Surgical treatment of diplopia in Graves' Orbitopathy patients
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Citation for published version (APA):
GENERAL INTRODUCTION

AIMS AND OUTLINE OF THIS THESIS
GENERAL INTRODUCTION

A 45-year-old lady presents with the following complaints: Since eight months she feels agitated, she easily loses her temper and she has lost weight. Her eyelids have become swollen, her eyes are red, irritated and often teary and above all bulging. She hardly recognizes herself looking in the mirror. Her marriage broke down and now she faces the possible loss of her job as a teacher at a primary school as well, due to the recently developed double images. She cannot drive a car anymore. She becomes more and more isolated. When we explain to her that we she will need a long rehabilitation process, she starts crying……. This patient typically presents with symptoms of Graves’ Orbitopathy.

Graves’ Orbitopathy (GO) is an auto-immune disease that affects women four times more often than men. Besides the aesthetic changes, GO causes a number of functional impairments with a great impact on daily life activities. Therefore, it is understandable, that quality of life studies show that GO-patients consider themselves severely afflicted by their disease. More severely, for instance than insulin-dependent diabetes mellitus patients.\(^1\)

A major cause of GO-induced changes in quality of life is the development of double images as a result of inflammation of the extraocular muscles. In the treatment of these double images (diplopia), the orthoptist plays a significant role. This thesis will focus on the surgical treatment of the diplopia and on the psychosocial impact of this treatment.

ORTHOPTICS

WHAT IS ORTHOPTICS?

Orthoptics is a paramedic profession complementary to ophthalmology. Orthoptists focus on diagnosis and non-surgical treatment of strabismus, visual development problems, refraction errors and eye motility disorders, in both children and adults. Orthoptists have a close working relationship with ophthalmologists, especially with oculoplastic surgeons, and neuro- and pediatric ophthalmologists. The word orthoptics is originally a junction between the Greek words ὀρθός orthos, ‘straight’ and ὀπτέιν, ‘sight’.
HISTORY
Orthoptics

From ancient times on, philosophers were puzzled by the concept of space. During the course of history, the idea of real or physical space evolved, filled with measurable objects, the so-called objective space. Another definition of space is a psychological process, a mental perception of the observer based on sensorimotor information. This is also referred to as subjective space. For example, the location of an object (objective space) is different compared to the localization (subjective space) of an object. This is shown in Figure 1: both foveas have the same subjective direction (the window plane) and the objects are seen in a common visual direction. This phenomenon is the foundation of binocular fixation e.g. binocular single vision. Descartes was the first to mention the concept of a sensorineural system in a theory of vision.

![Figure 1](image1.png)

**Figure 1.** (left) Hering’s fundamental experiment about the discrepancy between objective and subjective localization From: Campos and von Noorden (2002).

**Figure 2.** (right) Wheatstones’ stereoscope (1938). The right eye sees plate E reflected in a mirror A. The left eye sees E’ via A’. The two images are combined into one (in depth). From: Crone (2003).

The insights into the neuroanatomic and neurophysiological backgrounds of binocular single vision and stereopsis developed about a hundred years later, after the invention of the stereoscope (Fig. 2) by Wheatstone (1802 – 1875) and the successive application of this instrument in the treatment of squint by Javal (1839 – 1907). Javal showed that binocular single vision was often recoverable by stereoscopic exercises and his pupils Priestly Smith and Worth took it upon themselves to revise treatment of squint in England. In fact, Worth (1869 – 1936) – in spite of his insistence that a defect of the (central) fusion faculty was the
underlying cause of squint – contributed a great deal to the development of orthoptic training and from then several schools of orthoptics were founded in England\textsuperscript{2, 4-5}.

Ernst Maddox (1860 – 1933) had a great interest in orthoptic treatment of squint in children. He invented among others, the Maddox rod, the Maddox double prism and the Maddox wing, all devices which measure deviations of the eyes. His daughter Mary Maddox worked with him; she was probably the first woman to take up orthoptic treatment in the capacity of a ‘medical auxiliary’. Maddox and his daughter inspired many others in England to study the orthoptic investigation and treatment of strabismus\textsuperscript{4-6}.

However, in 1938 Chavasse resisted against the orthoptic training of squint. He emphasized that the motor aspect of binocular vision was more significant to restore the straight eye position\textsuperscript{7}. His exercises focused on the motor aspects of strabismus complemented by strabismus surgery. In the 1970’s it became apparent that both aspects were important to achieve or regain normal binocular vision\textsuperscript{4}.

**Orthoptics in the Netherlands**

To confirm or dismiss the theory of the origins of squint of Chavasse, Zeeman (1879 – 1960) (Fig. 3) promoted the conservative treatment of strabismus and founded a strabismus clinic at the Wilhelmina Gasthuis in Amsterdam in 1940 (later the Academic Medical Center)\textsuperscript{8}. Members from this clinic (Hagedoorn, Keiner, Velseboer, Roelofs, Crone and others) were leading researches interested in the physiology and pathophysiology of binocular vision and ocular motility disorders. For example, Crone (1918 – 2012)(Fig. 3), published his magnus opus ‘Diplopia’, a highly informative book on motility disturbances and binocular vision.
As a result of this interest in strabismus the ‘Dutch School for Orthoptic Assistants’ was started in Amsterdam in 1956. Robert Crone was greatly involved as a teacher and as medical director of the school. Together with Joan Hagedoorn, patient care was combined with scientific work on fixation disparity, heterophoria, normal and abnormal binocular vision. Crone contributed significantly to the standard of the orthoptic profession in the Netherlands and the Dutch orthoptists honored him with an honorary membership of their association. In 1958, the first 8 orthoptists graduated and founded the Dutch Orthoptic Association. Nowadays, orthoptists have a Bachelor of Science degree after following a four year fulltime program at the University of Applied Health Science in Utrecht and the Dutch Orthoptic Association counts over 350 members.

Alongside the strabismic part of the clinic, Amsterdam founded their first orbital center of the Netherlands in the early 60’s. Due to the sharp increase of orbital fractures caused by mopeds and the turbulent 60’s, Bleeker (1915 – 1997) (Fig. 3) and later Koornneef (1945 – 2001) focused their treatment and research on the orbital part of ophthalmology. The first international orbital symposium held in Amsterdam in 1968 gained an enormous interest and by now, the orbital center treats a wide variety of orbital diseases, of which Graves’ Orbitopathy is a significant one.

Surgical treatment

In ancient times, a squinting eye was seen as an ‘evil’ eye. In the 7th century, eye masks were advised to correct this evil eye and encourage the eyes to look straight (Fig. 4). Until the late 18th century, the surgical interventions on the eye muscles were not yet possible. The first person who tried to correct strabismus by means of surgery was Taylor (1703 – 1772). He made an incision of the conjunctiva of the deviated eye and covered the straight eye. Of course, this therapy was not successful. It was Dieffenbach (1792 – 1847) in Germany who actually changed the eye position by unfastening the muscle from the eye.

Figure 4. Masks to correct strabismus.
Franciscus Cornelis Donders (1818 – 1889), father of ophthalmology in the Netherlands, stressed in his work ‘On the anomalies of accommodation and refraction of the eye’ (1864) the relation between accommodation and convergency and the co-relation between hypermetropia and esotropia\(^2, 11\). However, prescribing hypermetropic glasses only cures patients with a specific type of esotropia. The surgical techniques developed further and during the end of the nineteenth century, both weakening procedures (tendon weakening, recession) and strengthening procedures (tendon tucking, resection) were invented. During the 20\(^{th}\) century, surgery on the oblique muscles and transposition procedures became feasible to correct the deviation\(^12\).

**BASICS OF ORTHOPTICS RELEVANT TO THIS THESIS**

**Normal binocular vision and diplopia**

Binocular vision is the ability to see with two eyes simultaneously. Double vision (diplopia) proves that a patient at least has a sensory input into both eyes. To perceive only one image with two eyes (binocular single vision), the image in both eyes has to fall on identical spots in each retina (corresponding points) (Fig. 5, left).

However, if an image falls on retinal points with a small horizontal separation (disparity), depth perception is perceived. When the disparity between the retinal points is too large, it is impossible to see one image and diplopia occurs (Fig. 5, right).

![Figure 5](image.png)

**Figure 5.** Left: Normal binocular single vision. The image (star) falls on corresponding retinal points and is perceived as a single image. Right: Esotropia in the right eye with normal retinal correspondence. The image (star) falls on non-corresponding retinal points (a and b) which causes a double image.
The development of binocular single vision takes place during early childhood. Only when both eyes are aligned, binocular single vision can develop. If a constant misalignment between both eyes (strabismus) occurs during early childhood, the visual cortex suppresses the image of the deviated eye. This process (amblyopia) is irreversible in time, but helps the patient to function in daily life.

**Measurements**

**Binocular vision**

The first quote of the famous orthoptic textbook of Campos and von Noorden states under the heading of “the eyes as a sensorimotor unit”: “The two human eyes with their adnexia and nervous system connections form an indivisible entity”\(^3\).

To measure the quality of this binocular system, several orthoptic tests are available. Some tests focus on the sensory and other on the motor aspects of the oculomotor system. To get the most reliable results, it is important to test the patient’s system of binocular single vision under circumstances as natural as possible and on different viewing distances. *Bagolini striated glasses* are most frequently used to test the quality of binocular vision (Fig. 6)\(^{13}\). It gives information about the presence of binocular single vision, diplopia or suppression, both at near and distance fixation.

![Figure 6. Bagolini striated glasses.](image1)

![Figure 7. Prims bars.](image2)

![Figure 8. Fresnel prims.](image3)

With help of the additional prism bars (Fig. 7), the orthoptist can analyze if prisms can be of help in correcting the double vision (Fig. 8).

The part of the objective visual space in which the patient has single vision is called the *field of binocular single vision* (BSV). Measurement of this field gives information about the daily life situation of the patient. In case of lack of fusion, the field of perceived BSV can be limited\(^{14}\). The Maddox screen and Harmswand are suitable to measure this field\(^{13, 15}\) although in limited gaze directions. A larger field can be tested with the Goldmann perimeter (Fig. 9).
strabismus

It is of great importance to measure the squint angle at both distance and near. Differences in angles between both distances could influence the surgical treatment plan. The amount of strabismus can be measured objectively and subjectively. In general the best test to measure the angle objectively in GO patients is with help of the prism cover test (PCT)\textsuperscript{15-31}. With the prism bars the amount of horizontal and vertical deviation can be accurately measured at near and distance up to 40°. In case of a larger angle of strabismus, additional prisms have to be used. Care has to be taken to hold the prisms in the Prentice position rather than in the frontal plane, otherwise measurement errors occurs easily\textsuperscript{32}.

To test the angle of strabismus subjectively, the Lancaster Hess chart\textsuperscript{16, 23, 33-38}, the Maddox screen\textsuperscript{39} and Harmswand at 2½ meters\textsuperscript{15, 40-42} are used in patients with GO. All three tests measure the deviation in nine positions of gaze. The results in the nine positions can be drawn schematically and give information about the involved eye muscles, the stability of the disease and is of help when making a surgical plan for strabismus correction (Fig. 10).

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**Figure 10.** Amsterdam motility diagram showing the eye position in nine directions of gaze including the cyclodeviation of the eyes in primary position, up- and downgaze (exc = excyclodeviation).
motility

In testing ocular motility, distinction between binocular (version) and monocular (ductions) eye movements must be made. In patients with GO, ductions are often impaired due to the restrictive eye muscles due to inflammation. To monitor the progress of the disease and to make the best choice of therapy, ductions have to be measured carefully. In general, abduction, adduction, elevation and depression are all important to measure. This can be done semi-quantitatively by ranking the ductions from 0 – 4, with 0 indicating full ductions and 4 no movement possible in that direction\textsuperscript{20,43}. For more accuracy, Flanders and Hastings (1997) divided the ductions in 7 steps\textsuperscript{44}. Quantitatively, the most appropriate device is the Goldmann perimeter\textsuperscript{45-47} or the motility meter\textsuperscript{48} (Fig. 11).

cyclodeviation

Four out of the six eye muscles cause a primary or secondary amount of a rotary eye movement (incyclo- or excyclodeviation) (Table 1). To perceive and/or maintain binocular single vision, the amount of cyclodeviation may not exceed 8°\textsuperscript{49}. To restore the field of BSV in GO-patients, it is important to know if any bothersome cyclodeviation exists. Furthermore, eye muscle surgery can change the amount of cyclodeviation. Both pre- and postoperatively, accurate measurement in primary position, up- and downgaze is necessary. However, measuring the secondary gaze positions with the Maddox Double Rod test can give measuring errors\textsuperscript{50}. For that reason, the Harmswand or the cycloforometer of Franceschetti (Fig. 12) are preferred.

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GRAVES’ ORBITOPATHY AND DIPLOPIA TREATMENT

GRAVES’ ORBITOPATHY
Graves’ disease is an autoimmune disease affecting the thyroid gland, the orbits and the legs. In patients with eye involvement, the disease is called Graves’ Orbitopathy (GO). The most frequent sign of the disease is eyelid retraction, followed by protrusion of the eye (proptosis). This proptosis is a result of swelling of the eye muscles in an early stage of the disease and increase of the volume of the orbital fat in a later stage. Due to the increased exposure of the anterior part of the eyeball, patients complain of tearing, photophobia, and/or a gritty sensation of the cornea. In addition, they may have eyelid swelling, chemosis and double vision. Sight loss appears in the severe cases, if the optic nerve becomes compressed.

Although the association between hyperthyroidism and exophthalmos was already described in the 12th century, it was the Irish doctor Robert James Graves in 1835 who was the first to publish the syndrome. Only 5 years later, the German doctor Karl Adolph von Basedow did the same, independently from Graves. For that reason, both the names of Graves and von Basedow are linked to the disease. Synonyms for GO are Graves’ Ophthalmopathy (used by endocrinologists), Thyroid Associated Ophthalmopathy (TAO) (used in the UK), Thyroid Eye Disease (TED) (used in the USA) and Thyroid-Related Orbitopathy (TRO) (not frequently used).

GO is primarily associated with hyperthyroidism (80%), but patients can also be euthyroid (10%) or even hypothyroid. (10%). The disease primarily affects women (female : male ratio 4:1) with the highest risk to develop GO around the age of 40 – 60 years. In the USA, the prevalence of Graves’ disease is 1:90, of whom about 50% develop GO. In contrast, the incidence of Primary Open Angle Glaucoma is 1:136 and of Age Related Macula Degeneration 1:175. The severity, duration and expression of GO differs significantly between patients as does the impact of the disease on the patients’ quality of life. Generally, the disease first tends to get worse (active phase), followed by a slow decrease in severity and ends with a stable stage (inactive phase). Treatment is fitted to this natural course of the disease. During the active phase, immunosuppressive treatment is aimed at prevention of progression of the disease. After the active phase, the inactive phase follows,
which is confirmed by a period of stability of 3 – 6 months\textsuperscript{15, 57, 64}. During the inactive phase, functional and rehabilitative surgery is performed, starting with orbital decompression, followed by strabismus surgery and finally by eyelid corrections\textsuperscript{57}. Decompression surgery can be required during the active phase of the disease when there is a threat of blindness and insufficient response to medical or radio therapeutic treatment.

**Diplopia**

Diplopia in GO patients is the result of a loss of elasticity of the swollen extraocular muscles following the inflammatory process. The extraocular volume increases due to edema formation following secretion of high amounts of glucosaminoglycans by activated orbital fibroblasts\textsuperscript{65}. This induces duction impairment in the contralateral gaze. Along with the levator muscle, the inferior and medial rectus muscles are most frequently involved. The belly part of the muscle is mainly affected, the tendon usually keeps its original shape\textsuperscript{65}. This restrictive type of strabismus is often bilateral and asymmetric, which results in intractable diplopia. Any GO patient may develop diplopia, but in up to 64\% GO-patients, diplopia develops after decompression surgery \textsuperscript{66-68, 69-72}. If the eye muscles are impaired asymmetrically, normal binocular single vision cannot be established.

**DIPLOPIA TREATMENT**

**Torticollis**

Patients with diplopia due to GO often try to compensate with an abnormal head position (torticollis). Due to the elevation impairment, the chin is elevated to avoid looking up. When the abduction impairment is predominantly on one side, a head turn can help to reach the field of BSV. Although a torticollis avoids diplopia, most patients suffer from neck pain. Therefore, this cannot be seen as a permanent solution.

**Prisms**

During the active phase or if the diplopia is mild, Fresnel press-on membrane prisms can be worn on glasses (Fig. 8)\textsuperscript{15, 74-78}. The prism changes the direction of the image in the primary position to the correct retinal spot and the often large range of fusion makes it possible to regain single vision\textsuperscript{15}. The incomitant aspect of the strabismus per se is not a contradiction for the use of Fresnels\textsuperscript{74}, however no optimal field of binocular single vision (BSV) can be achieved\textsuperscript{78}. The Fresnel prisms are available in a range of strengths, which enables adjustments when the angle of strabismus changes. Nevertheless, strong Fresnel prisms
cause vision loss and distortion\textsuperscript{74}. If long term stability is reached, the amount of prisms is low and the eye motility is the same in all directions of gaze, prisms can be grinded into the glasses. In many cases, the eye motility is highly incomitant and the deviation is too large to correct with prisms, therefore other measures are needed.

**Occlusion**

One of the most frustrating issues for patients with GO is the time needed to confirm stability of the disease. In the meantime, if prisms are not achievable, occlusion of an eye to overcome diplopia may be the only possible treatment. However, if one eye is occluded, the visual field is severely restricted and patients often suffer from a tired fixating eye. In some cases, occlusion is a permanent option, when all other efforts to gain a useful field of BSV, have failed. Eye patches, occluder contact lens or frosted glasses are examples of occlusion\textsuperscript{79}.

**Surgery**

The goal of strabismus surgery is to reach a useful field of BSV around primary position and down gaze\textsuperscript{44,80-84}, but a wide variety of success criteria is mentioned in literature. To reach this goal, the orthoptic status must be stable for 3 – 6 months\textsuperscript{33,85-87}. A thorough surgical plan has to be established within a team of orthoptists and ophthalmologists, verifying ductions, eye motility, amount of cyclodeviation and contribution of secondary muscle actions. Due to the incomitant type of strabismus, additional surgery is often necessary to reach the desired goal\textsuperscript{85}.

The ideas about the cause of squint in GO-patients changed over time. In 1944, Rundle and Wilson reported a bilateral and symmetrical ‘paralysis’ of elevation, which they thought was caused by a dysfunction of the superior rectus muscle and potentially of the inferior oblique muscle\textsuperscript{63,88}. Following this conception, Miller treated these GO-patients with a single recession of the inferior rectus and adhesiolysis of the inferior oblique\textsuperscript{89}. He also stated that if limitation in elevation was absent, a resection of the underacting muscle had to be performed. In all cases, the forced duction test was found to be essential in this process to identify the involved muscle\textsuperscript{90}. In contrast to the ‘paralytic hypothesis’, Braley (1953)\textsuperscript{91} and later Smith and Soll (1960) suggested that the inferior rectus muscle was the primary cause of restriction of elevation due to a fibrous infiltration\textsuperscript{92}. We now know he was right. Smith and Soll suggested lengthening of the involved muscle instead of performing a strengthening procedure\textsuperscript{88,93}.  


Chapter 1

Nowadays, surgery of the eye muscles is based on either one of two concepts: the duction concept or the deviation concept. In the duction concept, the surgeon evaluates at the time of surgery the position of the eye muscle during active or passive motility\textsuperscript{21, 22, 88-96}. The deviation concept is based on the measured squint angle prior to the surgery\textsuperscript{84, 97-99}. Several modifications are based on these two concepts\textsuperscript{98}.

In general, resections of the eye muscles in GO are avoided and recessions are preferred\textsuperscript{15, 85, 100, 101}. In some cases resection can be considered after preceding maximal recession surgery\textsuperscript{102}. With regard to recession, different techniques are used, such as recession with fixed sutures\textsuperscript{25, 98}, adjustable sutures\textsuperscript{20, 44, 76, 80, 87, 103-107}, relaxed muscle technique\textsuperscript{83, 108} and lengthening procedures with scleral graft or Tutopatch\textsuperscript{88, 109}. The most common complication is overcorrection, especially seen after inferior rectus recession\textsuperscript{85, 104, 105, 111, 112}. However, the advantage of these lengthening procedures is that the arc of contact of the muscle with the eye remains. This would prevent duction impairment in the direction of the operated muscle postoperatively and lower the chance of overcorrection. Till present, randomized control trials are not available to confirm or counter this theory. Moreover, for each method chosen, the success and reoperation rate shows a wide variation\textsuperscript{42, 44, 83, 84, 113, 114}. Furthermore, the effect of surgery can and should be measured both in an objective and subjective way. Measuring change in quality of life appears to be a major outcome in evaluation of surgery in this patient group\textsuperscript{59}.

Quality of life

After enduring all stages and treatments of the disease, eventually, patients with GO seem to acquiesce in their situation and again gain in their quality of life (QoL). Nonetheless, this process is long and with a lot of obstacles. A survey among 120 patients up to 17 years after diagnosis revealed that 52% found their appearance to be abnormal and 38% were unhappy as a consequence. Another third of the patients reported eye discomfort\textsuperscript{115}. Obviously, GO is a chronic disease which permanently effects patient’s QoL\textsuperscript{116}. A disease specific questionnaire to measure the quality of life in GO-patients was designed by Terwee \textit{et al.}(1998)\textsuperscript{117} and another by Fayers and Dolman (2011)\textsuperscript{118}. Both questionnaires are validated and are used in different countries\textsuperscript{28, 119-122}. By now, only one study evaluated the change of QoL after strabismus surgery\textsuperscript{121}.

In addition to the disease specific QoL questionnaire, Yeatts \textit{et al.} (2005) added mental health questions to evaluate mood en psychological factors of the disease\textsuperscript{62}. This study
showed that social and vocational function was significantly impaired. Another study showed a psychological depressed mood in a group of moderate to severe GO-patients. This was especially significant in patients who suffered from proptosis and diplopia. More recently, the same psychosocial characteristics were found in a patient group undergoing orbital decompression surgery. Future studies are necessary to explore this area of the QoL more in depth.

**AIMS AND OUTLINE OF THIS THESIS**

The primary goal of this thesis is to evaluate the effect of different surgical procedures to correct diplopia in GO-patients. Additionally, analysis of the effect of treatment on the quality of life plays a major role in this thesis.

To make multicenter studies possible in this field, this thesis starts with a paper comparing the outcome of objective tools for measuring ductions and cyclodeviation (chapter 2). In chapter 3, 4 and 5 we will analyze the outcome of bilateral inferior rectus muscle recession, uni- and bilateral medial rectus muscle recession and combined superior rectus and inferior rectus muscle recession. In addition, the effect of the surgery on outcome of ductions, cyclodeviation, squint angle and stability of the postoperative orthoptic status are evaluated. A review of success criteria in this patient group is necessary to present a proposal for success criteria (chapter 6). Finally, two prospective studies on the outcome of the QoL questionnaire and the field of BSV after strabismus surgery in this patient group will be discussed (chapter 7 and 8).
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