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Graves' orbitopathy: lessons from Representational Art

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Abstract

Graves' orbitopathy (GO) is an autoimmune orbital disorder which occurs most commonly in patients with Graves' disease, less frequently in patients with chronic autoimmune thyroiditis. Full-blown GO is characterized by exophthalmos, swelling and inflammation of periorbital soft tissues, extraocular muscle dysfunction (responsible for diplopia) and may evolve into relevant functional and disfiguring sequelae which impair quality of life. GO may very rarely sight-threatening due to optic neuropathy or corneal breakdown. This study reviews a series of articles dealing with figurative works of art (sculpture and painting) from the Hellenistic age up to a few years ago, that represent real-life individuals or ideal models with features of GO. Clinical evaluation and a hypothetical ideal treatment is proposed for some selected subjects who appear in the portraits, based on updated clinical and management criteria.

KeyWords: Graves' disease, Graves'orbitopathy, Endo&Art, Exophthalmos, Strabismus

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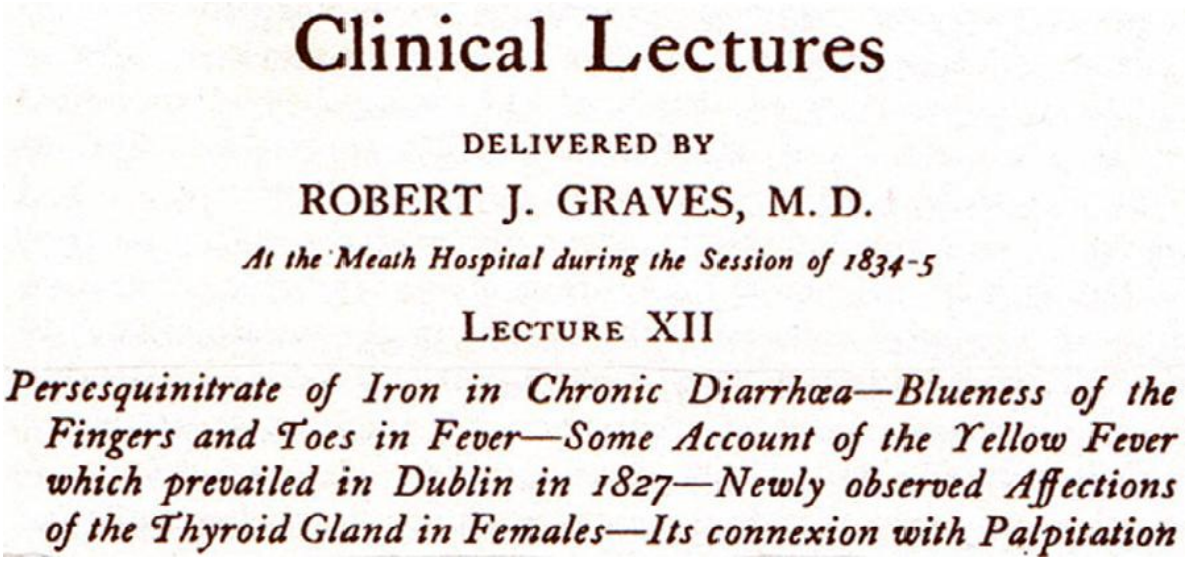
Introduction

Graves' disease is the most common cause of hyperthyroidism in iodine-sufficient areas, with a prevalence >1% in the general population [1]. Graves' orbitopathy (GO) is its most frequent extra-thyroidal expression affecting about 25–30% of Graves' patients. Robert J Graves was the first physician to fully describe GO in 1835 [2] yet anecdotally reported [3]. In his Clinical Lectures (Fig.1) eye symptoms evident in one woman were described as follows : "*The eyeballs were visibly enlarged, to such a degree the eyelids were unable to shut during sleep and when trying to close the eye. When the eyes were open the white of the eyes could be seen in the breadth of several lines around all of cornea*". Ocular disease was associated with thyroid enlargement and palpitations. The association of these clinical features was subsequently defined as the Merseburg triad, historically characterizing Graves' disease.

Fig. 1 Front page of the Clinical Lectures by R.J.Graves [2]



Clinical Lectures

DELIVERED BY

ROBERT J. GRAVES, M. D.

At the Meath Hospital during the Session of 1834-5

LECTURE XII

Persesquinitrate of Iron in Chronic Diarrhœa—Blueness of the Fingers and Toes in Fever—Some Account of the Yellow Fever which prevailed in Dublin in 1827—Newly observed Affections of the Thyroid Gland in Females—Its connexion with Palpitation

Graves'orbitopathy: clinical features and state of the art of management

GO is an autoimmune disorder of the orbit, mostly occurring in patients with Graves' disease, less frequently in euthyroid/hypothyroid patients with chronic autoimmune thyroiditis [4]. It is widely accepted that the orbital disease is triggered by recognition by immune competent cells (T lymphocytes) of one or more antigens shared by the thyroid and the orbit, such as the thyrotropin receptor (TSHR) or its peptides, possibly the insulin-like growth factor-1 (IGF-1) presented by professional antigen-presenting cells (dendritic cells, B-cells) [5]. This triggers a cascade of events, such as proliferation of orbital fibroblast, including stem cell-derived fibrocytes, expansion of the adipose tissue, infiltration and enlargement of extraocular muscles, secretion of cytokines, secretion of glycosaminoglycans, increased water content in the volume [5]. The resulting increase in orbital tissue volume mechanically explains the clinical features of GO, including exophthalmos, swelling and inflammation of periorbital soft tissues, extraocular muscle dysfunction (responsible for diplopia) [6]). GO has a self-remitting natural course, lasting 2-3 years [4], but sequelae are common, including persisting exophthalmos, strabismus (due to fibrotic changes in the extraocular muscles), and eyelid malposition, which may need rehabilitative surgery. Quality of life is often severely impaired, because of the disfiguring and dysfunctional features of the disease [7, 8]

Clinical diagnosis of GO is straightforward in many instances, but it may be tricky in asymmetric or unilateral forms [9]. Early diagnosis is of paramount importance to prevent as much as possible progression to more severe forms and/or to treat GO properly. To accomplish this, a strict interdisciplinary collaboration between endocrinologists, ophthalmologists, radiologists is required, preferably in joint thyroid-eye clinics. Management plan is based on definition of the activity and severity of the disease [4, 11]. GO is responsive to medical (immunosuppressive) treatments only in its active (inflammatory) phase, while in the inactive (burnt-out) phase can be only managed by rehabilitative surgery [11]. Definition of severity is important because mild forms of GO should not be treated with aggressive and potentially risky

treatments [11]. A useful and simple, although imperfect, tool to assess GO is represented by the Clinical Activity Score (CAS) [12].

Classification of severity includes mild, moderate-to-severe, and sight-threatening (very severe) GO. For GO of all degrees, general measures and preventive actions (removal of risk factors) are required. These include refrain from smoking, control of thyroid dysfunction (both hyperthyroidism and hypothyroidism), prevention of radioiodine-associated progression of GO by steroid prophylaxis, use of selenium supplementation (in mild GO), control of hypercholesterolemia, local treatments (lacrimal substitutes, ophthalmic gels at nighttime), use of dark glasses [4]). Mild GO usually does not require aggressive treatments which are not cost-effective. For moderate-to-severe and active GO, intravenous glucocorticoids are the first-line treatment, preferably in combination with mycophenolate [11, 13]. If response to a first course is partial, second-line treatments may include a second course of intravenous glucocorticoids as monotherapy or combined with orbital radiotherapy, oral glucocorticoids combined with cyclosporine or azathioprine, and biologics, including teprotumumab, rituximab, tocilizumab.The latter biologics, particularly teprotumumab, holds great promise, if reassuring long-term data on effectiveness and safety will be provided.

Graves' orbitopathy in Art

Until the publication of Robert Graves' Clinical Lecture [2], medical literature had not recognized or suspected the link between GO and hyperthyroidism, with the single exception of an almost anecdotal report by Caleb H. Parry, published in 1825 [3]. Graves' disease certainly occurred in humans, and exophthalmos was obviously evident since classical antiquity and in the larger and more evolved communities. To reconstruct a history of GO in representative Art, we reviewed the articles representing GO published in the Journal of Endocrinological Investigation, under the Endocrinology & Art heading, devoted to the description of fine art works depicting physical signs of endocrine disorders.

According to an interesting historical study [14], GO had been described by philosophers of classical Greece, including Plato and Aristotle, who probably, however, referred to mentally retarded (idiot) individuals with bulging eyes associated with a pug nose, likely resembling congenital hypothyroidism or endemic cretinism, rather than Graves' disease. The authors [14] reported that the historian Xenophon (V century BC) "*thought that exophthalmos denoted vigilance, better eyesight and clear-sightedness*", but the first statement of the relation between goiter and exophthalmos appeared in the Latin text of *Digesta of Corpus Juris CivilisJustinian*i in the sixth century, where a sentence reads "*quis natura gutturosus sit aut oculos eminentes habeat".* According to this article [14], the relationship between goiter and exophthalmos would go back to the text of the jurist Dometius Ulpianus (170-228 A.D.).

The most ancient art work reported was a Roman marble head of a women with clear signs of GO, described in 1911 by a Danish physician [15]. The statue by an unknown artist, realized in 2nd-3rd

century BC, is exposed at Ny Carlsberg Glyptotek©, Copenhagen, Denmark, and represents an unknown woman with exophthalmos and eyelid edema, suggesting that the portrayed lady was indeed affected by Graves' disease [15] (Fig.2). Clear features of GO are evident in a marble statue of the 4th century AC Roman Emperor Maximinus II Daia (Fig.3), described as a vicious and boorish tyrant [16]. We can postulate that both the sculptures depicted faithfully physiognomic features of the real models. Obviously neither the unknown artists nor the models themselves were aware of this endocrine disorder.

Fig.2 Detail of the statue of a Roman Matron [15]

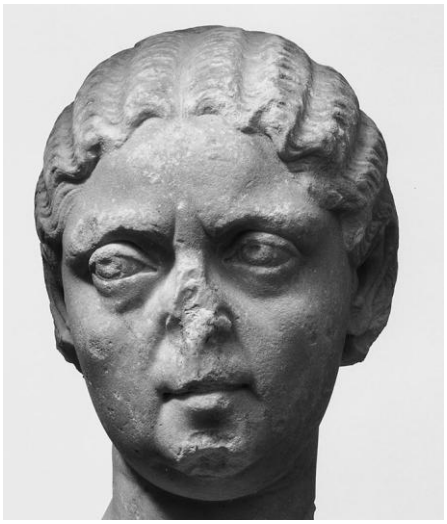


Fig. 3 Detail of the statue of the Roman Emperor, Maximinus Daia II [16]

To find representations of possible signs of GO in figurative art, it will be necessary to wait for the Renaissance. During the Middle Ages, in fact, painting was mainly devotional and the pictorial style had moved away from classical naturalism and the idealization of forms, particularly due to Byzantine influences and Gothic art. A drawing by Leonardo da Vinci (Fig.4), stored at Louvre Museum in Paris, is particularly impressive and is, probably the first representation of Graves' disease. The portrayed young lady exhibits clear features of Graves' disease including diffuse goiter and GO, characterized by bilateral exophthalmos, stare and palpebral edema. The model portrayed in the drawing has not been identified. At variance, in the magnificent painting by Albrecht Dürer, *"Virgin and Child with Saint Anne"*, [18] Saint Anne reproduces the features of the Artist's mother-in-law Elspet Tucher, certainly suffering from Graves' disease. The Saint shows clear features of GO, including bilateral exophthalmos, lower eyelid retraction, and left ophthalmoplegia in infralateralduction, as evident in the detail of the painting (Fig.5). Interestingly, a previous portrait of Elspet Tucher, few years earlier, showed the presence of diffuse goiter, but no ocular manifestations [19].

Fig. 4 Leonardo da Vinci'sfemale portrait [4]

Fig 5 St. Anne by Albrecht Dürer (detail) [18]

Of note are signs of GO we found in the portraits of Giovanbattista Tiepolo's wife and Queen Maria Carolina of Naples. Maria Cecilia Guardi, Tiepolo's wife, is portrayed in two paintings [20] with evident thyroid swelling and exophthalmos (Fig.6). Her neck is clearly round and enlarged and the eyes are big and bulging.

A Maria Carolina's portrait [21] depicts the middle-aged Queen showing exophthalmos more evident in the right eye, associated with upper eyelid edema and hyperpigmentation, mild lower eyelid retraction, and, possibly, mild conjunctival hyperemia; a slight thyroid swelling is also apparent (Fig.7). At the time of the portrait, the Queen was about 50 years of age. Should the Queen have been affected with Graves' disease, her premature death might have been caused to a stroke due to a thromboembolic event secondary to atrial fibrillation [4].

Fig. 6 Tiepolo's wife (details) [22]

Fig.7 Queen Maria Carolina (detail) by G.Crestadoro [21]

The case of Lenin's wife, Nadezda Konstantinovna Krupskaya [22], is different: it is well known, in fact, that the woman suffered from Graves' disease. Photographic portraits and the oil portrait clearly testify physical signs of the disease (Fig.8). Thus, we examined the portraits of three people from real life, Tiepolo's wife, Queen Maria Carolina and the first lady of the Bolshevik revolution.

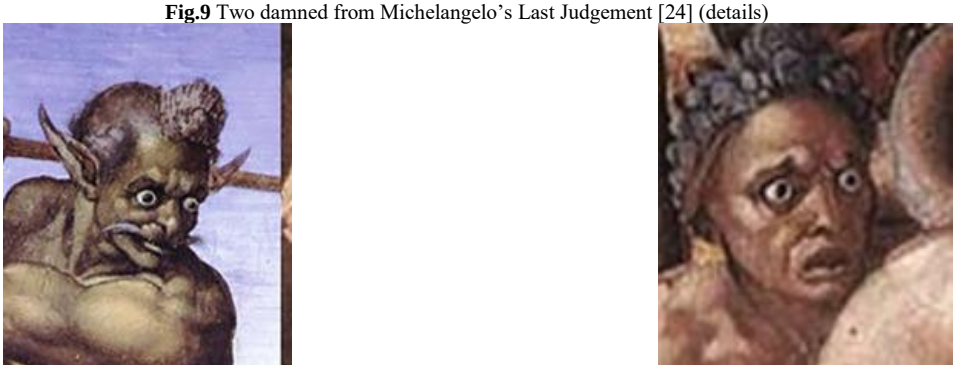
Fig 8 Portrait of Nadezda Konstantinovna Krupskaya by I. Kosmin [22](detail)

In the first case GO is suspected on the basis of two different art works in which the woman was employed as a model of mythological characters. In the second case signs of GO appear in a portrait depicting the Queen in maturity, while there was no evidence of GO in a juvenile portrait, and Maria Carolina's clinical history includes a cerebral thromboembolic event and atrial fibrillation which are consistent with Graves' disease [21].

Of great interest was the finding of characters, who apparently had severe GO, in the *Last Judgment* of the Sistine Chapel by Michelangelo Buonarroti [23]. It is evident that the artist intended to

represent, by painting eyes out of their sockets (pseudo-exophthalmos), the state of mind and moral attitude of the damned, rather than the physical signs of the endocrine disorder (Fig.9).

Fig.9 Two damned from Michelangelo's Last Judgement [24] (details)



The intent of Francisco Goya in the creation of the most famous of the "*Black Paintings*" (Fig.10) was probably similar. Saturn devouring his own children expresses violent suffering and great mental distress. Almost a century later, when those ocular changes were recognized as manifestations of Graves' disease even outside the medical literature [24] , the Italian futurist painter Sexto Canegallo [25] painted severe GO to represent a state of mind, namely hate (Fig.11).

Fig.10 Francisco Goya y Lucientes: Saturn devouring one of his Children. Prado Museum Madrid, Spain

Fig 11 Detail of Sexto Canegallo painting [26]

GO is represented in a recent graphic novel by the American artist Emil Ferris (Fig. 12), who draws the disfiguring effects of the disease as a monstrosity. The graphic novel is indeed entitled "*My Favorite Thing Is Monsters*" [26]. Finally, severe GO is depicted in a painting (Fig. 13) by the young American painter Natalie Frank, whose work is also inspired by the Goya's "*Black paintings*" (Fig. 10). Frank's painting is particularly impressive, since it depicts a long-lasting GO, severe, but poorly active. In fact, a few inflammatory signs are present in a framework of

asymmetric exophthalmos, more pronounced in the right eye, while eyelid retraction, as well as eye muscle restriction are evident, particularly in the left eye, associated with a corneal opacity which impairs vision and reduces the quality of life [27].

Fig. 12 Drawing by Emil Ferris [25]

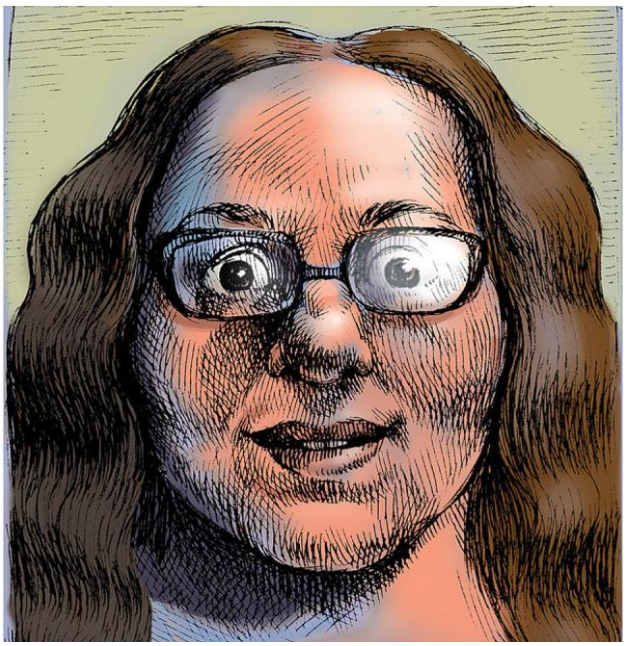


Fig.13 Natalie Frank: Portrait 3(blue) [26]

Last but not least is the representation of a mother with child by Otto Dix [28]. The mother appears skeletal and the inspection of reddish cheeks, hair glued to the forehead with sweat and evident ocular signs, support the diagnosis of (undiagnosed and untreated) Graves' disease, even in the absence of visible thyroid enlargement (Fig.14).

Fig.14 Detail of the painting by Otto Dix

A cultural fun

Based on the few inspection elements that can be obtained from the evaluation of the art works, we have attempted to assess GO and to indicate the possible treatment for each "patient". To this

purpose, we selected some of the above art works (Table1), including the Roman emperor Maximinus II Daia (Fig.3) , the wife of Giovanbattista Tiepolo (Fig.6) , the Queen of Naples and Sicily (Fig.7) and the wife of Lenin(Fig.8) , as well the anonymous lady portrayed by Leonardo da Vinci(Fig.4).

Table 1. Clinical characteristics and treatment of selected cases

Art Work detail	Author-Year	Ref.	Clinical evaluation	Treatment
	Unknown-3rd-4th Century AC	[16]	Stare, exophthalmos, upper and lower lid retraction, right eye hypertropia	Restore euthyroidism, local treatment (eye drops, ocular gel at nighttime), reassess when euthyroid
	Leonardo-1500 circa	[17]	Palpebral edema, possible extraocular muscle dysfunction	Local treatment, eyelidsurgery?
	Tiepolo-1744	[20]	Palpebralswelling, asymmetric exophthalmos (more pronounced in the left eye), possible extraocular muscle involvement	Local treatment, rehabilitative surgery (orbital decompression, squint surgery and/or eyelid surgery)
	Crestadoro-1791	[21]	Orbital swelling, mild exophthalmos and upper lid retraction in the right eye	Local treatment, rehabilitative surgery (orbital decompression and/or eyelid surgery in the right eye)
	Kosmin-1933	[22]	Marked periocular soft tissue changes, possible mild chemosis in the left eye, bilateral exophthalmos, lower lid retraction	Local treatment, rehabilitative surgery (orbital decompression and/or eyelid surgery in the right eye)

The statue of the Roman Emperor, whose death was likely due to severe hyperthyroidism (thyroid storm) shows a marked lid lag (stare), exophthalmos, possible hypertropia in the right eye. Euthyroidism should be promptly restored by antithyroid drug treatment, local treatment (eye drops during the day, ocular gel at bedtime) should be given to protect ocular surface; the ocular situation should be reassessed after correcting thyroid hyperfunction.

The lady's portrayed by Leonardo da Vinci shows palpebral edema and possible extraocular muscle dysfunction; no active treatment is needed, except for local treatment to protect ocular surface, but rehabilitative surgery (squint surgery and/or eyelid surgery) might be offered to this young woman.Tiepolo's wife also shows bilateral exophthalmos, more pronounced in the left eye, possible extraocular muscle dysfunction, mild-to-moderate palpebral edema, but otherwise limited signs of inflammation. Also in this case, medical management should be limited to local treatment, but

rehabilitative surgery (left eye decompression and/or squint surgery and/or eyelid surgery) might be considered. The same considerations can be made for the Queen of Naples and Sicily, as her GO appears poorly active. Both ladies should be informed that orbital decompression may be associated with the occurrence of post-operative diplopia.

Finally, Lenis' wife has the features of moderate-to severe but inactive GO. As for the previous cases, intravenous glucocorticoids or other immunosuppressive would probably have limited beneficial effects, if any. Rehabilitative surgery (orbital decompression followed by eyelid surgery, if needed) might be offered if her disease has a relevant impact on her quality of life.

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