Short-tau inversion-recovery (STIR) sequence magnetic resonance imaging evaluation of orbital structures in Graves’ orbitopathy

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Objective: To evaluate the orbital structures and to establish correlations with disease activity and severity in patients with Graves’ hyperthyroidism and orbitopathy (GO) using short-tau inversion-recovery (STIR) sequence magnetic resonance imaging (MRI).

Methods: Observational, cross-sectional, case-control study. Twenty-eight patients with euthyroid status after treatment and GO (GO group) and 15 control subjects (control group) were included. Patients underwent a complete ophthalmologic examination and were then assessed according to the EUGOGO (European Group on Graves’ Orbitopathy) recommendations. Muscle cross-sectional areas, orbital tissue volumes and the signal intensity ratio (SIR) from the most inflated extraocular muscle were calculated using a STIR-T2 weighted sequence MRI. Correlations between clinical and MRI measurements were analyzed.

Results: Enlargements in the cross-sectional areas and volumes were significant for most EOMs (p<0.001), but not for the lateral rectus muscle cross-sectional area. A significant difference in SIR values between patients with GO and control subjects (p<0.001) was found. No significant correlations were found between muscle cross-sectional areas, orbital tissue volumes, SIR values and the clinical activity parameters.

Conclusions: Given the small sample size of our study, with the obvious need for larger clinical trials, we were unable to demonstrate that the STIR sequences in MRI are a sensitive tool in assessing patients with longstanding GO in order to detect inflammatory changes and activity follow-up, possibly because it is in inactive phase. Meanwhile, it is still necessary to continue performing a thorough clinical evaluation in the therapeutic management of GO.

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Palabras clave:
Orbitopatía de Graves
Músculos extraoculares
Resonancia nuclear magnética
Exoftalmos
Actividad clínica (CAS)

Evaluación de la órbita mediante secuencias short-tau inversion-recovery (STIR) en resonancia nuclear magnética en la orbitopatía de Graves

Resumen

Objetivo: Evaluar las estructuras orbitarias mediante secuencias short-tau inversion-recovery (STIR) en resonancia nuclear magnética (RNM) y establecer correlaciones con los signos de actividad clínica (CAS) y severidad en pacientes con hipertiroidismo y orbitopatía Graves (OG).

Métodos: Estudio clínico de casos y controles, observacional y transversal. Veintiocho pacientes en estatus eutiroido post-tratamiento y OG (grupo OG) y 15 sujetos controles (grupo control) fueron evaluados. Se realizó una exploración oftalmológica completa a los participantes y se determinó la actividad y severidad de la OG, según recomendaciones EUGOGO (Grupo Europeo en Orbitopatía Graves). Áreas de sección transversal de los músculos extraoculares (MOE), volúmenes de los tejidos orbitarios y ratios (SIR) de intensidad de señal del MOE más inflamado fueron calculados usando secuencias STIR-T2 en RNM. Se establecieron correlaciones entre variables.

Resultados: Los incrementos en las áreas de sección transversal y volúmenes fueron significativos en la mayoría de los MOE (p<0,001), pero no en el área de sección transversal del recto lateral. Se encontraron diferencias significativas en valores SIR entre ambos grupos (p<0,001). No se establecieron correlaciones significativas entre la totalidad de sección transversal de los MOE, volúmenes de los tejidos orbitarios, valores SIR y signos de actividad clínica.

Conclusiones: Dado el tamaño muestral del estudio, con la necesidad obvia de estudios más amplios, no podemos demostrar que las secuencias STIR en RNM sean una herramienta sensible para evaluar cambios inflamatorios y actividad clínica en la OG de larga evolución, posiblemente debido a que no ha una fase inactiva.

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Introducción

Graves’ orbitopathy (OG) is a self-immune process associated to thyroid disease that involves the retro-ocular space. In most cases, its diagnostic is based on the coexistence of typical ocular signs and hyperthyroid symptoms, abnormal thyroid functional tests or high antibodies level. OG is characterized by inflammation, congestion, hypertrophy and fibrosis of orbital fat and muscles, involving thickening of tissue and particularly extrinsic ocular muscles (EOM). The evaluation of OG activity is important to predict medical treatment results because it is more effective in the active phase. Mourits et al. established clinical activity signs (CAS) in OG and found they were related to immunosuppressant treatment response. However, in many patients the OG activity is not clinically clear because both active and inactive OG can exhibit severe ocular signs, making it impossible to take adequate therapeutic decisions without the help of neuroimaging techniques.

Nuclear magnetic resonance (NMR) can assist to differentiate between active and inactive OG and perhaps to select patients who would probably respond to immunosuppressant treatment. The short-tau inversion-recovery (STIR) sequences suppress the fatty signal and allows a more adequate assessment of pathological tissues. The STIR signal intensity is directly related to the increase of relaxation in T2 caused by increased actual content in tissue, and correlates with the inflammatory activity in OG. The most sensitive measurements to assess the involvement of EOM in OG were the volume and maximum cross-sectional area. Recently, Mayer et al. reported that the more inflamed EOM signal intensity correlated with CAS. However, some authors argue that the NMR study does not substitute clinical evaluation.

In this study the orbital structures were assessed with STIR sequences in NMR in patients with Graves’ hyperthyroidism and OG, establishing correlations with the activity and severity of the disease.

Patients and methods

In this observation and transversal clinical case and control study 28 consecutive patients with Graves’ hyperthyroidism and OG were assessed (OG group; 24 females and 4 males; mean age, 47.5 years; range, 26–72 years) and 15 healthy subjects (control group; 12 females and 3 males; mean age, 50.73 years; range, 35–67 years). The inclusion criteria were: patients with Graves’ hyperthyroidism and OG, in thyroid treatment and biochemical euthyroid status. The exclusion criteria were: orbital inflammations of unknown origin, euthyroid or hypothyroid OG, previous immunosuppressant treatment with steroids, previous orbital radiotherapy and orbital surgical decompression. All participants signed an informed consent. The study protocol was approved by the Ethics Committee of the Príncipe de Asturias University Hospital and the Guadalajara University General Hospital. The procedures fulfilled the principles of the Helsinki Declaration. All the participants underwent a complete ophthalmological
exploration, assessing OG activity and severity on the basis of the EUGOGO group (European Group for Graves Orbitopathy).15

**Nuclear magnetic resonance**

A Philips Gyroscan NRM units were utilized (Philips Medical Systems, Best, The Netherlands) operating at 1.5 T with surface antenna. The study protocol included images (FFE-3D)-T1 in the axial plane, images (TSE)-T2 in the axial plane and a sequence of images (STIR)-T2 with suppression of fat in the coronal plane. These images were analyzed in a semi-automatic manner (ViewForum R5.1V1L1 SP1, Philips Systems).

In TSE-T2 axial sequences in the neurocular playing a line was drawn up between the frontal processes and the perpendicular distance in millimeters from the angle of the cornea to the line, taken as a measure of exophthalmos. In coronal STIR-T2 sequences at 10 mm of the posterior pole of the ocular globe the EOM transversal section areas were determined for each subject of the study12; and the volumes were obtained by multiplying the sum of all the transversal section areas by the thickness of the cut and gap. Accordingly, the following EOM measurements were calculated: upper eyelid/upper rectus elevator complex, middle rectus (MR), inferior rectus (IR), lateral rectus (LR) and upper oblique. In addition, the total area of EOM was calculated, total orbitary volume (TOV), total muscular volume (TMV), total fat volume (TFV) and muscular and fat volume (MFV), obtained by adding TMV and TFV.

Similarly, in coronal STIR-T2 sequences the maximum signal was determined in the most inflamed EOM utilizing a standard triangular interest region of 1 mm² and calculating its ratio with the signal intensity of the ipsilateral temporal muscle (ITM), which was taken as a standard reference as it is never involved in OG (Fig. 1).

**Statistical analysis**

The relationship between a categorical and quantitative variables was analyzed comparing mean values with the t for Student test if the normality and the variance in quality conditions were fulfilled; otherwise, the U Mann–Whitney nonparametric test was applied. The relationship between two quantitative variables was assessed with Pearson’s or Spearman’s correlation coefficient. Values of p < 0.05 were taken to be statistically significant. The statistical data was processed utilizing SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA).

**Results**

The demographic data and clinical characteristics of patients in the OG group are shown in Table 1.

**Measures of EOM cross-section and volume measures**

In eight patients the reliability of MR volume measurements was assessed by means of the intraclass correlation coefficient (ICC). The estimated intra-observer variability was of 0.988 with CI 95% from 0.966 to 0.996, p < 0.0005.

**Fig. 2** shows the measures of these EOM cross-section and volume areas in the control and OG groups for both orbits. No statistically significant differences were observed between groups in what concerns the measures of these cross-section areas for the LR muscle but said differences were found in the rest of EOM. The volume measures in the OG group were found to be significantly increased in all EOM. In addition, in the OG group a significant correlation between the cross-section areas and volumes of the MR muscles was observed (r Spearman = 0.449, p < 0.001) and IR (r Spearman = 0.511, p < 0.0005), but not in the rest of EOM. Similarly, the overall EOM cross-section had a significant correlation with TMV (r Spearman = 0.507, p < 0.0005), and MFV (r Spearman = 0.458, p < 0.001).

**Exophthalmos and radiological measures of orbitary tissues**

Table 2 shows the mean values of exophthalmos, orbital tissue volumes and ITM in the OG and control groups for both

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**Table 1 – Clinical evaluation of patients with Graves orbitopathy.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>47.5 SD 11.53</td>
</tr>
<tr>
<td>Male/female</td>
<td>4/24</td>
</tr>
<tr>
<td>EG evolution time, years</td>
<td>5.42 SD 3.81</td>
</tr>
<tr>
<td>OG evolution time, years</td>
<td>4.28 SD 3.68</td>
</tr>
<tr>
<td>Antithyroid medication</td>
<td>25 (92.59)</td>
</tr>
<tr>
<td>Previous radium-iodine therapy</td>
<td>14/34 (40.74)</td>
</tr>
<tr>
<td>Previous thyroidectomy</td>
<td>4 (14.61)</td>
</tr>
<tr>
<td>Tobacco consumption</td>
<td>15 (55.55)</td>
</tr>
<tr>
<td>T4 levels, ng/dl</td>
<td>1.12 SD 0.94</td>
</tr>
<tr>
<td>TSH levels, mIU/l</td>
<td>1.19 SD 1.99</td>
</tr>
</tbody>
</table>

Data expressed in mean and standard deviation (SD), and percentages.

GD: Graves’ disease; GO: Graves orbitopathy; T4: thyroxine; TSH: thyrotropin.
orbits. The differences were significant for all the assessed parameters.

The exophthalmos measure had a significant correlation with several orbital tissue volume measures (Table 3) and also with the TMV/TOV ratio (r Pearson = 0.328, p < 0.05) and the MFV/TOV ratio (r Pearson = 0.449, p < 0.001), but not with the TFV/TOV ratio. These ratios were calculated to standardize the volume of each orbital tissue with TOV.

The TFV/TOV ratio was analyzed to determine the involvement of orbital tissues in orbital volume increases. The mean values of the TFV/TOV ratio were of 5.67 SD 1.16 in the control group and 5.02 SD 1.41 in the OG group (p > 0.05), indicating that the increase of TFV and TMV was proportional in patients with OG.

The ITM values exhibited a significant correlation with TMV (r Spearman = 0.388, p < 0.05) and exophthalmos (r Spearman = 0.288, p < 0.05), but not with TFV, MFV or with the overall EOM cross-section areas.

Associations between clinical activity and severity of OG and radiological measures in NMR

In our study only 18% of patients had active OG with CAS ≥ 3. No significant correlations were found between CAS and exophthalmos, overall cross-section area of EOM, TMV, TFV or ITM. On the basis of the clinical severity measures, city patients exhibited slight OG, 25 patients moderate OG and none of the patient had severe OG. The severity degree was significantly correlated with exophthalmos (p < 0.01), but not with the overall cross-section area of EOM, TMV, TFV or ITM. Table 4 shows the correlations between the various severity degrees of OG and the assessed radiological parameters.

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**Table 2 - NMR data summary: exophthalmos, volume measures and ITM values in the most inflamed EOM.**

<table>
<thead>
<tr>
<th></th>
<th>Control group (N = 30)</th>
<th>GO group (N = 56)</th>
<th>Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exophthalmos, mm</td>
<td>18.18 SD 2.26</td>
<td>23.16 SD 3.99</td>
<td>5.04 (3.47–6.60)</td>
<td>0.001</td>
</tr>
<tr>
<td>TOV, mm³</td>
<td>37.860 SD 5.500</td>
<td>42.320 SD 8.430</td>
<td>4.460 (1.070–7.860)</td>
<td>0.006</td>
</tr>
<tr>
<td>TMV, mm³</td>
<td>4.240 SD 6.200</td>
<td>5.500 SD 2.150</td>
<td>1.260 (650–1.880)</td>
<td>0.0001</td>
</tr>
<tr>
<td>TFV, mm³</td>
<td>24.040 SD 5.040</td>
<td>27.620 SD 6.540</td>
<td>3.580 (840–6.320)</td>
<td>0.012</td>
</tr>
<tr>
<td>MFV, mm³</td>
<td>28.280 SD 5.260</td>
<td>33.180 ± 8.050</td>
<td>4.890 (1.640–8.150)</td>
<td>0.002</td>
</tr>
<tr>
<td>ITM</td>
<td>2.89 SD 0.97</td>
<td>3.80 ± 0.94</td>
<td>0.9081 (0.47–1.34)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data expressed as mean and standard deviation (SD).
EOM: extrinsic ocular muscles; NMR: nuclear magnetic resonance; ITM: signal intensity ratio; TOV: total orbitary volume; TMV: total muscular volume; TFV: total fatty volume; MFV: muscular and fatty volume.

**Table 3 - Correlations between exophthalmos and volume measures in NMR.**

<table>
<thead>
<tr>
<th>Correlated variables</th>
<th>r Spearman</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exophthalmos vs TMV</td>
<td>0.339</td>
<td>0.01</td>
</tr>
<tr>
<td>Exophthalmos vs TFV</td>
<td>0.286</td>
<td>0.035</td>
</tr>
<tr>
<td>Exophthalmos vs MFV</td>
<td>0.289</td>
<td>0.032</td>
</tr>
</tbody>
</table>

NMR: nuclear magnetic resonance; TFV: total fatty volume; MFV: muscular and fatty volume; TMV: total muscular volume.

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**Figure 2 − Box diagrams (mean with interquartile amplitude) showing (A) the cross-section areas (mm²) and volumes (mm³) of extrinsic ocular muscles (EOM) in control and OG groups (Graves orbitopathy): upper eyelid elevator complex/superior rectus (GRS) (p < 0.0005 and p < 0.001, respectively), inferior rectus (IR) (p < 0.0005 and p < 0.05, respectively), median rectus (MR) (p < 0.0005 and p < 0.005, respectively), lateral rectus (LR) (p > 0.05 and p < 0.05, respectively), and superior oblique (OS) (p < 0.01 and p < 0.0005, respectively).**
Table 4 – Comparisons between GO severity and various NMR values.

<table>
<thead>
<tr>
<th></th>
<th>Palpebral aperture</th>
<th>Hertel exophthalmometry</th>
<th>Subjective diplopia</th>
<th>Keratitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r Spearman p</td>
<td>r Spearman p</td>
<td>Mean differences p</td>
<td>Mean differences p</td>
</tr>
<tr>
<td>Exophthalmos</td>
<td>0.260 0.068</td>
<td>0.569 0.001</td>
<td>2.796 0.008</td>
<td>0.116 0.886</td>
</tr>
<tr>
<td>Overall EOM</td>
<td>0.330 0.022</td>
<td>0.350 0.015</td>
<td>28.965 0.039</td>
<td>7.414 0.475</td>
</tr>
<tr>
<td>TMV</td>
<td>0.202 0.168</td>
<td>0.412 0.004</td>
<td>1.821 0.199</td>
<td>0.556 0.341</td>
</tr>
<tr>
<td>TTV</td>
<td>0.370 0.010</td>
<td>0.361 0.013</td>
<td>3.443 0.137</td>
<td>3.742 0.011</td>
</tr>
<tr>
<td>ITM</td>
<td>0.115 0.459</td>
<td>0.291 0.055</td>
<td>0.646 0.143</td>
<td>0.477 0.248</td>
</tr>
</tbody>
</table>

EOM: extrinsic ocular muscles; OG: Graves orbitopathy; NMR: nuclear magnetic resonance; ITM: signal intensity ratio; TFV: total fatty volume; TMV: total muscle volume.

* Mann–Whitney U-test.

Discussion

In our study the activity and the severity of OG in patients with Graves’ hyperthyroidism were assessed clinically and with STIR NMR images. The results revealed the absence of significant correlations between the overall EOM cross-section area and CAS. However, the overall area had a significant correlation with some severity measures such as palpebral opening, Hertel exophthalmometry and the presence of subjective diplopia. Mayer et al.14 reported that the measures of the EOM cross-section areas at the point of maximum muscle inflammation in STIR and T1 images had a poor correlation with CAS. However, in both sequences the changes in the measures of these areas did have a significant correlation with changes in CAS, supporting the idea that isolated measures of the EOM cross-section areas are not enough to establish an adequate assessment of OG clinical activity.

Other studies on associations between the muscular thickening and clinical activity in OG were not conclusive either, possibly due to the absence of uniformity in the NMR measuring methods and the difficulty in determining the EOMs16 volumes. Accordingly, EOM thickening assessment should be based on normal values obtained from control subjects within the same NMR unit. In contrast with previous studies17–19 our results reported EOM thickening in the majority of patients but without a significant correlation with CAS. One possible explanation to this is that the OG a group of our study is made up by a high number of patients with long OG evolution (mean OG evolution time: 4.28 years; range: 0.5–11 years), suggesting that the majority of these patients had entered the scarring phase thereof and therefore it is unlikely that they will be active. Accordingly, muscular volume increase would represent fibrosis and fatty degeneration of the muscles, and this of course does not influence in CAS although a certain degree of inflammation cannot be excluded. The authors believe that CAS is difficult to assess in patients with long-standing OG because it does not represent the typical inflammatory activity of the disease. For example, eyelid swelling is a difficult to interpret sign of CAS because frequently the swelling is a consequence of orbital volume increases and of fatty herniation, and this is different from eyelid infiltration edema typical of the active phase. Conjunctival hyperemia is also difficult to assess because a small palpebral retraction or exposure could cause a conjunctival injection which is unrelated to OG activity. The presence of keratitis has also been associated to conjunctival injection and exposure. For all these reasons, the authors believe that CAS is less precise to assess long-standing OG.

The coronal plane is most frequently utilized to assess the size of EOM11,20,21 because all the rectus muscles are visualized in the same image. Utilizing muscle volume ratios between patients with OG and control subjects, we found that the muscle which thickened the most was MR (ratio: 1.48) and IR (ratio: 1.36), as was also found in other studies.4,20 In addition, we found significant differences in the measures of the EOM cross-section areas and volumes with the exception of the cross-section area and volume of the LR muscle. The oblique course of EOM in the orbit would explain the distortion of its cross-section areas in the coronal plane, with LR being the most distorted muscle. Szucs-Farkas et al.12 reported that in patients with OG the volume of the rectus muscles with the exception of LR can be estimated by a simple measure of the cross-section areas in an adequately selected coronal plane. Utilizing the same plane we have shown that the measures of these cross-section areas are appropriate only to estimate the MR and IR volumes, possibly due to the small number of patients in our study.

EOM and orbitary sets are the main tissues involved in orbital content increase in OG. In this regard, previous studies have calculated the prevalence of muscle and fatty tissue increase in OG, establishing associations with the ophthalmological and endocrine characteristics of these patients.22 In our study, the participation of EOM was clearly predominant and the main cause of exophthalmos. Even though the increase of TFV exceeded the growth of TMV in absolute terms, the TFV ratio (1.15) between patients with OG and control subjects was lower than the TMV ratio (1.3). Nishida et al.24 also reported the participation of orbital fat in exophthalmos degrees in patients with OG. In contrast, Kvetny et al.15 reported diminished orbital fat volume, possibly because swollen muscles compressed orbital fat. One explanation would be that it is impossible to compare studies in which the clinical status of OG, such as severity and CAS, is not included because in Graves’
disease the muscular volume depends on the severity of the orbitopathy.

In STIR sequences the signal intensity of the most inflated EOM has been correlated with the activity of OG.\textsuperscript{10,14,25,26} In accordance with previous studies,\textsuperscript{3,14,26} our results revealed significant differences in the ITM values between patients with OG and control subjects (p < 0.0005), which suggests the presence of edema in EOM; but in our case we did not find significant correlations between the ITM values and CAS signs, which is probably due to the small sample size of our study (power test = 22%). An additional possible explanation would be that the high ITM values of our patients, most of whom had long-standing OG, match the presence of congestive orbital edema due to venous flow reduction caused by the compression effects of thickened EOMs instead of inflammatory edema. Thus, in order to differentiate between inflammation and congestion it would be more appropriate to determine the ITM values in NMR with gadolinium.\textsuperscript{26}

As for the future, it is foreseeable that new NMR technologies such as relaxometry NMR, high resolution NMR at 3.0T or NMR/positron emission tomography (NMR/PET) with the utilization of specific molecules will provide an improved assessment of OG activity. Due to the small size of this study and the obvious necessity of larger studies, we cannot demonstrate that STIR sequences in NMR are a sensitive tool to assess inflammatory changes and clinical activity in long-standing OG, possibly because it is in the inactive phase.

Conflict of interests

The authors have no conflict of interests to declare.

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