Lachrymal gland involvement in Graves' Ophthalmopathy (GO): a useful magnetic resonance imaging - derived marker of GO activity.

Gagliardo C [2*], Radellini S[1*], Morreale Bubella R[3], Falanga G[2], Richiusa P[1], Vadalà M [3], Ciresi A[1], Midiri M [2], Giordano C[1]

[1]Section of Endocrinology, Department of Health Promotion Sciences Maternal and Infantile Care, Intenal Medicine and Medical Specialities (PROMISE), University of Palermo, Italy

[2]Section of Radiological Sciences, Department of Biomedicine, Neuroscience and Advanced Diagnostics, University of Palermo, Italy

[3]Section of Ophthalmology, Department of Biomedicine, Neuroscience and Advanced Diagnostics, University of Palermo, Italy

* these authors contributed equally to this work.

Radellini Stefano, MD – Endocrinologist e-mail: rdlsfn@gmail.com

Gagliardo Cesare, MD – Neuroradiologist e-mail: cesare.gagliardo@unipa.it

Morreale Bubella Raffaella, MD – Ophthalmologist e-mail: rmorreale@email.it

Falanga Giorgia, MD – Neuroradiologist e-mail: giorgiafalanga@gmail.com

Richiusa Pierina MD – Endocrinologist e-mail: pierinarichiusa@libero.it

Vadalà Maria, MD – Ophthalmologist e-mail: maria.vadala@unipa.it

Ciresi Alessandro MD – Endocrinologist e-mail: alessandro.ciresi@unipa.it

Midiri Massimo, MD - Full Professor of Radiology e-mail: massimo.midiri@unipa.it

Giordano Carla, MD - Full Professor of Endocrinology e-mail: carla.giordano@unipa.it

Running title: Lachrymal gland involvement in Graves' Ophthalmopathy

Key words: Graves' Ophthalmopathy, Lachrymal gland, Orbital MRI, CAS

ha eliminato: Biomedical Department of Internal and Specialist Medicine

ha eliminato: Section of Radiology

ha eliminato: Department of Biopathology and Medical Biotechnologies, University of Palermo, Italy

ha eliminato: Experimental Biomedicine and Clinical Neuroscience,

Abstract

Background: Lachrymal gland (LG) involvement in patients with Graves' Ophthalmopathy (GO) has been considered as a potential cause of the associated GO symptoms and different studies found that the LG measurements were significantly higher in patients with GO than healthy controls. The aim of this study was to evaluate LG involvement, through measurement of herniation compared the interzygomatic line using magnetic resonance imaging (MRI), in patients with different GO activity.

Methods: Thirty-two consecutive Caucasian patients (10 M, 22 F, mean age 49.5, IR 30-68 yrs), affected by GO were enrolled and grouped in group A (16 with inactive GO, CAS<3) and B (16 with active GO, CAS≥3) according to their GO activity. All patients underwent clinical, biochemical and morphological thyroid assessment, complete ocular evaluation and orbital MRI examination.

Results: No significant difference was found for the hormonal parameters and thyroid ultrasound-derived parameters between the two groups. TRAb levels were slightly higher, although not significantly, in group B than group A [2.76 (0-40) *vs.* 1.74 (0-13.8) UI/L; p=0.073)]. The LG herniation measurement evaluated by MRI was significantly higher in group B for both right [10.1 (7.3-17) *vs*. 7 (0-13.4) mm; p=0.004)] and left [8.5 (6.6-13) *vs*. 5.8 (0-12) mm; p=0.026)] eye than group A. A linear positive correlation was found between TRAb levels and LC herniation (Rho 0.462, p=0.009) in all patients.

Conclusions: Measurement of LG herniation seems to be a good marker of the disease and GO activity, although further larger studies are needed to better understand this association.

Introduction

Thyroid-associated orbitopathy, also termed Graves' ophthalmopathy (GO), is the most common extrathyroidal manifestation of Graves' disease (GD), although it may also be rarely associated with euthyroid or hypothyroid autoimmune thyroiditis (1,2)

GO is a chronic inflammatory autoimmune disease targeting the intra-orbital structures, with an estimated incidence of GO in 16 women or 3 men per 100,000 person per year. About three-quarters of GD patients do not have any GO at diagnosis, and moderate-to-severe and severe forms represent no more than 5-6% of cases (3,4). Subclinical eye involvement is quite common. In about 70% of adult patients with GD, computed tomography (CT) could reveal subclinical extraocular muscle enlargement (5). The thyroid-stimulating hormone receptor (TSH-R) is the best-known autoantigen, also expressed on orbital fibroblasts and adipocytes (6,7). The serum levels of TSH-R autoantibodies (TRAb) positively correlate with the clinical features of GO. These constitute an independent risk factor for disease severity and progression (8,9). The inflammatory process leads to orbital fibroblast proliferation, increased glycosaminoglycan synthesis and secretion, and differentiation of preadipocytes into adipocytes (7,8). Fibroadipose tissue expansion and the extraocular muscle infiltration in a rigid anatomic site like the orbit cause clinical manifestations of GO like exophthalmos, periorbital soft tissue swelling, the possible extraocular muscle dysfunction with diplopia and more severe form with optic nerve compression (10). Clinical management of GO is the most important challenge for clinicians and early diagnosis and correct staging of GO and its inflammatory activity is important for timing and choice of treatment (11). In the early stage, patients with GO may commonly have photophobia, excess tearing and grittiness probably associated with a widened vertical palpebral fissure, and exophthalmos, which may accelerate dehydration of the eyes (12,13). However, other studies suggest direct LG involvement leading to a decrease in tear secretion (14,15). Different studies, CT-based (16,17,18) and, more recently, MRI-based (19), found that the LG volume was significantly higher in patients with GO than in healthy controls. To date no data are available about the difference in LG involvement between patients with different levels of GO activity. Since different treatment strategies are required for patients with active and inactive GO (20), the aim of this study was to evaluate a simple quantitative MRI-derived parameter able to evaluate LG involvement (in terms of gland herniation) in relation to GO activity.

Materials and Methods

Thirty-two consecutive Caucasian patients, 10 men and 22 women, median age 49.5 years (IR 30-68), affected by GD with a diagnosis of GO were enrolled from June 2013 until November 2015 in our Outpatients Clinic at the Endocrinology Section of the University of Palermo. Exclusion criteria were previous orbital-cranial radiotherapy and immunosuppressive treatment for GO. All patients gave their informed consent after approval by the local Ethical Committee. The diagnosis of GD was based on standard criteria (4), including increased serum concentrations of free thyroxine (FT4) and triiodothyronine (FT3), undetectable serum thyrotropin (TSH), positive tests for TRAb, diffuse goiter by palpation or ultrasonography, and homogeneous pertechnetate uptake at thyroid scan. Six out of 32 patients underwent total thyroidectomy while 26 patients received thyrostatic therapy with methimazole 10-20 mg daily according to the severity of the hyperthyroidism. All patients underwent clinical, biochemical and morphological thyroid assessment, complete ocular evaluation and an orbital MRI examination on the same day as the endocrinological examination.

Commentato [CG1]: da togliere per la versione blinded

Thyroid evaluation

Serum FT4, FT3, TSH and TRAb were measured by Electro-chemiluminescence immunoassay (E411 Roche device; normal values in our laboratory are: 7-17 pg/mL, 2-4.4 pg/mL, 0.2-4 µUI/mL and < 1.58 U/L respectively).

In patients who never underwent thyroidectomy, among the thyroid ultrasound parameters we evaluated thyroid lobe anteroposterior diameters (APD) and the right and left inferior thyroid artery peak systolic velocity (PSV), using a Philips device.

Ophthalmological evaluation

The examination included presence of diplopia, evaluation of ocular proptosis by Hertel Exophthalmometry (HE), ocular pressure measurement, lid retraction measurements and soft tissue signs to calculate the clinical activity score (CAS) according to the European Group On Graves' Orbitopathy (EUGOGO) consensus statements (21) for both eyes. All patients were divided into two groups according to their GO activity: group A (32 eyes of 16 patients) with inactive GO (CAS<3) and group B (32 eyes of 16 patients) with active GO (CAS≥3).

Imaging assessment and lachrymal gland herniation measurement

All subjects underwent orbital MRI scan at the Radiology Section of the University of Palermo. A 1.5 Tesla MRI scanner (Signa HDxt; GE Medical Systems; Milwaukee, WI, USA) was used for orbital evaluation with an 8-channel phased-array head coil. A fast three-plane scout scan was used to localize the region of interest. Axial planes were then planned parallel to the optic nerve (number of slices accordingly adjusted to include all of orbits); coronal planes were planned perpendicular to the axial plane (scan range was from lens to mid pons). The protocol employed was as follows: axial T2-weighted (w) Fast Spin Echo (FSE) with fat saturation (FAT-SAT) (acquisition matrix: 288x256; slice thickness 3 mm; spacing 0,3 mm; TR 5452 ms; TE 119,088 ms; ETL 17; NEX 3), axial T1-w FSE (acquisition matrix: 288x224; slice thickness 3 mm; spacing 0,3 mm; TR 295 ms; TE 16,248 ms; ETL 3; NEX 2), axial T1-w FSE with FAT-SAT (acquisition matrix: 288x224; slice thickness 3 mm; spacing 0,3 mm; TR 490 ms; TE 16,248 ms; ETL 3; NEX 2) and coronal T2-w FSE (acquisition matrix: 288x256; slice thickness 3 mm; spacing 0,3 mm TR 6332 ms; TE 117,6 ms; ETL 17; NEX 3). After intravenous (i.v.) administration of 0.1 mmol/kg of gadobenate dimeglumine (MultiHance®; Bracco Imaging SpA, Milano, Italy) the axial T1-w FSE FAT-SAT sequence was repeated and then an axial three-dimensional Enhanced Fast Gradient Echo (3D-EFGRE) inversion recovery for fat tissue (acquisition matrix: 256x256; slice thickness 1,2 mm;

Commentato [CG2]: da togliere per la versione blinded spacing 0,2 mm; TR 9,676 ms; TE 3,272 ms; IT 26 ms; FA 12; NEX 2) scan was acquired. Multi-planar reconstructions (MPR) were obtained from the 3D-EFGRE sequence using a 3-mm slice thickness and an average reconstruction algorithm. MRI findings were evaluated in consensus by two experienced neuroradiologists (C. G., G. F.). Lachrymal gland herniation was evaluated on axial MRI FSE-T2w sequences by drawing a line between the right and left ventral zygomatic border (interzygomatic line). This line is commonly drawn at the level of the lens to evaluate the amount of proptosis (from there, a perpendicular line is taken to the apex of the globe, depicting the measurement of proptosis considering a Hertel-index of ≥22 mm pathological). We also drew the interzygomatic line at the level of the maximum depicted lachrymal glands herniation on post-gadolinium axial T1-w FSE FAT-SAT (or 3D-EFGRE's MPRs) sequences and, taking a perpendicular line, we measured the amount of lachrymal gland parenchyma protruding anteriorly (i.e.: lachrymal gland herniation).

All the MRI reconstructions and measurements were performed with independent workstations using the length and perpendicular lines tools of the Horos software (<https://www.horosproject.org/>), a free, open-source medical image viewer software based upon OsiriX and other open-source medical imaging libraries available under the GNU Lesser General Public License, Version 3 (LGPL-3.0).

Statistical analysis

the Statistical Packages for Social Sciences (SPSS) version 20 was used for data analysis. Normality of distribution for the continuous variables was assessed with the Kolmogorov-Smirnov test. Data were presented as a median and interquartile ranges (IR) for continuous variables, rates and proportions for categorical data. The differences between the two groups of patients were evaluated with the Mann–Whitney test (non-parametric test), as they were continuous variables without normal distribution. Univariate correlations among continuous variables were determined by Spearman's test. To evaluate the independent variables influencing gland herniation, a linear regression model was used. A p value <0.05 was considered statistically significant.

Results

The clinical, biochemical and ultrasound parameters of 32 patients, grouped according to CAS, are shown in Table 1. The two groups were matched for gender, age, BMI. No difference was found for the thyroid biochemical and ultrasound parameters. TRAb levels were slightly higher, although not significantly, in group B [2.76 (0-40) *vs.* 1.74 (0-1.3.8) UI/L; p=0.073)] than A (Table 1).

The ophthalmological clinical parameters are shown in Table 2. No differences between the two groups of patients were found for all the evaluated parameters, except for diplopia, which was significantly more prevalent in patients with active than inactive GO (81 *vs*. 31%; p=0.003).

The MRI-derived characteristics of LG are shown in Table 2. LG herniation was significantly higher for both right [10.1 (7.3-17) *vs*. 7 (0-13.4) mm; p= 0.004)] and left [8.5 (6.6-13) *vs.* 5.8 (0-12) mm; p=0.026] eyes in group B than A (Figure 1 and 2).

Similarly, MRI-derived proptosis (Hertel-index) was significantly higher for both right [23.3 (20-27.7) *vs.* 20 (15.1-26.2); p= 0.021] and left [23.7 (18-26.9) *vs.* 19.8 (13.3-26.2) mm; p= 0.036] eyes in group B than A. A linear correlation was found between TRAb levels and LG herniation measurement (Rho 0.462, p=0.009) in all patients (Figure 3).

ha eliminato:

Discussion

In this study we demonstrated significantly higher LG herniation, evaluated by the use of MRI orbital examination, in patients with active than those with inactive GO. This parameter appears useful for the differentiation between inactive and active GO and was correlated with TRAb levels.

Early diagnosis of GO and correct grading of the inflammation activity have primary importance in GO management (11). Indeed, medical therapy by corticosteroids in the early stages of the disease is considered useful to reduce inflammation and to obtain GO remission but is useless in fibrotic end-stages (11). The CAS, proposed by Mourits et al., is a validated scoring system for the identification of the active phase of the autoimmune process (22). This system is based on the assessment of inflammatory signs and symptoms (pain, eyelid and conjunctiva erythema, chemosis, eyelid oedema) to distinguish acute inflammatory from fibrotic GO. These parameters have a high predictive value for the outcome of immunosuppressive treatment in GO patients (22, 23). According to the 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 (11,22,24). In this study, we demonstrate that MRI-derived LG herniation is a good and simple parameter to differentiate inactive from active GO, which could be useful to improve the diagnostic ability of CAS in some clinical cases. Indeed, other studies which evaluated orbital MRI combined with CAS, demonstrate that no patients with CAS < 3 have really inactive GO (25,26). The most important limits of the CAS are operator-dependent evaluation and imperfect differentiation of the various degrees of inflammation activity. Indeed CAS 3 as well as CAS 6 are considered to show active GO in the same way (25,27). Furthermore, the CAS attributes the same value to the various signs and symptoms, each of which probably has different importance. Therefore, CAS could require integration with other imaging-based examinations (1, 25, 28,). Orbital US is the simplest examination to perform the measurement of muscular diameters but it is not able to evaluate the orbital apex and is very operator-dependent. CT does not estimate muscle composition so it is not able to directly identify inflammation and crystalline exposure to ionizing radiations limits its use (29). Many recent studies have validated the utility of MRI in GO (29). Orbital MRI is able to obtain detailed orbital anatomy representation and could differentiate inflammatory from fibrotic alterations of orbital tissue (30,31). Fat suppression/saturation MRI techniques (i.e.: short tau inversion recovery or STIR, difference in resonance frequency with water by means of frequency selective pulses or CHESS, Dixon method, spectral presaturation with inversion recovery or SPIR) have been found to be useful in detecting oedema in extra-ocular muscles which present longer T2 relaxation times than healthy controls (25,27,30,31,32). Other authors suggest using diffusion-weighted imaging to detect extra-ocular muscles damage at a very early stage (33), though conventional echo-planar pulse sequences are hardly applicable to this kind of study because of many artifacts that could affect imaging quality.

The present study focuses on LG involvement evaluation in patient with GO. Previous studies, performed in patients with GO, found a greater volume of LG evaluated by CT than those of healthy controls (16,17,18). Recently, a study conducted by Hu et al evaluated the importance of LG, based on 3.0 Tesla MR imaging, in the diagnosis of GO patients. This study showed a significant difference in LG volume between GO and healthy controls, without difference between inactive and active GO patients (19). To date a simple LG quantitative parameter that could correlate with the GO staging has not yet been found. Our study demonstrates that LG involvement could also be assessed by means of herniation using a simple quantitative measurement, although with the limits related to the small sample and the lack of evaluation in healthy controls. In addition, LG herniation could also be related to the growth of retro-orbital structures, as demonstrated by the significant higher proptosis evaluated by MRI for both eyes in patients with active GO than in those of patients with inactive GO in our cohort. However, LG involvement may also have an independent pathogenic role in GO, as demonstrated by the study by Eckstein et al, who found the presence of TSHR in LG tissues (14). These data are agreement with our study, which demonstrates a linear correlation between LG herniation and TRAb levels.

In conclusion, the present study evaluated the role of a simple quantitative measurement of LG herniation for GO staging, based on conventional MRI pulse sequences. This method, which is not time-consuming, could be easily adopted in daily practice (especially if compared to manual or semiautomatic volume-based methods). The results can be summarized as follows: measurement of LG herniation seems to be a good marker of GO activity as evidenced by the significant difference between the two groups of patients, proving useful to differentiate between active and inactive GO. The correlation between TRAb levels and the degree of LG herniation may suggest a bigger role of

LG involvement in the pathogenesis of GO. Future studies in a larger group of patients with different degrees of GO activity will confirm these preliminary data.

Author Disclosure Statement

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Corresponding author:

Carla Giordano, MD - Full Professor of Endocrinology
Piazza delle cliniche, 2
90127 Palermo, PA – Italy
email: carla.giordano@unipa.it
tel: +39 091 655 21 10

References

1 Bahn RS 2010 Graves' ophthalmopathy. N Engl J Med 362:726-738.

2 Perros P, Hegedüs L, Bartalena L, Marcocci C, Kahaly GJ, Baldeschi L, Salvi M, Lazarus JH, Eckstein A, Pits S, Bodoridis K, Anagnostis P, Ayvaz G, Boschi A, Brix TH, Currò N, Konuk O, Marinò M, Mitchell AL, Stankovic B, Törüner FB, von Arx G, Zarković B, Wiersinga WM 2017 Graves' orbitopathy as a rare disease in Europe: a European Group on Graves' Orbitopathy (EUGOGO) position statement. Orphanet J Rare Dis 12:72

3 Bartley GB 1994 The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmstead County, Minnesota. Trans Am Ophthalmol Soc 92:477–588.

4 Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, Pariani N, Gallo D, Azzolini C, Ferrario M, Bartalena L 2013 Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed Graves' hyperthyroidism seen at a single center. J Clin Endocrinol Metab 98:1443–1449.

ha eliminato:

5 Enzmann DR, Donaldson SS, Kriss JP 1979 Appearance of Graves’ disease on orbital computed tomography. J Comput Assist Tomogr 3:815–819.

6 Moshkelgosha S, So PW, Deasy N, Diaz-Cano S, Banga JP 2013 Cutting edge: retrobulbar inflammation, adipogenesis, and acute orbital congestion in a preclinical female mouse model of Graves' orbitopathy induced by thyrotropin receptor plasmid-in vivoelectroporation. Endocrinology 154:3008–3015.

7 Iyer S, Bahn RS 2012 Immunopathogenesis of Graves' ophthalmopathy: the role of TSH receptor. Best Pract Res Clin Endocrinol Metab 26:281–289.

8 Khong JJ, Selva D 2016 Pathogenesis of thyroid eye disease: review and update on molecular mechanisms. Br J Ophthalmol 100:142-150

9 Smith TJ, Hegedüs L 2016 Graves’ desease. N Engl J Med 375:1552-1565

10 Dolman PJ 2012 Evalueting Graves’ Orbitopaty. Best Pract Res Clin Endocrinol Metab 26:229-248

11 Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, Perros P, Salvi M, Wiersinga WM, European Group on Graves' Orbitopathy (EUGOGO) 2016 The 2016 European Thyroid Association/European Group on Graves’ Orbitopathy Guidelines for the Management of Graves’ Orbitopathy. Eur Thyroid J 5:9–26

12 Gilbard JP, Farris RL 1983 Ocular surface drying and tear film osmolarity in thyroid eye disease. Acta Ophthalmol (Copenh) 61:108-116.

13 Khurana AK, Sunder S, Ahluwalia BK, Malhotra KC 1992 Tear film profile in Graves' ophthalmopathy. Acta Ophthalmol (Copenh) 70:346-349.

14 Eckstein AK, Finkenrath A, Heiligenhaus A, Renzing-Köhler K, Esser J, Krüger C, Quadbeck B, Steuhl KP, Gieseler RK 2004 Dry eye syndrome in thyroid-associated ophthalmopathy: Lacrimal expression of TSH receptor suggests involvement of TSHR-specific autoantibodies. Acta Ophthalmol Scand 82:291-297.

Codice campo modificato

15 Jacobson DH, Gorman CA 1984 Endocrine ophthalmopathy: Current ideas concerning etiology, pathogenesis and treatment. Endocr Rev 5:200-220.

16 Harris MA, Realini T, Hogg JP, Sivak-Callcott JA 2012 CT dimensions of the lacrimal gland in Graves orbitopathy. Ophthal Plast Reconstr Surg 28:69-72.

17 Bingham CM, Harris MA, Realini T, Nguyen J, Hogg JP, Sivak-Callcott JA 2014 Calculated computed tomography volumes of lacrimal glands and comparison to clinical findings in patients with thyroid eye disease. Ophthal Plast Reconstr Surg 30:116-118.

18 Huh HD, Kim JH, Kim SJ, Yoo JM, Seo SW 2016 The change of lacrimal gland volume in Korean patient with Thyroid-associated Ophthalmopathy. Korean J Ophthalmol 30:319-325.

19 Hu H, Xu XQ, Wu FY, Chen HH, Su GY, Shen J, Hong XN, Shi HB 2016 Diagnosis and stage of Graves' ophthalmopathy: Efficacy of quantitative measurements of the lacrimal gland based on 3-T magnetic resonance imaging. Exp Ther Med 12:725-729.

20 Bartalena L, Pinchera A, Marcocci C 2000 Management of Graves' ophthalmopathy: Reality and perspectives. Endocr Rev 21:168-199.

21 Bartalena L, Baldeschi L, Dickinson AJ, Eckstein A, Kendall-Taylor P, Marcocci C, Mourits MP, Perros P, Boboridis K, Boschi A, Currò N, Daumerie C, Kahaly GJ, Krassas G, Lane CM, Lazarus JH, Marinò M, Nardi M, Neoh C, Orgiazzi J, Pearce S, Pinchera A, Pitz S, Salvi M, Sivelli P, Stahl M, von Arx G, Wiersinga WM 2008 Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid 18:333-346.

22 Mourits MP, Prummel MF, Wiersinga WM, Koornneef L 1997 Clinical activity score as a guide in the management of patients with Graves' Ophthalmopathy. Clin Endocrinol. (Oxf) 47:9-14.

23 Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L 2009 Treatment modalities for Graves' ophthalmopathy: systematic review and meta-analysis. J Clin Endocrinol Metab 94:2708-2716.

ha eliminato: Bartalena L, Baldeschi L, Dickinson AJ, Eckstein A, Kendall-Taylor P, Marcocci C, Mourits MP, Perros P, Boboridis K, Boschi A, Currò N, Daumerie C, Kahaly GJ, Krassas G, Lane CM, Lazarus JH, Marinò M, Nardi M, Neoh C, Orgiazzi J, Pearce S, Pinchera A, Pitz S, Salvi M, Sivelli P, Stahl M, von Arx G, Wiersinga WM 2008 Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid 18:333-346.¶

ha formattato: Inglese americano

24 Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R 1989 Clinical criteria for the assessment of disease activity in Graves' Ophthalmopathy: a novel approach. Br J Ophthalmol 73:639-644.

25 Tachibana S, Murakami T, Noguchi H, Noguchi Y, Nakashima A, Ohyabu Y, Noguchi S 2010 Orbital magnetic resonance imaging combined with clinical activity score can improve the sensitivity of detection of disease activity and prediction of response to immunosuppressive therapy for Graves' Ophthalmopathy. Endocr J 57:853-861.

26 Kirsch EC, Kaim AH, De Oliveira MG, von Arx G 2010 Correlation of signal intensity ratio on orbital MRI-TIRM and clinical activity score as a possible predictor of therapy response in Graves' orbitopathy – A pilot study at 1.5 T. Neuroradiology 52:91-97.

27 Prummel MF, Gerding MN, Zonneveld FW, Wiersinga WM 2001 The usefulness of quantitative orbital magnetic resonance imaging in Graves' Ophthalmopathy. Clin Endocrinol (Oxf) 54:205-209.

28 Hoang JK, Eastwood JD, Glastonbury CM 2010 What's in a name? Eponyms in head and neck imaging. Clin Radiol 65:237-245.

29 Muller-Forell W, Kahaly GJ 2012 Neuroimaging of Graves' orbitopathy. Best Pract Res Clin Endocrinol Metab 26:259-271

30 Mayer EJ, Fox DL, Herdman G, Hsuan J, Kabala J, Goddard P, Potts MJ, Lee RW 2005 Signal intensity, clinical activity and cross sectional areas on MRI scans in thyroid eye disease. Eur J Radiol 56:20-24

31 Tortora F, Cirillo M, Ferrara M, Belfiore MP, Carella C, Caranci F, Cirillo S 2013 Disease Activity in Graves' Ophthalmopathy: Diagnosis with Orbital MR Imaging and Correlation with Clinical Score. Neuroradiol J 26:555-564.

32 Higashiyama T, Iwasa M, Ohji M 2017 Quantitative Analysis of Inflammation in Orbital Fat of Thyroid-associated Ophthalmopathy Using MRI Signal Intensity. Sci Rep 7:16874.

ha formattato: Colore carattere: Automatico

ha eliminato: Tachibana S, Murakami T, Noguchi H, Noguchi Y, Nakashima A, Ohyabu Y, Noguchi S 2010 Orbital magnetic resonance imaging combined with clinical activity score can improve the sensitivity of detection of disease activity and prKirsch EC, Kaim

ha eliminato: ediction of response to immunosuppressive therapy for Graves' Ophthalmopathy. Endocr J 57:853-861.¶

ha eliminato: <#>Kirsch EC, Kaim AH, De Oliveira MG, von Arx G 2010 Correlation of signal intensity ratio on orbital MRI-TIRM and clinical activity score as a possible predictor of therapy response in Graves' orbitopathy – A pilot study at 1.5 T. Neuroradiology 52:91-97.¶

Codice campo modificato

Codice campo modificato

Codice campo modificato

ha formattato: Nessuna sottolineatura, Inglese americano

ha formattato: Inglese americano

Codice campo modificato

Codice campo modificato

Codice campo modificato

Codice campo modificato

Codice campo modificato

Codice campo modificato

Codice campo modificato

Codice campo modificato

Codice campo modificato

33 Kilicarslan R, Alkan A, Ilhan MM, Yetis H, Aralasmak A, Tasan E 2015 Graves' ophthalmopathy: the role of diffusion-weighted imaging in detecting involvement of extraocular muscles in early period of disease. Br J Radiol 88:20140677.

Codice campo modificato

Codice campo modificato

Codice campo modificato