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Graves' orbitopathy: current imaging procedures

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Summary

In patients with Graves' orbitopathy (GO), magnetic resonance imaging (MRI) is a valuable tool to distinguish the acute inflammatory active disease from fibrotic, inactive end stage disease in demonstrating interstitial oedema within the extraocular muscles on coronal TIRM-sequences. MRI is the modality of choice to identify active inflammatory changes and to assess any immunomodulatory treatment response. MRI is always required in doubtful cases, as e.g., asymmetrical orbital involvement, to exclude any other orbital pathology and the clinical suspicion of dysthyroid optic nerve compression in Graves' orbitopathy. Computed tomography (CT) provides precise imaging of the osseous periorbital structures, but does not reveal information on the disease activity in most cases. It is therefore the method of choice to plan CT-guided orbital decompression surgery in the inactive phase of GO.

Key words: Graves' orbitopathy; magnetic resonance imaging; TIRM-sequences; computed tomography

Introduction

Diagnosis of Graves' orbitopathy (GO) is based on the typical eye signs and symptoms, the evidence of thyroid auto-immunity and the exclusion of other orbital pathologies, as none of the eye signs are specific for GO. Normally diagnosis of GO is evident, due to the bilateral symmetric aspect of the orbitopathy in patients with a history of Graves' hyperthyroidism. However, in 15% of all GO patients, GO may present predominantly with unilateral eye changes or may precede or follow the onset of Graves' disease. Bilateral orbital involvement is found on imaging in 50–75% of GO patients presenting clinically with asymmetric or unilateral eye findings. Especially in the latter cases, it is important to exclude other diseases by orbital imaging [1, 2].

Management of thyroid eye disease is based on three treatment arms. Firstly, treatment of the underlying dysthyroid disease to obtain a euthyroid state as soon as possible and to subsequently maintain it. Secondly, immunosuppressive treatment of the inflammatory orbital disease with high dose corticosteroids and/or orbital radiotherapy and, thirdly, surgery. When treating patients with GO, it is important to distinguish the acute inflammatory early stage from fibrotic, inactive end stage disease. The acute stage is characterised by an interstitial oedema of the extraocular muscles and orbital tissues that responds to immunosuppression or orbital radiotherapy. In the fibrotic end stage, the extraocular muscles are scarred and do not respond to anti-inflammatory treatment, hence necessitating a surgical approach [3]. According to these treatment options, imaging modalities have to be selected to answer specific clinical questions for further treatment, in addition to the Clinical Activity Score (CAS) and the NOSPECS-classification [4, 5]. The modified NOSPECS-classification was devised in 1977 as a way of summarising the severity of GO, with an assumed rank order attached to the various clinical features. **N**OSPE**CS** is a mnemonic of initials of the features that should be assessed clinically, such as **N**o signs, **C**orneal involvement or **S**ight loss.

Advantages and disadvantages of the radiological imaging modalities as well as their specific indications in the diagnostic work-up and the follow-up in the treatment of GO are discussed.

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Magnetic Resonance Imaging

MRI: technical basics, imaging protocol

In Magnetic Resonance Imaging (MRI), the two main relaxation times T1 and T2 can be used to differentiate tissue types depending on their proton density. Additionally, a certain weighting in T1 or T2 can be achieved by applying special prepulses, to distinguish water and fat. In Graves' orbitopathy, strong T2-weighted (-w) and fat suppressed images, so called TIRM- (Turbo-Inversion Recovery-Magnitude) sequences, have been found to be useful in detecting not only oedema, and therefore to define inflammation in extraocular muscles, but also to exclude other orbital pathology (fig. 1) [6]. On T1-w images, contrast enhancement with gadolinium, in combination with fat saturation, are helpful tools to detect intense signal enhancement of the extraocular muscles or the eyelid, which is the case in the acute, inflammatory stage (fig. 2) [7, 8]. In GO the standardized MR-imaging protocol includes coronal fast spin echo T1-w and T2-w TIRM sequences in transverse and coronal planes, with 3 mm slice-thickness.

MRI in GO: imaging findings

Indications for MR-imaging in GO are listed in table 1. Morphological imaging criteria, suggestive for GO on MRI (and CT) are a bilateral, spindle-like thickening usually of multiple extraocular muscles (EOM) over 5 mm, with relative sparing of the muscle insertion to the globe, an increase of intra- and extraconal fat, both with bulging of the orbital septum and proptosis of the globe anterior to the interzygomatic line. Compression of the optic nerve in the orbital apex or impression of the lamina papyracea, similar to a spontaneous decompression, can be detected (table 2).

MRI in GO: differential diagnosis

The most frequent disease mimicking Graves' orbitopathy is orbital myositis. Clinically GO is usually painless and most frequently involves the inferior and medial rectus muscles. On imaging, the inserting tendon of the EOM are not usually involved, the muscles are sharply defined, show a fusiform appearance separated by fat and

Table 1

Indications for MR-imaging in Graves' orbitopathy (modified according to [6]).

Uncertain diagnosis
Graves' disease and decreased vision
Graves' orbitopathy vs other cause of orbital disease
Uncertainty of best treatment
Immunosuppressive therapy in active vs surgical intervention in inactive GO
Dysthyroid Optic Neuropathy (DON) vs noncompressive optic neuropathy
Amount of proptosis
Monitor progress or response to treatment

Table 2

Suggestive MR- and CT- imaging findings for GO (modified according to [6]).

Exclusion of other causes such as orbital mass, infection or vascular lesion
Mostly bilateral proptosis
Increase of intra- and extraconal fat
Bowing of the medial orbital wall ("Coke-bottle sign"), impression of the lamina papyracea
Intracranial fat prolaps along the superior orbital fissure
Increased orbital fat density
Enlargement of extraocular muscles
Spindle-like thickening, tendinous insertion of globe spared
Rectus muscles involved: inferior > medial > superior rectus / levator complex
Oedema / Contrast-enhancement
Lipomatous, fibrous changes
Compression of the optic nerve in the orbital apex, compressive dysthyroid optic neuropathy (DON)

Figure 1

Coronal, strong T2-w image (TIRM) with fat suppression of the orbit. Voluminous thickening of all orbital muscles with oedematous changes, pathognomonic for active Graves' orbitopathy.

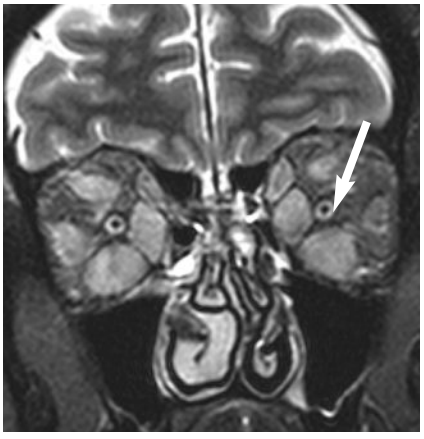


Figure 2

Coronal T1-w, gadolinium enhanced images with fat saturation.
a) Normal aspect of normally moderate enhancing extraocular muscles.
b) Marked contrast-enhancement of enlarged orbital inferior and medial rectus muscles bilaterally.

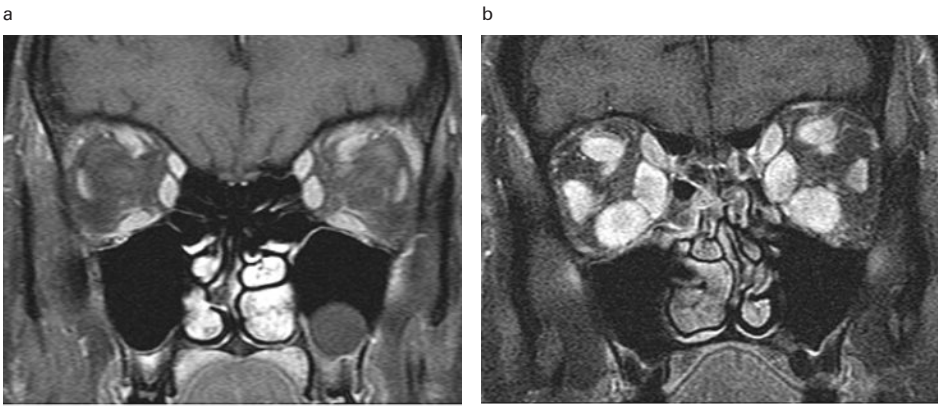
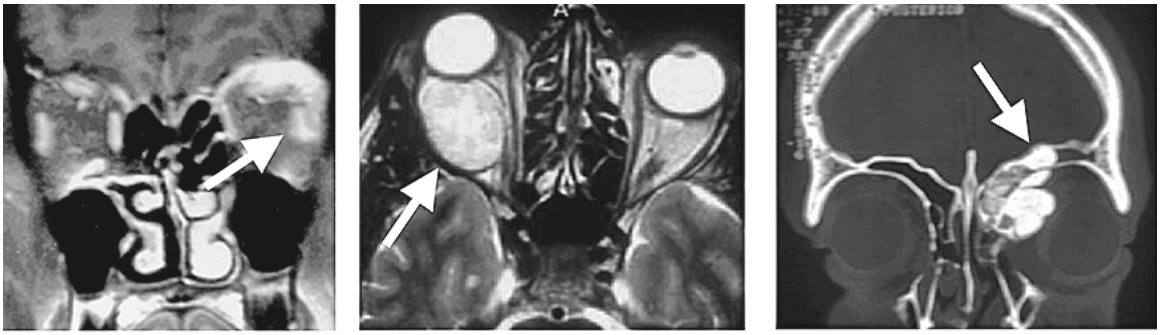


Figure 3

Examples of differential diagnoses mimicking unilateral Graves' orbitopathy.
a) Coronal fat saturation, post contrast T1-w images. Orbital myositis with increased thickness of the left lateral rectus muscle with dense contrast enhancement, combined with a soft tissue mass in the superlateral extraconal space (arrow).
b) Axial T2-w sequence. Intraconal haemangioma of the right orbit (arrow).
c) Coronal CT, bone window. Large primary osteoma of the left frontal sinus with broad extension into the left orbit (arrow).



a b c

the periosteum not infiltrated. In addition, myositis is usually painful and may involve any EOM. The inserting tendons of the ill defined muscle are usually involved, showing an inward bowing of the medial contour of the muscle, with the fat between the muscle and the periosteum usually infiltrated (table 3; fig. 3a) [9]. An overview of the broad spectrum of the differential diagnosis of GO is given in table 4 (fig. 3b, 3c).

Table 3

Differentiation between Graves' orbitopathy and orbital myositis [9].

	Graves' orbitopathy	Myositis
Clinic		
Onset	Weeks to months	Days
Pain	Mild	Severe
Eyelid position	Retraction frequent	Ptosis frequent
Steroid response	Incomplete, slow	Unusually complete, fast
Imaging		
Bilateral	Frequently	Seldom
Muscle involved	Usually > one	Rarely > one
Muscle borders	Regular, no fat noise	Irregular, fat noise
Muscle tendon	Not involved	Involved

Table 4

Differential Diagnosis of Graves' orbitopathy.

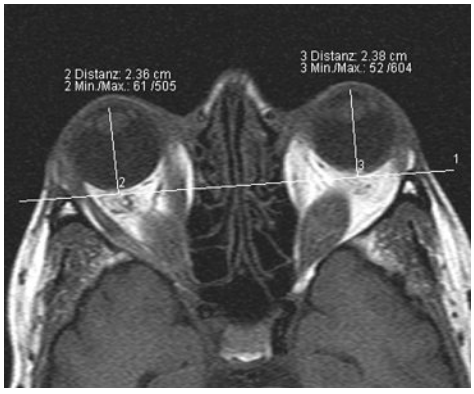
Myositis, major DD, see table 3.
Local form of pseudotumour
Infection
Intra-/extraconal soft tissue tumours
Haemangioma (fig. 4b)
Dermoid
Rhabdomyosarcoma
Orbital pseudotumour
Lymphoma
Neurofibroma
Metastasis
Vascular
Arteriovenous-fistula (AVF) of cavernous sinus
Arteriovenous malformation (AVM)
Osseous Tumours
Nasal cavity
Sinuses (fig. 4c)

MRI in GO: advantages

On axial T1-w sequences, the amount of proptosis can be measured very precisely, compared to the clinically measured Hertel-index. On imaging, a line is drawn between the right and left ventral zygomatic border, the so called interzygomatic line, at the level of the lens. From there, a perpendicular line is taken to the apex of the globe, depicting the measurement of proptosis. Normally, ⅓ of the globe is located behind the interzygomatic line and a Hertel-index of ≥22 mm is pathological (fig. 4). Additionally, T1-w images without fat saturation are helpful in detecting fatty muscle degeneration. These fatty or fibrotic muscle changes demonstrate no contrast-enhancement on the comparable fat-saturated T1-w-images (fig. 5). Strong T2-w TIRM-sequences have been found to be useful in detecting oedema in inflamed extraocular muscles. The signal intensity from inflamed extraocular muscles is known to correlate with the CAS and therefore has an impact on the two treatment options immunosuppression or surgery [10, 11]. During follow-up, the response to treatment can be monitored by measurements as the Signal Intensity (SI) and the Signal Intensity Ratio (SIR).

Figure 4

Transverse T1-w spin echo sequence without fat-saturation to define the amount of exophthalmos. Representative image from the standardized imaging protocol in a female patient (W.H., 1948) with active Graves' orbitopathy. Distances (No. 2, 3) from the apex of cornea to the interzygomatic line (No. 1) given as Hertel- index: right 23.6 mm; left: 23.8 mm.



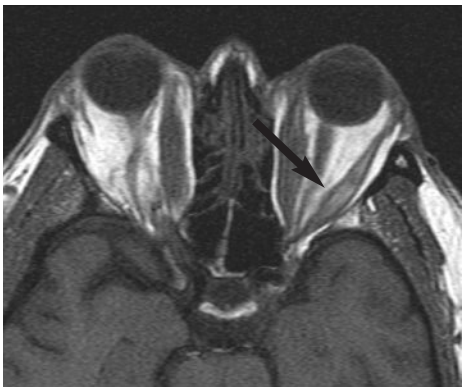


Figure 5

Transverse T1-w spin echo sequence of the orbit without contrast or fat saturation. Male patient with diagnosis of clinically active Graves' orbitopathy (G.Ch., 1942). Lipomatous and fibrous changes of the left lateral rectus muscle, as a sign of long standing disease (arrow). Marked bilateral exophthalmos; Hertel index right: 24 mm, left: 27 mm.

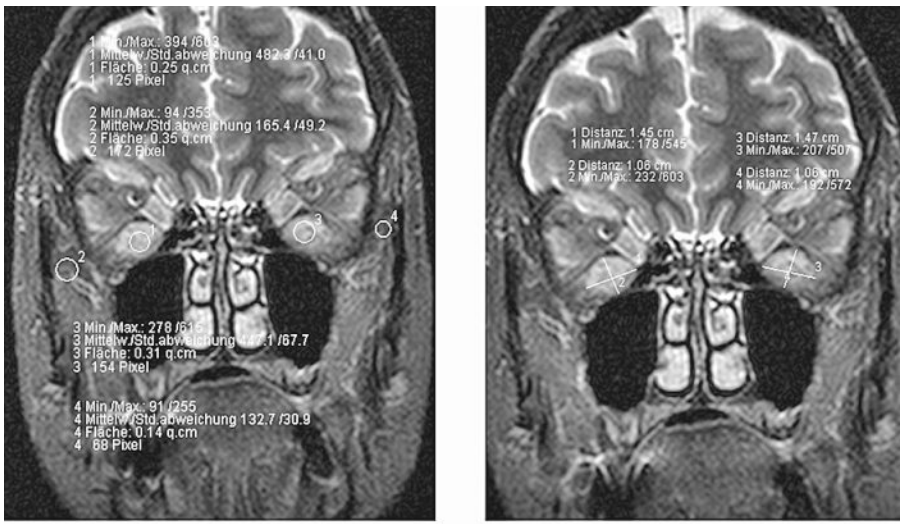
To define active tissue inflammation, the SI from the brightest muscle, and therefore, the muscle with the most evident oedematous changes, can be measured with a cross section area, set within the most inflamed extraocular muscle. A SIR is calculated as the SI of the most inflamed extraocular and the adjacent temporalis muscle as a reference standard (fig. 6a). The extraocular muscle cross-sectional area calculated from coronal TIRM-sequences is known to be measured slightly greater than on comparable coronal T1-w images (fig. 6b) [12]. This is mostly due to the higher sensitivity of TIRM sequences to susceptibility with augmentation of tissue borders; additionally it may suggest perimuscular inflammation [10].

The advantages and disadvantages of MR-imaging in GO are listed in table 5. The former advantage of MRI permitting examination in several planes without movement of the patient is no longer a significant benefit compared to CT, as the new multi-slice CT-techniques are now able to provide the same planes in one run in equal reconstruction time frames.

Table 5

Advantages and disadvantages of MR-imaging in Graves' orbitopathy.

Advantages
Detailed imaging of orbital anatomy
High soft tissue contrast
Multiplanar reconstructions
Thin sections
Interstitial oedema
Rectus eye muscles
Orbital fat
Lack of ionising radiation
Disadvantages
Evaluation bony structures
Detection of calcification
Pat. cooperation/claustrophobia
Investigation time ≈30 min.
Electronic implants
Pace maker
Spinal cord stimulator
Relative expensive ≈300 Euro



a b

Figure 6

Coronal T2-w TIRM fat suppression sequences. a) Measurement of amount of oedema. Region Of Interest (ROI) set in the inferior rectus muscle and the temporalis muscle of each side, in the active stage of disease. The Signal Intensity Ratio (SIR) is expressed as a ratio of the signal intensities of the inflamed extra-ocular muscle to the (in GO never inflamed) temporalis muscle.
b) Measurement of the cross sectional areas of the thickest muscle, both on the left and right orbit.

Computed tomography

CT: technical basics, imaging protocol

Based on different X-ray absorption, fat and water have low densities and hence appear black in contrast to the denser muscles, optic nerve and very bright bony structures on CT. In the orbit, the presence of intra- and extraconal fat acts as a "natural contrast medium", which allows high spatial resolution of orbital soft tissues. Therefore, preoperative CT examinations of the orbit are routinely performed without additional application of intravenous contrast agents, which are indicated to increase the inherent tissue differences by enhancement of the extraocular muscles, if MRI is not available. Orbital CT is routinely performed using a spiral technique, which allows reconstructions in any plane (fig. 7), normally with

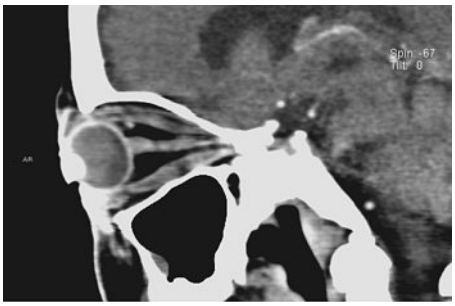


Figure 7

Parasagittal CT image of the orbit with intravenous contrast agent. Reconstruction along the axis of the optic nerve.

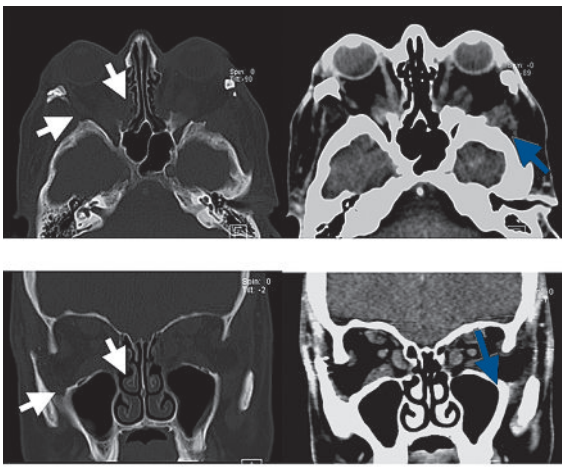


Figure 8

Axial a) and coronal b) 3 mm CT reconstructions of the orbit, both in bone- and soft-tissue windows settings. (Pat. G.Y., female, 1962).
Follow-up after bilateral medial and lateral decompression surgery (white arrows). Bilateral extrusion of extraconal fat lateral to the removed orbital walls on the soft tissue images (blue arrows).

3 mm slices in the axial and the coronal plane, both in bone and soft tissue windows settings. In contrast to direct coronal scanning, these reformations avoid artefacts from dental or other metal jaw implants.

CT in GO: indication, advantages

Today CT is mostly used as an additional method to MRI for preoperative planning of the osseous structures, perioperative navigation guided decompression of the orbit and to monitor the follow-up for the orbital surgeon after decompression surgery (fig. 8). A further indication for CT of the orbit is an uncertain orbital pathology if MRI is not available. CT imaging patterns in Graves' orbitopathy are shown in table 2.

The benefits of CT are a short investigation time, a precise imaging of the orbital bones and moderate costs. Limitations are the radiation exposure to the lens and rather poor information about the disease activity (table 6) [13, 14]. Despite the fact that adverse reactions are uncommon, iodinated contrast agents must not be used in patients with Graves' disease.

Table 6

Advantages and disadvantages of CT-imaging in Graves' orbitopathy.

Advantages
Precise imaging:
Bony structures
Calcification
Sinus
Orbital apex
Good availability
Short examination time ≈5 min
Moderate costs ≈200 €
Electronic implants possible
Disadvantages
Disease activity
Relative long multiplanar reconstruction times ≈30 min.
Radiation exposure 0.5 mSv/2 mm slices (total lens dose: 40 mSv/exam.)

Ultrasound

Diagnostic ultrasound in eye diseases is performed using high frequencies (8 MHz) as a standardised transocular A- and B-scan procedure (fig. 9). Ultrasound diagnosis of GO is based on the following points: no mass lesion, orbital tissues appear enlarged with a heterogenous reflectivity, thickening of the bellies of at least two extraocular eye muscles, enlarged subarachnoid space of the optic nerve in case of dysthyroid optic neuropathy and thickened periorbital tissue. The internal reflectivity of extraocular eye muscles is low in patients with active disease due to oedematous inflammatory infiltration and irregularly high in fibrotic end stage disease [15, 16]. The main advantages of orbital ultrasound are its low cost and the lack of ionising radiation, with a relatively short examination time (≈15 min.) to monitor anterior / midorbital therapeutic response in experienced hands. The main disadvantage is its high intra- and interobserver variability concerning accurate muscle measurements. Furthermore, the quality of information on the posterior orbit as well as the bony orbital walls is significantly inferior to MRI and CT [6].

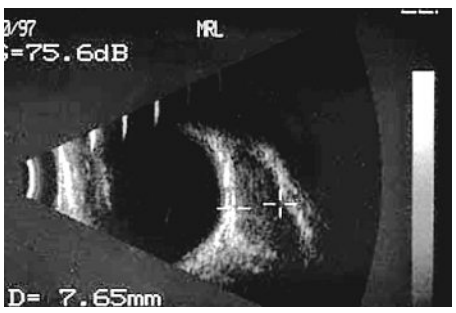


Figure 9

Transocular B-scan ultrasound with thickened extraocular muscle (marked).

Conclusion

Is orbital imaging always necessary in GO? In our own experience the answer is "yes". Even in patients with mild orbitopathy, presenting with typical subjective complaints such as retrobulbar pain and gritty sensations as well as objective signs of GO such as lid swelling, lid retraction, motility impairment and proptosis, imaging helps to support the diagnosis and provides a baseline examination with additional information in the decision making for immunomodulatory therapy and for follow-up.

Imaging is always required in doubtful cases, such as asymmetrical orbital involvement, to exclude any other pathology, the clinical suspicion of optic nerve involvement in GO and to plan orbital decompression.

MRI is able to differentiate the two activity states, in demonstrating interstitial oedema on coronal TIRM-sequences within the extraocular muscles in active disease. MRI is therefore the modality of choice to identify active inflammatory changes and to assess treatment response, additionally due to its lack of ionizing radiation.

Short investigation time, precise imaging of the orbital apex and especially of the osseous structures and moderate costs are advantages of CT. As CT does not reveal information on the disease activity, it is the method of choice to plan orbital decompression surgery in the inactive phase.

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