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DIAGNOSTIC NEURORADIOLOGY

Diagnostic accuracy of short-time inversion recovery sequence in Graves' ophthalmopathy before and after prednisone treatment

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Abstract
Introduction In Graves' Ophthalmopathy, it is important to distinguish active inflammatory phase, responsive to immunosuppressive treatment, from fibrotic unresponsive inactive one. The purpose of this study is, first, to identify the relevant orbital magnetic resonance imaging signal intensities before treatment, so to classify patients according to their clinical activity score (CAS), discriminating inactive (CAS<3) from active Graves' Ophthalmopathy (GO) (CAS>3) subjects and, second, to follow post-steroid treatment disease.
Methods An observational study was executed on 32 GO consecutive patients in different phases of disease, based on clinical and orbital Magnetic Resonance Imaging parameters, compared to 32 healthy volunteers. Orbital Magnetic Resonance Imaging was performed on a 1.5 tesla Magnetic Resonance Unit by an experienced neuroradiologist blinded to the clinical examinations.
Results In pre-therapy patients, compared to controls, a medial rectus muscle statistically significant signal intensity ratio (SIR) in short-time inversion recovery (STIR) (long TR/TE) sequence was found, as well as when comparing patients before and after treatment, both medial and inferior rectus muscle SIR resulted significantly statistically different in STIR. These increased outcomes explain the inflammation oedematous phase of disease, moreover after steroid administration, compared to controls; patients presented lack of that statistically significant difference, thus suggesting treatment effectiveness.
Conclusion In our study, we proved STIR signal intensities increase in inflammation oedematous phase, confirming STIR sequence to define active phase of disease with more sensibility and reproducibility than CAS alone and to evaluate post-therapy involvement.

Keywords Graves' Ophthalmopathy · Oedematous phase · SIR in STIR

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Introduction

Graves' Ophthalmopathy (GO) is a chronic inflammatory autoimmune disease of periorbital tissue and conjunctiva, as well as of retrobulbar structures, e.g. extraocular muscles (EOM). The most frequent GO clinical signs are eyelid erythema, oedema, chemosis, upper eyelid retraction, proptosis (exophthalmos), restricted ocular motility as well as sight-threatening complications of compressive optic neuropathy and corneal ulcerations. Clinical manifestations of GO are evident and severe in only 3–5 % of patients. In fact, GO is

more often characterized by subclinical course, and its presentation can be heterogeneous since not all features are present in every patient [1–3].

The most important pathogenic factors are the human thyroid-stimulating hormone receptor autoantibodies (hTRAb). The autoimmune attack determines swelling of the extra-ocular muscles in association with an increase in orbital connective tissue and fat volume and consequent restrictive ophthalmoplegia [4, 5].

Two phases characterize the GO clinical course:

1. Active phase, histologically characterized by mononuclear-cells infiltrations, proliferating fibroblasts, oedema and enlargement of orbital muscles many times their normal size;
2. Inactive or chronic phase, identified by fibrosis and fatty infiltrations of muscles, causing the extension of fibrous strands into adjacent adipose tissue [1, 6].

The distinct diagnosis of classical GO is based on clinical presentation and laboratory results thus without the need for any further imaging.

Four mandatory objectives should be taken into account in the first evaluation of clinically suspected GO patients:

1. To support clinical diagnosis of GO by Imaging
2. To identify disease phase, in order to establish correct treatment
3. To assess disease severity and, therefore, indication to treatment
4. To follow post-treated disease

In this study, we have considered the validated scoring system clinical activity score (CAS), proposed by Mourits et al, to identify the disease phase distinguishing inflammatory from non-inflammatory GO [7]. In agreement with the European Groups on Graves' Orbithopathy (EUGOGO) recommendations, CAS >3 defines active GO, thus responding to radiotherapy with positive predictive value (PPV) of 65 % and negative predictive value (NPV) of 56 % [7–9].

Moreover, another scoring system is the well-known NOSPECS classification, first introduced by Werner in 1969, representing a summary of signs and symptoms further modified in 1977. This classification system categorizes thyroid-associated orbitopathy (TAO) patients in six different classes and is still used today, although minor changes in clinical disease, as well as active and quiescent phases of TAO, are difficult to distinguish through NOSPECS criteria. [10, 11].

The aim of this study is, first, to identify the most relevant pre-treatment orbital MRI signal intensities, on short-time inversion recovery (STIR) with long repetition time (TR)/echo time (TE) and on contrast-enhanced T1 sequences with fat saturation, performed within the same day of patient's clinical evaluation, so to best discriminate patients presenting a CAS <3 (suspected non-inflammatory or inactive GO) from patients with a CAS >3 (suspected inflammatory or active GO) and, second, to follow post-treatment disease. Further, diagnostic advantages in the evaluation of GO and improvement of accuracy in the detection of the disease activity by orbital MRI have also been described.

Materials and methods

Patients characteristics, protocols and clinical evaluations

Between October 2011 and November 2012, an observational study was conducted on thirty-two diagnosed GO consecutive patients (12 males and 20 females, mean age of 56.81 years) in different phases of thyroid disease, derived from clinical (Table 1) and orbital MRI signs. These patients were examined after treatment too. Moreover, thirty-two normal volunteers (12 males and 20 females, mean age of 51.20 years) were enrolled in the study, as control group. MRI signal intensities ascertained from healthy volunteers played an important role as they contributed to a more heterogeneous sample, allowing robust results to be carried out.

The inclusion criteria were ocular symptomatology in patients exhibiting a proved history of Graves' thyroid disease or even confirmed by related clinical and laboratory signs and above all presenting with bilateral manifestation. Healthy volunteers showed normal MRI scans.

Exclusion criteria were orbit diseases such as trauma, optic neuropathy, other inflammatory diseases of unknown origin, previous orbital radiotherapy or surgery, previous immunosuppressive steroid and antithyroid treatments lasting more than 12 weeks before MRI examination.

All patients, as well as volunteers, gave informed consent to take part in the contrast-enhanced orbital MRI studies. The protocol was approved by the local ethical board in our hospital and therefore has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Patients were clinically observed through CAS by two different operators one by one (blind), assigning a rating for each

Table 1 Patients' clinical and orbital MRI signs

	Range (min–max)	Median	Reference values
TSH (UI/ml)	0.001–3.19	0.7	0.4–4.0
FT3 (pg/ml)	2.6–9.60	3.8	1.5–5.9
FT4 (pg/ml)	6.8–21.7	11.9	5.2–15.8
hTRAb (UI)	0.1–46	7.65	<1.5

Males 12 (37.5 %), females 20 (62.5 %)

parameter and finally calculating the total score in relation to the scheme in Table 2.

All patients were subjected to a 6-month MRI evaluation follow-up, after a 3-month treatment consisting of intravenous administration of metilprednisone 500 mg twice per day a week for 12 weeks, followed by oral prednisone tapering therapy for 2 months.

MRI analysis

All patients were subjected to Magnetic Resonance Imaging within the same day of the clinical evaluation. Orbital MRI was performed on a 1.5 tesla MRI unit (Magnetom Symphony, Siemens Medical Systems, Erlangen, Germany) with an Imaging protocol consisting of the following sequences: axial turbo spin-echo (TSE) T2-weighted images (parameters: repetition time/echo time/Nex=3350/116/2 with a 259×384 matrix, field of view (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, inversion time 50 ms), 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, acquired on a plane perpendicular to the optic nerve (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), and axial 3D fat-suppressed T1-w volumetric interpolated breath-hold examination (VIBE) images (parameters: repetition time/echo time/Nex=8/2,46/3 with a 205×256 matrix, FOV 200 mm, one slab with 52 slices per slab and 1-mm slice thickness without gap).

Table 2 List of scores attributable to each parameter to calculate CAS value

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

Clinical activity score (CAS) (amended by EUGOGO after Mourits et al [7]): 1, spontaneous orbital pain; 2, Gaze evoked orbital pain; 3, eyelid swelling that is considered to be due to active (inflammatory phase) GO; 4, eyelid erythema; 5, conjunctival redness that is considered to be due to active (inflammatory phase) GO; 6, chemosis; 7, inflammation of caruncle OR plica; 8, increase of >2 mm in proptosis; 9, decrease in uniocular ocular excursion in any one direction of >8°; 10, Decrease of acuity equivalent to 1 Snellen line. For initial CAS, only score items 1–7; Patients assessed after follow-up can be scored out of 10 by including items 8–10

Contrast-enhanced images were obtained immediately following intravenous (IV) administration of 0.1 ml/kg of gadobutrol 1.0 mol (Gadovist, Bayer Schering Pharma, Berlin, Germany) consisting of axial 3D fat-suppressed T1-w VIBE images and coronal fat-suppressed T1-w images copying the same parameters as the pre-contrast phase.

MRI scans were assessed by an experienced neuroradiologist blinded to clinical examinations.

Since GO most frequently involves the inferior and medial rectus muscles, as demonstrated in literature [4, 6, 12], the neuroradiologist positioned region of interests (ROIs) avoiding the Magnetic inhomogeneity artifacts from the bone/air of maxillary sinus. ROIs were drawn around the inferior and medial rectus muscles on coronal acquisitions, from anterior origin of the muscles to the orbital cavity apex, considering the so-called 'hot spot' method [13] where hot spot is defined as the highest-signal area within the most inflamed muscle. The values in the highest-signal-intensity area were calculated, and the resulting 'average' value [13] was considered together with its corresponding standard deviations. This second method represents the mean signal intensity over the whole cross section of the most inflamed extra-ocular muscle at the hot spot. The most inflamed muscle was selected as the one with the highest-signal intensity on STIR sequence in MRI.

This evaluation was performed by positioning ROIs in the same position before and after treatment. These measurements were repeated two times to make results more reproducible, thus showing no significant differences in the two evaluations.

Moreover, these measured signal intensities were set in proportion to those of the ipsilateral temporal muscle to calculate the signal intensity ratio (SIR), a more objective and reproducible indicator. The temporal muscles were considered as reference standard since they are not involved in Graves' disease and because of their structural similarity and close anatomical relationship to the EOM (Figs. 1, 2, and 3) [4, 6].

Therefore, a wide number of single-muscle variables were obtained in both patient and volunteer groups considering SIR related to FS T2- and to gadolinium-enhanced FS T1-weighted images.

Statistical analysis

Statistical analysis was performed using SPSS 20 (Statistical Package for Social Science) software.

All MRI signal intensities were reported as mean standard deviation (SD), and both examined muscle signal intensity ratio (SIR) referred to the ipsilateral temporal one were pointed out.

CAS, STIR and enhanced T1 inferior and medial rectus muscle signal intensity ratios, normalized to ipsilateral temporal muscle, were evaluated on group analysis, using the paired samples *t* test, before and after treatment. The same

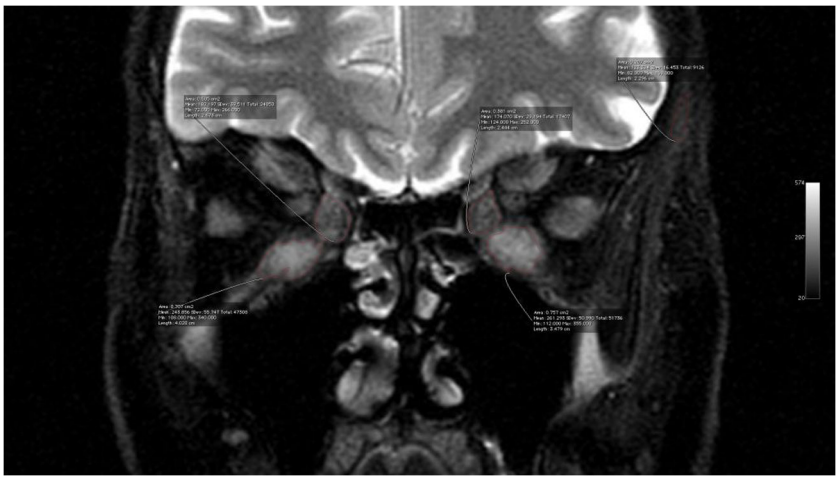

Fig. 1 Coronal T2 FS image showing ROI on extraocular muscles

parameters entered into the Correlation Analysis and were performed using the Spearman test.

Moreover, a Multiple Regression Analysis was assessed considering MRI measurements as variables to estimate the most significant predictive value resulting from the examined Magnetic Resonance sequences.

A p value of <0.05 was considered as significant.

Results

Among the thirty-two GO patients, most presented over 3 points CAS (n=31), while only one had a less 3 points CAS (n=1). Those patients with CAS >3 presented a range value from 3 to 5 mean (M)±standard deviation (SD), 4.4±0.68.

Obviously, all thirty-two normal volunteers had a CAS value of 0.

From now onwards, we refer to each MRI signal intensity according to its short notation (Table 3), arbitrary defined for statistical analysis. Table 4 (paired samples test) shows the means, standard deviations (SD) and confidence interval of difference of MRI pre- and post-therapy signal intensities studied in GO patients and controls as well as their full interchange.

In our group, most of the examined patients (n=31) showed post-treatment regressive symptoms, clinically evaluated and proved by the correlated CAS range value included between 1 and 4 (2.58±0.72).

When comparing pre versus post-treated patients, medial rectus signal intensity ratios (SIR) from cross-sectional area on enhanced T1 sequence (Pre_Rmed SIR T1 + c.a.) resulted significantly higher (p≤0,038) than post-treatment SIR (Post_ Rmed SIR T1 + c.a.), also, pre-therapy medial rectus muscle SIR measured in STIR (Pre_Rmed STIR SIR) resulted significantly increased SIR (p≤0.001) than the post-therapy SIR (Post_ Rmed STIR SIR), as well as inferior pre-treated group rectus muscle signal intensity ratios (p≤0.00001) in STIR (Pre_Rinf STIR SIR) were higher than that of the post-treated one (Post_ Rinf STIR SIR).

Comparing pre-therapy patients to controls (Fig. 4), medial rectus cross-sectional area SIR in STIR (Pre_Rmed STIR SIR) resulted significantly higher SIR (p≤0.0002) together with

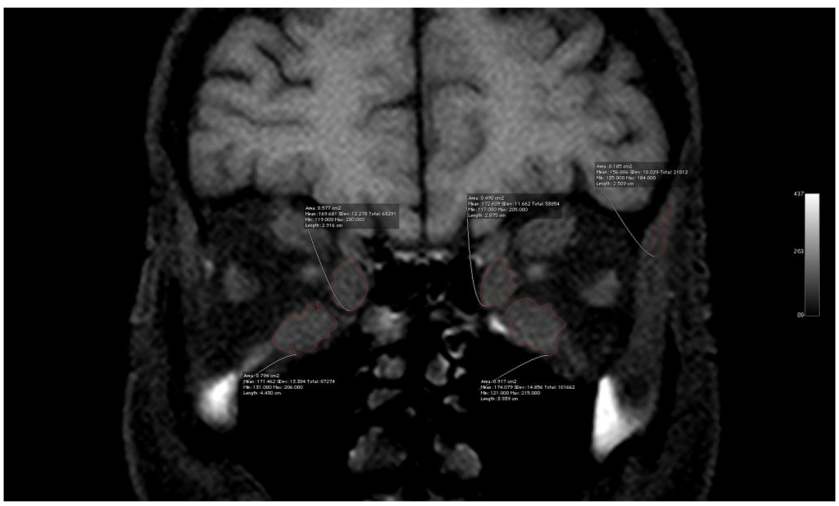

Fig. 2 Coronal FS T1-unenhanced image showing ROI on bilateral inferior and medial rectus muscles

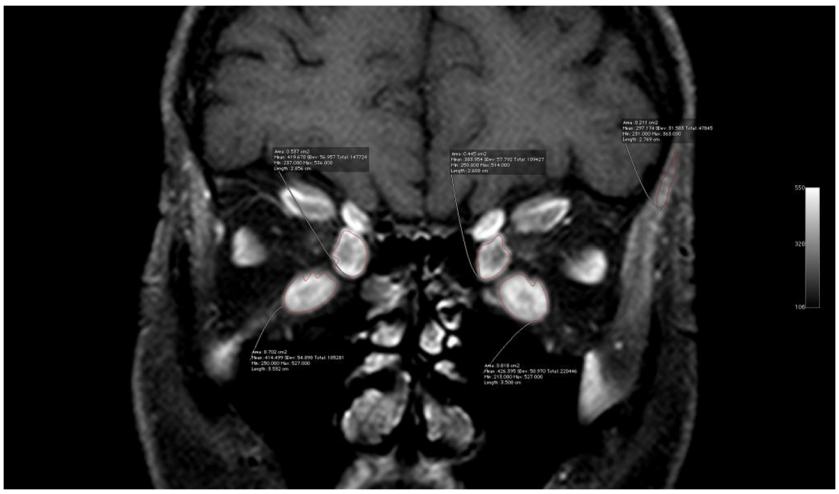

Fig. 3 Coronal FS T1-enhanced image showing ROI on inferior and medial rectus muscles

more significantly increased ($p \leq 0.002$) inferior rectus muscle SIR (Pre_Rinf STIR SIR); similarly, on enhanced T1 sequence, medial rectus SIR significantly increased (Pre_Rmed SIR T1 + c.a. ; $p \leq 0.00001$) as well as the inferior rectus muscle SIR (Pre_Rinf SIR T1 + c. a. ; $p \leq 0.00001$).

Comparing treated patients to controls, the enhanced T1 medial rectus cross-sectional area SIR (Post_Rmed SIR T1 + c.a.) was found significantly higher ($p \leq 0.0004$) than the one (Norm_Rmed SIR T1 + c. a.) in volunteers; similarly, results are derived from Post_Rinf SIR T1 + c. a., showing a higher statistical value ($p \leq 0.0003$) than the one in controls (Norm_Rinf SIR T1 + c. a.). However, when compared to controls, no statistical significance was derived between both post-treatment STIR medial and inferior rectus muscle SIR (Post_Rmed STIR SIR, $p \leq 0.238$; Post_Rinf STIR SIR, $p \leq 0.642$) and the related SIR in volunteers.

In the pre-therapy group, medial and inferior rectus muscle CAS values significantly correlated with corresponding SIR mean values both on enhanced T1 and STIR sequence, as showed respectively for Pre_Rmed SIR T1 + c.a. ($p<0.007$), Pre_Rinf SIR T1 + c. a. ($p<0.002$), Pre_Rmed STIR SIR ($p<0.001$) and Pre_Rinf STIR SIR ($p<0.017$). Moreover, MRI STIR medial and inferior rectus muscle signal intensities significantly correlated with the equivalent intensities on enhanced T1 sequence (SIR T1 + c. a., $p<0.002$); data not detected after treatment.

Furthermore, it was ascertained that Rmed STIR SIR had the highest discriminatory power of 0.905 (95 %, confidence interval (CI)=[0.828–0.982]) in classifying CAS >3 patients, acquiring both high sensitivity and specificity (SE 1.00 and SP 0.78), at the optimal cut-off of 2.23, whilst Rinf SIR T1 + c.a. had a discriminatory power of 0.843, (95 %, CI=[0.745–0.941]), acquiring a sensitivity of 0.75 and a specificity of 0.78, at the optimal cut-off of 1.71.

Table 5 shows all the MRI signal discriminatory powers and the related optimal cut-off.

Therefore, a patient presenting a Rmed STIR SIR ≥2.23 would be classified into CAS >3 group, only with one wrong classification (false-positive) on five measurements; however, even if Rinf SIR T1 + c.a. showed the same specificity, its sensibility of 75 % may be considered unsatisfying.

By defining the 'stepwise' procedure based on the multiple linear regression model, Rmed STIR SIR and Rmed SIR T1 + c.a. presenting a multilinear regression coefficient of $R=0.3907$ (standard error 0.167) and $R=1.07$ (standard error 0.517) were found to be the most significant predictors.

Moreover, D' Agostino-Pearson test on residuals resulted insignificant ($p=0.9931$, multiple correlation coefficient of 0.63), suggesting a very good model fitting and the respect of normality assumption. After therapy, CAS values ranged from 1 and 4 (M=2.58 and SD=0.72).

Table 3 List of MR signal notations

Rinf STIR SIR	Signal intensity ratio in STIR sequences in inferior rectus muscle
Rmed STIR SIR	Signal intensity ratio in STIR sequences in medial rectus muscle
Rinf SIR T1+ c.a.	Enhanced T1 signal intensity ratio of the inferior rectus muscle
Rmed SIR T1 + c.a.	Enhanced T1 signal intensity ratio of the medial rectus muscle

c.a. Contrast agent

Discussion

Symptomatic patients presenting the active phase of disease more often report dry and gritty ocular sensation, photophobia, excessive tearing, double vision and a pressure sensation behind the eyes. Moreover, suddenly appeared or modified altered appearance and double vision are specific for active disease. Particularly, worsening on waking, eventually

Table 4 Paired samples test

Pairs		Differences					t	DF	*p* (two-tailed)
		Mean	SD	Standard error of the mean	95 % Confidence interval of the difference				
					Lower	Upper			
1	Pre_RmedSIRT1 + c.a. and Post_Rmed SIR T1 + c.a.	−,24	,63	,11	−,47	−,01	−2,16	31	,038
2	Pre_Rinf SIR T1 + c.a. and Post_Rinf SIR T1 + c.a.	−,20	,63	,11	−,43	,023	−1,83	31	,076
3	Pre_Rmed STIR SIR and Post_Rmed STIR SIR	1,10	,92	,16	,77	1,43	6,77	31	,001
4	Pre_Rinf STIR SIR and Post_Rinf STIR SIR	,73	,80	,14	,44	1,02	5,15	31	,00001
5	Pre_Rmed SIR T1 + c.a. and Norm_Rmed SIR T1 + c.a.	,35	,46	,08	,18	,52	4,29	31	,00001
6	Pre_Rinf SIR T1 + c.a. and Norm_Rinf SIR T1 + c. a.	,36	,42	,07	,21	,51	4,81	31	,00001
7	Pre_Rmed STIR SIR and Norm_Rmed STIR SIR	1,24	1,18	,21	,81	1,67	5,91	31	,0002
8	Pre_Rinf STIR SIR and Norm_Rinf STIR SIR	,80	1,3	,23	,33	1,27	3,47	31	,002
9	Post_Rmed SIR T1 + c.a. & Norm_Rmed SIR T1 + c.a.	,60	,61	,12	,38	,81	5,55	31	,0004
10	Post _Rinf SIR T1 + c.a. and Norm_Rinf SIR T1 + c.a.	,56	,55	,10	,37	,76	5,81	31	,0003
11	Post _Rmed STIR SIR and Norm_Rmed STIR SIR	,14	,64	,11	−,10	,37	1,20	31	,238
12	Post _Rinf STIR SIR and Norm_Rinf STIR SIR	,07	,82	,14	−,23	,36	,47	31	,642

*Pre_* Pre-treatment patients, *Post_* post-treatment patients, *Norm_* healthy volunteers, *DF* degree of freedom

painful, intermittent diplopia 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), determining optic nerve compression in the orbital apex.

Early diagnosis has primary importance in GO management, avoiding permanent injuries to the patients (proptosis, sight impairment). Medical corticosteroid therapies in early stages of disease reduce the inflammation and let the GO remission, though useless in fibrotic end-stages. So, early diagnosis and treatment would cause at least partial remission, up to 65 % of cases [14].

The CAS scoring system evaluates disease activity and response to immunosuppressive therapy but actually does not fully describe the overall status of GO [3, 15]. This method is widely used through the reported correlation between pre-treatment CAS and post-immunomodulating therapy outcome (retailed positive predictive value of 80 % and negative predictive value of 64 % [16]). Anyway, Mourits' study never demonstrated CAS <3 patients having inactive GO [7, 15], especially since in Mourits' report, 10 of 13 CAS <3 patients responded to immunosuppressive treatment [3, 15, 17] therefore showing that CAS alone could not detect active GO adequately [15].

Significant CAS limits consist in the lack of evaluation of various inflammation levels as well as its operator-dependent low sensibility and subjectivity [2, 5, 15]. Furthermore, the score attributes the same value to various different factors, thus missing diversifications. Therefore, CAS requires the integration with other modalities [15, 18, 19], as orbital

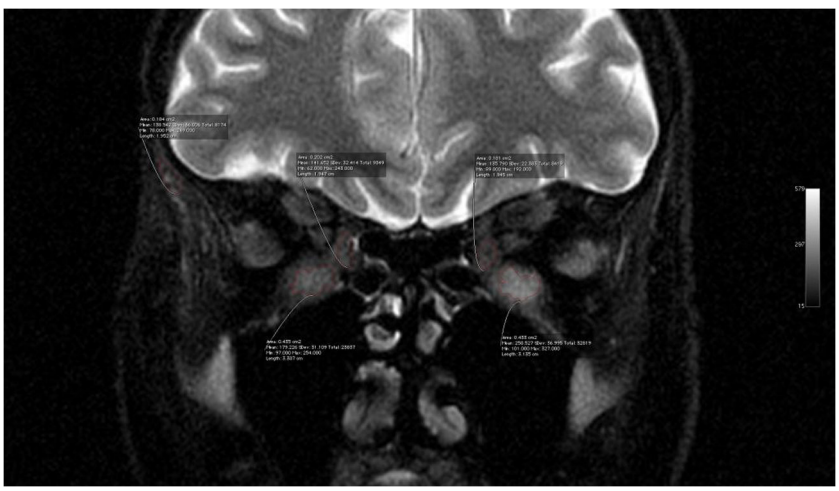

Fig. 4 Coronal T2 FS image after corticosteroid therapy showing ROI on extraocular muscles

Table 5 Discriminatory power and diagnostic test characteristics

MRI measurements	AUC [95%CI]	Optimal cut-off	Sensibility (SE)	Specificity (SP)
Rinf STIR SIR	0,756 [0.637–0.875]	1.79	1.00	0.50
Rmed SIR STIR	0,905 [0.828–0.982]	2.23	1.00	0.78
Rinf SIR T1 + c.a.	0,843 [0.745–0.941]	1.71	0.75	0.78
Rmed SIR T1 + c.a.	0,794 [0.683–0.905]	1.91	0.50	0.97

ecography and CT/MRI to determine disease activity and severity [20].

Orbital CT is useful in detecting extra-ocular muscle enlargement and proptosis degrees, but not muscle composition and the inflammation phase; moreover, consequent crystalline irradiation prevents its use in follow-up.

Computed tomography (CT) is an invaluable Imaging modality in the evaluation of TAO, using X-rays and their variable absorptions within the many orbital structures to quantify and qualify orbital pathologies. CT as a tool to quantify muscle enlargement, similar to ultrasound (US), is therefore a valuable aid to the clinical exam. Studies suggest parallels between total extraocular muscle volumes and medial rectus muscle width at the mid-orbital level, and medial rectus muscle width with clinical extraocular muscle restriction, periorbital oedema, and optic neuropathy in those with TAO. Unlike US and MRI, CT involves radiation and cannot precisely assess disease activity, in fact, even if oedema of extra-ocular eye muscles or of intra-orbital or periorbital can be recognized, oedema involving optic nerve is not detected. CT, however, remains a fast, available, relatively inexpensive, and highly reproducible test, although the possible assessment of the optic nerve itself is less specific than that of MRI. Contrast administration is oftentimes reserved, then, for cases of optic nerve pathology or vision loss [21]. Moreover, after iodinated contrast agent administration, CT can show an active inflammation, but since the hyperthyroid metabolism of many patients, contrast administration should be avoided (27).

Instead, MRI gives all the information of both ecography and CT, discovering muscle oedema, because of its intrinsic capability to characterize tissue. Many recent studies are validating the utility of MRI in GO because of detailed orbital anatomy Imaging (characterizing high soft tissue, through thin sections and multiplanar reconstructions), lack of ionizing radiation and examination reproducibility. So the ability to differentiate inflammatory from fibrotic orbital tissue alterations allows to choose the right treatment; moreover, Imaging is always required in doubtful cases to exclude any other pathology and in evaluating the clinical suspicion of optic nerve involvement, thus to plan orbital decompression [12]. Anyway, as already described, classical GO presentation does not need any further distinct Imaging finalized to diagnosis.

In GO, the standardized MRI protocol includes fast spin-echo T1-w and T2-w STIR sequences on 3-mm slice thickness transverse and coronal planes [12].

In our study, when comparing pre-treated patients to controls, medial and inferior rectus muscle intensities were significantly different in both STIR (Rmed STIR SIR, $p=0.0002$; Rinf STIR SIR, $p=0.002$) and enhanced T1 sequences (Rmed SIR T1 + c.a., $p=0.00001$; Rinf SIR T1 + c.a., $p=0.00001$). This result attests the utility of these sequences in detecting extra-ocular muscle oedema, especially referring to the relaxation T2 time found longer than in healthy controls [5, 15, 22], confirming EOM inflammatory involvement [1–4, 12, 13] occurring earlier than ocular symptomatology, as well as showing at least one EOM MRI involvement in 50 % of patients on subclinical phase [23].

Furthermore, in the pathologic group, both muscle SIRs in STIR sequence significantly correlated with enhanced T1 one ($p=0.002$), leading to suppose STIR to be the handler than enhanced T1, thus interestingly avoiding contrast medium. Moreover, medial rectus muscle signal intensity ratio in STIR sequence (Rmed STIR SIR) was found to be the most capable MRI parameter to assign a subject to CAS <3 or CAS >3 group at the optimal cut-off value of 2.23, then, presenting the highest proportion of identified actual positives [Sensitivity (SE) 1.00] and the lowest proportion of false positives [high Specificity (SP) 0.78].

MRI is able to differentiate the two disease states, demonstrating extraocular muscle interstitial oedema on coronal STIR sequences in the active disease.

Inflamed extraocular muscle signal intensity is known to correlate with CAS, therefore having a strong impact on the two treatment options: immunosuppressants or surgery [12, 15, 22, 24]. CAS alone could not detect active GO sufficiently, and orbital MRI could predict the response to corticosteroid therapy more accurately than CAS alone [15]. Although the 'fine tune' of thyroid values is often enough, management of GO is mainly based on three treatment arms:

1. Treatment of the underlying dysthyroid disease and maintenance of a euthyroid state (anti-thyroid drugs, total thyroidectomy, and/or ^{131}radioiodine)
2. Immunosuppression with high-dose corticosteroids and/or orbital radiotherapy
3. Surgery (sequential orbital decompression, squint and lid surgery)

Moreover, T2 sequence lets us observe therapeutic effect [25]; as found in our study, when comparing steroid-treated

patients to controls, in fact, both medial and inferior rectus muscle signal intensities on STIR did not show any statistically significant difference, confirming therapy effectiveness; anyway, this result is in contrast with the increase in both muscle different signal intensities on enhanced T1. This outcome could be justified by the unclear role of T1 sequence contrast enhancement of EOMs in GO acute inflammatory stage, determined by the multitude of pathogenetic factors (microcirculation injury due to muscle enlargement and inflammatory infiltration versus vascular congestion, caused by oedema and interstitial inflammatory infiltration [4, 6, 10, 11]), thus leading to the diagnostic accuracy of STIR sequences in detecting both active and inactive phases, with the outstanding advantage of avoiding contrast injection.

Eye muscle oedema is observed in the subclinical stage of the disease, usually characterized by eyelid retraction, larger lid fissure and decreased eyelid impact frequency. This leads to the great aim to detect those patients at risk and responders to immunosuppressive treatment in early and even pre-clinical stages in order to prevent progression and deterioration of pre-clinical GO. The diagnosis actually relies on the well-known risk factors like history, symptoms, clinical signs, smoking, and serology for the development or deterioration of GO. Therefore, a MRI SIR cut-off value is considered an 'objective' method able to enhance the reliability of these risk factors. From our data, we statistically calculated a cut-off value of 2.23 for a CAS ≥3, which usually defines active GO.

As reported in literature, the existence of subclinical stage of this condition is well known, but in our study, patients presented bilateral clinical signs, so they could not be considered in this pathological phase. Moreover, as previously described in the pre-therapy group, medial and inferior rectus muscle CAS values significantly correlated with corresponding SIR mean values both on enhanced T1 and STIR sequence.

The valid indication of MRI supporting clinical assessment in classical presentation of GO is represented by the possibility to determine disease activity in particularly severe cases. Many recent studies are validating the utility of MRI in GO because of detailed orbital anatomy Imaging (characterizing high soft tissue, through thin sections and multiplanar reconstructions), lack of ionizing radiation and examination reproducibility [12].

Response to immunosuppressive therapy in correlation to MRI derives from the previously described T2 sequence able to show immunosuppressive therapeutic effect [15, 25]. In fact, in our study, we proved that both the medial and inferior rectus muscle signal intensities on STIR did not show any statistically significant difference when comparing steroid treated patients to controls, thus confirming therapy effectiveness. Moreover, the significant improvement after treatment demonstrates that orbital MRI imaging combined with CAS can detect active GO more sensitively than CAS alone, and also predict the response to IV or oral GC for GO more accurately than CAS alone. This leads to the main role of MRI in follow-up, to control the muscle signal intensity changes related to therapeutic effect.

From the clinical findings and orbital imaging, we know that in GO, inferior and internal EOMs are more frequently involved than the superior, lateral, and oblique muscles. In our study, when comparing to controls, a significant statistical difference resulted from pre-treated medial and inferior rectus muscle towards the non-pathologic ones in both STIR and enhanced T1 sequences, thus explaining the utility of the relaxation T2 time [5, 15, 22], confirming EOM inflammatory involvement [1–4, 12, 13] occurring earlier than ocular symptomatology.

Furthermore, in the pathologic group, medial rectus muscle signal intensity ratio in STIR sequence (Rmed STIR SIR) was found to be the most capable MRI parameter to assign a subject a CAS >3 group at the optimal cut-off value of 2.23, leading to its interpretation as the most significant muscle intensity to refer to.

Our study is not without limitations. The first one is the reproducibility of the data, due to the signal dependence on specific MRI equipment. This limit could be in part overcome because of the evaluation of signal intensity ratio in STIR, assessed by means of a robust statistical method. Furthermore, since SIR represents a more objective and reproducible measure, our statistical comparison results are more reliable. Therefore, one of the study priority is actually represented by the reproducibility improvement and the development of orbital tissue evaluation common scale, even on different MRI equipment. The second one is represented by Imaging data elaboration executed by only one neuroradiologist, placing ROIs in pre- and post-treatment MRI.

Conclusion

In our study, we proved that STIR signal intensities increase in inflammation oedematous phase of disease even though on T1-w images, gadolinium contrast enhancement in combination with fat saturation represents a helpful tool to detect extraocular muscle or eyelid intense enhancement [6, 12, 26]. So we bear out MRI STIR sequence to establish activity phase of disease with more sensibility and reproducibility than CAS alone [15] and to evaluate post-therapy EOM involvement, supported by the related obtained optimal cut-off of 2.23.

As recommended by Cakirer et al. [6], our report contributes to improve the use of this technique to predict the severity, type of treatment, and prognosis of the disease.

In conclusion, our study supports the diagnostic accuracy of STIR signal intensity ratios in identifying active inflammatory

changes as well as in assessing follow-up and the treatment response, implementing MRI capability, so underlining its well-known lack of ionizing radiation and above all the proved contrast medium sparing, in order to fit Imaging together with clinical evaluation in a more evident way.

Conflict of interest We declare that we have no conflict of interest.

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