperpigmented too (Tellas’s sign) and when placing the stethoscope’s capsule over the closed eyelids a systolic murmur could be heard (Snellen-Rieseeman’s sign) (12). The fold between upper eyelid and eyeball is narrowed when closing the eyes (Russel - Fraser’s sign) and the eyes seem to be situated at different levels because of tanned appearance of skin (Mann’s sign) (13). Elevator muscle of upper eyelid is spastic (Abadie’s sign) and the same trend is noticed while patient is looking down so consequently the eye closes faster (Boston’s sign) (6). □

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of oculopathy is mainly oriented towards exophthalmos which is usually on one side when of local causes and

bilateral when of systemic causes (13). Exophthalmos could be occasioned by cavernous sinus thrombosis, meningiomas, retroocular tumors (eg. choromas in acute myeloid leukemia), granulomatous diseases, uremia, accelerated and malignant arterial hypertension, chronic alcoholism, obstructive lung disease, superior mediastinum compressions, Cushing’s syndrome a.o. (14). Ophthalmoplegia should be differentiated from the one accompanying diabetes mellitus, miastenia gravis, myopathies, blepharochalasis, dermatochalasis, and facial nerve palsy. In the last case Revilland’s sign help in differential diagnosis as patient is not able to close the eye on affected side (15). Are also noticed: Charles-Bell’s sign (visualization of physiologic superior-external ocular deviation when eyes closed), Nero’s sign (because of lagophthalmos the affected eye seems to be deviated upwards), Souque’s sign (when inviting the patient to close the eyes the eyebrows appear longer on affected side) (14).

In order to evaluate the severity of ophthalmopathy there have been imagined a lot of grading systems, the most used of them being the very much alike 6 stages ophthalmologists



FIGURE 1. CM, age 44 female; Graves ophthalmopathy with obvious Stellwag, Moebius, Darlimple and Enroth signs

Score	NOSPECS classification	NOSPECS features	AATG features
0	N	No symptoms or signs	No signs or symptoms
1	O	Signs, no symptoms	Palpebral ptosis or retraction
2	S	Soft tissue involvement	Oedema, chemosis, conjunctivitis
3	P	Exopthalmos	Exopthalmos > 2 cm
4	E	Extraocular muscle involvement	Extraocular muscle involvement
5	C	Corneal involvement	Keratitis
6	S	Sight loss or impairment	Optic nerve involvement

TABLE 1. NOSPECS and AATG classification of Graves ophthalmopathy (16)

acronym NOSPECS and the classification of The American Association for Thyroid Gland (AATG) (Table 1) (16). Also of great importance, especially for monitoring the response to treatment is the 10 points maximum Disease Activity Index scale (Table 2) (2). □

TREATMENT

The management of the condition should be performed and evaluated in a team formed by an endocrinologist and ophthalmologist with a wide experience in such conditions (17).

General points. First of all, the patient should be encouraged to quit smoking if he is a smoker, having in mind that smoking stimulates the synthesis of TSH receptor antibodies and efforts should be made in the direction of achieving euthyroidian status (10). Ocular lubricants must be prescribed as well as complete close of the eyes using adhesive trips during the sleep is welcome. It is mandatory to wear protective sun glasses and UV filters creams on the eyelids (14).

Medical treatment. Elevated thyroid hormones require administration of antithyroid drugs

such as carbimazole, methimazole and propylthiouracil, credited to block entrance of iodine into follicles (18). Generally these drugs are considered of equivalent efficiency but on a randomized trial testing methimazole appeared to be almost three times more efficient than propylthiouracil (19). Radio iodine (¹³¹I) is also used but needs months or years to validate its effect of partially or totally destroy of the thyroid. Moderate-severe opthalmopathy is an absolute contraindication without glucocorticoids association (20). Synthetic thyroid hormones will be administrated as many patients become lifelong hypothyroidians due to radioiodine or surgical removal of the gland (21). When mental status changes persist after restoration of euthyroidism treatment with beta blockers and psychotropic drugs may be required but also mild sedatives and tranquilizers could be helpful. Beta blockers may provide benefits reducing ocular changes, cardiac extra-work, profuse perspiration and tremor, have anxiolytic effect and reduces conversion of thyroxine into triiodothyronine but doses should be gradually risen up to 80 mg per day for propranolol (22). Glucocorticoids reduce orbital oedema but

Feature	Points	Clinics
Pain	1	Pain, oppressive feeling on or behind eye over past 4 weeks
	1	Pain on attempted eye movement over past 4 weeks
Redness	1	Red eyelids
	1	Diffuse conjunctival injection covering at least 25% of eyeball
Swelling	1	Swollen eyelid
	1	Swollen caruncle
	1	Proptosis invreasing more than 2 mm over past 1-3 months
	1	Chemosis
Loss of function	1	Reduced eye movement
	1	Reduced visual acuity
Score	10	

TABLE 2. Disease activity index (2)

their administration must frequently associate orbit irradiation. Diuretics may have a slight effect on orbit, facial and pretibial oedema (23).

Surgical treatment is often required in spite of obtaining euthyroidism. Dollinger and Naffzier were the first surgeons to describe orbital decompression techniques (24) Preoperatively all patients must undergo a complete clinical examination and ophthalmologic evaluation followed by a CT or IRM of orbit and sinuses (17).

Medial wall decompression requires a septoplasty followed by endoscopic ethmoidectomy and sphenoidotomy and a maxillary antrostomy. Then medial orbit wall is fractured and lamina is gently removed and periorbita must be incised to allow orbital fat liberation and provide decompression. Alternative approaches to medial wall include transcutaneous and transcaruncular ways (25).

Lateral wall decompression could be performed through the upper lid incision, lateral, vertical and canthotomy incisions continuing with the dissection of lateral orbit wall periosteum (24).

Inferior wall decompression is addressed to the orbital floor and it is performed transorally or via endoscopy through the maxillary sinus (26).

Superior wall decompression is reserved for the situation when an extensive amount of decompression is needed and implicates the dissection of orbital roof periosteum (27, 28).

Recent advances. It appears that Enterecept, a TNF α inhibitor that binds TNF α thus interfering with its biological activities is effective in Graves` ophthalmopathy (29) as well as Rituximab (30). Rituximab is a monoclonal antibody against CD20 antigen expressed on the surface of B lymphocytes which are implicated in the secretion of antibodies against TSH- receptor (30,31). Other new potential candidates for routine treatment of Graves` ophthalmopathy are antioxidants, intravenous immune globulins and somatostatin and its analogues (1,32). Other targets in Graves` ophthalmopathy are TNF, TNF Receptor, IL1 receptor, TGFB, CD20, CD28, CD3, CD154 resulting in increased self immune tolerance (33).

Response to treatment. In order to predict the response rate of medical treatment, HLA assaying, Doppler ultrasound evaluation of thyroid vascularization, thyrotropin releasing hormone and thyroid stimulatory hormone recep-

tor antibody status have been suggested to ensure a high predictive rate (34). Treatment outcome after use of radioiodine could be indicated by thyroid size, severity of biochemical hyperthyroidism, radioiodine uptake and turn over but so far none of these tests have been adopted generally or proved substantial clinic use (34).

Recent studies on treatment strategies. Corticosteroids treatment has a response rate of 66,9% as a trial involving 834 patients treated for moderate and severe Graves` exophthalmos suggests that intravenous corticosteroids administered in weekly pulses are more effective (74,6%) and has fewer side effects than daily oral administrated corticosteroids (55,5% response), though there exists a lack of standardization in different studies (35). Three observational studies reported on treatment response to orbital radiation suggested an overall favorable outcome of 40% up to 97% of patients, the main risk being the radiation retinopathy developed with a risk of 2% in 10 years (36). In the opinion of National Institute for Health and Clinical Excellence retrobulbar irradiation appears safety and efficient and is particularly indicated for patients without obvious benefits from other therapies (37). There are a few studies on somatostatin and intravenous immunoglobulin for Graves` exophthalmos and as the results are somehow contradictory it is stated that these treatments are of marginal or unproven value (38). A study conducted in 2010 compared the effectiveness of Rituximab in patients with corticosteroid resistant disease using clinical activity score, peripheral lymphocytes flow cytometry, proptosis, strabismus, treatment side effects and regulatory T cells activity (39). Rituximab improved eye changes and vision ($p < 0.03$) after only 2 months of administration and results remained stable and relapse rates were zero (38). Glucocorticoids intravenous pulses are the most accepted approach for patients with moderate to severe disease as a recent trial evaluating the response after 12 weeks of high-dose intravenous corticosteroid pulses showed a statistically significant advantage over oral daily treatment with fewer adverse events and lower mortality rates but the cumulative dose should not exceed 8 g and the fractioned doses should not be administered on consecutive days (40). Other recent study suggests that low doses of orally administered prednisone (0.2mg/kg) during 6 weeks has the

same effectiveness as a standard doses of 0.5 -1mg/kg (41). For antithyroid drugs relapse rates are about 30-50 (after discontinuation and TSH receptor antibodies remain positive at the end of administration in about 52% of smoking patients and in 82% of non smokers (41). Selenium administration seems to improve significantly the quality of life in Graves` ophthalmopathy the usual score and orbit inflammation, the beneficial effect being obvious after 6 months of 100mg administered twice a day (42). The same study evaluated the effect of pentoxifylline as a potent antimedator drug but the results were not concludent (42). Selenium is credited to enhance the effect of methimazole (43). □

CONCLUSIONS

Basedow-Graves ophthalmopathy is a condition characterized by polymorphic signs and symptoms. Its diagnosis requires some clinical skills especially in early stages combined with imagistic studies. Euthyroidism must always be a primary aim. Medical approaches are often efficient and sufficient but many patients become subject to surgery techniques which can properly decompress the orbit providing functional and esthetic results. Among surgical approaches, medial wall decompression appears to provide effective reduction of exophthalmos but every therapeutic step should be decided by a team of specialists incorporating endocrinologists, ophthalmologists, otolaryngologists, endoscopists and even plastic surgeons.

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