Disease Activity in Graves' Ophthalmopathy: Diagnosis with Orbital MR Imaging and Correlation with Clinical Score

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SUMMARY – *In Graves' ophthalmopathy (GO) it is important to distinguish acute inflammation at an early stage, responsive to immunosuppressive treatment, from inactive fibrotic end stage disease, unresponsive to the same treatment. The purpose of this study was to identify the most relevant signal intensities on orbital MR imaging with contrast administration both to classify patients according to their clinical activity score (defined by a cut-off value of 3) and to make a prediction of patient's CAS. Such threshold was considered as widely used in literature. Sixteen consecutive patients with a diagnosis of GO in different phases of thyroid disease based on clinical and orbital MR imaging signs, and six normal volunteers were examined. Orbital MR imaging was performed on a 1.5 Tesla MR Unit. MR scans were assessed by an experienced neuroradiologist, blinded to the clinical examinations. We found a statistical correlation between CAS and both STIR and contrast enhanced T1-weighted sequences. There was also a statistically significant correlation between STIR and contrast-enhanced T1 images disclosing the possibility of avoiding the injection of contrast medium. Our study proved that signal intensity values on STIR sequence increase in the inflammatory oedematous phase of disease. We confirmed the correlation between signal intensities on this sequence and CAS, showing an increase in signal intensity proportional to the CAS value. So we validated MRI use to establish the activity phase of disease more sensitively than CAS alone.*

Introduction

Graves' ophthalmopathy (GO) is a chronic inflammatory autoimmune disease of periorbital tissue and conjunctiva, as well as retrobulbar structures, e.g. extraocular muscles (EOM). The diagnosis of GO is often evident, due to the bilateral symmetric aspect of the orbitopathy in patients with a history of Graves' hyperthyroidism. Mandatory objectives in the first evaluation of patients with clinically suspected GO, in order to establish the correct treatment, are: 1) to support the clinical diagnosis of GO by imaging; 2) to identify the disease phase; 3) to assess the disease severity.

The clinical activity score (CAS), proposed by Mourits et al. [1], is a validated scoring system for the identification of disease phase. The system is based on the assessment of inflammatory signs and symptoms (pain, eyelid and conjunctiva erythema, chemosis, eyelid oedema) to distinguish inflammatory from non-inflammatory GO. The system is widely used because of its high predictive value for the outcome of immunosuppressive treatment in GO patients [2]. According to the European Groups on Graves' Orbitopathy (EUGOGO) recommendations, CAS≥3 defines active GO with a positive predictive value (PPV) of 65% and negative predictive value (NPV) of 56% for response to radiotherapy [1,3,4]. However, the CAS system is an examiner-dependent method, and is inadequate for monitoring changes in clinical manifestations until the symptom completely

resolves [5-7]. Moreover, in Mourits et al.'s study, many patients with a CAS of 1 or 2 showed a significant response to immunosuppressive treatment [8,7], and the CAS cut-off value of 3, as stated by European Groups, did not prove suitable for the Asian population [5-7]. So there is no exact correspondence between CAS alone and the real clinical condition of GO.

Therefore, as largely reported in literature, clinical score should be integrated by imaging modalities to improve the diagnostic accuracy [7,9,10], i.e. orbital ultrasound (US), computed tomography (CT) and magnetic resonance (MR). Orbital MR imaging is widely reported to detect not only other pathologies such as orbital mass, infections or vascular lesions, but also to identify oedema and so distinguish active from inactive GO. This is due to the high contrast resolution of MRI allowing the differentiation between signal intensity of fibrous and inflammatory tissue on strong T2-weighted (w) fat-suppressed images, derived from TIRM (Turbo-Inversion Recovery-Magnitude) sequences [5,7,11-15]. Furthermore, many studies report the possibility to quantify different signals using STIR protocols or measuring T2-relaxation time, so realizing an objective assessment [13].

The purpose of our study was to identify the most important MR signal intensities on STIR images and on T1-w imaging after contrast administration, performed on the same day as the patient's clinical evaluation, that best discriminate patients with a CAS>3 (sus-pected non-inflammatory or inactive GO) from patients with a CAS≤3 (suspected inflammatory or active GO). The diagnostic advantages in the evaluation of GO and the improvement of accuracy in detecting disease activity using orbital MR imaging are also further described.

Materials and Methods

Patient characteristics, protocols and clinical evaluations

Between October 2009 and May 2010, 16 consecutive patients (seven men and nine women; mean age 49.19 years), with a diagnosis of GO in different phases of thyroid disease, and six normal volunteers (three men and three women; mean age 50.12 years) were enrolled.

In particular, patients with ocular symptomatology with a proven history of Graves' thyroid disease or with clinical and laboratory signs of Graves' disease, ascertained during the first clinical evaluation, were enrolled (inclusion criteria). Baseline serum thyroid parameters are reported in Table 1. Patients with other orbit diseases such as trauma, optic neuropathy, other inflammatory diseases of unknown origin, previous orbital radiotherapy or surgery, previous immunosuppressive treatments with steroids and antithyroid treatment for more than 12 weeks before MR examination

Table 1 Baseline serum thyroid parameters.

	Range (min – max)	*Median*	*Reference values*
TSH UI/ml	0.001-5.45	1.23	0.4-4.0
FT3 pg/ml	2.41-9.60	3.7	1.5-5.9
FT4 pg/ml	6.8-21.7	10.3	5.2-15.8
hTRAb* U/l	0.2-40	5.75	<1.5
N° males: 7 (43.7%); N° females: 9 (56.3%)			

Table 2 Range of scores attributable to each domain making up the CAS value.

Domains	*Scores*
Conjunctival chemosis	0 – 1 – 2
Conjunctival redness	0 – 1
Eyelid erythema	0 – 1
Eyelid swelling	0 – 1 – 2
Spontaneous orbital pain	0 – 1
Gaze evoked orbital pain	0 – 1

were excluded. All patients gave informed consent and volunteers gave consent to take part in the contrast-enhanced orbital MR studies. The protocol was approved by the local ethical board of our hospital.

Two CAS were assessed for each patient by two independent "blinded" operators, who assigned a rating for each domain that make up the score at issue, according to the scheme reported in Table 2. Therefore, CAS values were derived from the sum of all ratings assigned by each operator. The meaning of "blinded" refers to the fact that the two operators were blinded to the patient's clinical conditions, to prevent certain information leading to conscious or *subconscious* bias on their part, invalidating the results.

MR imaging analysis

All patients were subjected to resonance on the same day as the clinical evaluation. Orbital MR imaging was performed on a 1.5 Tesla MR Unit (Magnetom Symphony, Siemens Medical Systems, Enlangen, Germany) with an imaging protocol consisting of axial turbo spin echo (TSE) T2-w images (parameters: repetition time/echo time/Nex = 3350/116/2 with a 259×384 matrix, FOV 240 mm and a 5 mm slice thickness with no gap), axial fat-suppressed (FS) TSE T2-w images (parameters: repetition time/echo time/Nex = 3960/115/3 with a 248×320 matrix, FOV 220 mm and a 4 mm slice thickness with a 0.4 mm space between slices), coronal fat-suppressed TSE T2-w images (parameters: repetition time/echo time/Nex = 3960/115/3 with a 248×320 matrix, FOV 210 mm and a 3.6 mm slice thickness with a 0.4 mm gap), coronal fat-suppressed T1-w images (parameters: repetition time/echo time/Nex = 472/15/3 with a 448×512 matrix, FOV 210 mm and a 3 mm slice thickness with no gap), axial 3D fat-suppressed T1-w VIBE images (parameters: repetition time/echo time/Nex = 8/2,46/3 with a 205×256 matrix, FOV 200 mm, 1 slab with 52 slices per slab and 1 mm slice thickness without gap). Coronal fat-suppressed T1-w images were acquired on a plane perpendicular to the optic nerve.

Contrast-enhanced images were obtained immediately after IV administration of 0.1 ml/kg of Gadobutrol 1.0 mol (Gadovist; Bayer Schering Pharma, Berlin, Germany) and consisted in axial 3D fat-suppressed T1-w VIBE images and coronal fat-suppressed T1-w images with the same parameters as the pre-contrast phase.

Figure 1   Coronal T2 FS image showing ROI on extraocular muscles.

Figure 2   Coronal FS T1-unenhanced image showing ROI on bilateral inferior and medial rectus muscles.
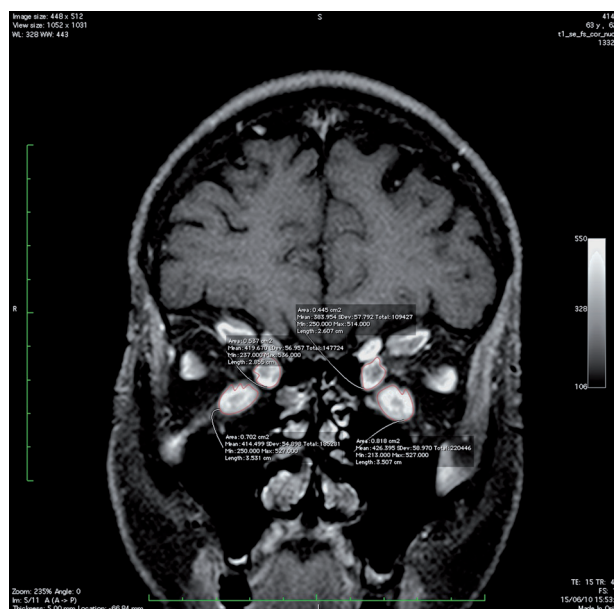

Figure 3 Coronal FS T1-enhanced image showing ROI on inferior and medial rectus muscles.

Table 3 List of MR signal notations.

STIRRinf	Signal intensity value in STIR sequences in inferior rectus muscle
STIRRmed	Signal intensity value in STIR sequences in medial rectus muscle
T1SNZinf	Signal intensity in T1 without contrast medium in inferior rectus muscle
T1SNZmed	Signal intensity in T1 without contrast medium in medial rectus muscle
T1CONinf	Enhanced-T1 signal intensity of the inferior rectus muscle
T1CONmed	Enhanced-T1 signal intensity of the medial rectus muscle
STIRtemp	Signal intensity value in STIR sequences in temporal muscle
T1tempSNZ	Signal intensity in T1 without contrast medium in temporal muscle
T1tempCON	Signal intensity in T1 with contrast medium in temporal muscle
SIRretINF	Signal intensity ratio in inferior rectus muscle
SIRretMED	Signal intensity ratio in medial rectus muscle
SIRT1retINF	Signal intensity ratio in T1 in inferior rectus muscle
SIRT1retMED	Signal intensity ratio in T1 in medial rectus muscle
CMSIRretINF	Signal intensity ratio between the signal intensities of inferior rectus muscle and the ipsilateral temporalis muscle
CMSIRretMED	Signal intensity ratio between the signal intensities of medial rectus muscle and the ipsilateral temporalis muscle

MR scans were assessed by an experienced neuroradiologist, blinded to the clinical examinations. Because GO most frequently involves the inferior and medial rectus muscles [5,11-13], the neuroradiologist positioned ROIs avoiding the magnetic inhomogeneity artifacts from bone/air of the maxillary sinus. ROIs were drawn around the right and left edges of the above-mentioned muscles on coronal acquisitions, from the anterior origin of the muscles to the orbital cavity apex.

We approved the values in the area of the highest signal intensity as a resulting number without a quantity and representing mean value and standard deviations. Moreover these measured signal intensities were set in proportion to those of the ipsilateral temporal muscle to calculate the signal intensity ratio (SIR), which is a more objective and reproducible indicator. The temporal muscles are considered the reference standard because they are spared from Graves' disease and because of their structural similarity and close anatomical relationship to the EOM [5,11,12]. (Figures 1 to 3). Therefore, a wide number of variables were obtained, considering SIR related to FS T2 and gadolinium-enhanced FS T1-w images, for each muscle in both the patient and the volunteer groups.

Statistical analysis

The most important MR signal intensities that best discriminate a suspected non inflammatory or inactive GO patient (CAS≤3) from a suspected inflammatory or active GO patient (CAS>3) were detected using the new Random Forest (RF) algorithm [16]. This approach simultaneously models the relationship between an outcome (i.e. CAS) and multiple potential predictor variables (i.e. MR signal intensities) by building 100,000 trees where, for each tree, a subset of both observations and MR signals were randomly chosen. Moreover, for each MR signal evaluated, RF provided a relative measure of how much this signal should be relevant to discriminate suspected inflammatory from non-inflammatory patients, among the other predictors. Since the RF algorithm scrambles all the available data, by the use of permutation and bootstrapping methods, the most accurate evaluation of relative variable importance was provided for each predictor at issue, even with a small number of observations. To confirm the validity of the RF findings, a discriminatory power of each MR signal intensity was assessed by estimating the area under the receiver operating characteristic (ROC) curve, along with its 95% confidence interval (95%CI)
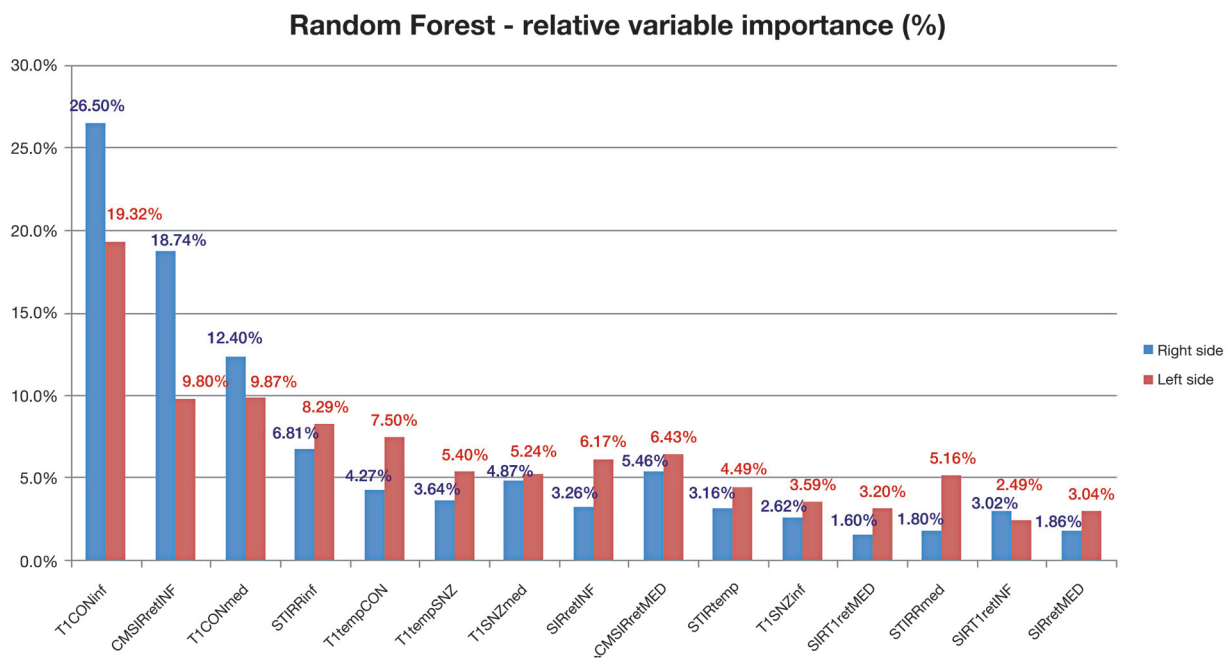
Figure 4 Relative variable importance attributed by the Random Forest algorithm to all left and right MR signals intensities to discriminate "inactive GO" (CAS≤3) from "active GO" (CAS>3) patient groups.

estimated by the DeLong method [17]. The optimal cut-off was assessed by jointly maximizing sensitivity and specificity. Sensitivity and specificity, computed at the optimal cut-off, were also reported. An evaluation of the statistical power acquired to detect a specific area under the ROC curve, using a one-sided z-test, was also provided. A p value ≤ 0.05 was considered for statistical significance. All statistical analyses were performed by evaluating left and right MR signal measurements separately, and using R software (Ver. 2.12, random Forest and Diagnosis med and packages).

Results

CAS values assessed in all patients by the two independent operators were perfectly concordant. The reader can find a list of all notations used to define each MR signal intensity in Table 3.

Among all patients that represent the whole sample, 13 had CAS≤3 and represented those with suspected non-inflammatory or "inactive GO" group, whilst nine patients had CAS>3 and represented the others with suspected inflammatory or "active GO" group. The RF algorithm showed that the most important signal

that best discriminates the two patient groups was the enhanced-T1 signal intensity of the inferior rectus muscle (T1CONINF): indeed the relative variable importance attributed by the algorithm was 19.3% and 26.5% for the left and right muscle sides, respectively. The next important signal was the signal intensity ratio between the signal intensities of inferior rectus muscle and the ipsilateral temporalis muscle (CMSIRRETINF): a relative variable importance of 9.8% and 18.7% were attributed for the left and right muscle sides, respectively. A graphic representation of all MR signals (measured on left and right sides) relative variable importance, sorted from the highest to the lowest percentages, is also reported in Figure 4. The estimated area under ROC curve (AUC) of all left and right MR signals, along with its 95%CI and the optimal cut-offs are reported in Table 4. As previously found by the RF algorithm, T1CONINF seemed to confirm the most important predictor that best discriminates patients belonging to the "active GO" group from patients belonging to the "inactive GO group", with the highest discriminatory power both for left signals (AUC=0.942, 95%CI = [0.86 - 1.00]) and for right signals (AUC=0.983, 95%CI = [0.94 - 1.00]), acquiring the maximum sensitivity of 0.88 and maximum specificity of 0.86

at the cut-off of 532 for the left signal, whilst the maximum sensitivity of 0.89 and maximum specificity of 1.00 at the cut-off of 546 for the right signal. A sample of nine patients from the "active GO" group and 13 from the "inactive GO" group achieved 83% power to detect an area under ROC curve greater than or equal to 0.80, under the null hypothesis of 0.50 at a significance alpha level of 0.05. The ratio of the standard deviation of the responses in the "active GO" group to the standard deviation of the responses in the "inactive GO" group was assumed to be 1. Furthermore, a graphic representation of the ROC curves for T1CONINF and CMSIRRETINF (left and right) signals, are reported in Figure 5.

Discussion

GO is a chronic inflammatory autoimmune disease, more often associated with Graves' hyperthyroidism, but it may exist in patients with euthyroid or hypothyroid chronic autoimmune thyroiditis. The most important pathogenic factors are the TSH receptor auto-antibodies, sharing as targets TSH receptors localized on orbital fibroblasts and adipocytes. The

autoimmune attack determines swelling of the extra-ocular muscles in association with an increase in orbital connective tissue and fat volume, with consequent restrictive ophthalmoplegia [5,11,12]. The most common GO clinical signs include eyelid erythema and oedema, chemosis, upper eyelid retraction, and proptosis (exophthalmos) [17], restricted ocular motility but also sight-threatening complications of compressive optic neuropathy and corneal ulcerations. The clinical manifestations of GO are evident and severe in only 3-5% of patients. The disease is more often characterized by a subclinical course; sometimes presentation can be heterogeneous because not all features are present [6,8,19].

In 15% of all patients, GO may present predominantly with unilateral eye changes or may precede or follow the onset of Graves' disease [11]. 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 [13,20,27].

Two phases characterize the GO clinical course [19]: 1) "active phase", histologically characterized by mononuclear cell infiltration, pro-

Table 4 Discriminatory power and test characteristics at the optimal cut-off for all MR signals measured both on left and on right sides.

	Left signals		Right signals	
	AUC (95%CI)*	*Optimal cut-off (SE, SP)***	*AUC* (95%CI)*	*Optimal cut-off (SE, SP)***
STIRRinf	0.839 (0.66 - 1.00)	255 (SE = 0.88, SP = 0.71)	0.846 (0.68 - 1.00)	244 (SE = 1.00, SP = 0.62)
STIRRmed	0.777 (0.58 - 0.98)	206 (SE = 1.00, SP = 0.57)	0.752 (0.54 - 0.96)	255 (SE = 0.67, SP = 0.77)
T1SNZinf	0.665 (0.43 - 0.90)	192 (SE = 1.00, SP = 0.50)	0.718 (0.49 - 0.94)	211 (SE = 0.78, SP = 0.69)
T1SNZmed	0.772 (0.58 - 0.97)	183 (SE = 1.00, SP = 0.57)	0.803 (0.62 - 0.99)	192 (SE = 1.00, SP = 0.62)
T1CONinf	0.942 (0.86 - 1.00)	532 (SE = 0.88, SP = 0.86)	0.983 (0.94 - 1.00)	546 (SE = 0.89, SP = 1.00)
T1CONmed	0.857 (0.70 - 1.00)	511 (SE = 0.88, SP = 0.79)	0.906 (0.78 - 1.00)	514 (SE = 1.00, SP = 0.77)
STIRtemp	0.696 (0.48 - 0.91)	81 (SE = 0.88, SP = 0.50)	0.701 (0.48 - 0.92)	81 (SE = 0.89, SP = 0.62)
T1tempSNZ	0.777 (0.59 - 0.97)	158 (SE = 0.88, SP = 0.71)	0.786 (0.59 - 0.98)	155 (SE = 1.00, SP = 0.54)
T1tempCON	0.777 (0.57 - 0.98)	293 (SE = 0.75, SP = 0.79)	0.769 (0.56 - 0.98)	302 (SE = 0.67, SP = 0.92)
SIRretINF	0.759 (0.52 - 0.99)	3.70 (SE = 0.50, SP = 1.00)	0.778 (0.58 - 0.98)	2.74 (SE = 0.89, SP = 0.62)
SIRretMED	0.616 (0.34 - 0.89)	2.68 (SE = 0.63, SP = 0.71)	0.667 (0.43 - 0.90)	2.38 (SE = 0.89, SP = 0.46)
SIRT1retINF	0.661 (0.32 -1.00)	1.22 (SE = 1.00, SP = 0.14)	0.654 (0.31 - 1.00)	1.28 (SE = 0.89, SP = 0.31)
SIRT1retMED	0.692 (0.27 - 1.00)	1.00 (SE = 1.00, SP = 0.00)	0.671 (0.30 - 1.00)	1.08 (SE = 1.00, SP = 0.00)
CMSIRretINF	0.853 (0.69 - 1.00)	1.61 (SE = 1.00, SP = 0.64)	0.940 (0.84 - 1.00)	1.73 (SE = 1.00, SP = 0.85)
CMSIRretMED	0.763 (0.56 - 0.96)	1.60 (SE = 1.00, SP = 0.64)	0.859 (0.71 - 1.00)	1.82 (SE = 0.67, SP = 0.92)

AUC = Area under the receiver operating characteristic curve, along with bootstrap 95% confidence interval. ** *SE* = Sensitivity, *SP* = Specificity.
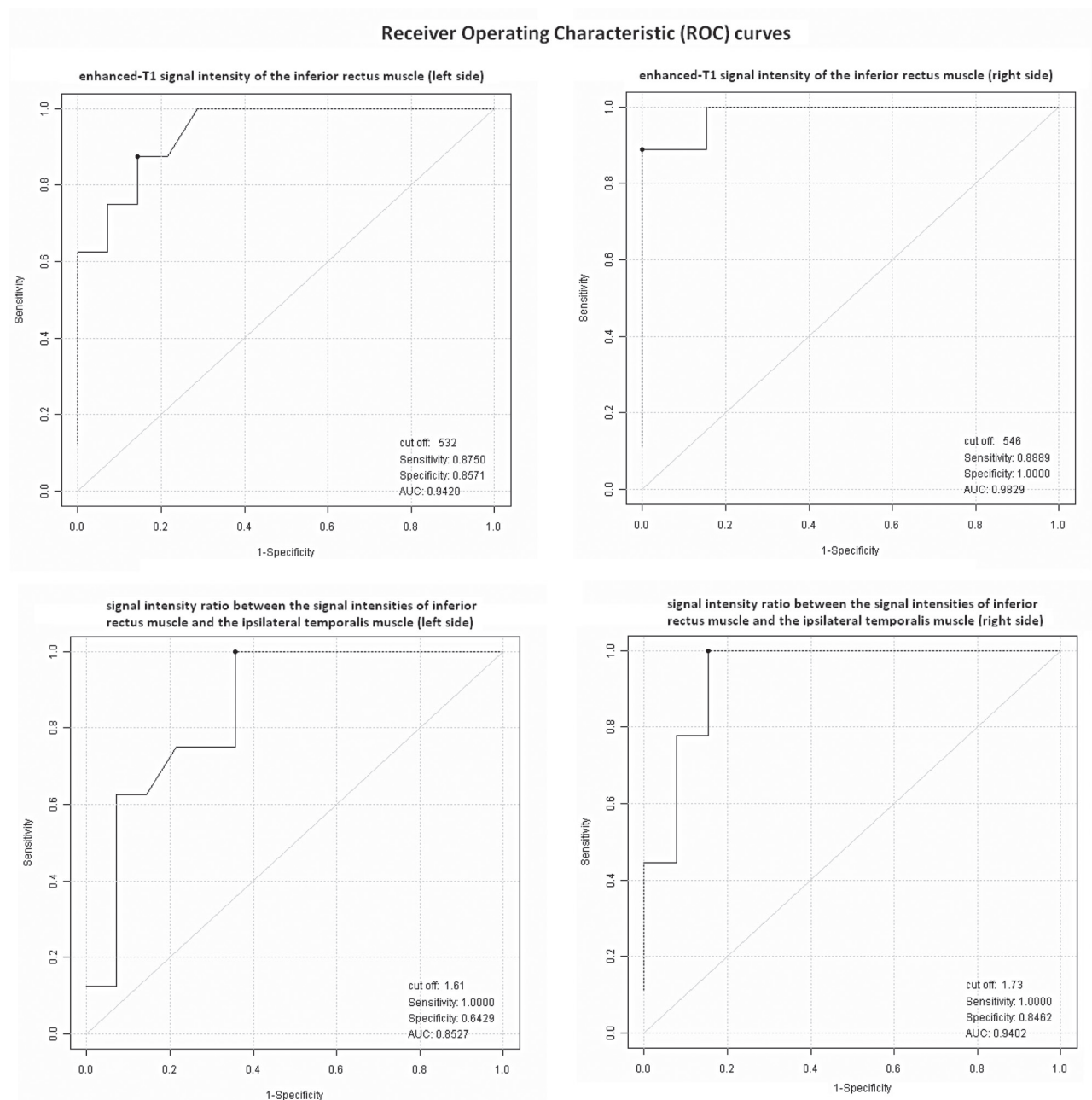
Figure 5 Receiver operating characteristic (ROC) curves of enhanced-T1 signal intensity of the inferior rectus muscle (left and right sides) and signal intensity ratio between the signal intensities of the inferior rectus muscle and the ipsilateral temporalis muscle (left and right sides), on discrimination between "active GO" and "inactive GO" patients. The optimal cut-off was assessed by jointly maximizing test sensitivity and specificity.

liferating fibroblasts and oedema within the extra-ocular and levator muscles, lachrymal glands and adipose tissue with consequent oedema and enlargement of muscles; 2) "inactive or chronic phase", characterized by fibrosis and fatty infiltrations of muscles causing the extension of fibrous strands into adjacent adipose tissue [5,11,12].

Patients presenting the active phase of disease are more often symptomatic, reporting a dry and gritty ocular sensation, photophobia, excessive tearing, double vision and a pressure sensation behind the eyes.

Specific symptoms of active disease are sudden appearance or change in altered and double vision. In particular, worsening on

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waking intermittent diplopia eventually associated with pain is strongly suggestive of active GO.

Permanent alterations in visual functions, such as blurred vision or altered colour perception, are potential markers of dysthyroid optic neuropathy (DON) with optic nerve compression in the orbital apex, and they are associated with active disease. However, clinicians should specifically seek these symptoms in all patients suspected of having active disease, as they are not always reported and considering that treatment of DON is obligatory.

Early diagnosis has primary importance in GO management, because an appropriate treatment can avoid permanent injuries (proptosis, sight impairment). Medical therapy by corticosteroids in the early stages of disease is useful to reduce the inflammation and to obtain GO remission, but it is useless in fibrotic endstages. Early diagnosis and treatment would therefore lead to at least partial remission in up to 65% of cases [22].

The CAS scoring system evaluates disease activity and response to immunosuppressive therapy. Because CAS determination requires two clinical examinations, some authors proposed a modification that allows determination of CAS in a single session [21]. This method is widely used because of the reported correlation between pretreatment CAS and post-immunomodulating therapy outcome in GO patients characterized by a retailed PPV of 80% and a NPV of 64% [2]. However, Mourits et al.'s study never demonstrated that patients with CAS<3 have inactive GO [7,11]. Moreover, in Mourits et al.'s' report, ten out of 13 patients with CAS<3 were responders to immunosuppressive treatment [7,8,21]. Finally, this method does not fully describe the overall status of GO, especially in the seven-item form [7,8]. These results, therefore, show that CAS by alone cannot adequately detect active GO [7].

The significant limits of CAS consist in the lacking evaluation of the various levels of inflammation activity, so any improvement or exacerbation does not alter the score until it completely resolves, and low sensitivity and subjectivity because of the operator dependence [5-7]. Furthermore the score attributes the same value to the various factors, each of which probably has different importance, thereby missing a diversification. Therefore CAS requires the integration with other modalities [7,9,10].

Clinical assessment and imaging methods like orbital US, CT and MRI are used to determine disease activity and severity. Orbital US

is the least expensive and simplest examination to perform and allows good evaluation of muscular diameters and reflectivity, but it is not able to study the orbital apex, so will not yield information on the optic nerve, and is characterized by an apparent inaccuracy because of variability in orbital tissue measurement [23]. Orbital CT is useful in detecting enlargement of extra-ocular muscles and in evaluating optic nerve and proptosis degrees. However, irradiation of the crystalline is the greatest limit of CT which prevents its use in follow-up [17]. Furthermore, CT does not estimate muscle composition and so it is not able to identify inflammation. In fact, in our study there is no correlation between muscle diameters and CAS, confirming the literature stating that muscle thickness alone is not a measure of the degree of inflammation [23].

MRI gives all the information of both US and CT and in addition is able to detect muscle oedema, because of its capacity to characterize tissues. Many recent studies have validated the utility of MRI in GO because of its features: detailed imaging of orbital anatomy (consisting of high soft tissue contrast with the possibility of characterizing tissues, thin sections and multiplanar reconstructions), lack of ionizing radiations, standardization of study protocol with consequent examination reproducibility. So this modality will differentiate inflammatory from fibrotic alterations of orbital tissue and so discriminate the active from the inactive phase to select the right treatment. STIR sequences, in particular, have been found useful in detecting oedema in extra-ocular muscles which present T2 relaxation times longer than healthy controls [5,7,24]. Moreover, T2 sequences allow us to observe the therapeutic effect [25].

An accurate interpretation of pathological alterations of EOM and periorbital tissue can suggest the correct therapeutic approach and can even provide pre-clinical information in patients with Basedow's disease without ocular symptoms. There is growing evidence [6,8,11,13,19,29], in fact, that EOM inflammatory involvement can occur earlier than ocular symptomatology and a recent study reports the involvement of one EOM at least on MR examination in 50% of patients of the presented case series, characterized by subjects in subclinical phase [26].

In agreement with some of the literature, we confirm the probable multifactorial pathogenesis of GO if we consider that we found no correlation between the blood levels of anti-TSH receptor antibodies and MR signal intensity values or CAS [7,23].

Orbital imaging is always necessary, 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, helping to support the diagnosis and providing a baseline examination with additional information in the decision making for immunomodulating therapy and for follow-up[13].

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[13,28]. MRI is able to differentiate the two activity states, demonstrating interstitial oedema on coronal TIRM sequences within the extraocular muscles in active disease: It is therefore the modality of choice to identify active inflammatory changes and to assess treatment response, additionally thanks to its lack of ionizing radiation[13].

In GO the standardized MR imaging protocol includes coronal fast spin echo T1-w and T2-w TIRM sequences in axial and coronal planes, with 3 mm slice thickness[13]. The signal intensity from inflamed extraocular muscles is known to correlate with the CAS and therefore has an impact on the two treatment options, that are immunosuppressants or surgery[7,13,24,27]. CAS alone could not detect active GO sufficiently and orbital MR imaging could predict the response to corticosteroid therapy more accurately than CAS alone[7].

Our study proved that signal intensity values on STIR sequence increase in the inflammatory oedematous phase of disease. We confirmed the correlation between signal intensities on this sequence and CAS, showing an increase in signal intensity proportional to the CAS value. So we validated MRI use to establish the activity phase of disease more sensitively than CAS alone[7]. T1-w images after contrast medium injection, associated with fat saturation, are a helpful tool to detect intense enhancement of the extraocular muscles or the eyelid[12,13,15].

However, the role of EOM contrast enhancement on T1 sequences in the acute inflammatory stage of GO remains unclear. Some studies demonstrated decreased contrast enhancement because of microcirculation injury, attributable to muscle enlargement and inflammatory infiltration. On the contrary, our study, in agreement with some previous literature[11], demonstrated a direct proportion between STIR values and enhanced-T1 images, i.e. the increased enhancement during the active phase, as a result of vascular congestion, caused by oedema and interstitial inflammatory infiltration[12,30,31].

Moreover, we found that enhanced T1 signal intensities are the most reliable MR signals to assign a subject to the group with CAS<3 or CAS>3 at the cut-off value of 529. Furthermore, if the signal intensity ratio between the signal intensities of the inferior rectus muscle and the ipsilateral temporalis muscle is linearly combined with the STIR signal intensities of the inferior rectus muscle and the unenhanced-T1 signal intensities of the same muscle, it would most likely predict the exact CAS value.

A fundamental limit of our study is the reproducibility of the data due to the dependence of the signal on specific MR equipment. This limit was in part overcome as the evaluation of the relative importance that each MR signal acquired in predicting the proper CAS group was assessed by means of a robust statistical method[16]. Furthermore, since SIR with contrast signals were defined as a ratio, the presence of correlations with CAS would be more reliable as objective and reproducible indicators. Therefore, improvements in reproducibility and the development of a common scale for orbital tissue evaluation, even in different MR systems, currently represents one of the most important priorities. As recommended by Cakirer et al.[12], our report contributes to use and improve this technique in order to predict the severity, type of treatment, and prognosis of the disease.

In conclusion, our study supports the diagnostic accuracy of the CAS and implements its prediction capabilities, in order to fit imaging and clinical evaluation with more strength. Therefore, the final results can be a more objective assessment and fair treatment settings or even pre-clinical information in patients with Graves' disease.

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