Chapter 5

Graves' Ophthalmopathy Imaging Evaluation

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1. Introduction

Graves' ophthalmopathy (GO), known as Graves' orbitopathy or thyroid eye disease (TED), is an autoimmune disorder and the main extrathyroidal expression of Graves' disease (GD). GO occurs mainly, but not exclusively, in patients with Graves' disease (up to 50% of GD patients have clinically apparent ophthalmopathy). The major clinical risk factor for developing thyroid eye disease is smoking. Moreover, radioactive iodine used to treat hyperthyroidism can worsen GO. There is an age-specific and gender-related distribution of GO, and the annual incidence is 0.4% for women and 0.1% for men but this largely reflects the increased incidence of GD in women [1]. In addition to GD, thyroid eye disease can also be seen in chronic autoimmune thyroiditis, albeit is far less common and occurs in 2–5% of these patients [2]. Although the link between GD and GO is still not totally clear, the close association between onset of GD and the development of GO suggests that both disorders would have common pathogenic mechanisms [3]. The ocular involvement of GD is explained by the expression of receptor for thyroid-stimulating hormone (TSH-R) present not only in the thyroid follicular cells but also in adipocytes, and fibroblasts located in the orbit, and lymphocytes infiltrating orbit tissues [3]. Likewise, the signs and symptoms of GO occur due to inflammatory reaction and subsequent fibrosis of the orbital components, including orbital connective tissue, and the extraocular muscles [4]. Inflammatory cell infiltration of extraocular muscles is associated with increased secretion of glycosaminoglycans and osmotic retention of water. The muscles become enlarged, sometimes up to eight times their normal size, and may compress the optic nerve. Subsequent degeneration of muscle fibers eventually leads to fibrosis, which exerts a tethering effect on the involved muscle resulting in the muscle dysfunction and ophthalmoplegia. Infiltration of interstitial tissues, orbital fat and lacrimal glands with lymphocytes, plasma cells, macrophages and mast cells along with accumulation of glycosaminoglycans and

retention of fluid cause an increase in the volume of orbital content and secondary elevation of intraorbital pressure, which may itself cause further fluid retention within the orbit [4].

In general, GO can be divided into two clinical stages: the earlier inflammatory (congestive) stage and the late fibrotic (quiescent) stage. The inflammatory stage is marked by edema and deposition of glycosaminoglycans in the extraocular muscles. This results in the clinical manifestations of orbital swelling, proptosis (exophthalmos), diplopia due to restricted ocular motility, periorbital edema, and lid retraction. At this stage the eyes are red and painful. This tends to remit within 3 years and only 10% of patients develop serious long-term ocular problems. The fibrotic stage is a convalescent phase and may result in further restrictive myopathy and lid retraction. The most serious complication of GO is optic neuropathy, caused by compression of the optic nerve or its blood supply at the orbital apex by the congested and enlarged recti. Such compression, which may occur in the absence of significant proptosis, may lead to severe but preventable visual impairment.

The first step in diagnosis of thyroid-associated ophthalmopathy in an individual patient is the ophthalmological examination performed by ophthalmologist. Then, dedicated specialized imaging methods need to be employed in selected clinical situations in GO patients. For example, muscle enlargement, and not retrobulbar fat accumulation, is associated with an increased risk for development of dysthyroid optic neuropathy, which may lead to partial/total loss of vision [5]. As shown by computer tomography (CT) and magnetic resonance imaging (MRI), the swelling of extraocular muscles and disappearance of adipose tissue in the apex of the orbit is suggestive for active development of dysthyroid optic neuropathy [6]. Also, a stretched optic nerve is associated with an increased risk for visual loss [6], thus it should be confirmed with particular imaging modality and the therapy should be immediately provided. In principle, thyroid-associated ophthalmopathy is a bilateral condition, but it can occur unilaterally in about 20% of all GO patients [7]. Indeed, Graves' disease is the most common cause (20–30%) of unilateral exophthalmos [8]. Since a variety of other neuro-ophthalmic disorders require consideration when the unilateral proptosis or malposition of the eyelid are detected, including a retrobulbar tumors, myasthenia gravis, myositis, lymphoma, metastasis, arterio-venous malformation, carotid-sinus cavernous fistula, infection, diffuse or focal idiopathic orbital inflammation with mass effect, or illusory ptosis of the opposite eyelid, the comprehensive neuroimaging should be implicated. Therefore, all patients with unilateral eye disease suspected to GO development should undergo broad orbital imaging, involving several diagnostic methods, to exclude an alternative diagnosis. Apart from the comprehensive diagnosing of GO, clinical imaging is also indicated for the control checkup in the course of the thyroid-associated ophthalmopathy, especially for examination of the disease activity, what may predict the onset and response to therapy.

In this chapter, we will highlight the use of different imaging techniques, such as ultrasonography, computer tomography, magnetic resonance, and nuclear medicine-based examinations in the assessment of patients with Graves' ophthalmopathy for diagnostic purposes and to provide information about the optimal indications for use of each imaging method in the clinical setting.

2. Orbital imaging evaluation in Graves' ophthalmopathy

Radiological neuroimaging of Graves' ophthalmopathy plays an important role in the differential diagnosis and interdisciplinary management of patients with GO. Orbital imaging especially can be helpful in establishing the diagnosis of GO, because it objectively describes the morphological abnormalities of the orbital structures. Likewise, it is estimated that orbital imaging reveals anomalies in 90% of patients with Graves' disease [9]. Based on the selected imaging techniques, it is possible to establish the degree of extraocular muscle and orbital fat enlargement, exclude other coexisting orbital pathology, clarify a confusing clinical set of symptoms, and perform surgical planning [10]. Importantly, the signs and symptoms of thyroid ophthalmopathy usually develop within one year after the thyroid gland dysfunction onset, but up to 20% of subjects with exophthalmos may exhibit euthyroidism [11]. Moreover, the widespread availability of CT and MRI have made early detection of exophthalmos possible, and the imaging presentation of GO may even precede clinical signs of hyperthyroidism and significant changes in related laboratory tests. Therefore, it is postulated that abnormal imaging findings may be a sign of early thyroid disease that subsequently need to be diagnosed in detail [12-13]. Consequently, it is important to provide accurate diagnosis based on specific radiological findings and to propose the following testing to rule out the thyroid dysfunction in yet euthyroid patients.

Certainly, the commonly used imaging modalities posses the selected advantages and disadvantages for their use in specific clinical situations in case of GO patients. Some selected techniques have been reserved for patient examination in different phases of the disease activity. For example, the assessing of vascularity around extraocular muscles is achieved with the contrast-based CT and MR imaging techniques. On the contrary, the assessment of local tissue edema is accomplished with the dedicated MRI sequences, and quantitative monitoring of inflammation activity may require the radionuclide scintigraphy. Nevertheless, the search for optimal method to characterize the selected GO features necessary for different diagnostic and therapeutic purposes is not yet completed.

2.1. Ultrasound-based imaging evaluation of Graves' ophthalmopathy

Ultrasonography (US) is a non-invasive, well-established imaging modality, that is widely used in clinical practice and it enables the evaluation and measurement of extraocular muscles, general assessment of the optic nerve status, detection of the existing gross edema or the enlargement of lacrimal glands [14-16]. Especially, US may be conveniently used to investigate some of the orbital muscle parameters. First ultrasonography-based evidence that extraocular muscle enlargement can be documented directly by US was given by Werner and coworkers in 1974 [17]. From this time, several groups have proposed selected methods for detection and analysis of the thickness of the extraocular muscles and it was determined that their thickness expands with increasing disease severity [18]. However, this technique has also been found by several groups to have limited accuracy and not to be as effective as CT and MRI studies [19-22]. Especially, ultrasound investigation do not include all the extraocular muscles, thus sensitivity and specificity of this imaging modality is getting lower. Moreover, US examination

of the orbit is not enough detailed in delineating the relationship of orbital pathology with soft-tissue structures located in the orbits, nor is it reliable in imaging lesions of the posterior part of the orbit, where compression of the optic nerve often occurs. Likewise, US has strong limitations in imaging of the bone elements of the orbit. In addition, the accuracy of measurements in US examination is strongly dependent on investigator's experience and qualifications. In the concise analysis of differences between orbital MRI and US imaging that was performed in 43 patients with orbitopathy and developed diplopia, the US has not provided sufficient degree of information on muscles and connective tissue that, in contrast, was obtainable by MRI [21]. Nevertheless, US permits to some extent for differential diagnosis of proptosis due to the high degree of similarity between the right and left eye, and the diagnosis of symmetric muscle enlargement is valuable in distinguishing the GO from other similar but often unilateral ophthalmologic disorders [18].

Changes in ocular blood flow may alter the functions of the retina and retinal pigment epithelium and may affect the prognosis of different ophthalmological disorders, including TED. Ocular hemodynamic changes have been reported in GO by several authors using different techniques, including Heidelberg retina flowmeter, ocular blood flow tonography, and oculodynamometry [23-25]. In general, the numerous factors may cause alterations in ocular blood flow in patients with Graves' disease. It is assumed that in hyperthyroidism, increased systemic blood pressure, increased intraocular pressure, and orbital inflammation may affect ocular blood flow [26]. Color Doppler imaging (CDI) is a sonographic imaging technique that permits for non-invasive assessment of blood flow velocity in orbital vessels, and thus, it has been used to study the ocular blood flow in patients with GO. Importantly, it allows for simultaneous imaging of the anatomic structures by B-mode ultrasonography with superimposed color-coded vascular flow. The orbital venous congestion and decreased flow velocity in the superior ophthalmic vein measured with CDI have been found in GO subjects by several groups [26-28]. Similarly, Li et al. and Alp et al. found independently the significantly lower value of the peak systolic velocity (PSV) of blood flow in the central retinal artery in GO patients compared to controls [26,29]. Additionally, Li et al. observed in the same vessel the decreased end diastolic velocity (EDV) of blood flow and the resistance indexes (RIs) significantly increased [29]. Besides, Perez-Lopez et al. measured the changes in retrobulbar blood flow parameters in 14 GO patients before and after decompression surgery and found that in inactive moderate-to-severe GO, the RIs of central retinal artery and ophthalmic artery were preoperatively significantly higher compared to healthy subjects. After decompression surgery, the authors observed a significant decrease of calculable US parameters, such as resistive index (RI), which occurred in both ocular arteries mentioned above. These results may indicate that increased RI of inactive GO might be due to orbital extrinsic compression of vascular structures and decompression surgery leads to significant decreases of the RIs of different orbital arteries [30]. Moreover, Doppler ultrasound parameters of the retrobulbar arteries have been related to the clinical activity score, suggesting increased arterial blood flow velocity in patients with active GO due to inflammation of the orbital tissues [31]. Some studies have showed that evaluation of the impaired arterial vascularization of the orbit and the optic nerve in inactive GO may indicate the necessity of performing the earlier decompression surgery to prevent dysthyroid optic neuropathy in these patients. Altogether, these findings

raise the possibility that CDI measurements represent a clinically useful tool in adjunction to basic ultrasonography for diagnosis and follow-up of GO and, to some extent, for the evaluation of its activity. However, it is necessary to take into account that there are certain limitations that need to be recognized, when interpreting data obtained by retrobulbar CDI measurements. As expected, there is a high intraobserver variability, and even higher the interobserver variability, when the consecutive measurements are performed by two observers in one patient. Therefore, the adequate training is mandatory to allow reproducible CDI measurements. In addition, another limitation of retrobulbar CDI measurements is that it can be influenced by proximal carotid artery stenosis and this abnormality should be excluded prior to retrobulbar CDI. Finally, the resolution of CDI is insufficient up until today to provide reliable volumetric vascular flow measurements. Hence, a high flow velocity in an artery supplying the eyeball does not necessarily reflect the high flow, but may also reflect a stenosis or constriction at the site of measurement. Despite the mentioned limitations, CDI has an important advantage over the other imaging techniques as it is noninvasive, it requires no contrast or radiation, and is available in almost every hospital setting. Nevertheless, according to authors of the recent report on the use of colour Doppler imaging for assessment of retrobulbar blood flow, it is not relevant for routine use in current clinical practice [32].

2.2. Computer tomography-based imaging evaluation of Graves' ophthalmopathy

Computer tomography imaging can distinguish abnormal structures of different tissue density based on their differing X-ray absorption properties. Generally, CT is the preferred imaging modality for the diagnosis of patients with GO because of its ability to visualize bone and soft tissues of the orbit. The orbital fat that acts as a natural contrast medium allows for good spatial and density resolution of orbital structures [33]. As analyzed on the large GO patient cohort, the extraocular muscles most frequently affected are the medial and inferior recti followed by superior and lateral recti, which were involved less frequently and less severely. Importantly, the two or more muscles were enlarged in 70% of patients with ocular involvement [34-35]. The extraocular muscles affected by GO appear to be enlarged in a fusiform fashion with sharp borders [36]. The attempts to establish normative measurements of thickness of the extraocular muscles have been performed by several groups based on national and international cohorts of patients [37-39]. However, the assessment of muscle enlargement is often subjective and requires comparison with the opposite orbit and prior qualitative experience in CT imaging analysis.

Clinical symptoms of GO derive from the discrepancy between limited space of the orbit and expansion of pathologically affected orbital tissues. CT permits to evaluate the differences in orbital soft tissue volumes and densities that are different in GO patients compared to healthy controls. For example, studies using three dimensional CT showed the increase in volume of extra-ocular muscles alone in 20% of 40 subjects with GO, and 28% of GO patients presented only the increased orbital fat tissue volume, however, almost half of the patients had augmented volume of both analyzed structures of the orbit, i.e. muscles and fat [40]. These results indicate that orbital changes might be presented separately as the myogenic and the lipogenic abnormal forms. Furthermore, Regensburg et al. determined by CT imaging that orbital fat

density was significantly higher in GO patients than in the normal population and it negatively correlated to orbital fat volume. They also found a positive correlation between orbital fat density and muscle volume or muscle density [38]. The same group proposed the useful method for calculating orbital soft tissue volume using a manual segmentation technique for CT scans. Based on their results, this technique seems to be reliable and might be an accurate tool for diagnostic follow-up evaluation of GO patients [41]. A decade ago, Nishida et al. hypothesized that orbital fat volume has larger influence on proptosis induction than increased extraocular muscle volume [42]. Recently, Fang et al. observed in CT imaging that orbital fat changes were more important in mild proptosis than in severe one [11]. Imaging-based studies are not only important for the diagnosis of GO, but they can aid in the evaluation of disease activity. Changes observed in sequential measurements of the extraocular muscles obtained with CT may be related to clinical activity of the disease as muscular involvement occurs early in GO and it may correlate with other clinical signs [43]. Other abnormal findings in the orbits that may be determined by CT are a dilated superior ophthalmic vein and abrupt angulations of the posterior muscle belly [44].

Computer tomography is also valuable for the evaluation of the orbital bone wall structures and their remodeling. For example, in long-lasting GO a spontaneous bony orbit decompression could be noted with an impression of the normally parallel laminae papyraceae, which create the medial orbital walls, and then leading to the so-called "Coca Cola sign", when GO has bilateral occurrence and forms the shape typical for internationally-known bottle of Coca-Cola [45]. Orbital CT is the modality of choice to particularly examine the osseous structures of the orbital apex, the sinus, and the intra-orbital elements for the orbital decompression surgery planning. In this notion, CT imaging is recommended pre-and postoperatively in order to define the site and extent of the bony decompression.

Compressive optic neuropathy, which occurs in approximately 5% of patients with thyroid eye disease, is caused by direct compression of the optic nerve at the orbital apex. Such compression in general occurs due to enlarged extraocular muscles [46]. However, optic nerve function in thyroid eye disease may be also compromised by other mechanisms. There have been described several cases of dysthyroid optic neuropathy without apparent orbital apex congestion in which the combination of increased orbital fat volume, shallow orbits, and/or outbowing of the medial orbital wall caused sufficient anterior ocular displacement to allow linear antero-posterior stretching of the optic nerve [47]. As the CT-based examination in patients with dysthyroid optic neuropathy often reveals crowding of the optic nerve at the orbital apex by enlarged extraocular muscles [46], thus several methods have been proposed to delineate the degree of crowding of the optic nerve at the orbital apex using CT imaging that comprised the radiologist-based subjective judgment of the appearance of the apex, quantization of the total extraocular muscle volume by using an image analyzer [48], or just the linear measurements of the amount of orbital height or width occupied by the extraocular muscles at a selected point in the orbit (e.g. the middle between the posterior surface of the globe and the orbital apex) [49]. As a result, every of the above-mentioned methods has shown independently that optic nerve dysfunction is more common in crowded orbit and less common in uncrowded orbit. Birchall et al. described an additional CT sign that has a high

correlation with the presence of optic nerve dysfunction in patients with dysthyroid optic neuropathy, which is the hernia of orbital fat raising out 2-4 mm from the superior orbital fissure [50].

The muscles are usually involved bilaterally in GO and they present a "fusiform" appearance due to characteristic sparing of the muscle tendons. The enlarged muscles produce not only the apical crowding in the orbit, but also venous congestion what can be clearly noticeable in the CT scans performed with intravenous contrast enhancement. As the inflammation starts naturally in the extraocular muscles, it has a crisp, well-defined border within the affected muscle, and thus can be distinguished from pseudotumors. The another characteristic sign, helping in differential diagnosis of Graves' orbitopathy versus orbital myositis, is lack of the involvement of the muscle tendon into the inflammatory process. In the later, the tendon should present swelling and enlargement. Consequently, the inflammatory process leaks from the intramuscular tissue into the intraorbital fat and produces streaking within the fat giving a characteristic 'dirty fat' sign inside the orbit. Concurrently, the medial rectus muscle enlargement may produce the deformation or even the breakage of delicate lamina papyracea of the orbital bony wall. These imaging features are efficiently diagnosed and monitored with CT, especially obtained in the coronal plane [51]. However, the apical crowding is assessed better on coronal planes of MRI scans.

Altogether, CT scanning of the orbits is non-invasive, simple, fast, and cost-effective imaging technique. Findings such as spindle-shaped thickness >4 mm of more than one of the extraocular muscles without involvement of the corresponding tendon, with preferential involvement of the inferior and medial rectus, followed by the superior and lateral rectus muscles, apparent increase in orbital fat volume and the compression of the optic nerve at the orbital apex ("crowded orbital apex syndrome") are the most important morphological diagnostic criteria of GO, when analyzing the axial and coronal CT scans [52]. For the above reasons, and especially because of lower costs and better availability than the MR equipment, the CT imaging should be considered first imaging step in diagnostic evaluation of GO and other thyroid-associated diseases. Moreover, CT provides precise imaging of the osseous periorbital structures, therefore this is the method of choice to plan CT-guided orbital decompression surgery in the inactive phase of GO. To the limitations of this imaging modality belong the radiation exposure to the organism, and especially to the eye lenses. Moreover, CT does not reveal information on the disease activity in most cases. It is also important to be aware that there is a risk for thyrotoxicosis development due to the performance of CT with commonly used iodinated contrast agents.

2.3. Magnetic resonance-based imaging evaluation of Graves' ophthalmopathy

The main advantages of MRI are the excellent soft-tissue contrast, obtainable with a great spatial tissue resolution, compared even to a high-resolution CT imaging and absence of ionizing radiation during the examination. Therefore, MRI is the preferred modality for soft tissue imaging. In orbital MR imaging, slices ranging from 3 to 5 mm are used, normally oriented in the transverse and coronal direction and, along to the optic nerve, in the parasagittal plane. One of the neuroimaging protocols proposed in the literature for examination of the

orbits with MRI is comprised of spin-echo T1-weighted sequences in the axial and coronal planes with 3-mm-slice thickness, multi-echoes T2-weighted sequence in the coronal plane, and short time inversion recovery (STIR) sequence in the coronal plane. Paramagnetic contrast-enhanced images are acquired with T1-weighted sequence with fat-suppression in the axial, coronal and sagittal oblique planes [53]. Our currently used MRI protocol for examination of GO patients is given in Table 1.

Sequence Number	Sequence Name	TR / TE ms	Resolution	Slice Thickness mm	Slice Spacing mm	FOV cm	Contrast Medium
1	3-plane, Gradient Echo, 3-pl T2* FGRE, whole brain	3000 ms / 102 ms	512 × 512	5	5	30.0	No
2	Oblique, Ax T2 Propeller, bulbus	3000 ms / 102 ms	512 × 512	5	15	24.0	No
3	Oblique, Ax T2 FRFSE, bulbus	3000 ms / 102 ms	512 × 512	3	0.3	16.0	No
4	Oblique, Ax T1 FSE, bulbus	575 ms / Minimal Full	512 × 512	3	0.3	16.0	No
5	Oblique, R-SAG T1 FSE, bulbus	475 ms / Minimal Full	512 × 512	2	0.2	14.0	No
6	Oblique, L-SAG T1 FSE, bulbus	475 ms / Minimal Full	512 × 512	2	0.2	14.0	No
7	Oblique, COR T1 FSE, bulbus	575 ms / Minimal Full	512 × 512	3	0.3	14.0	No
8	Oblique, COR STIR, bulbus	2975 ms / 68 ms	512 × 512	3	0.3	14.0	No

Table 1. MR-imaging protocol used in GE Signa HDxt MR apparatus with 8-channel HR head coil for patients with thyroid-associated ophthalmopathy.

Importantly, the T1-weighted MRI sequence offers a better contrast resolution for evaluating the orbit structures and measurement of the thickness of the intra-orbital muscles [54]. In contrast, the pathophysiological conditions of the muscles could be better evaluated on T2-weighted MRI sequences [55]. Moreover, the STIR sequences suppress the fatty signal and allow a more adequate assessment of pathological tissues. Not affected extraocular muscles are defined with a low signal intensity on T1-weighted sequences and low to intermediate signal intensity on T2-weighted sequences, with evident and clear edges. Due to the immense vascular supply of the orbital muscles the strong contrast enhancement is observed during the examination with paramagnetic contrast mediums (e.g. gadolinium containing agents).

Morphological imaging criteria, suggestive for GO on MRI are a bilateral, spindle-like thickening of normally multiple extraocular recti muscles over 5 mm and an increase of intra- and extra-conal fat, both leading to exophthalmos (Figure 1A-C). MRI imaging is specifically advantageous for clinical diagnosis of exophthalmos, because it depicts a clear outline of the eye globe that allows precise measurements. In the clinical setting, exophthalmos is usually measured manually with a Hertel exophthalmometer. The average measurement is around 13.5 mm, and the difference between bilateral eye protrusions should be within 2 mm. However, this manual diagnostic method has poor reproducibility due to the orbital interval, variance of eye diameter as a result of ametropia, exophthalmometer variance and instrument operator bias. In contrast, on axial T1-weighted sequences, the level of proptosis can be measured very precisely, compared to the clinically measured Hertel-index [56]. On imaging, a interzygomatic line is drawn between the right and left ventral zygomatic border. From there, a perpendicular line, representing the value of Hertel-index in mm, is taken to the apex of each globe, thus depicting the measurement of proptosis. Physiologically, 1⁄3 of the globe is located behind the interzygomatic line and a Hertel-index of ≥ 22 mm is pathological and indicates exophthalmos (Figure 1A).

Although changes in extraocular muscle size and increased amounts of orbital fat can be assessed with CT, the orbital soft tissue edema and water content changes in the extraocular muscles can be only assessed by MRI imaging. There are several studies indicating the specific applications of MRI imaging in establishing of the disease phase due to the ability to estimate the water content in orbital tissues. Especially, the images from strong T2-weighted and fat suppressed sequences have been found to be useful in detecting tissue edema [44]. Inflammatory process of the extra-ocular muscles can be detected in MRI independently from the size of the muscles [21]. Young and colleagues proposed to employ in GO patients the MRI turbo inversion recovery magnitude (TIRM) sequences used with short inversion times (80–150 ms). These strong T2-weighted and fat-suppressed images have been found to be useful in detecting edema and therefore, TIRM sequences can be used to define inflammation in extra-ocular muscles [57]. Specifically, the STIR signal intensity, which is directly related to the raise of relaxation in T2 time caused by increased abnormal content in the analyzed tissue, correlates with the inflammatory activity in GO [58]. STIR-sequence MRI may also detect peri-muscular inflammation [59]. Importantly, Kirsch et al. reported that the difference in T2-STIR versus T1-STIR would be helpful to distinguish inflammatory edema of the extra-ocular muscles from intra-orbital congestion due to reduced venous outflow [60]. Therefore, the results of MRI examination have a great therapeutic impact, identifying inflammatory and edematous alterations in orbital muscles that are critical to achieve a good outcome of the anti-inflammatory treatment, which is effective only in the active phase of the disease. Likewise, increase in the signal intensity on T2-weighted sequences was associated with a good response to methylprednisolone pulse therapy [61]. Also, longer T2 relaxation times in the extraocular muscles before treatment were associated with a good response to orbital irradiation [62]. Moreover, individual STIR imaging was useful for predicting the outcome of immunosuppressive therapy [61]. On the other hand, the T1-weighted images with contrast enhancement and in combination with fat saturation are helpful to detect intense signal enhancement of the eyelid, which is also affected in the inflammatory GO stage [63]. Interestingly, the decrease of

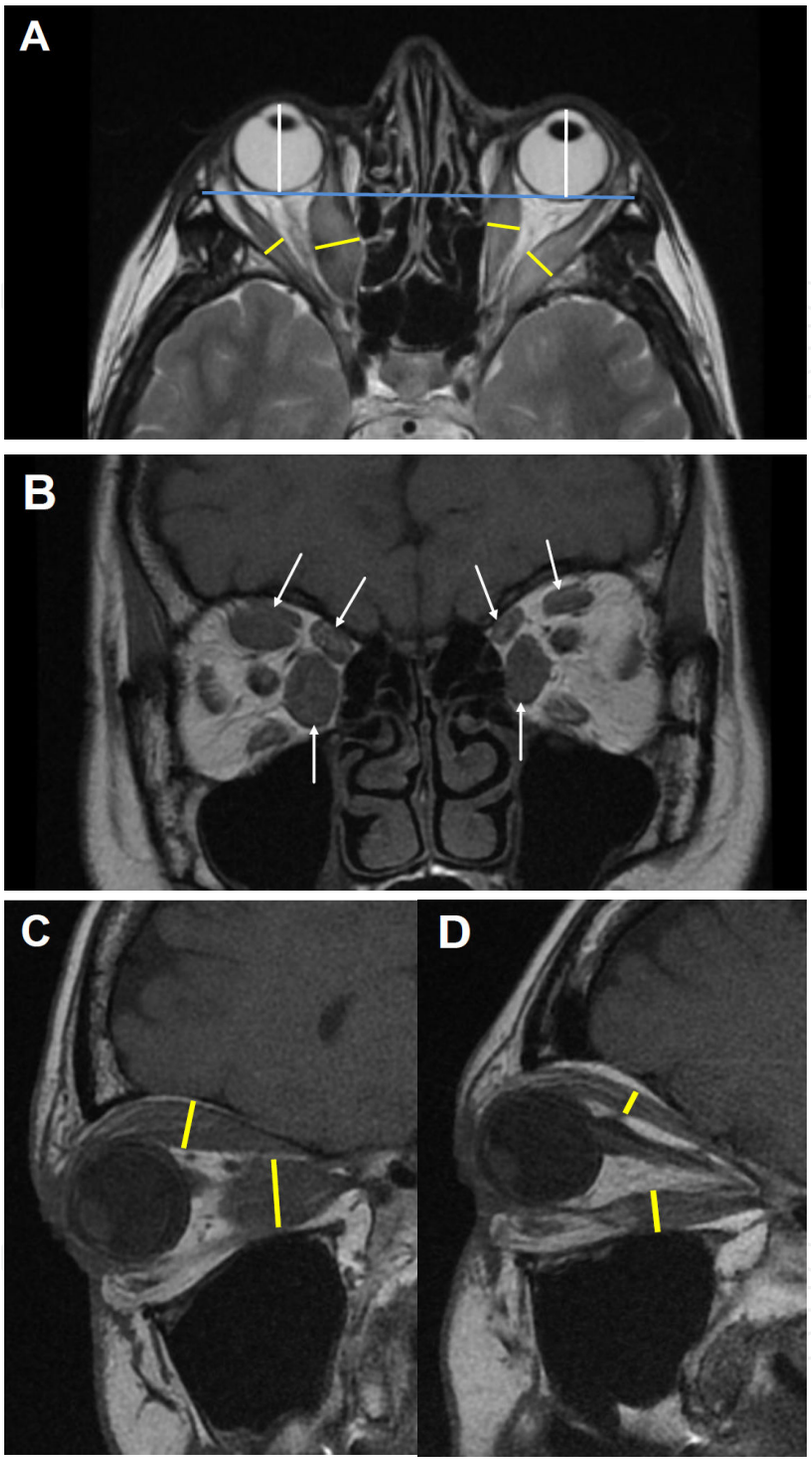

Figure 1. 59-year-old female patient with diagnosis of clinically active Graves' orbitopathy. (A) Axial T2 FRFSE MR image of orbits without contrast shows marked bilateral exophthalmos as indicated by interzygomatic line (blue line) and Hertel-index (perpendicular white lines). This image shows also the largest diameters (yellow lines) perpendicular to long axis of medial and lateral rectus muscles in both orbits. (B) Unenhanced T1 FSE coronal image of orbits shows the transverse sections of the thickest extraocular muscles in both orbits (arrows). (C) and (D) Unenhanced T1 FSE sagittal images parallel to optic nerve show corresponding maximal diameters (yellow lines) for inferior rectus muscle and for superior muscle group of right (C) and left (D) orbit.

T2 relaxation times of the extraocular muscles in response to immunosuppressive therapy occurs even in spite of unchanged laboratory markers during and after the treatment [64]. Nagy et al. found that T2 relaxation times on MRI provided more diagnostic and prognostic information than other applied eleven clinical and laboratory factors [21]. In summary, the major result of the above studies is the relationship between response to therapy and pre-therapeutic value of the T2 times of relaxation in MRI sequences. Consequently, the measurement of T2 before giving the therapy might play a role in the prediction of the reversibility of orbital tissue abnormalities (e.g. muscle thickening, increased fat volume), and favors the choice of anti-inflammatory therapy regimens in GO patients.

MRI is also a valuable tool that can be used to detect other features of the active inflammatory phase of the disease that include lacrimal gland hypertrophy, palpebral edema, anterior displacement of the orbital septum and optic nerve stretching. On the contrary, gradual decreasing of signal intensity of intra-orbital muscles on T1-and T2-weighted sequences suggests the presence of chronic fibrotic alterations that clinically correspond to chronic phase at the Rundle's curve of disease activity [65]. Hyper-intense intramuscular foci on T1-and T2-weighted sequences are suggestive of chronic fat degeneration [66]. Of note, chronic fat degeneration may also be identified at CT imaging through hypodense areas corresponding to fat infiltration of muscle tissue [53]. The above-mentioned findings indicate the presence of the non-congestive phase of the disease with restricted ocular motion secondary to extraocular muscle fibrosis and subsequent loss of elasticity in association with volume reduction of the muscles [66]. Recently, the dynamic contrast-enhanced MRI (DCE-MRI) technique that is used for assessment of microcirculation was able to establish the correlation between disease activity and the microcirculation characteristics of extraocular muscles in patients with GO [63, 67-68]. The natural consequence of the pressure at the orbital apex by increased volume of orbital contents, and resulting overcrowding and stretching of the optic nerve is the compressive optic neuropathy, in which the nerve diameter at the orbital apex has been found to be significantly reduced in MRI imaging. The high-resolution volume acquisition (T1-w-3D) with curved multiplanar reformatting process can be used to measure the optic nerve diameter along its entire length, and thus it can be used to predict possible optic nerve compression. The group of Dodds et al. has demonstrated in MRI modality a reproducible decrease in mean nerve diameter as it extends posterior from the globe in patients with chronic GO [69]. Importantly, this situation may occur even in orbits without increased muscle indices but with clinical signs of optic neuropathy. An additional sign of nerve compression is intracranial fat prolapse in the orbital apex [44].

In conclusion, MRI remains a valuable tool in the care of patients with GO, despite its limited usage due to the time-consuming and a relatively high cost, as well as the still reduced availability, and magnetism contraindicated in patients with certain types of implants. MRI offers extraordinary images of orbital anatomy, except for bony structures, and has an ability to quantify muscle enlargement that outperforms the results obtained from other modalities such as the US and CT imaging. MRI modality is the most effective tool not only in establishing the initial diagnosis but also in diagnosing of the disease stage and immune activity of GO for predicting therapeutic efficacy and of the potential harmful disease complications (damage to

the optic nerve), what makes it a unique instrument in determining the proper treatment and monitoring of the therapeutic response.

2.4. Radionuclide-based imaging evaluation of Graves' ophthalmopathy

Direct neuroimaging methods (US, CT and MRI) play currently a significant role as an aid in the diagnostic process and clinical evaluation of patients with endocrine ophthalmopathy, however, there is no sufficient imaging modality that could be applied to determine with a high sensitivity and specificity the GO activity. It is suggested that intervention using immunosuppressive drugs will be most successful, if applied in the phase of active inflammation. Therefore, to decide, when the treatment should be given, it is important to determine the phase of the disease in an individual patient. One of such imaging possibilities gives octreotide scintigraphy so-called "octreoscan". Previously, it was observed that accumulation of octreotide, a somatostatin analogue labelled with radioisotope indium-111, binds in the thyroid and the orbit to the somatostatin receptor in patients with active GO [70]. Octreotide uptake was significantly higher in patients with active GO compared to those with non-active GO, and the observed high orbital radionuclide activity decreased after therapy. Postema and colleagues have also performed thyroid octreoscan in patients with confirmed Graves' disease and in controls [71]. In this study, the thyroidal octreotide accumulation was increased in thyrotoxicosis, and was almost absent after radioiodine-induced hypothyroidism. The cause of specific orbital and thyroid uptake of octreotide is not well known yet. Most probably, the orbital uptake of octreotide in GO is caused by the expression of somatostatin receptors on the surface of both activated T lymphocytes and fibroblasts, which infiltrate the orbital and thyroid tissues in patients with GO [72-73]. Radio-labeled octreotide accumulated within the orbits can be detected via single-photon emission CT (SPECT), and may serve as a marker of disease activity [70]. On the other hand, the octreoscan does not provide information on inactive patients nor gives any anatomical and morphologic information on the orbit. Importantly, although several studies have found a relation between octreoscan uptake and severity of GO [74-76], the others did not find such a correlation [77-78]. Due to the above-mentioned results indicating substantial limitations of octreoscan (i.e. high demand of the technique in terms of accuracy needed for prediction, inter-observer variance, significant price, modest availability, a non-negligible radiation burden of patients, long acquisition protocol and relative lack of specificity), it is not recommended by some specialists to use it as a routine imaging procedure in a regular clinical practice with GO patients [79-80].

In contrast to octreotide labeled with In-111, the orbital SPECT with other radionuclide tracers has been proposed as clinically suitable protocols for activity evaluation of Graves' ophthalmopathy and differential diagnosis of GO cases sensitive or resistant to the immune suppressive therapy. Indeed, the diethylenetriamine pentaacetic acid labeled with technetium-99 (Tc-99m DTPA) has been indicated as suitable radiopharmaceutical for such examination [81]. The theoretical basis of this method is that the high capillarisation in the orbit and edematous swelling of orbital tissues may be reflected on SPECT images, as the Tc-99m DTPA uptake has been reported as related to the inflammatory process, and signal disappearing with the resolution of the inflammation. The Tc-99m DTPA complex (molecular weight 492 Da),

administered intravenously, marks the high capillarization of inflammation sites leaving the vascular bed through damaged capillary walls. It goes out into the interstitial fluid and binds to polypeptides present in the extracellular fluid at inflammation sites [82]. This may explain the high DTPA uptake in GO since the orbital inflammation is a basic pathophysiological process in GO. The determination of periorbital inflammation tissue by testing with intravenously given Tc-99m DTPA may identify the patients that will benefit from anti-inflammatory treatment. This protocol was clinically tested by Galuska et al., who was able to visualize the active retrobulbar inflammation in GO patient by Tc-99m DTPA SPECT [83]. Moreover, Ujhelyi et al. found that the mean retrobulbar Tc-99m DTPA uptake is useful to estimate GO activity and may predict the effectiveness of immunosuppressive therapy with corticosteroids in GO patients [84]. Especially, patients included in this study with Tc-99m DTPA uptake score above 12.28MBq/cm^3 were more likely to respond to corticosteroid treatment. Another promising method for the diagnosis of inflammatory state is SPECT technique, which uses polyclonal and monoclonal antibodies labeled with technetium-99 (Tc-99m). This technique was previously reported to allow the use of polyclonal human immunoglobulin gamma labeled with Tc-99m (Tc-99m HIG) as a radiopharmaceutical tool in the evaluation of the disease activity in GO [85]. Recently, Lopes and colleagues proposed Tc-99m anti-TNF-alpha scintigraphy based on labeling of a human monoclonal antibody directed against TNF-alpha molecule, commercially known as adalimumab, with technetium-99, as a promising method for the diagnosis of active ocular disease [86]. This method is based on the demonstration of TNF-alpha as one of the cytokines involved in the initial active phase of GO development. They reported the successful use of Tc-99m-anti-TNF-alpha scintigraphy in case of unilateral exophthalmos in which intense uptake of anti-TNF-alpha antibody was observed, indicating the development of active retrobulbar inflammation that may be related with active phase of GO.

Concurrently, the positron emission tomography (PET) appears also as promising tool for diagnosing of active phase of GO. PET is a noninvasive diagnostic method that has been used as a mean for differential diagnosis of inflammatory and malignant processes and it offers the ability to perform functional and metabolic assessment in cases of the absence of any tissue structural alteration [87]. One of its main advantages over other methods is its ability to detect early inflammatory stages prior to structural changes in the tissue [88]. Recently, García-Rojas et al. demonstrated in PET combined with CT (PET/CT) imaging a significant correlation between extraocular muscle uptake of 18-fluorodeoxyglucose (18-FDG) radiotracer and GO developed in hyperthyroid patients [89]. These studies indicate that modern PET/CT imaging modality may provide the valuable clinical information and may be a helpful tool in detecting, localizing, and quantifying the GO inflammation. Ultimately, in the same line of work, Pichler et al. reported the case of subclinical hyperthyroidism due to Graves' disease without presenting exophthalmos in a 53-year-old woman. Application of specific radiotracer Ga-68-DOTA-NOC for high-resolution hybrid PET/CT imaging comprised of gallium-68 radionuclide demonstrated marked accumulation at the thyroid and the right rectus inferior muscle in this patient. Therefore, this specific imaging modality revealed active Graves' orbitopathy in a single extraorbital muscle. The authors concluded that the Ga-68 labeled PET tracers may provide the possibility to evaluate the status of activity in any single extraorbital

muscle in hybrid imaging of PET with CT [90]. Whether novel radiopharmaceutical, such as Ga-68-DOTA-NOC, which has a stronger discriminative capability for detecting active endocrine orbitopathy than octreotide will achieve clinical applicability similar to technetium-99-labelled tracers, it remains to be demonstrated in the future.

In conclusion, the nuclear medicine-based imaging continues to be important in the diagnosis and management of thyroid-associated ophthalmopathy. Although, the previously used SPECT technique known as octreoscan presents nowadays the restricted clinical application [91] due to its high costs, relative lack of specificity (i.e., the number of false positives in other inflammatory or non-inflammatory orbital disorders), and a non-negligible radiation burden, some other SPECT-based methods including technetium-related scintigraphy with the new target-based modalities (i.e. antibodies against selected pro-inflammatory molecules), can be used in the reliable evaluation of patients with unilateral/bilateral active GO. Particularly, the better image quality due to the high energy of technetium, the lower radiation dose for patients and personnel, and the short acquisition protocol favor scintigraphy with Tc-99m-over In-111-labeled compounds [92]. In the near future, the modern PET/CT imaging technique may still improve significantly the process of the treatment selection and the outcome in patient with GO. The results of the currently reported studies demonstrated that PET/CT imaging modalities are able to recognize the early active phase from the late stable stage of the disease and to predict the response to anti-inflammatory treatment in majority of GO patients. Especially, the hybrid PET/CT imaging modality provides valuable and useful information for the diagnosis, characterization, and therapeutic decision in cases, where clinical doubts and uncertainties exist.

3. Predicting therapeutic efficacy and disease activity based on orbital neuroimaging

The activity and severity are important pathophysiological characteristics in Graves' orbitopathy and have implications for the treatment, although the biologic activity of ophthalmopathy is neither synonymous nor coincident with the clinical severity of the eye disease. Severity of GO is defined by the functional impairment and should be categorized using an examination form and a photographic color atlas, which includes the clinical signs of the disease [5]. The European Group of Graves' Orbitopathy (EUGOGO) suggests classifying the GO severity, based on subjective symptoms and objective signs, into three categories: sight-threatening, moderate-to-severe, and mild GO [93]. On the other hand, the activity of GO is related to the presence of inflammatory signs in the orbits. It can be measured using the *Clinical Activity Score* (CAS) classification that is based on the classical features of inflammation (pain, redness, swelling, and impaired function). In the CAS ten-point scoring system, which was developed by Mourits et al., one point is given for each of the following 10 items: painful, oppressive feeling on and behind the globe during the past 4 weeks; pain attempted up, side, or down gaze during the past 4 weeks; redness of the eyelid; diffuse redness of conjunctiva covering at least one quadrant; swelling of the eyelid; chemosis; swollen caruncle; increase of proptosis of ≥ 2 mm during a period of 1–3 months; decrease of eye movements in any direction ≥ 5° during

a period of 1–3 months; and decrease of visual acuity of ≥ 1 line(s) on the Snellen chart during a period of 1–3 months. A score ≥ 3 defines an active GO [94]. The second classification, *NOSPECS* mnemonic, is a useful alternative reminder of what should be assessed in patients with Graves' orbitopathy regarding severity, but it is of lesser practical value [5]. Importantly, the clinical problem in GO is not the establishing of the diagnosis of the disease, because this is quite obvious from the clinical presentation, but the treatment of the eye symptoms in an individual patient. Patients with the immunologically-active ophthalmopathy need the anti-inflammatory treatment, and patients with inactive disease require a completely different treatment course, including rehabilitative surgery (strabismus surgery, eyelid surgery, etc.). In general, the decision for anti-inflammatory treatment with steroids or irradiation is based on objective findings of detailed ophthalmological examination. However, it is important to be able to predict, if the patient will benefit from immunosuppression, as some patients might improve without such therapy, whereas in some patients with a severe course of the disease the initial choice of immunosuppressive steroid dosage may be too low. In contrast, patients with the immunologically inactive orbit will only suffer from the serious adverse reactions of otherwise ineffective immunosuppressive therapy given to them. Furthermore, there are always the questions demanding the rapid answer that include the decision whether to continue or to stop the anti-inflammatory therapy in patients with mild but persisting inflammation, and when is the right moment for surgical rehabilitation, which should not be done in patients at risk for further deterioration due to the high disease activity. The clinical decisions in GO patients are often difficult, and it is extremely important for the clinicians to be able to distinguish the specific phases of Graves' orbitopathy. Of note, in the last decade as many as one-third of patients did not respond to given immunosuppressive treatment [95]. Most of these cases were due to lack of the active stage of disease in the course of the therapy. In such scenarios, more discriminative information of better quality is needed to establish the activity phase of the disease and to make the best treatment decision. For this reason, several groups have assessed the predictive value of several potential activity parameters to predict response to therapy including duration of the eye disease, the CAS score, urinary glycosaminoglycan (GAG) excretion, serum cytokine levels, serum levels of TSH-receptor autoantibodies [91,94,96-98]. Lastly, even genetic factors might influence treatment outcome as several HLA markers have been shown to indicate good or bad response to immune therapy [99]. Notwithstanding, some of these parameters could predict a response to treatment only to some extent, while others could predict to some extent a lack of the therapeutic response. This means that probably a combination of different parameters may be necessary to accurately predict the response to the treatment in the particular patient. In this notion, several recent clinical and experimental studies have found evidences that the selected neuroimaging modalities would be valuable in measuring the disease activity to predict therapeutic outcomes in GO patients. Especially, there are two imaging modalities that seem to be highly supportive to detect disease activity, including MRI and radionuclide-based imaging.

MRI has currently emerged as a valuable tool in the evaluation of disease activity in patients with GO as it can illustrate in detail the inflamed regions of orbits. More than two decades ago, Just *et al.* described that in MRI sequences an increased T2 time in the eye muscles before treatment was associated with a good response to orbital irradiation [62]. This first report was

confirmed by two others indicating that the T2 time decreases after immunosuppressive therapy, what suggests a transition from an edematous and inflammatory state into a fibrotic chronic stage [100]. In particular, there was established strong positive correlation between the clinical activity score of GO and the T2 relaxation time and ratio of signal intensity in STIR sequences in T2-weighted and fat suppressed images [61]. Moreover, Mayer et al. found, that the area of highest signal intensity within the most inflamed extra-ocular muscle, and the average cross-sectional signal intensity of the most inflamed extra-ocular muscle reliably correlated with CAS, and this was maintained as disease activity changed over time [59]. Recently, the correlation between disease activity and the microcirculation characteristics of extraocular muscles has been demonstrated in GO using sophisticated dynamic contrast-enhanced MR imaging [68]. This novel technique is based on the hypothesis that the pathological changes occurring at different stages of GO might impact the microcirculatory status of extraocular muscles differently, and therefore induce distinct contrast-enhancement characteristics on DCE-MRI images, which might serve as indicators for activity estimation. Furthermore, to improve the sensitivity of detection of active phase of the disease and therefore the prediction of the response to immunosuppressive therapy, over CAS alone, the combination of the orbital MR imaging and CAS estimation was proposed by Tachibana et al. [101]. They reported that the orbital MR imaging combined with CAS could improve the sensitivity of differentiation between the active and inactive GO form and especially the CAS and the maximum of T2 relaxation times of extraocular muscles (maxT2RT) showed significant positive correlation. Interestingly, 40% of GO patients included in this study were positive by only MR imaging and all these GO patients presented significant improvement after intravenous immunosuppressive therapy due to active GO diagnosis by MRI classification, what indicates the importance of the orbital MR imaging for the diagnosis of active GO. Recently, Le Moli et al. determined positive correlation between CAS score and ratio of extraocular muscles area to the total orbit area measured in CT imaging modality [43].

Similarly, several radionuclide-based imaging methods have been proposed recently to evaluate disease activity in GO. Importantly, the obtained image evaluation and orbital uptake fraction calculation of the selected radiotracers could provide the qualitative (image-based) and quantitative (numerical) information on disease activity. Historically, the imaging of orbital uptake of In-111-labeled octreotide detected by scintigraphy was presented as a sensitive method to estimate immunologic disease activity in GO patients [70]. However, further studies indicated the low specificity for this method, therefore, its clinical applicability is strongly limited nowadays [33,40]. Subsequently, SPECT imaging of the orbits using Tc-99m-labeled DTPA have been proposed by several reports [102-103]. This method has been accepted for evaluation of GO disease activity allowing a rapid imaging at an acceptable cost, and in addition, the successful management of GO has been associated with the decrease in orbital uptake of radiotracer [84]. In addition, to improve the sensitivity of detection of active GO phase, and therefore the prediction of the response to immunosuppressive therapy, over clinical activity score (CAS) alone, the combination of Tc-99m DTPA SPECT imaging and CAS estimation was proposed by Galuska et al. [104]. They reported that Tc-99m DTPA SPECT imaging provides essential supplementary information to traditional CAS evaluation in assessing GO activity. Likewise, Szabados et al. reported recently the results of the study in

which they measured the inflammatory activity in the retrobulbar region using Tc-99m DTPA SPECT before and after external radiation to determine whether this method is suitable for predicting the effectiveness of the anti-inflammatory therapy [105]. They found in the group comprised of thirty-two patients with suspected active GO that a high initial DTPA uptake may predict the response to orbital radiation therapy, therefore the orbital SPECT with Tc-99m DTPA may be a suitable technique for the selection of GO patients for radiation therapy [105].

Furthermore, the different imaging methods, which were developed recently, applying scintigraphy of Tc-99m-labeled compounds, including polyclonal and monoclonal antibodies against inflammatory-related molecules (e.g. TNF-alpha), gave a new perspective in the diagnostic approach of active GO, which could be diagnosed with high sensitivity and specificity [85-86]. The preliminary results obtained from the group of 25 GO patients with different CAS score suggest that scintigraphy with Tc-99m-labeled anti-TNF-alpha might be a promising procedure for the evaluation of active orbital inflammation in GO [106]. Lately, the high-resolution PET/CT have been introduced to clinical practice for improved detection, disease grading, and follow-up of patients with GO in order to optimize the treatment in the inflammatory GO phase. Several novel radiotracers have been employed in PET/CT imaging, including gallium-68 and fluor-18 to supply valuable information on localizing and quantifying of GO-related inflammation in retrobulbar tissues [89-90]. Importantly, the availability of novel PET tracers for high-resolution and hybrid imaging in PET/CT enables to evaluate selectively the actual status of immune activity in any single extraorbital muscle.

Altogether, the precise quantitative evaluation of clinical disease activity and prediction of the outcome of immunosuppressive therapy in GO are reserved nowadays for only selected orbital neuroimaging modalities such as MRI and nuclear medicine-based imaging using gallium or technetium scintigraphy. Importantly, there are some limitations to the imaging studies of GO activity. For example, as the histological validation by extraocular muscle biopsy, which is the "golden standard" in diagnosis evaluation, is not available on regular basis in case of the orbits, the discussion about morphology-related changes observed in images obtained by different imaging modalities are speculative to some extent. Moreover, although MRI and radionuclide-based imaging may show increased edema in the muscles and inflammatory process in the orbital tissues during the active phase, however both modalities tend to be less helpful in therapeutic surgical planning since no detail about bone architecture is provided in these techniques.

4. Conclusion

Diagnosis of Graves' orbitopathy is usually given by careful ophthalmological examination when clinical manifestations occur. The main symptoms of the orbitopathy derive from the discrepancy between limited space of the orbit and expansion of pathologically affected orbital tissues. Therefore, in most patients, CT and MRI of the orbit confirm diagnosis by showing enlarged extraocular muscles (without involvement of the tendon) and/or increased orbital fibroadipose tissue. Although extra-ocular muscle enlargement can be documented

directly by ultrasonography, the CT scan or MRI highly improve the measurements (i.e. thickness and volume) by direct visualizing the retro-bulbar muscles in their entire length and at the apex of the orbit, where their augmentation is responsible for dysthyroid optic neuropathy. The orbital neuroimaging is especially required in asymmetrical or, particularly, unilateral forms of GO, to rule out that exophthalmos, swelling of periorbital tissue, inflammation, or diplopia exist due to disorders other than GO. The MRI is the preferred modality for soft tissue imaging. As a basic rule, T1-weighted images are best for anatomic details, while T2 images give more information about the different tissue composition. Compared with MRI, computer tomography is less expensive, more available in the national health system and faster to perform, however, is less efficient in the evaluation of soft tissue changes and might not reveal details that could be important in the assessment of disease activity. In addition, the iodinated contrast medium usage for CT imaging should be limited in patients with Graves' disease. On the other hand, MRI provides a precise quantitative evaluation of clinical disease activity and may predict the outcome of immunosuppressive therapy for GO. As a consequence, there is potential for MRI in the evaluation of the therapeutic outcomes of new drugs for GO [45].

The history of the disease, physical examination, and neuroimaging findings can all provide important data on the actual phase of the disease process. But they can also be equivocal or confusing. The orbital cavity is a particularly difficult area for quantitative analysis. It contains various anatomical structures, which are small in size and have significantly different densities, structures, and shapes as well as complicated spatial relationships. This leads to various artifacts that can significantly affect the final results of applied neuroimaging. In addition to this, individual variability strongly affects the established range of standard parameters important for correct disease diagnosis [55]. Diagnostic uncertainties have to be weighed against the benefits and risks of therapy with systemic immunosuppressive treatment, radiation, or surgical orbital decompression.

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