Orbital decompression in Graves' orbitopathy: state of the art and novel perspectives
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Chapter 11

General Discussion

Orbital Surgery in Graves' Orbitopathy:
Where We Are, What Are the Novel Perspectives,
What Are Its Concealed Messages?
Where we are

In ancient times lacking any background experience, accurate tools, technology to guide the comprehension of diseases and adequate prescription drugs our ancestors struggled to learn how to repair the human body. Surgery came into being and with it, human life became more sophisticated. Man lived longer, and having gained a knowledge of themselves sufficient to break the boundaries built by ignorance, ultimately increased their quality of life. Later in eras wherein religious views took precedence over medicine and logic, surgical advancement was difficult. Some of the surgical technology developed in ancient times surpassed anything available in the modern world until the 18th or 19th century. Most of the knowledge we now have was obtained from prehistoric exploits. Skull trephination and craniotomy performed by abrasion, scraping, crosscut sawing, and drilling are the oldest known surgical techniques used by primitive people for decompression of the brain after fracture or epidural haemorrhages, to cure epilepsy or osteomyelitis.

The indications for modern decompression surgery for GO are not too dissimilar from those which motivated the invention of surgery in ancient times, and the greatest bulk of it, bone decompression, conceptually continues to be based on principles and techniques similar to those for cranial trephination from as early as 7000 or even 20 000 years ago. Stone lancets and obsidian curettes, already used successfully in up to 80% of such prehistoric surgery, have been substituted by more sophisticated equipment. Nevertheless, abrasion, scraping, crosscut sawing, and drilling are still in current use in the great majority of surgery for treating raised intraorbital pressure responsible of signs and symptoms of GO.

Modern bone orbital decompression surgery in GO started in 1911 when Dollinger proposed the removal of the lateral orbital wall, which had been already used by Kroenlein for the excision of an orbital dermoid cyst, as a possibility to increase the volume of the bony orbit in GO. Till since many other osteotomies and approaches have been proposed, abandoned, modified and performed with minimally invasive techniques or more extensive incisions each carrying its distinctive advantages and disadvantages as discussed in the paper included in chapter 6.

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Where we are

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Skull trephination and craniotomy performed by abrasion, scraping, crosscut sawing, and drilling are the oldest known surgical techniques used by primitive people for decompression of the brain after fracture or epidural haemorrhages, to cure epilepsy or osteomyelitis.²,³ The indications for modern decompression surgery for GO are not too dissimilar from those which motivated the invention of surgery in ancient times, and the greatest bulk of it, bone decompression, conceptually continues to be based on principles and techniques similar to those for cranial trephination from as early as 7000³, or even 20000 years ago.⁴ Stone lancets and obsidian curettes, already used successfully in up to 80% of such prehistoric surgery²,³,⁵, have been substituted by more sophisticated equipment. Nevertheless, abrasion, scraping, crosscut sawing, and drilling are still in current use in the great majority of surgery for treating raised intraorbital pressure responsible of signs and symptoms of GO.

Modern bone orbital decompression surgery in GO started in 1911 when Dollinger⁶ proposed the removal of the lateral orbital wall, which had been already used by Kroenlein⁷ for the excision of an orbital dermoid cyst, as a possibility to increase the volume of the bony orbit in GO. Till since many other osteotomies and approaches have been proposed, abandoned, modified⁷-²⁶ and performed with minimally invasive techniques or more extensive incisions each carrying its distinctive advantages and disadvantages as discussed in the paper included in chapter 6.²⁷ Starting from the end of the 1990s, the osteotomy entailing the removal of the lateral orbital wall, and in particular its deep portion, has
regained popularity\textsuperscript{23, 24, 26}, roughly reiterating what had been proposed one century before by Dollinger, when he described his pristine form of bone decompression surgery.\textsuperscript{6}

In essence, over time, human reasoning has not produced any substantial conceptual innovation in the field of decompression surgery, or of its execution. An exception was the introduction of fat decompression in 1920\textsuperscript{28}, which, however, never reached the popularity of its bone counterpart.

Real new short term conceptual breakthroughs in orbital surgery for GO appear to be very unlikely. Collective awareness which also extended to the possible discovery of specific immunological therapy, has been recently stated in “the Amsterdam declaration on GO” \textsuperscript{29, 30}, and it was also maintained that the overall quality of patient care can be implemented by reducing the inequality in expertise and delivery of existing treatments.\textsuperscript{30-32}

Recently introduced technical advances\textsuperscript{33}, and most importantly implementation of the scarce evidence and quality of literature concerning available surgical treatment for GO \textsuperscript{34-36} can also play a positive key role in the amelioration of surgical care, including orbital decompression.

\textit{Technical advances}

Technical advance in the field of decompression surgery has undeniably been substantial, and there is further potential.\textsuperscript{33} The current use of high-speed rotary instrumentation has facilitated the possibility of deeper lateral wall osteotomies than that achievable by means of conventional bone nibbling rongeurs.\textsuperscript{26} This has resulted in the possibility of more effective exophthalmos reduction\textsuperscript{24, 26}, but grinding with cutting-burrs or diamond-burr tips in tight spaces, such as those available in orbital surgery, has a potential, not negligible, risk of damage to soft orbital tissues or the dura. Ultrasonic bone removal recently proposed for orbital surgery represents a promising field of technical development.\textsuperscript{37, 38} Hand pieces which transmit 25-29 kHz vibrations can easily selectively carve/cut only mineralized tissues. The reliability of ultrasonic bone curettes in orbital surgery, however, still needs to be tested against large numbers, and issues of concern about possible damage to soft tissues when using such devices have been arisen in neurosurgery.\textsuperscript{39} Technical innovations for decompression surgery, however, are limited when compared with those that are already available and constantly implemented for other rehabilitative surgical procedures.
procedures for GO such as blepharoplasty, forehead plasty, and eyebrow lift. This is the result of the benefits of technical solutions from the commercial dynamic world of cosmetic surgery.  

Decompression surgery: evidence and quality of the literature

A clear methodology is a basic requirement for any scientific paper. In clinical science a plain definition of the treatment, the circumstances under which it is administered, and an unambiguous description of the treated patient population are essential ingredients. These criteria guarantee that results are repeatable and that meaningful comparisons can be made among studies. Most articles on the outcome of decompression surgery do not fulfil these criteria. They are chiefly based on retrospective case series with inhomogeneous methodologies and definitions, heterogeneous anatomical and pathological substrates, none standardized modalities and timing of pre- and postoperative clinical assessments, differences in surgical techniques, modality, location, and amount of removed bone or fat. Consequently surgical choices continue to be left to local tradition and surgeons’ experience rather than being based on evidence that links the patient’s specific needs, and their background characteristics to one or another surgical approach.

At present patients’ access to high standard surgical treatments is still not prompt or available in many countries, and not many are the centres of excellence or the international organizations with a referral adequate enough to produce randomized clinical trials in the field of decompression surgery. Although a document such as the Amsterdam declaration might instigate a medium term desirable implementation in surgical care for patients with GO, it is not unforeseen that retrospective case series will continue to remain the commonest study design for decompression surgery.

While the evidence of the literature might not be easily implemented, its quality can. Limitations can be overcome, and overstatements and conceptual axioms are liable to critical review, thus potentially generating novel data and perspectives useful for clinical practice or future research.

The main ambition of this thesis was to stimulate a move towards a more systematic reporting and analytical style which can, more reliably and comprehensively, allow present
and future generations to use the data in clinical practice, the planning of new clinical trials and meta-analysis.

**Novel perspectives**

If present and future studies are to be used and interpreted adequately, it is essential that sufficient information be provided regarding the methods of data collection, and baseline characteristics: male gender, older age and heavy smoking are patient characteristics that are known to be associated with more severe orbital disease.\(^{41, 43}\) Preoperative Hertel values, extent and location of the osteotomy performed during decompression surgery, and differences in manipulation of the periorbita, are factors known to affect the extent of exophthalmos reduction.\(^{26, 44-51}\) Precise data collection, listing of inclusion and exclusion criteria followed by a careful evaluation of predecompression characteristics of the cohort and groups under evaluation are therefore essential methodological requirements. Only in this way can it be clear to whom the results of a survey apply, and whether or not the groups under evaluation present differences or are homogeneous.

All these methodological limitations, and misleading statements regarding the negative effects of long standing GO and previous orbital radiotherapy on the outcome of decompression surgery were addressed in the study published in chapters 2, and 3. A clear methodology and careful analysis of the results allowed us to compare homogeneous patient populations and to conclude that a long duration of GO and orbital radiotherapy do not have an adverse effect on decompression surgery\(^{52, 53}\), and that there was a decreased risk for developing post decompression diplopia in long duration GO as compared with shorter duration.\(^{52}\) Such strict methodology as in the papers included in chapters 2 and 3\(^{52}\), \(^{53}\) was used in the case control study included in chapter 5 aimed at quantifying, in clinical practice, the previously unpublished contribution of popular lateral wall osteotomy to exophthalmos reduction and the influence of such an osteotomy on consecutive diplopia.\(^{27}\)

We concluded that a deep lateral wall is an effective although not always available zone of possible orbital volume expansion, and that it is connected with a minimal incidence of decompression induced diplopia when performed as part of a 3-wall decompression through a coronal approach.
Despite the retrospective nature of these studies\textsuperscript{27, 52, 53}, they had the merit of showing that validity can be increased, by respecting as much as possible symmetry with strict methodology, and that bias and confounding factors can be controlled by adopting clear inclusion/exclusion criteria and by careful comparison of the groups under consideration for demographics and preoperative characteristics.

The prospective trial included in chapter 4 was aimed at a better assessment of outcome following decompression surgery. Demographics and pre decompression characteristics were addressed similarly to the studies included in chapter 2, 3, and 5. The context of the study allowed us to review the “time honoured axiom” which links the best results with the highest exophthalmos reduction and the lowest incidence of induced diplopia, and to assess the results of decompression surgery based on a novel methodology. The novel appraisal method with descriptive figures (achievement or not of the preoperative target) and easily interpretable quantitative indexes, precisely defined the extension of applied surgery and its outcomes, to whom they pertain and, empowered the survey to disclose new findings regarding pre-decompression characteristics and surgical results. The study showed that different pre-decompression medical regimens and the duration of orbitopathy at decompression may influence the targets to be pursued by decompression surgery and that the development of GO at an older age, with associated low Hertel readings necessitates targets in decompression surgery other than exophthalmos reduction, and that the “best results” are linked to the achievement of the desired targets which may or may not include reduction of exophthalmos. Additionally the paradigm that amount of exophthalmos reduction is proportional to the extent of the osteotomies was shown not to be always valid.

Although the novel appraisal method of this study took into account a large proportion of the variables which can play a role in determining the outcomes of decompression surgery, it still remains sub optimal. Morphology of the orbital cavity and its osteology, compliance of the soft orbital tissue, lipogenic versus the myogenic variants of the disease, all of which are potential determinants of surgical outcome, were not considered. The novel appraisal and the generated indexes, however, can already be of some benefit for straight forward study comparisons, patient counselling, and can be a valuable tool for balancing risks benefits when changing invasivity of the procedure during the course of surgery. This then might represent a step towards the final goal of a desirable, and as much as possible,
evidence based customized approach to orbital decompression. Customization may be required in unconventional situations as well, such as the case of a patient with an enlarged supernumerary extraocular muscle presented in chapter 9.54

While future studies on decompression surgery will likely fine tune and expand the evaluation criteria, the existing list should stimulate reflection among practising orbital surgeons.

Diplopia has a considerable impact on the patient’s quality of life, is a feared, debilitating eventual consequence of decompression surgery, and it often deters patients and physicians from undertaking decompression rehabilitative surgery. In the vast majority of cases, however it is correctable with straightforward surgery performed under topical anesthesia. Induced diplopia should therefore be considered a treatable side effect rather than a real complication of decompression surgery. Decompression surgery can also result in improving diplopia and instruments such as the diplopia index (ID) as proposed in the paper included in chapter 4 could prove to be valuable for study comparisons, or when counselling both, patients without or with diplopia about to undergo decompressions.

Only the irreversible, disabling or unwanted consequences resulting from decompression surgery should be considered real complications. Trigeminal neuralgia is one of them. In chapter 10 the case of a patient with GO who developed a traumatic neuroma and trigeminal neuralgia of the infraorbital nerve subsequent to inferomedial orbital decompression is presented.55 This previously unreported complication is unlikely to respond to any treatment and deserves to be mentioned when counselling patients about to undergo inferomedial decompression.

Concealed messages of orbital surgery

Careful clinical observations, particularly in a multidisciplinary setting can lead to new insights on pathogenesis as discussed in chapters 7 and 8.57-58 Orbital fibroblasts are key to the pathogenesis of GO. Fibroblasts from GO patients produce excess matrix glycosaminoglycans, and can differentiate into fatlike adipocytes. Proliferation of orbital fibroblasts is dependent on appropriate activation of T helper (TH) cells. However, effective T cell help requires the local expression of co-stimulatory molecules.59, 60 The discovery that orbital fibroblasts can express co-stimulatory molecules, such as CD40, and
MHC class II molecules, suggests that T-cell activation in orbital tissue can occur without the traditional antigen presenting cells. Activation or perpetuation of the inflammatory cycle can be sustained through the presentation of autoantigens by orbital fibroblasts. Inflammatory stimuli, for example, lipopolysaccharide and proinflammatory cytokines like interferon-γ (IFN-γ) can also drive the autoimmune process. These and other inflammatory signal mediators may be induced or released at the time of surgery leading to reactivation of disease as seen in the patients discussed in chapter 7.

Inflammation and infection have been suspected to trigger GO. The case described in chapter 8, extends and confirms that genetics play a role. A patient received a bone marrow transplant from a donor who years later developed Gaves’ hyperthyroidism. The recipient patient developed Graves’ hyperthyroidism and orbitopathy before the donor. While donor and recipient were siblings, the earlier onset in the recipient suggests that a preferential recruitment and expansion of orbital tissue responsive T cells occurred. Immunity constituted after BMT is not the same as during embryogenesis. The checks and counter check between self and non self are not as tightly established following BMT. Certain Treg populations may be missing, predisposing the recipient to certain viral infections or autoimmune disease. GO obviously is no exception to this state of affairs. The fact that orbital fibroblasts may bypass normal control mechanisms may be a further aggravating factor in the early onset of disease in this BMT patient.

While the exact mechanisms underlying the pathogenesis of GO will come from basic research, critical clinical observations as those presented in chapters 7 and 8 may help to drive such research and provide valuable information for basic scientists.
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