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Chapter 7

Reactivation of Graves’ Orbitopathy after Rehabilitative Orbital Decompression

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Abstract

Objective: To present and discuss three cases of apparent reactivation of Graves’ orbitopathy (GO) after orbital decompression and to evaluate the incidence of this phenomenon.

Design: Observational case series and retrospective follow-up study.

Participants: A few weeks after surgery 2 patients with GO (patients 1 and 2), treated at our institution with rehabilitative bony orbital decompression during the static phase of the disease showed clinical and radiologic evidence of reactivated orbitopathy. After this observation, a sample of 249 patients who had consecutively undergone the same treatment for the same reason before the second of the 2 observed patients was selected for this study.

Methods: The records of the selected patients were retrospectively reviewed searching for cases presenting with clinical and radiologic evidence of GO reactivated as a consequence of any type of bony orbital decompression. Patients treated with perioperative systemic glucocorticoids or who had concurrent periorbital diseases, injuries, or surgeries, or who had immunocompromised conditions or a follow-up of ≤2 months, were excluded.

Main Outcome Measures: Incidence of reactivation. Clinical history, clinical and radiologic characteristics, treatment modalities, and time course of the reactivation in patients presenting with this phenomenon.

Results: Decompression surgery took place between 1994 and 2000. Eleven patients were excluded for having been treated with perioperative glucocorticoids. Only 1 patient (patient 3) presented with reactivation. The incidence of the phenomenon that we regard as reactivation of GO after rehabilitative bony orbital decompression was therefore 1.3% (3/239). In all 3 patients, the reactivation took place a few weeks after surgery, after an early normal convalescence period and could be controlled with systemic immunosuppression or orbital radiotherapy. None of the patients we report developed further episodes of reactivation during the follow-up period (mean, 7.5 years).

Conclusions: Based on its clinical characteristics, we suggest naming our observation delayed decompression related reactivation and we propose using its acronym DDRR when referring to it. Although DDRR appears to be a rare event, it is important for physicians and patients to be aware of its possible occurrence with rehabilitative decompression surgery.
**Introduction**

In Graves’ orbitopathy (GO), signs and symptoms progressively increase in severity during an early dynamic, active, inflammatory phase; later, they become milder and relatively stable during a consecutive inactive, postinflammatory static phase. Prompt restoration of stable euthyroidism and immunosuppression, when necessary, may decrease the duration of the dynamic phase and reverse the tendency to progress toward more severe symptomatology. During the dynamic active phase, patients with functional complications such as optic neuropathy or exposure keratopathy can benefit from surgical expansion of the bony orbit when medical therapy fails.

Bony orbital decompression is the mainstay therapy for the treatment of stable alterations such as exophthalmos, periorbital congestion, and retro-ocular tension that typify the inactive postinflammatory phase of the disease. Worsening of the disease after bony decompression surgery performed for functional reasons during the inflammatory phase has been described, but it is debatable whether the phenomenon should be considered the natural progression of the active phase despite surgical intervention or a direct consequence of surgery.

In this paper, we present and discuss clinical history, clinical and radiologic characteristics, treatment modalities, and time course of a few cases of apparent reactivation of GO after orbital decompression performed for aesthetic rehabilitation during the inactive phase of the disease. Because we are unaware of previous reports of this phenomenon and could not find references to it in a computerized search using MEDLINE, we chose to evaluate its incidence by means of a retrospective survey.

**Patients and methods**

Our survey is an observational case series and retrospective follow-up study. A few weeks after surgery 2 patients (patients 1 and 2) treated with bony orbital decompression surgery at our institution for aesthetic rehabilitation during the inactive, postinflammatory phase of GO started showing clinical signs and symptoms and computed tomography (CT) evidence of reactivated orbitopathy. A sample of 249 records of patients with GO who had consecutively undergone the same treatment for the same reason before the second of the 2 observed patients were retrospectively reviewed to assess the incidence and clinical characteristics of the phenomenon, which appeared subsequent to orbital decompression.
Inclusion Criteria
All patients presenting with clinical signs and symptoms of reactivated orbitopathy together with CT or magnetic resonance imaging evidence of increased extraocular muscle volume soon after rehabilitative bony orbital decompression surgery, carried out through any approach, were included as patients presenting reactivation of the orbitopathy subsequent to orbital decompression.
All patients not presenting with such characteristics were included as patients who did not present reactivation subsequent to orbital decompression.
Exclusion Criteria
Patients treated with perioperative systemic glucocorticoids or who had concurrent periorbital diseases, injuries, or surgeries, or who had immunocompromised conditions or a follow-up of ≤ 2 months, were excluded.
For the second of the observed patients, a 5-year follow-up period was chosen to accommodate the variable active phase duration of GO and we decided to invite for a final examination any patient included in the retrospective study as having reactivation of the orbitopathy. The latter included 1) evaluation of severity and activity of the orbitopathy respectively by means of “no signs or symptoms, only signs, soft tissues involvement with symptoms and signs, proptosis, extraocular muscle involvement, corneal involvement, sight involvement” (NOSPECS) classification, which in our clinic is applied scoring right and left sides separately, and clinical activity score (CAS), and 2) the following blood tests: triiodothyronine, thyroxine, free thyroxine, thyroid stimulating hormone, thyrotropin binding inhibiting immunoglobulins, and thyroid peroxidase autoantibodies.

Results
The cohort of patients that we studied underwent decompression between 1994 and 2000. Eleven treated with perioperative systemic glucocorticoids to prevent postoperative oedema at the surgical site were excluded. Only 1 patient (patient 3) could be included in this study together with patients 1 and 2 as presenting reactivation of the orbitopathy subsequent to rehabilitative decompression. There were 236 patients who did not present reactivation. The incidence of the phenomenon that we regard as reactivation of GO after rehabilitative bony decompression surgery was therefore 1.3% (3/239). Demographics and pre- and post-decompression prominent clinical characteristics of patients 1, 2, and 3 are summarized
in Table 1. The clinical history as well as characteristics and time course of the phenomenon presented by the 3 patients are reported below.
**Patient 1**

A 48-year-old Caucasian female presented with hypothyroidism in 1984 when she was 32. In early 1997, she developed bilateral GO, left more severe than right, that was treated with oral glucocorticoids between May 1997 and March 1999 and with orbital irradiation (2 Gray × 10 sessions = 20 Gray) in July 1997.

The patient was first seen at our center in June 1999. In January 2000, she was admitted for left rehabilitative inferior orbital decompression. The operation was carried out via an anterior transinferior fornix approach.

From the first examination at our center, the patient was euthyroid on levothyroxine replacement therapy and had presented with stable inactive orbitopathy. On admission for decompression, eyelid aperture was normal bilaterally; Hertel values were 16 mm right, 20 mm left; best-corrected visual acuity (BCVA) (pin hole) was right 20/25, left 20/30; and according to NOSPECS classification, the severity of the orbitopathy was 2ab, 300, 4aa, 50b (class 6 could not be scored due to a known amblyopia left > right). Clinical activity score was 0+/7. Bilateral limitation of elevation and diplopia in up gaze above 22 degrees were recorded. Orbital CT scan showed enlargement of the extraocular muscles more in the left orbit than in the right (Figure 1, top).

The first postoperative review carried out 10 days after surgery was unremarkable with minimal left periorbital aedema and symmetric Hertel readings of 16 mm. Starting from the third postoperative week, the clinical picture began to deteriorate progressively and for this the patient attended our outpatient clinic 4 weeks after surgery. This time the typical signs and symptoms of active orbitopathy were unequivocally present. Eyelid aperture was 15 mm on both sides, Hertel readings were 22 mm right and 19 mm left, and BCVA was unchanged as compared with preoperative BCVA. According to NOSPECS classification, the severity of the orbitopathy was 2ab, 300, 4aa, 50b (class 6 could not be scored due to a known amblyopia left > right). Clinical activity score was 7+/10 with signs of activity being more evident on the right non decompressed side. A bilateral limitation of elevation and diplopia in up gaze above 10 degrees was present. In addition, the volume of the extraocular muscles was consistently increased when pre- and post-decompression CT scans were compared (Figure 1).

Oral glucocorticoids (prednisone, total dose of 2.59 g; initial dosage of 60 mg/day tapered down over 15 weeks) administered starting in early April 2000 inactivated the orbitopathy.
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Oral glucocorticoids (prednisone, total dose of 2.59 g; initial dosage of 60 mg/day tapered down over 15 weeks) administered starting in early April 2000 inactivated the orbitopathy. Exophthalmos decreased on the left to 17 mm; the right side remained 22 mm. In March 2002, the patient underwent a right rehabilitative inferomedial orbital decompression through an inferior fornix approach. This time the postoperative course was uneventful and right exophthalmos decreased to 17 mm. Bilateral eyebrow ptosis correction and upper lid blepharoplasty followed in February and July 2003, respectively.

The orbitopathy remained stable without signs of reactivation up to the last examination performed in May 2006, 6.3 years after the phenomenon that we regard as reactivation subsequent to rehabilitative orbital decompression. The patient has been euthyroid with levothyroxine replacement therapy, and thyroid autoimmunity has been abnormal for the entire review period at our institution (Table 1).

Patient 2

A 71-year-old Caucasian female was diagnosed with hyperthyroidism in 1969 at the age of 43. In September 1972, a few weeks after subtotal thyroidectomy, she developed GO with optic neuropathy. For this she was first treated with oral glucocorticoids and then with lateral orbital decompression bilaterally.

She first presented to our center in December 1981 (at age 52) with a disfiguring clinically inactive orbitopathy. The severity of the orbitopathy scored as 2cc, 3bb, 4aa, 500, and 600 with NOSPECS classification. Eyelid aperture was 14 mm right, 16 mm left; Hertel readings were 26 mm right, 28 mm left; and BCVA was 20/20 both sides.

In July 1994, clinical signs of active orbitopathy became evident. Hertel values rose to 30 mm right and 31 mm left, and BCVA dropped to 20/30 bilaterally. For this she was treated with a bilateral inferomedial orbital decompression through a translid approach in August 1994.

In 1995, several functional and aesthetic eyelid surgical procedures were carried out. Thereafter, for some years, the orbitopathy remained stable. Her BCVA was 20/30 and Hertel values 28 mm bilaterally; CAS was 0+/7. The patient was euthyroid and disturbed by a retro-ocular pressure feeling and symptoms related to exposure keratopathy.

In an attempt to improve her symptoms in September 2000, it was decided to proceed with a third orbital decompression, as despite 2 previous decompression procedures, most of the medial and lateral bony orbit was still intact (Figure 2, top). The procedure was carried out bilaterally by means of a combined transcaruncular and upper skin-crease approach.
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After surgery, periorbital edema did not subside as expected, and starting from the third postoperative week typical clinical signs of active orbitopathy were clearly evident (Figure 3). NOSPECS classification and CAS worsened to 2cc, 3cc, 4cc, 5bb, 6aa, and 7+/10 respectively. In addition, postoperative orbital CT scans showed an increased enlargement of extraocular muscles as compared with preoperative ones (Figure 2). Her BCVA did not worsen and Hertel values remained unchanged despite the extensive osteotomies.

In April 2001, the patient underwent simultaneous treatment with IV and oral glucocorticoids (IV methylprednisolone, total dose 6 g, 1 g/day at days 1, 2, 3, 8, 9, and 10 followed by oral prednisone, total dose, 2.73 g, initial dosage of 40 mg/day, starting at day 15 and tapered down over 17 weeks) combined with orbital irradiation (2 Gray × 10 sessions).

By the end of 2001, her orbitopathy was inactive, Hertel values decreased to 22 mm right and 23 mm left, eyelid swelling was greatly reduced, and BCVA was 20/20 bilaterally. Ophthalmic signs and symptoms remained stable, and evidence of active orbitopathy has been absent through the last examination performed in May 2006, 5.7 years after the phenomenon that we regard as decompression-related reactivation. Since the time of the last decompression, the patient has remained biochemically euthyroid with levothyroxine replacement therapy and presented abnormal thyroid autoimmunity (Table 1).

Patient 3

A Caucasian female who was 51 years old at the time of our retrospective observation presented with hyperthyroidism and diffuse goiter in 1993 at the age of 48. She was initially treated with antithyroid drugs and later with block replacement therapy.

In September 1994, the patient developed GO; she was treated with low-dose oral glucocorticoids until May 1995, when she was first seen at our institution. At that time, she presented with a moderately severe, inactive orbitopathy. Her NOSPECS classification was 2bb, 300, 400, 5aa, 600, and her CAS 0+/7. She presented an increased eyelid aperture (14 mm right, 17 mm left), Hertel readings were 21 mm right, 22 mm left, and BCVA was right 20/20, left 20/25. Ocular motility and the field of binocular vision were normal. The patient also presented a mild form of psoriasis. The clinical picture was unchanged when in December she was admitted for bilateral inferomedial orbital decompression. A coronal
approach was used and on postoperative day 10, exophthalmos was reduced to 19 mm bilaterally; no double vision was present.

Starting from postoperative week 3, the patient experienced increased retro-ocular pressure feeling, double vision in primary position of gaze, foreign body sensation, and profuse tearing; psoriasis worsened simultaneously. When she was examined 4 weeks after surgery NOSPECS classification was 2cc, 300, 4bb, 500, 600 and CAS 5+/10. Eye movements were reduced in every direction of gaze, Hertel readings were not worsened, and BCVA was unchanged as compared with preoperative acuity. The volume of extraocular muscles was increased on postoperative CT when compared with preoperative (Figure 4).

Orbital irradiation (2 Gray × 10 sessions) administered in May 1996 produced inactivation of the orbitopathy. In March 1997, the patient underwent successful horizontal squint surgery, and 1 month later she was treated with bilateral upper lid lengthening.

At the end of 1997, Hertel values of 14 mm right, 15 mm left, persistent bilateral upper lid lateral flare, and the presence of puffy eyelids were recorded. Despite the eyelid alterations, the patient refused any further rehabilitative surgical procedure.

Signs and symptoms of the orbitopathy remained stable, and evidence of reactivation has been absent through the last examination performed in June 2006, 10.6 years after the phenomenon that we regard as decompression-related reactivation.

From the first examination at our institution to April 1999, when she was treated with I\(^{131}\), the patient had been euthyroid under antithyroid drugs and levothyroxine replacement therapy. After April 1999 and to the last examination, the patient remained metabolically stable with levothyroxine replacement therapy. The patient’s thyroid autoimmunity had never been investigated until the most recent follow-up, when it was found to be grossly abnormal (Table 1).
Figure 1. Coronal computer tomography scans of the orbits in patient 1. (Top) Predecompression scan. The left extraocular muscles were enlarged more than the right. (Bottom) Postdecompression scan 1 month after surgery. The right orbital floor was removed, and a consistent enlargement of the extraocular muscles was present bilaterally.

Figure 2. Coronal computer tomography scans of the orbits in patient 2. (Top) Scan before the third orbital decompression. The extraocular muscles were moderately enlarged, and the medial orbital wall and part of the lateral were intact bilaterally. (Bottom) Scan 3 weeks after the third decompression. The medial and the lateral orbital walls were removed, and the extraocular muscles were severely enlarged bilaterally.
Figure 1. Coronal computer tomography scans of the orbits in patient 1. (Top) Predecompression scan. The left extraocular muscles were enlarged more than the right. (Bottom) Postdecompression scan 1 month after surgery. The right orbital floor was removed, and a consistent enlargement of the extraocular muscles was present bilaterally.

Figure 2. Coronal computer tomography scans of the orbits in patient 2. (Top) Scan before the third orbital decompression. The extraocular muscles were moderately enlarged, and the medial orbital wall and part of the lateral were intact bilaterally. (Bottom) Scan 3 weeks after the third decompression. The medial and the lateral orbital walls were removed, and the extraocular muscles were severely enlarged bilaterally.

Figure 3. Patient 2. (Top) The patient before the third orbital decompression. No signs of active orbitopathy were present. (Bottom) The patient 3 weeks after the third orbital decompression. Signs of active Graves’ orbitopathy were evident.

Figure 4. Coronal computed tomography scans of the orbits in patient 3. (Top) Predecompression scan. A moderate enlargement of the extraocular muscles was present bilaterally. (Bottom) Postdecompression scan 3 weeks after surgery. Right and left medial orbital wall, and right orbital floor osteotomies were evident; the extraocular muscles were severely enlarged bilaterally.
Discussion

Graves’ orbitopathy is a T-cell-mediated autoimmune disorder, closely associated with Graves’ disease. The immune mechanisms underlying the orbitopathy as well as the primary autoantigens involved in the disease are poorly characterized. A consensus has emerged that orbital fibroblasts are key to the pathophysiology of GO. Indeed, fibroblasts from patients with GO produce excess matrix glycosaminoglycans, including hyaluronan, are very proliferative, and can differentiate into fatlike adipocytes. Proliferation of orbital fibroblasts is dependent on proper activation of T helper (T_H) cells. These CD4^+^-expressing T lymphocytes are able to recognize (auto)antigens present in major histocompatibility complex (MHC) class II molecules by antigen presenting cells (APC). This initial trigger leads to the expression of T-cell surface receptors, such as CD40 ligand (CD40L), which can interact with CD40 expressed on the surface of APC. This CD40-CD40L signaling is a crucial step for efficient activation of T-cell effector functions.

Of special interest is the discovery that orbital fibroblasts express CD40 and MHC class II molecules, thus suggesting that proper T-cell activation can also be achieved through presentation of autoantigens by fibroblasts. The activated T lymphocytes then produce increased cytokines driving activation and proliferation of fibroblasts, thus leading to fibroblast-associated diseases like GO. In agreement, it has been shown that activation by the CD40-CD40L signaling induces orbital fibroblasts to synthesize excess hyaluronan and proinflammatory cytokines.

Proper activation of APC can be achieved not only by T_H cells but also by inflammatory stimuli, for example, lipopolysaccharide and proinflammatory cytokines like interferon-\(\gamma\), which is produced during an infection/inflammatory process. In light of this, the inflammatory process induced by surgery may be a sufficient stimulus for proper activation of APC.

Interestingly, MHC class II molecules expressed by orbital fibroblasts can be upregulated by interferon-\(\gamma\). The increased expression of MHC class II molecules together with the CD40-CD40L signaling would allow the fibroblasts to present autoantigens and fully activate the T cells.

Therefore, the exposure of soft orbital tissues to pathogen components / endogenous microbial flora as well as the surgical trauma may lead to proper activation of professional

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This CD40-CD40L signaling is a crucial step for efficient activation of T-cell effector functions. Of special interest is the discovery that orbital fibroblasts express CD40 and MHC class II molecules, thus suggesting that proper T-cell activation can also be achieved through presentation of autoantigens by fibroblasts. The activated T lymphocytes then produce increased cytokines driving activation and proliferation of fibroblasts, thus leading to fibroblast-associated diseases like GO. In agreement, it has been shown that activation by the CD40-CD40L signaling induces orbital fibroblasts to synthesize excess hyaluronan and proinflammatory cytokines. Proper activation of APC can be achieved not only by T H cells but also by inflammatory stimuli, for example, lipopolysaccharide and proinflammatory cytokines like interferon-γ, which is produced during an infection/inflammatory process. Interestingly, MHC class II molecules expressed by orbital fibroblasts can be upregulated by interferon-γ. The increased expression of MHC class II molecules together with the CD40-CD40L signaling would allow the fibroblasts to present autoantigens and fully activate the T cells. Therefore, the exposure of soft orbital tissues to pathogen components / endogenous microbial flora as well as the surgical trauma may lead to proper activation of professional APC, and perhaps orbital fibroblasts. These events singularly, or in combination, might have induced the processing and presentation of normally sequestered self-antigens with possible reactivation of GO. In this respect, genetic factors may have also played a role. Clearly, more research is required to decipher the mechanisms underlying the phenomenon that we described as related to surgical decompression. Investigation of patients presenting this phenomenon may also be useful in uncovering valuable information regarding the etiology of GO itself. We could directly or retrospectively observe reactivation of the disease after orbital bony decompression in a restricted number of patients. We described 3 of a sample of 239 Graves’ patients decompressed for rehabilitative reasons and not treated with perioperative systemic glucocorticoids. At the time of surgery, 2 of these patients had alteration of thyroid autoimmunity; information regarding the third patient was not available. In all of them, thyroid autoimmunity was altered at the time of the last evaluation. The incidence of the complication that we described appears to be on the order of 1.3%. It is a rare event that in our series of patients could be controlled with systemic immunosuppression or orbital radiotherapy. None of the patients we reported developed further episodes of reactivation during the period of our observation. Our estimated incidence, however, could have been biased. Our calculation was based on patients referred to a tertiary center who can be expected to have a somewhat more problematic disease, resulting in an overestimation. We do not think that this was the case because the entire case scenario of patients affected by GO is referred to our institution. On the other hand, we excluded patients treated with perioperative glucocorticoids, which may have resulted in an underestimation; we cannot exclude that in some of them glucocorticoids could have prevented the trigger of the reactivation or jeopardized its clinical manifestations. This is unlikely, however, because all received glucocorticoids to prevent postoperative aedema and not to treat a disease suspected for reactivation. Besides these considerations, we found the exclusion of patients treated with perioperative glucocorticoids correct from a methodologic viewpoint. Our purpose was in fact to evaluate the incidence of reactivation in a cohort of patients as similar as possible to cases 1 and 2, who represented our prototypes of reactivation and who did not receive corticosteroids perioperatively. The phenomenon that we described consists in the onset of the typical signs and symptoms of active GO with radiologic evidence of extraocular muscles enlargement after...
rehabilitative orbital decompression and after a normal convalescence period of a few weeks soon after surgery. Based on its clinical characteristics, we propose naming our observation *delayed decompression-related reactivation*, or DDRR.

A similar phenomenon had been previously described by Wai *et al.* after cataract extraction. Severe reactivation of GO took place 3 weeks after surgery in a patient who had presented inactive orbitopathy for 24 years. The authors hypothesized that trauma and pressure in the retrobulbar space induced by retrobulbar anesthesia triggered local inflammatory and immune responses, which in turn caused progression of GO. That conclusion was in keeping with the concept of Rapoport *et al.* that trauma and/or pressure explains, at least in part, the distribution of the extrathyroidal manifestations of Graves’ disease.

Before this case, Hamed and Lingua reported previously unsuspected GO in 8 patients out of a series of 58 who developed dysthyroid strabismus after cataract extraction. If in some of these cases it appeared that the diplopia may have been masked before surgery by the impaired vision, in others there was a clear progression of GO in the following months, suggesting that the surgical procedure may have contributed to aggravating the disease.

To our knowledge, reactivation of GO after rehabilitative orbital decompression has not been reported. The findings we described present several similarities to those described as subsequent to cataract extraction, which is by far a more common ophthalmologic intervention. In our cases, as in Wai *et al.*’s and Hamed and Lingua’s, GO worsened a few weeks after surgical trauma, and the phenomenon was invariably bilateral despite unilateral cataract extraction in all their cases and despite unilateral orbital decompression in one of ours.

Although DDRR is a rare complication, we feel that it is an event which deserves to be known by physicians and to be mentioned to those patients with GO undertaking surgical rehabilitation by means of orbital decompression.
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