ARTICLE IN PRESS

Journal of Cranio-Maxillo-Facial Surgery xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Graves-Basedow ophthalmopathy surgical approaches: Open vs Endoscopic

Valerio Facchini [a], Alessandro Piccirilli [a,*], Walter Colangeli [a], Aleksandr Kapitonov [a], Flavia Maesa [a], Iacopo Iachini [b], Evaristo Belli [a]

[a] U.O. Chirurgia Maxillo-Facciale, Ospedale Sant'Andrea di Roma, Facoltà di medicina e psicologia, Università di Roma "La Sapienza", Italy
[b] Maxillofacial Surgery Unit, Azienda ULSS 2 Ospedale di Castelfranco Veneto, via dei Carpani, 16/Z, 31033, Castelfranco Veneto, (Treviso TV), Italy

ARTICLE INFO

Handling editor: Emeka Nkenke

Keywords:
Graves-basedow ophthalmopathy
Endoscopic orbital decompression
Open orbital decompression
Exophthalmos

ABSTRACT

Graves-Basedow's disease (GBD) is an autoimmune pathology that affects the thyroid and is characterized by the presence of goiter, hyperthyroidism, ophthalmopathy, and dermopathy. Graves-Basedow ophthalmopathy (GBO) is a set of inflammatory and infiltrative alterations of the orbital tissue that affects 40–90% of subjects suffering from GBD. Our study aims to investigate the differences in the clinical outcomes of patients treated with two different techniques: the classic open and the more modern endoscopic. A retrospective clinical study was carried out from the year 2011 until the year 2020 to evaluate the clinical outcomes of two different surgical techniques for the treatment of GBO. Eighteen patients were given surgical indications, 12 males and 6 females aged between 37 and 69 years (average age 48.5 years), for a total of 36 orbits. From the year 2011 to the year 2014, all patients were treated with the open orbital decompression technique; from 2015 onwards, patients were subjected to orbital decompression with the endoscopic transnasal approach. Pre- and postoperative ophthalmometry, reduction of proptosis, and reduction of oculo-orbital index were compared for the two techniques. As evidenced by the statistical analysis carried out on the sample before and after surgical treatment, there is a statistically significant difference between ophthalmometry and the Oculo-Orbital Index (IOO) values; this indicates that surgical orbital decompression with two walls (floor and medial wall) is effective in reducing exophthalmos. The positive result is also confirmed by the reduction of proptosis, measured in millimeters, averaging 1.7 mm. In the analysis of data relating to the two different patient groups, treated respectively with endoscopic orbital decompression (Technique 1) and classical open orbital decompression (Technique 2), the results obtained show that there is no statistically significant difference between the results of the two techniques. Therefore, the choice of surgical approach is at the discretion of the surgeon. It is our opinion that orbital decompression with the endoscopic transnasal technique should be an absolute indication in all patients who have clinical and radiographic signs of involvement of the optic nerve at the orbital apex (crowded apex syndrome) thanks to the ability of this technique to add and decompress the optical channel at the apex. For all other patients with GBO, the endoscopic technique of orbital decompression can be indicated as a first-line surgical approach considering the absence of skin scars and the best aesthetic results.

1. Introduction

Graves-Basedow's disease (GBD) is an autoimmune pathology that affects the thyroid and is characterized by the presence of goiter, hyperthyroidism, ophthalmopathy, and dermopathy (Graves; Bürgi, 2009). It is the most frequent cause of hyperthyroidism with an incidence around 1–2 cases per 1000 inhabitants per year and a prevalence of about 2.5–3%; it affects more frequently the female sex with an F/M ratio of 5–10/1 in the third and fourth decades of life. GBD is a pathology characterized by strong familiarity in the Caucasian race, as evidenced by the existence of genetic factors such as the association between the expression of HLA-B8 and DR3 antigens and the appearance of disease; the association with polymorphisms of genes located on chromosome 2Q33 in relation to susceptibility in the production of autoantibodies has also been documented.

The hyperthyroidism that characterizes this disease is caused by the presence of autoantibodies directed against the TSH receptor in the serum of affected patients. These lead to an overstimulation of the

* Corresponding author.
E-mail addresses: valerio.facchini1@gmail.com (V. Facchini), alessandro.piccirilli@uniroma1.it (A. Piccirilli), walter.colangeli@alice.it (W. Colangeli), dr.kapitonov.aleksandr@gmail.com (A. Kapitonov), flavia.maesa@gmail.com (F. Maesa), iacopo.iachini@gmail.com (I. Iachini), evarbell@libero.it (E. Belli).

https://doi.org/10.1016/j.jcms.2024.06.004
Received 31 August 2023; Received in revised form 11 February 2024; Accepted 8 June 2024
Available online 15 June 2024

Please cite this article as: Valerio Facchini et al., *Journal of Cranio-Maxillo-Facial Surgery*, https://doi.org/10.1016/j.jcms.2024.06.004

thyroid gland cells with an increase in the circulating hormones FT3 and FT4.

The symptomatological cortex of GBD is characterized by a variety of multisystemic manifestations, including cardiopalms, asthenia, sweating, weight loss, diarrhea, anxiety, agitation, and neuropsychic instability. Clinical signs include goiter, tachycardia, finger tremors, dermal affections, and eye signs. The latter define the framework of Graves-Basedow ophthalmopathy (GBO), which is a set of inflammatory and infiltrative alterations of the orbital tissue that affects 40–90% of subjects suffering from GBD.

Of these patients, about 60% report eye discomfort due to eyelid retraction; 35% have diplopia or impaired proptosis, and 3–7% will develop a serious and threatening complication such as dysthyroid optic neuropathy. A multidisciplinary team of endocrinologists, ophthalmologists, and maxillofacial surgeons supports the diagnosis and the treatment of GBO. Thanks to a careful clinical analysis of symptoms and signs, a laboratory analysis aimed at the assessment of the thyroid condition, and a careful study through imaging methods such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US), it is possible to define the diagnosis and the degree of activity and severity of the pathology.

Our study aims to investigate the differences in the clinical outcomes of patients treated with two different techniques: the classic open and the more modern endoscopic.

2. Materials and methods

A retrospective clinical study was carried out from the year 2011 until the year 2020 to evaluate the clinical outcomes of two different surgical techniques for the treatment of GBO.

Eighteen patients were given surgical indications, 12 males and 6 females aged between 37 and 69 years (average age 48.5 years), for a total of 36 orbits. From the year 2011 to the year 2014, all patients were treated with the open orbital decompression technique; from 2015 onwards, patients were subjected to orbital decompression with endoscopic transnasal approach.

The sample, therefore, included two groups of patients: the first group consisting of 8 patients, subjected to orbital decompression with the open technique (OT); the second consisting of 10 patients, subjected to orbital decompression with the endoscopic technique (ET). Pre- and postoperative ophthalmometry, reduction of proptosis, and reduction of oculo-orbital index were compared for the two techniques.

All the patients came from the Diagnosis and Therapy of Thyroid Orbitopathy day hospital service of the same hospital; here, they followed periodic endocrinological and oculistic assessments. During the day hospital, each patient was evaluated for.

- Medical history: age, sex, previous or current treatment for GBO, surgery for strabismus, previous orbital radiotherapy, thyroidectomy, previous ocular pathologies, possible topical therapy.
- Symptoms: photophobia, watery eyes, irritation, dryness, tightness, foreign body sensation, diplopia, spontaneous pain, or movement.
- Objective examination: assessment of upper and lower palpebral edema, upper and lower palpebral hyperemia, conjunctival hyperemia, chemosis, plica/caruncula edema, eyelid opening, upper and lower eyelid retraction, lagophthalmos, corneal appearance and proptosis; in particular, proptosis values were evaluated using the Hertel ophthalmometer.
- Index of Severity.
  •Activity Index (CAS).
  •Motility of the eyes. • Diplopia.
  •Visual acuity.
  •Tonometry.
  •Field of view.
  •Imaging examination (MRI, CT)

For each patient, the pre-operative measurement of the degree of proptosis was performed using the Hertel ophthalmometer; the IOO, considered as the percentage of the maximum vertical distance of the orbital cavity on the maximum horizontal distance assessed on the interzygomatic distance calculated as the maximum distance between the points on the anterior part of the zygomatic arch, was collected through the study of axial CT images. For the 10 patients endoscopically treated, the Fusion Navigation System, Medtronic™ was used. All surgeries were performed under general anesthesia.

- OPEN TECHNIQUE

The surgical open procedure begins with a cutaneous incision under the eyelid. It also can be performed tranconjunctivally to avoid the scar. The orbital floor is blunted, and the orbital floor and the lamina papyracea are then exposed and resected, resulting in orbital decompression and subsequent immediate reduction in proptosis. It is important to preserve a bony bridge together with the infra-orbital canal, avoiding downward displacement of the eyeball. The lateral wall of the orbit can also be resected in the more severe cases by performing a second cutaneous incision. The Olivari lipectomy is then performed. Upper blepharoplasty is finally performed.

- ENDOSCOPIC TECHNIQUE

The surgical endoscopic procedure begins with a partial uncinectomy and the opening of the natural ostium of the maxillary sinus. An antrostomy and an ethmoidectomy are practiced by exposing the medial wall of the orbit. It continues to the opening of the sphenoidal sinus. Once the lamina papyracea is exposed, the sphenoidotomy is widened laterally exposing the posterior limit of the medial orbital wall. The optical tubercle is identified and gently drilled and dislocated, exposing the tendinous annulus of Zinn and widening the optical hole. The lamina papyracea is gently milled and removed with a spatula; the exposed periorbit is longitudinally incised. Once the latter has been removed, the extraconic fat is exposed. The endoscopic decompression continues by removing the orbital floor up to the infra-orbital canal. By incisions of the periorbit, the extraconic fat is released. To avoid the formation of sinews between periorbital and nasal septum, silicone foil is placed. At the end of the procedure, two nasal swabs are placed and held for 72 h.

The patients of both groups were monitored in the post-operative course, with an evaluation of the degree of reduction of proptosis by means of the Hertel ophthalmometer; the IOO was calculated again through the study of post-operative CT images performed 3 months after surgery. For patients of the second group, an endoscopic examination was carried out following the removal of nasal swabs. The silicone foils were removed in the fourth week after surgery.

The data used to compare the outcomes of the two different surgical techniques were.

- Ophthalmometry (mm)
  •IOO (%)
- Reduction of proptosis (mm)

The collected data were processed with the SPSS IBM 24.0 software. Descriptive statistical analysis was carried out for the quali-quantitative variables (sex, age, pre- and post-surgical ophthalmometry, pre- and post-surgical IOO, postoperative proptosis reduction, surgical technique used). Student's T-test was performed to compare continuous variables.

3. Results

Patients are numbered in progressive order; for each, age, CAS, the values of ophthalmometry for the right and left eye recorded before and after surgery, the surgical technique used, the IOO for the right and left eye measured before and after surgery, and the reduction of proptosis for the right and left eye are listed (see Table 1).

Table 2 shows the data relating to the descriptive statistics carried out on the pre-operative sample; in particular, the minimum value, the maximum value, the mean, and the standard deviation of age, sex, ophthalmometry of the right and left eye, and IOO of the right and left eye were calculated.

For the parameters considered, ophthalmometry (Table 3a) and IOO (Table 3b), paired samples T-test was carried out to assess whether there is a statistically significant difference between the average pre- and post-operative values for both eyes.

As can be seen from the above tables (Tables 3a and 3b), the p values are all below 0.0001, indicating that there is a statistically significant difference between the averages of the pre- and post-operative values. To verify if there is significance between the two surgical techniques used in the two groups of patients, the Independent Samples T-test was performed between the averages of the variables ophthalmometry, IOO, reduction of proptosis in both eyes. An analysis of the p values in Table 4 shows that none of the variables were less than 0.05, indicating therefore that there is no statistically significant difference in the outcomes of the two different surgical techniques used in the groups of patients suffering from GBO.

4. Discussion

Graves-Basedow's ophthalmopathy is the most frequent extra-thyroid manifestation of the disease. However, it can be found in patients with no history of hyperthyroidism or even in hypothyroid patients with Hashimoto's thyroiditis. The GBO, even in its mildest manifestations, has a profound impact on the quality of life of affected patients; therefore, an important objective would be to prevent the onset of ophthalmopathy progression.

A recent study that analyzed data in the literature indicates that the incidence rate of GBD is 13.9/100,000 inhabitants per year in the United States (Jacobson et al., 1997). In Europe, the prevalence is between 0.1 and 0.3 % (Tellez et al., 1992; Flynn et al., 2004). A European study found a higher prevalence of GBO in Caucasians (42%) than in Asians (7.7%) (Tunbridge et al., 1977). Bartley's study (Bartley, 1994) attests to the age-related incidence of GBO at 1/100,000 inhabitants per year for women and 2.9/100,000 inhabitants for men in the state of Minnesota; this study also shows a bimodal peak incidence, 40–44 years and 60–64 years in women, 45–49 years and 65–69 years for men.

About half of patients with GBD do not have clinically evident eye involvement, but in most of them, subclinical abnormalities can be found thanks to CT or MRI studies (Forbes et al., 1986). Severe forms of ophthalmopathy are found in about 3–5% of cases; eye disease is bilateral in 85–95% of cases, unilateral in 5–15% (Burch and Wartofsky, 1993).

The natural history of GBO is not yet fully clarified; a cohort study by Perros et al. (1995) observed a spontaneous regression of ocular manifestations in about 2/3 of patients, stability of eye disease in 20%, and worsening in 14% of patients observed for a long period. Nowadays, GBO appears to be less frequent and less severe than in the past; a review of clinical data for 100 patients with GBD from 1960 to 1990 showed a significant reduction in clinically relevant GBO, from 57% in 1960 to 32% in 1990 (Kendall-Taylor and Perros, 1998). This trend could be related both to the early diagnosis of hyperthyroidism and to the increased attention towards the initial ocular manifestations.

An important epidemiological peculiarity of GBO is its close link to cigarette smoking: numerous studies have documented that the prevalence of smokers among patients with GBO is higher than any other thyroid disorder, of an autoimmune or non-autoimmune nature (Bartalena et al., 1989, 1995; Prummel and Wiersinga, 1993; Pfeilschifter and Ziegler, 1996). A study that analyzed 1730 women showed that the prevalence of smokers stood at about 30% in patients suffering from non-toxic goiter, toxic nodular goiter, or thyroiditis of Hashimoto, while it was 48% in patients with GBD without ophthalmopathy and 64% in

Table 1
Data of the whole sample examined. * = Endoscopic Technique. ** = Open Technique.

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Age	37	62	55	37	60	38	39	69	64	41	51	37	61	54	53	55	50	48
CAS	5	5	3	2	7	4	4	1	2	2	3	5	5	3	3	3	5	7
Gender	M	F	M	F	F	M	M	M	F	M	M	M	F	M	M	M	M	F
Pre-surgery Ophthalmometry (right eye) (mm)	27	20	21	22	25	17,5	25	25	23	22,5	21,5	27	20	21	23	22,5	21,5	20
Pre-surgery Ophthalmometry (left eye) (mm)	25	22	20	22	23	20	25	25	23,5	23,5	20	25	22	20	23,5	23,5	20	27
Post-surgery Ophthalmometry (right eye) (mm)	25	19	19	20	23	17,5	22	21	22,5	22	18	25	19	19	22,5	22	18	20
Post-surgery Ophthalmometry (left eye) (mm)	23	21	18	20	22	18	23	22,5	22,5	23	18	23	21	18	22,5	23	18	23
Surgical Technique	ET*	ET	ET	OT**	OT	OT	OT	OT	OT	OT	OT	ET	ET	ET	ET	ET	ET	ET
Pre-surgery IOO (right eye) (%)	137,7	82,6	99,5	86,3	104,6	64,9	132,5	103,6	111,7	114,8	118	137	82	99	111,7	114,8	118	82,7
Pre-surgery IOO (left eye) (%)	114,4	98,7	100	95,6	104,6	102,1	137	109	108,4	122,4	122,5	114	98	100	108,4	122,4	122,5	98,7
Post-surgery IOO (right eye) (%)	117,4	70,6	81,4	75,3	90,6	64,9	111,5	86,6	106,7	107,6	96,8	117	70	81	106,7	107,6	96,8	82,7
Post-surgery IOO (left eye) (%)	107,4	85,7	88,4	84,6	90,6	76,8	122	97	101,4	118,8	103,6	107	85	88	101,4	118,8	103,6	85,7
Reduction of proptosis (right eye) (mm)	2	1	2	2	2	0	3	4	0,5	0,5	3,5	2	1	2	0,5	0,5	3,5	0
Reduction of proptosis (left eye) (mm)	2	1	2	2	1	2	2	2,5	0,5	0,5	2	2	1	2	10,5	0,5	2	2

Table 2
Data relating to the descriptive statistics carried out on the pre-operative sample.

	Age	Pre-surgery Ophthalmometry (right eye) (mm)	Pre-surgery Ophthalmometry (left eye) (mm)	Pre-surgery IOO (right eye) (%)	Pre-surgery IOO (left eye) (%)
Mean	48,9286	22,6786	22,5714	105, 3000	109,0500
Median	52,5000	22,2500	22,5000	104,1000	106,5000
Mode	37,00	25,00	20,00	64,9	100,00
Std. Deviation	13,90,332	2,80,526	2,01778	21,86,504	11,88,378
Lower	25,00	17,5	20,00	64,90	95,60
Upper	69,00	27,00	25,00	137,70	137,00

Table 3a
Data relating to the paired sample T test for the ophthalmometry.

Paired Differences								
				Confidence Interval				
	Mean	Std. Deviation	Mean Std. error	lower	Upper	t	Degree of freedom	p Value
Pre-surgery Ophthalmometry (right eye)/Post-surgery Ophthalmometry (right eye)	1,82,143	1,15,371	0,30,834	1,15,530	2,48,756	5907	13	<0,001
Pre-surgery Ophthalmometry (left eye)/Post-surgery Ophthalmometry (left eye)	1,64,286	0,60,219	0,16,094	1,29,516	1,99,055	10,208	13	<0,001

Table 3b
Data relating to the paired sample T test for the IOO.

Paired Differences								
				Confidence Interval				
	Mean	Std. Deviation	Mean Std. error	lower	Upper	t	Degree of freedom	p Value
Pre-surgery IOO (right eye)/Post-surgery IOO (right eye)	14,05714	6,55,471	1, 75,182	10, 27,257	17,84,172	8024	13	<0,001
Pre-surgery IOO (left eye)/Post-surgery IOO (left eye)	12,17,143	65,44,771	1,45,596	9,02601	15,31,684	8360	13	<0,001

Table 4
Statistical analysis of the outcomes of the two different surgical techniques used.

Independent Samples Test									
	Levene's Test for Equality of Variances				*t*-test for equality of means			95% CI	
	F	Sig	T	Degree of freedom (df)	p value	Difference of the averages	Difference of the standard error	Lower	Upper
Proptosis reduction (right eye)	5524	0,037	−0,421	12	0,681	−027,083	0,64,379	−1,67,352	1,13,186
Proptosis reduction (left eye)	2817	0,119	0,284	12	0,782	0,10,417	0,36,735	−069,622	0,90,455
Post-surgery Ophthalmometry (right eye)	3143	0,102	0,182	12	0,859	0,25,000	1,37,689	−2,74,999	3,24,999
Post-surgery Ophthalmometry (left eye)	0,016	0,903	−0,387	12	0,706	−0,45,833	1,18,433	−3,03876	2,12,210
Post-surgery IOO (right eye)	1277	0,281	−0,286	12	0,779	−2,93,333	10,24,115	−25,24,689	19,38,022
Post-surgery IOO (left eye)	0,605	0,452	−0,774	12	0,454	−5,76,667	7,45,485	−22,00940	10,47,607

patients with GBO. The pathogenetic mechanism behind the influence of smoking in the progression of GBO is not yet clear, but it is hypothesized that smoking could both exert a direct irritating effect and contribute to the modulation of the endorbital immune response (Bartalena et al., 1989).

The pathogenesis of GBO is complex and unclear. In fact, GBO is an autoimmune disease resulting from the interplay between genetic susceptibility, due to the presence of genes such as HLA, CTLA-4, and TCR, and environmental factors. Environmental factors play a dominant role in the development of this disease (Putta-Manohar and Perros, 2010).

Cigarette smoking is the most important exogenous factor and is associated with the GBO onset, its severity, and the reduced response to therapy. Stress causes a modification of the cell-mediated response from Th1 and Th2, with an increased susceptibility to the development of autoimmune pathologies. Radioiodine therapy, a possible treatment for hyperthyroidism, can induce a worsening of GBO for destruction of thyroid follicular cells with release of inflammatory cytokines, activation of T cells, and increased title of anti-TSH receptor antibodies (TRAb) (Putta-Manohar and Perros, 2010).

The pathogenesis of GBD can be summarized in three main mechanisms: inflammation of the periorbital soft tissues, excess production of glycosaminoglycans (GAGs) by orbital fibroblasts, and hyperplasia of adipose tissue (Putta-Manohar and Perros, 2010; Bartley et al., 1996; Dickinson and Perros, 2001; Bahn and Gorman, 1987; Clauser et al., 2001). The TSH receptor (R-TSH) is the main antigen involved in the pathogenesis of GBO, and a correlation has been found between the expression of orbital R-TSH and the severity of GBO. In addition, the highest expression of R-TSH is observed in active forms of GBO (Putta-Manohar and Perros, 2010). Other antigens (thyroglobulin, TPO, ocular muscle antigens) may be involved, but their role is not yet clear (Putta-Manohar and Perros, 2010). Orbital fibroblasts represent the main target of the autoimmune process, due to the loss of their normal function. In the orbital tissue are distinguished fibroblasts that express the glycoprotein Thy1 (Thy1+) and fibroblasts that do not express it (Thy1-). Thy1+ if exposed to IFNγ and TNFα, cytokines produced by Th1 lymphocytes, produce GAGs that accumulate in the perimysium of the extraocular muscles and cause edema and increased muscle volume18. Thy1-fibroblasts (pre-adipocyte) express R-TSH and, due to the stimulation of TRAb, differentiate into mature adipocytes with increased orbital adipose tissue and increased expression of R-TSH (Bartley et al., 1996).

Production of TGFβ causes differentiation of Thy1+ into myofibroblasts that participate in late-stage fibrosis of GBO (Bartley et al., 1996). In GBO, the prevalent involvement of muscle or adipose tissue in the orbit depends on the proportion of Thy1+ and Thy1-fibroblasts present in the orbita (Dickinson and Perros, 2001; Bahn and Gorman, 1987). In most cases, GBO develops with an active inflammatory phase followed by an inactive one. During this last phase, muscle edema along with increased collagen production inevitably leads to atrophy, fibrosis, and sclerosis of the extraocular musculature resulting in restrictive strabismus (Clauser et al., 2001).

At the same time, impaired intraorbital venous drainage contributes to the volumetric increase of the endorbital content. In particular, the thickening of the upper rectus muscle can lead to a reduction in venous flow due to compression of the superior ophthalmic vein (Clauser et al., 2001).

The ocular modifications that appear in this disease can then be classified into infiltrative and non-infiltrative. The first ones, autoimmune, are characterized by the infiltration of pro-inflammatory cells in the retroocular tissues and in the extraocular muscles with consequent proliferation of fibroblasts, production of collagen and GAGs, up to the edema and fibrosis. Non-infiltrative modifications include spastic retraction of the eyelid. These modifications therefore allow classifying GBO into two different forms: type 1, characterized by stimulation of retroocular adipose tissue and connective tissue, and type 2, characterized by extraocular myositis with edema, lymphocytic infiltration, and muscle necrosis (Clauser et al., 2001).

About 50% of patients with GBD have ophthalmopathy symptoms. Many of the clinical manifestations of GBO are caused by the increased volume of orbital soft tissues that leads to an increase in pressure within the non-expandable bone cavity (Bartalena et al., 2008). The symptomatological cortex is related to eye exposure (dryness, photophobia, blurred vision, and excessive lacrimation); inflammation and congestion of periorbital soft tissues (sensation of retroocular pressure, conjunctival redness, palpebral edema; and involvement of extraocular muscles (pain associated with eye movement, limited ocular motility, and diplopia).

The two most frequent signs of GBO are upper eyelid retraction (90%) and proptosis (Barrio-Barrio et al., 2015). The staring wide-open eyes resulting from the retraction of the upper eyelid are a common aspect of presentation of these patients (Fig. 1a, b, and 1c).

Increased circulating levels of thyroid hormones and increased sympathetic activity are responsible at an early stage of eyelid retraction that, with time, becomes permanent due to the infiltration of the Muller muscle by lymphocytes and fibroblasts and the consequent scarring outcomes. The position of the eyelids in the neutral gaze position is considered in the evaluation of the retraction. The position of both eyelids is measured in reference to the sclera-corneal limbus which, in physiological conditions, is covered by the upper eyelid and only lapped by the lower. The retraction is measured as a positive value in mm[21].

Concerning proptosis, measurements are made considering an average orbital volume of 26 ml; therefore, an increase of only 4 ml will result in a proptosis of 4 mm[21].

Exophthalmos may be associated with eyelid edema, conjunctivitis, photophobia, headache, retroocular pain, and epiphora. Diplopia, on the other hand, results from ophthalmoplegia caused by hypertrophy of the extraocular muscles. The most involved muscles are the medial rectum and the lower rectum, resulting in limitation of lateral and upper gaze. In contrast, in an advanced stage, diplopia is caused by fibrosis of the eye muscles, which prevents adequate compliance in response to the contraction of antagonist muscles. Keratitis, conjunctival ulcers, and corneal degenerations may follow all of the above-mentioned phenomena (Bartalena et al., 2008; Barrio-Barrio et al., 2015).

About 3–7% of patients with GBO show very severe manifestations due to corneal exposure or to optic neuropathy (Neigel et al., 1988). Optic neuropathy is generally caused by compression of the optic nerve at the orbital apex by hypertrophic extraocular muscles. The typical

Fig. 1. a, b and c: lateral and frontal view of a clinical presentation with proptosis and upper eyelid retraction.

symptoms are represented by the desaturation of the colors and the blurred central vision; specific signs but not always present are the edema of the optical papilla and the afferent pupillary defect. Optic neuropathy is generally bilateral; monolateral in 1/3 of cases. Although these patients commonly have proptosis, optic neuropathy may appear even in the absence of significant exophthalmos, especially in those patients whose orbital septum limits the anterior dislocation of the eyeball resulting in increased retroocular pressure (Bartalena et al., 2008).

In the study of GBO, it is necessary to differentiate the concept of activity from that of severity. The first refers to the inflammatory process, the second to the quality of life of the patient or the risk of loss of visus. For a correct evaluation of the clinical manifestations of GBO, several classification systems have been described. In 1969, Werner (1969) developed the classification NO SPECS (No physical signs or symptoms, Only sign, Soft tissue involvement, Proptosis, Extraocular muscle signs, Corneal involvement, Sight loss).

Werner himself proposed the modified NO SPECS in 1977. This classification allows an assessment of the degree of severity only, not allowing an adequate distinction between the inflammatory phase and the stationary one. In 1989, Mourits et al. (1989) proposed the Clinical Activity Score (CAS), based on the study of the classic signs of inflammation (dolor, rubor, tumor, calor, and functio lesa), proposing it as a useful tool in discriminating between the active phase and the quiescent phase of the disease. To date, the most widely used classification systems are the VISA (Vision, Inflammation, Strabismus, Appearance) classification (Dolman and Rootman, 2006) and the EUGOGO (EUropean Group Of Graves' Orbitopathy) classification (Bartalena et al., 2008). Both systems are based on NO SPECS and CAS classifications and use different indicators for estimating activity and severity signs. They also provide the clinician with guidance for treatment.

- VISA

Developed by Dolman and Rootman in 2006, assesses four severity parameters.

Vision is estimated through the evaluation of visual acuity, pupillary reflexes, color vision, visual field, the study of the optic nerve, and visual evoked potentials. Inflammation is assessed through ocular pain at rest, movement-associated pain, and its daily variations, caruncular edema, chemosis, conjunctival redness, palpebral redness, and palpebral edema. Each item is awarded a score from the sum of which a score is obtained (max 10). Scores ≤ 4 are treated conservatively; scores ≥ 5 are subjected to treatments that are more aggressive. Strabismus is evaluated through three aspects: diplopia, duction movements, and restriction of duction movements. The appearance is evaluated through the ocular aesthetics aspects (protruding eyes, eyelid retraction, and fat pockets) and through the symptoms resulting from eye exposure (photophobia, dry eyes, watery eyes, and eye gritting). The scleral exposure, the functionality of the upper eyelid elevator muscle, the lagophthalmos, and proptosis are also evaluated.

- EUGOGO

Developed in 1999 and widely used, this classification is based on the study of parameters of activity and severity. The activity is assessed through the CAS. Taking into consideration 10 items, a score of 0 or 1 is assigned to each of them based on its absence or presence. Items are spontaneous orbital pain, orbital pain at movement, palpebral edema, palpebral erythema, conjunctival erythema, chemosis, inflammation of the caruncula, proptosis >2 mm, reduction of ocular excursion in any direction >8, and reduction of visual acuity. The first 7 items are evaluated on the first visit, and a score ≥ 3 is indicative of the GBO. During the follow-up, all 10 items are evaluated, and the cut-off of activity is set to a score ≥ 4. The severity is assessed through the evaluation of soft tissue inflammation, palpebral measurements, proptosis, ocular motility, corneal integrity, and optic neuropathy. The disease is then classified as mild, moderate/severe without vision impairment, and severe with vision impairment. The diagnosis in the evaluation of GBO requires a multispecialty approach involving ophthalmologists, endocrinologists, radiologists, and maxillofacial surgeons (Gonçalves et al., 2012). The endocrinological evaluation is aimed at identifying GBO by anamnesis, objective examination, and laboratory examinations. GBO is associated in 85% of cases with hyperthyroidism, in a small percentage of cases with hypothyroidism from chronic autoimmune thyroiditis, and in rare cases with normal thyroid function patients (Putta-Manohar and Perros, 2010). In the latter case, the thyroid correlation of GBO is possible thanks to autoantibodies, also useful as a prognostic factor (Eckstein et al., 2006, 2010; Gerding et al., 2000).

During the ophthalmologic evaluation, proptosis (considered positive if > 20 mm or if there is an asymmetry >3 mm between the two eyes), diplopia, optic neuropathy, and all previously reported eye signs and symptoms are evaluated.

Radiological examination with US, CT, and MRI plays an extremely important role in both diagnosis and follow-up of patients with GBO. For example, the CT allows the calculation of the oculus-orbital index (IOO) understood as the ratio between the degree of protrusion of the ocular globe multiplied by 100 and the axial length of the eye. Based on the values of the IOO, it is possible to classify the exophthalmos in three degrees: I degree, IOO <100%; II degree, IOO = 100%; III degree, IOO >100%. In the general population, IOO values are below 70% (Baujat et al., 2006).

Suggestive findings of Graves ophthalmology at TC/RMN are: mono or bilateral proptosis, fusiform thickening of extra-ocular muscles, with savings in muscle insertion on the eyeball, intra- and extra-conical fat increase, compression of the optic nerve at the apex of the orbit (Crowded orbital apex syndrome) or impression of the papiracea plate, and compression of the optic nerve at the apex of the orbit (Kahaly, 2001).

The maxillofacial evaluation is aimed at programming and performing the most appropriate surgical treatment for the resolution of the exophthalmos and related symptoms. Due to the characteristics of this clinical entity, adequate timing and treatment choices are required at different stages of the disease itself. Therapeutic measures for all GBO patients.

1. Restoring the euthyroid condition: it is a crucial point in the management of patients, as those with uncontrolled thyroid dysfunction are more likely to develop severe forms of ophthalmopathy (Bahn et al., 2011).
2. Conservative measures: all patients should be advised to take some general measures, such as artificial tears, goggles, natural ointments to protect the cornea.
3. Smoking abstention: smoking is the most important modifiable risk factor in GBO patients, and this risk is directly proportional to the number of cigarettes/day; affected smokers are more likely to develop severe forms and have worse responses to immunosuppressive therapies (Bahn et al., 2011; Bahn, 2010).

Treatment modalities are chosen based on the activity and severity of the disease. In mild ophthalmopathy, the most important treatment for this class of patients, whose disease often tends to self-limit, are local measures; a protocol is implemented to prevent progression based on the use of selenium (100 μg/bid) for the duration of 6 months. This approach has shown a significant improvement in the quality of life, a reduction in eye involvement, and a slowdown in progression to more severe forms of ophthalmopathy (Marcocci et al., 2011). Acute side effects of such treatment are periorbital edema, hair loss, and conjunctival hyperemia; these tend to regress at the end of radiant treatment. More rarely, more serious side effects can manifest, such as optic neuropathy, cataracts, and actinic retinopathy.

In the case of inactive disease (CAS <3), there are numerous rehabilitative surgical procedures available for patients with moderate-severe ophthalmopathy. An essential prerequisite for access to surgical treatments is the demonstration of a disease quiescence period of at least 6 months. Surgical procedures available include orbital decompression, surgery for strabismus, and eyelid surgery.

In patients whose dysthyroid optic neuropathy impairs visual function, urgent treatments are required, involving intravenous administration of high doses of corticosteroids (500–1000 mg/tid for 1 week). If the response is not adequate after one or two weeks of treatment or side effects appear, urgent orbital decompression surgical treatment is required. In cases of severe corneal exposure, treatment may be topical and may include botulinum toxin administration; it may also make use of tarsorrhaphy or even decompressive surgery in cases of severe exophthalmos.

The therapeutic rationale of orbital decompression is based on the demolition of orbital bone walls to allow the expansion of orbital content. After the first description by Dollinger (1911) in 1911, different decompression techniques have been described in the literature. In 1921, Lynch (1921) reported the medial transcutaneous approach; in 1930, Hirsh and Urbanek (Hirsch and Urbanek, 1930) described orbital decompression of the floor. Naffziger (1931) in 1931 described an interesting decompression of the orbital roof. Sewall (SEWALL, 1936) introduced an external pathway for medial orbital decompression in 1936. Walsh and Ogura (WALSH and OGURA, 1957) in 1957 realized two-wall orbital decompression: it was a demolition of the floor and the medial wall. In 1990, Kennedy et al. (1990) used the endonasal approach to the medial and inferior-medial wall of the orbit. Decompressive surgery is currently indicated in the inactive stages of the disease. Exceptions to this trend are represented by cases of dysthyroid optic neuropathy, corneal decompensation, and acute subluxation of the ocular globe, in which the severity of the clinical presentation requires timely intervention. There are 5 areas involved in orbital decompression: the adipose compartment, the floor, the lateral wall, the inferomedial complex, and the medial wall of the orbit.

The idea of intervening on the orbital content and no longer on the bone container for the decompression of dysthyroid orbitopathies was presented by Neven Olivari (1988), who published the first paper in 1988. The idea was later taken up by Trokel (Trokel et al., 1993) in the United States, and by Adenis (Adenis and Robert, 1994) in France, modifying the technique and coding it. Conceptually, the procedure has the objective of removing the orbital adipose tissue to determine muscle relaxation, a reduction in intraorbital pressure, and a reduction in the degree of proptosis. The orbital adipose tissue is not evenly distributed within the orbit; in fact, the greater volume (40%) is in the inferior-lateral quadrant, 25% in the inferior-medial quadrant, and 15% and 20%, respectively, in the supero-lateral and supero-medial quadrant. As for the results of this technique, the reduction of proptosis is in a range between 3.5 and 5.9 mm[49] with a linear correlation between the amount of adipose tissue removed and reduction of proptosis (Liao and Huang, 2011). In addition, this technique is associated with an average intraocular pressure reduction of 3.4 mmHg[51].

Post-operative complications are generally late; the Neven Olivari (Olivari et al., 1991) group reports an incidence of supraorbital anesthesia of 1.5–6%. New onset diplopia is reported in the range of 15–25% in some studies, while in others, it stands between 0- $_{3\%}$49.

Obstruction and chronic rhinosinusitis (due to the formation of sinews or intranasal herniation of orbital adipose tissue): An acute maxillary sinusitis, due to the obstruction of the ostium of the maxillary sinus by the periorbital herniated tissue is also possible. The results of this technique show a reduction of proptosis in a range between 2.5 mm and 8 mm[61]. The purpose of the clinical study was to investigate the efficacy and clinical outcomes of two surgical techniques used for the treatment of GBO: endoscopic orbital decompression and classical open decompression. As for bone decompression, there are four orbital walls subject to decompression: the floor, the medial wall, the lateral wall, and the roof of the orbit. Each of these can be surgically removed individually or in combination with the others. The orbital floor is rarely removed individually; more often it is associated with the demolition of the medial wall, in an inferomedial decompression. Whichever way of approach, the extent of bone removal can be very variable: the initial descriptions of the removal of the floor showed the extensive removal of the entire floor, both in the antero-posterior and the middle-lateral sense (Moran et al., 1972). Later, changes were made to the technique to avoid complications that followed such a demolitive approach. Also, for the medial wall, there are many possible extensions of the bone removal. The anterior limit of the bone removal is classically represented by the posterior lacrimal crest. Several authors agree that the anterior wall of the sphenoidal sinus is the posterior boundary of the dissection, but the dissection can be extended to the optic canal. As a superior extension, most authors describe the dissection up to the frontoethmoidal suture (Rootman, 2018). The results of the two-wall decompression are closely related to the extent of the dissection, the degree of opening of the periorbita, and the associated lipectomy. In the literature, a reduction of proptosis between 4 and 5 mm has been reported with the two-wall technique (Rootman, 2018). A more frequent complication (62% in patients approached transantrally, 10–35% in those approached transorbitally) is diplopia (Rootman, 2018). Much rarer complications (<1% of cases) are liquorrhea, palpebral and conjunctival edema, anesthesia, orbital hemorrhage, infections, and sinusitis (Rootman, 2018). Concerning the three-wall decompression, it refers to the orbital decompression obtained by the demolition of the lateral wall, the medial wall, and the floor of the orbit. The extent of the decompression in this technique can be variable; some authors describe the abatement of the deep lateral wall (Rocchi et al., 2012), others of the anterior lateral wall (Barkhuysen et al., 2009). The reduction of proptosis with this technique is within the range of 4.5 and 7.5 mm; the rate of onset of postoperative diplopia is between 10 and 15% (Chu et al., 2009). About the endoscopic transnasal approach to the orbit, of primary importance is the close anatomical relationship existing between the paranasal sinuses and the orbital content, summarized in the concept of the sinus-orbito-cranial interface (Dallan et al., 2014). Endoscopic visualization provided the surgeon with the ability to reach the medial orbital structures and the floor as well as the orbital apex, avoiding the creation of skin incisions, large bone alterations, and the risk of brain injury. Considering this, endoscopic orbital decompression is currently an accepted treatment for GBO. Careful preoperative planning is necessary: ophthalmological evaluation, examination of cranial nerve function, and radiological CT and MRI studies are crucial steps. Imaging studies allow an accurate study of the sinus-orbito-cranial interface (Castelnuovo et al., 2015). The transnasal approach to the orbital structures requires adequate instrumentation, and an aid to the surgeon is the image-guidance systems of neuronavigation; such systems can identify surgical instruments, calculate the position of the instrument tip in relation to the patient's structures, and project the instrument position on a previously obtained imaging study (CT or MRI). They allow an enhancement in the ongoing anatomical localization of the surgical procedure and offer the potential to reduce complications and improve outcomes. Such systems have, in fact, shown an accuracy comprised between 0.63 mm and 2 mm[60]. Postoperative complications are orbital hematoma, diplopia, enophthalmos, and nasal. As evidenced by the statistical analysis carried out on the sample before and after surgical treatment (ref. Tables 3a and 3b), there is a statistically significant difference between ophthalmometry and IOO values; this indicates that surgical orbital decompression with two walls (floor and medial wall) is effective in reducing exophthalmos. The positive result is also confirmed by the reduction of proptosis, measured in millimeters, averaging 1.7 mm. These results reflect those in the literature (Borumandi et al., 2011; Leong et al., 2009; European Group on Graves et al., 2009' Orbitopathy (EUGOGO)).

In the analysis of data relating to the two different patient groups (ref. Table 4), treated respectively with endoscopic orbital decompression (Technique 1) and classical open orbital decompression (Technique 2), the results obtained show that, however, there is no statistically significant difference between the results of the two techniques, confirming what the scientific community affirms. Therefore, the choice of surgical approach is at the discretion of the surgeon, based on his preferences and inclinations. It is our opinion, considering the variable character of the pathology, that the treatment of choice must be individualized, drawn on the characteristics, needs, and expectations of each patient. The classic open approach to orbital decompression, while effective in terms of proptosis reduction, requires skin incisions, osteotomies, and significant alterations of orbital structures, including the eyeball itself. Moreover, due to the conical shape of the operating field, this technique has the disadvantage of providing suboptimal visibility of the field, limited to the 1/3 front of the orbital cone, up to the equator of the globe. The endoscopic transnasal approach for orbital decompression, through the paranasal sinuses, allows approaching the orbit and its contents, guaranteeing the absence of eyelid skin scars, minor bruising, periorbital edema, and less post-operative pain/discomfort. Again, intraoperatively, it provides direct visualization of the orbital apex, offering the possibility of directly expanding the optical canal. This means that pressure on the optic nerve at the orbital apex can be directly reduced, and the risk of its involvement in any disease relapse can be reduced. Considering the ability of improved and more effective management of the optic nerve and satisfactory results in terms of recovery of visual acuity by patients treated with this technique, it would be desirable to carry out further prospective studies and on larger samples aimed at quantifying (through the evaluation of the evoked ocular potentials and visual campimetry) the real improvement of visual function.

5. Conclusion

In conclusion, it is our opinion that orbital decompression with the endoscopic transnasal technique should be an absolute indication in all patients who have clinical and radiographical signs of involvement of the optic nerve at the orbital apex (crowded apex syndrome). This is thanks to the ability of this technique to add and decompress the optical channel at the apex.

For all other patients with GBO, the endoscopic technique of orbital decompression can be indicated as a first-line surgical approach considering the absence of skin scars and the best aesthetic results.

For all these reasons, when applicable, the endonasal endoscopic orbital decompression technique for the treatment of GBO can be considered a safe and effective choice.

Declaration of competing interest

Authors declare that there are no relevant conflicts of interest.

Acknowledgements

This article has not been presented elsewhere and it is not under consideration from other journals. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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