Endocrine Journal 2010, **57** (10), 853-861

ORIGINAL

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

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Abstract. The aim of this study was to demonstrate that the addition of orbital magnetic resonance (MR) imaging can provide improvement in sensitivity of detection of active disease and the prediction of the response to intravenous glucocorticoid therapy (ivGC), over clinical activity score (CAS) alone. A prospective case series was studied at our institution. Forty eight patients were examined by CAS and orbital MR imaging. The maximum of T2 relaxation times of extraocular muscles (maxT2RT) and other parameters were evaluated by MR imaging. Thirty five of 48 patients underwent ivGC. Twenty of 35 patients, whose CAS was 2 points or less, were evaluated for the response to ivGC. The correlation between CAS and maxT2RT was evaluated. Differentiation of active and inactive GO was performed by CAS and orbital MR imaging. The response to ivGC was evaluated by CAS, orbital MR imaging and ophthalmic parameters. As a result, CAS and maxT2RT showed significant positive correlation (r=0.58, p<0.0001), and 15 patients were positive by CAS and orbital MR imaging. However, 20 patients were positive by only MR imaging. In those 20 patients, there was significant improvement after ivGC. We concluded that orbital MR imaging combined with CAS could improve the sensitivity of detection of active disease and the prediction of the response to ivGC. In addition, even if only one parameter of CAS is positive, further examination with orbital MR imaging is advised.

Key words: Orbital MRI, CAS, Graves' ophthalmopathy, Immunosuppressive therapy, Glucocorticoid

GRAVES' OPHTHALMOPATHY (GO) is a common complication of Graves' disease (GD), which reduces quality of life of GD's patients. Among the numerous means of evaluating GO activity proposed over the past few decades, CAS was proposed by Mourits *et al.* in 1989, and it is a common and widely used measure for evaluation of disease activity [1, 2]. However, CAS is a subjective measure whose result is highly dependent on the acumen of the examiner. In addition, it is an inadequate tool for monitoring changes of clinical manifestation as it employs binary scoring, whereby improvement of any individual feature does not alter the score unless it completely resolves [3]. Furthermore, there is no evidence that the cut-off value of CAS, 3 points or over, is appropriate for the Asian population whose facial features tend to be less sculptured. On the other hand, orbital MR imaging can evaluate the enlargement of extraocular muscles (EOMs), T2 relaxation time (T2RT) of EOMs, and signal intensity ratio (SIR). T2RT, which reflects a content of protons, is prolonged when the target tissue is more edematous than controls. Thus, prolonged T2RT is believed to represent active inflammation. By employing T2RT and SIR, orbital MR imaging can detect, not only the presence or absence of swollen tissue, but also objectively quantify the activity of inflammation hence predict the responsiveness to immu-

Received May 24, 2010; Accepted Jul. 24, 2010 as K10E-156
Released online in J-STAGE as advance publication Aug. 19, 2010

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nosuppressive therapy [4-7].

In Mourits' report, approximately half of patients who had 1 or 2 points in CAS showed significant response to immunosuppressive treatment [2]. This result indicated that CAS alone was inadequate for the evaluation of GO. Therefore, other modalities such as orbital MR imaging should be employed appropriately to improve the diagnostic sensitivity. Although there are many other modalities such as A-mode ultrasonography, octreoscan, and so on [8, 9], we limit the scope of this study to demonstrating the advantage of combining orbital MR imaging to CAS for the diagnosis of active GO.

Materials and Methods

Subjects

Forty-eight patients were examined for GO from August 2008 to October 2009. Recurrent cases of GO were excluded. All patients' profile was as shown in Table 1. They consisted of 12 men and 36 women, aged 49.9±2.2 (SE) yr. Twenty nine patients were treated for Graves' disease by oral antithyroid drugs, 4 patients were treated by radioiodine treatment, and 8 patients were treated by subtotal thyroidectomy. Seven patients did not receive treatment for Graves' disease. These 7 patients were euthyroid. Three of 7 patients were euthyroid Graves' disease and 4 had no GO. These 4 patients were examined since they had some subjective symptoms which indicated suspicion of GO, for example, mild proptosis, or mild eyelid swelling. The duration from the onset of GO was 6.7±0.6 (SE) months. The duration of the treatment for Graves' disease was 29.1±8.0 (SE) months. Eight of 48 patients were current smokers.

We measured free thyroxine (FT4), free triiodothyronine (FT3) and thyrotropin (TSH) levels by means of Elecsys FT4, Elecsys FT3 and Elecsys TSH (Roche Diagnostics GmbH, Mannheim, Germany) before evaluation. We also assessed thyroid stimulating antibody (TSAb) activity with a TSAb kit Yamasa (Yamasa Co., Tokyo, Japan) before evaluation. The reference range of these thyroid parameters was as follows. TSH was 0.5-5.0mU/L, FT4 was 11.6-21.9pmol/L, FT3 was 3.4-6.6pmol/L and TSAb was 0-180%. Their thyroid status was as follows. TSH was 0-39.7mU/L (median 0.26mU/L), FT4 was 5.1-100.4pmol/L (median 16.7pmol/L), FT3 was 3.7-41.4pmol/L (median 4.8pmol/L), and TSAb activity was 118-5458% (median 1296%). Hyperthyroidism or hypothyroidism at the time of the diagnosis of GO were corrected within about 2 months by antithyroid drug, potassium iodine, levo-thyroxine, and/or subtotal thyroidectomy.

Table 1 All patients' profile

All patients	
Age	49.9 (2.2)
Sex	
male	12
female	36
Treatment for GD	
antithyroid drug	29
radioiodine treatment	4
subtotal thyroidectomy	8
no treatment	7
Duration of the treatment for GD	29.1 (8.0) months
Duration from the onset of GO	6.7 (0.6) months
Smoking	
(+)	8
(-)	40

Numbers in parentheses are SEs.

Methods

CAS and orbital MR imaging

GO was diagnosed on the basis of CAS and orbital MR imaging. CAS was determined by the same endocrinologist before performing orbital MR imaging. CAS consisted of 7 parameters including spontaneous eye pain, eye pain upon eye movement, eyelid swelling, eyelid erythema, conjunctival redness, chemosis, and swollen caruncle. When CAS was 3 points or over, it was defined as active GO. We performed orbital MR imaging in all patients after evaluation with CAS. Patients were diagnosed of active GO independently regardless of CAS if they presented prolonged T2RT and enlargement of EOMs.

Parameters of orbital MR imaging

We evaluated maximum T2 relaxation times (maxT2RT), mean of T2 relaxation times of four rectus muscles (meanT2RT), and the sum of areas of four rectus muscles (areaSUM). The normal range of maxT2RT was defined as 80msec or below. AreaSUM was obtained on coronal sections by orbital MR imaging. The area of the rectus muscle on coronal section

Table 2 Orbital MR imaging parameters of normal subjects in our institution*

	Range	Mean
T2 relaxation times of extraocular muscles		
Superior rectus (msec)	49.7-62.5	56.7 (4.02)
Inferior rectus (msec)	48.3-69.5	58.2 (5.72)
Medial rectus (msec)	52.3-70.2	61.4 (4.85)
Lateral rectus (msec)	41.3-65.7	57.0 (4.92)
areaSUM (mm^2)	73.7-140.2	ND

*Evaluated by the same MR imaging system in Ohnishi's report.
Numbers in parentheses are SDs.

Table 3 The profile of three groups, CAS 0, CAS 1 or 2, and CAS positive

	CAS 0	CAS 1 or 2	CAS positive	
Age	41.8 (5.1)	49.3 (2.9)	55.4 (3.7)	p=0.10
Sex				
male	3	5	4	
female	5	20	11	p=0.60
Treatment for GD				
antithyroid drug	2	16	11	
radioiodine treatment	0	2	2	
subtotal thyroidectomy	2	4	2	
no treatment	4	3	0	p<0.05
Duration of the treatment for GD (month)	9.5 (19.3)	23.6 (10.9)	48.9 (14.1)	p=0.21
Duration from the onset of GO (month)	6.0 (2.5)	6.9 (0.8)	6.4 (0.9)	p=0.89
Smoking				
(+)	1	5	2	
(-)	7	20	13	p=0.81
maxT2RT	74.3 (5.1)	90.0 (2.9)	105.1 (3.7)	p<0.0001
meanT2RT	63.6 (3.0)	73.0 (1.7)	79.8 (2.2)	p=0.0003
areaSUM	113.0 (16.7)	163.2 (9.5)	171.9 (12.2)	p=0.0178

Numbers in parentheses are SEs.

was approximated by means of an ellipse of πab/4. Orbital MR imaging parameters of normal subjects, obtained from normal subjects, were as shown in Table 2 [6]. Orbital MR imaging was performed with a 0.5-T superconducting MR imaging system (FLEX ART; Toshiba, Tokyo, Japan).

Grouping

We divided those patients into two groups, one of which was 2 points or less in CAS (CAS negative group), and the other was 3 points or over (CAS positive group). In addition, the CAS negative group was divided into two groups, one of which was 0 points in CAS (CAS 0 group), and the other was 1 or 2 points (CAS 1or2 group). These groups' profile was as shown in Table 3.

Ophthalmic parameters

After evaluating the disease activity of GO, we evaluated exophthalmometer readings and eyelid widths in 20 patients of CAS negative group who underwent immunosuppressive therapy before and after treatment. All ophthalmic parameters were determined by the same ophthalmologist.

Treatment

Thirty-seven of 48 patients were diagnosed as active GO by orbital MR imaging and/or CAS. Thirty five of these 37 patients received immunosuppressive therapy. In this study, we evaluated 20 of 35 patients diagnosed as active GO by orbital MR imaging in CAS negative group. In these 20 patients, CAS was 0-2 points (median 1 points), maxT2RT was 80.1-121.3msec (median 93.6msec), meanT2RT was 64.1-92.5msec (median 71.9msec), and areaSUM was 91.7-234.2mm^2 (median 170.5mm^2) before treatment. Among these patients, 16 of 20 patients complained of diplopia.

Our immunosuppressive therapy was defined as intravenous glucocorticoid therapy (ivGC) with or without retrobulbar irradiation (RBI). One cycle of ivGC was 500 mg of methylprednisolone (mPSL) administered intravenously once per day for 3 consecutive days, after which 40mg of oral prednisolone (PSL) was prescribed for 4 consecutive days. IvGC was repeated 1-3 times (median 2 times) in 20 patients.

In addition, 15 of 20 patients underwent RBI to a total dose of 20 Gy delivered with a 4-MeV linear accelerator (ML-4M; Mitsubishi, Tokyo, Japan) after a simulation radiograph was obtained. Eleven patients did not undergo RBI, because of their age, their disease activity, or other complications (ex.; diabetic retinopathy). Patients were treated with opposed lateral fields. The radiation field was approximately 4 x 4 cm. The anterior border of the field was located just behind the lateral canthus of the eye. The field was angled 3° posteriorly to avoid irradiation of the contralateral lens. Patients were treated with twice-daily fraction at 1.0 Gy per fraction to a total dose of 20 Gy in 10 days. The radiation dose was calculated at the midline of the eye, which gave a uniform dose to both retroorbital regions. This technique was described by Donaldson *et al.* [10].

Evaluation

We performed orbital MR imaging and evaluated ophthalmic parameters within one week after ivGC. First, we evaluated the correlation between CAS and orbital MR imaging parameters, which are maxT2RT, meanT2RT, and areaSUM, the correlation between CAS and TSAb, and the correlation between orbital MR imaging parameters and TSAb. Second, we compared CAS negative group with CAS positive group in maxT2RT and meanT2RT. In addition, we compared active GO diagnosed by orbital MR imaging with that by CAS. Then, in CAS negative group, we also compared CAS 0 group with CAS 1 or 2 group in maxT2RT and meanT2RT. Finally, in CAS negative group, we evaluated the response to immunosuppressive therapy in maxT2RT, meanT2RT, areaSUM, CAS and ophthalmic parameters. We defined the normalization of maxT2RT and/or the reduction of areaSUM as positive response to treatment.

Statistical analysis

The statistical analysis was determined by one-way ANOVA, two-sided Student's *t* test, paired *t* test, Wilcoxon signed rank test, Pearson's correlation coefficient test or Spearman rank correlation. Difference with $p<0.05$ was considered significant.

Statistical analyses were performed with SAS JMP 5.1 (SAS Institute, Cary, NC).

Results

All 48 patients were available for analysis.

Before treatment, CAS was 0-5 points (median 2 points), maxT2RT was 63.6-138.5msec (median 91.8msec), meanT2RT was 58.4-97.3msec (median 71.7msec), and areaSUM was 70.6-267.5mm^2 (median 158.8mm^2). In 20 patients who were evaluated for response to immunosuppressive therapy, right exophthalmometer reading was 10-21mm (median 18mm), left was 11-23mm (median 18mm). Right eyelid width was 6-18mm (median 9.5mm), left was 7-16mm (10mm).

The correlation between CAS and orbital MR imaging

As shown in Fig. 1, we found significant positive correlation between CAS and maxT2RT ($r=0.61$, $p<0.0001$). We also found the same correlation between CAS and meanT2RT ($r=0.55$, $p<0.0001$). On the other hand, the correlation between CAS and areaSUM, was weak ($r=0.35$, $p=0.0139$).

The correlation between CAS and TSAb, and the correlation between orbital MR imaging parameters and TSAb

Of all parameters tested, only meanT2RT was significantly correlated with TSAb ($r=0.59$, $p=0.0001$).

The comparison of CAS negative group and CAS positive group in maxT2RT and meanT2RT

The maxT2RT of CAS negative group was

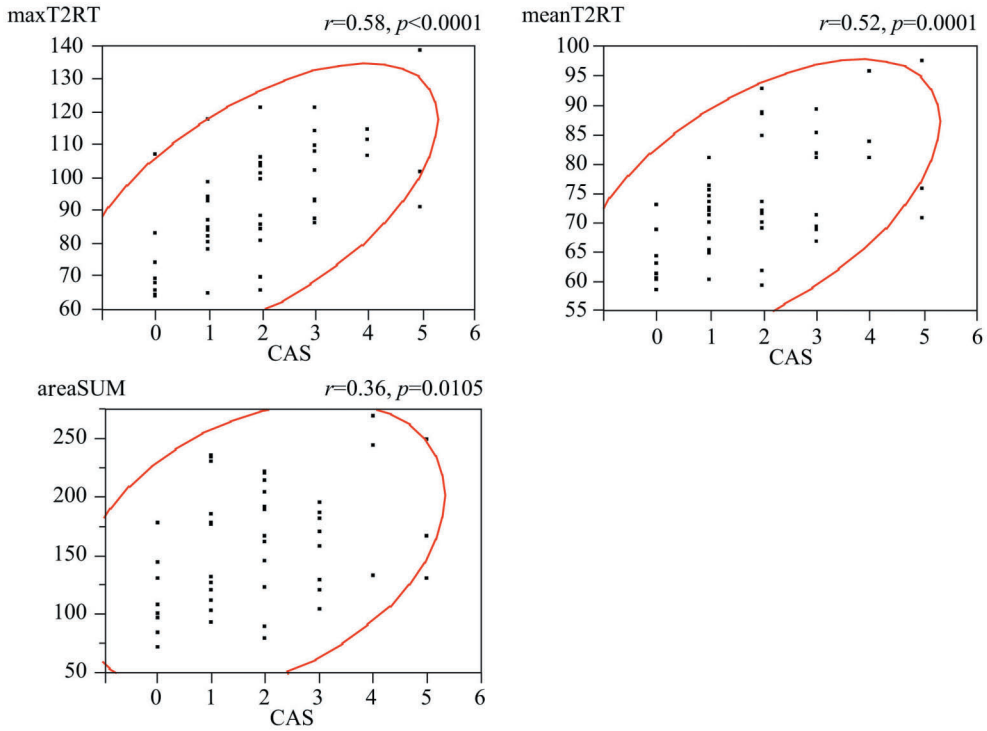

Fig. 1 We found significant positive correlation between CAS and maxT2RT (r=0.58, p<0.0001). We also found significant positive correlation between CAS and meanT2RT (r=0.52, p=0.0001). On the other hand, the correlation between CAS and areaSUM was weak (r=0.36, p=0.0105).

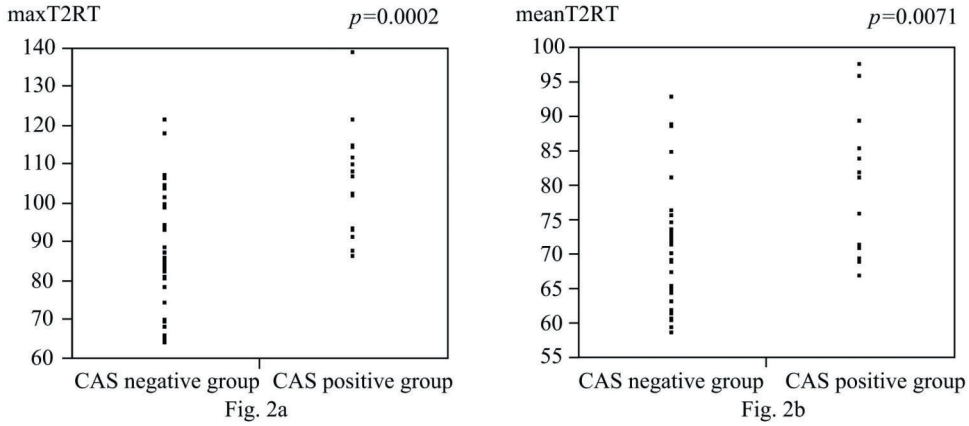

Fig. 2 2a: Significant statistical difference was found in maxT2RT between CAS positive and CAS negative groups. 2b: Significant statistical difference was also found in mean T2RT between CAS positive and CAS negative groups.

86.2±2.7 (SE) msec, and that of CAS positive group was 105.1±3.6 (SE) msec. These two groups showed significant statistical difference as Fig. 2a (p=0.0002). The meanT2RT of CAS negative group was 70.7±1.5 (SE) msec, and that of CAS positive group was 79.8±2.5 (SE) msec. In meanT2RT, these two groups showed significant statistical difference as Fig. 2b (p=0.0071).

The comparison of active GO determined by CAS and that determined by orbital MR imaging

CAS and orbital MR imaging both agreed in determining active GO in 15 of 48 cases and inactive GO in 11 of 48 cases. In 26 of 48 cases, the activity of GO which determined by orbital MR imaging is concordant with the activity by CAS. The coincidence rate of the diagnosis was 54.2%.

Table 4 The comparison of active GO determined by CAS and that determined by orbital MR imaging

Group	total No.	No. of active GO by orbital MR imaging
CAS positive group	15 cases	15 cases (100%)
CAS 1 or 2 group	25 cases	20 cases (80.0%)
CAS 0 group	8 cases	2 cases (25.0%)

The coincidence rate of the diagnosis between CAS and orbital MR imaging was 54.2%. Even if CAS was under 3 points, 20 of 25 patients in CAS 1 or 2 group and 2 of 8 patients in CAS 0 group were active GO by orbital MR imaging.

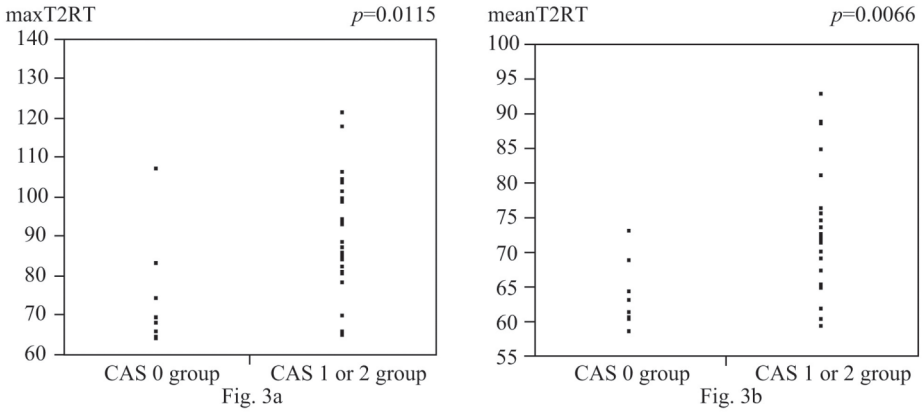

Fig. 3 3a: Significant statistical difference was found in maxT2RT between CAS 0 and CAS 1 or 2 groups. 3b: Significant statistical difference was also found in meanT2RT between CAS 0 and CAS 1 or 2 groups.

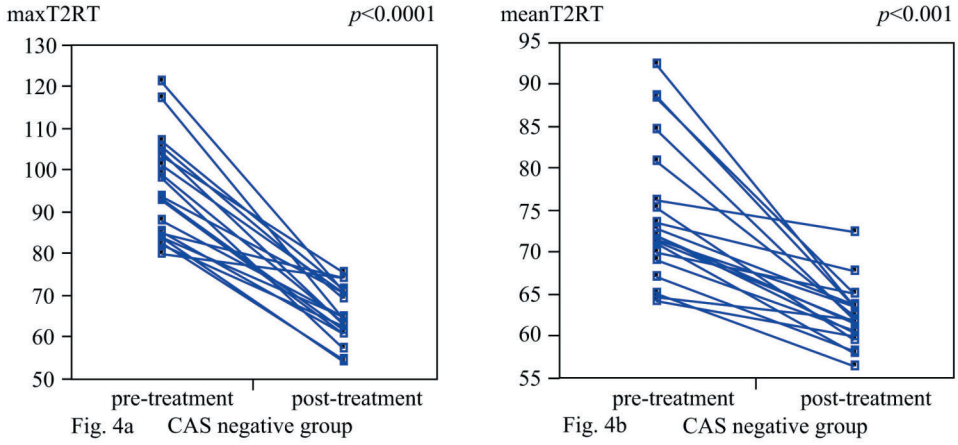

Fig. 4 4a: MaxT2RT was reduced significantly after immunosuppressive therapy. 4b: MeanT2RT was also reduced significantly after treatment.

In addition, in positive CAS group, all 15 cases were active GO by orbital MR imaging. Two of 8 cases in CAS 0 group, and 20 of 25 cases in CAS 1 or 2 group were active GO by orbital MR imaging (Table 4).

The comparison of CAS 0 group and CAS 1or2 group in maxT2RT and meanT2RT

The maxT2RT of CAS 0 group was 74.3±5.1 (SE) msec, and that of CAS 1 or 2 group was 90.0±2.9 (SE) msec. These two groups showed significant statistical difference as Fig. 3a (p=0.0115). The meanT2-RT of CAS 0 group was 63.6±3.0 (SE) msec, and that of CAS 1 or 2 group was 73.0±1.7 (SE) msec. In meanT2RT, these two groups also showed significant statistical difference as Fig. 3b (p=0.0066).

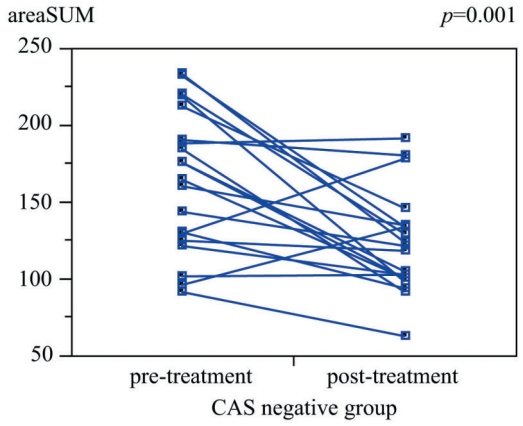

Fig. 5 AreaSUM was also showed significant reduction after treatment.

The response to immunosuppressive therapy in CAS negative group

CAS scores were reduced significantly ($p<0.001$) in all but two cases which were already CAS 0 before treatment. The maxT2RT was also reduced after treatment significantly as shown in Fig. 4a ($p<0.0001$). The meanT2RT and areaSUM showed the same results as shown in Fig. 4b and 5 ($p<0.001$, respectively). There was no case in which CAS and/or maxT2RT were increased. However, there were some cases which only areaSUM was increased after treatment. In ophthalmic parameters, both right and left exophthalmometer readings did not show significant improvement after treatment ($p=0.063$, $p=0.080$, respectively). Bilateral eyelid widths also showed no significant change after treatment ($p=0.507$, $p=0.497$, respectively).

Discussion

CAS is an accepted measure which can evaluate the disease activity of GO [1, 2, 11]. However, as described in the introduction, CAS is a subjective and qualitative measure, while orbital MR imaging is an objective and quantitative measure. Orbital MR imaging can detect not only EOM enlargement, but T2RT of inflamed EOMs [4-7, 12-14]. As described in the introduction, prolonged T2RT reflects edematous change of EOM due to inflammation. Some reports suggested that T2RT was more reliable in differentiating fibrotic enlargement of EOMs, with low disease activity, from inflammation and edema of EOMs, with high disease activity [6, 15]. Therefore, the information drawn from orbital MR imaging should supplement other clinical data allowing a comprehensive assessment of disease activity. In this respect, the correlation between CAS and orbital MR imaging parameters is vital, but reports about the correlation between CAS and MR imaging parameters are limited [12, 14, 16]. The edematous change of the orbital tissue increases CAS, and prolongs T2RT of EOMs [2, 6, 15, 17]. This change was caused by the inflammation of orbital tissue and the high pressure in the orbit due to swollen orbital tissue. In our study, we found significant positive correlation between CAS and orbital MR imaging parameters, particularly maxT2RT. Our results were compatible with these pathogeneses, and indicated that the supplement of orbital MR imaging to conventional parameters was appropriate. In addition, we found significant positive correlation between TSAb and meanT2RT. However, we were unable to find the correlation between TSAb and other orbital MR imaging parameters or CAS. The fact that maxT2RT did not correlate with TSAb demonstrates that the isolation of the single most inflamed EOM does not necessarily represent the activity of systemic disease. AreaSUM did not correlate with TSAb most likely because the mere size of the EOM did not represent current level of disease activity. CAS, which can be greatly influenced by the disease activity in one highly inflamed EOM, consequently did not correlate with TSAb.

We found significant statistical difference in maxT2RT and meanT2RT between CAS negative and CAS positive groups. On the other hand, our results also showed poor coincidence rate in the diagnosis of disease activity by CAS and orbital MR imaging. This suggests that although CAS reflects disease activity, CAS alone cannot sufficiently detect all active disease. Mourits *et al.* reported that GO patients whose CAS was over 4 of 10 points had a good response to glucocorticoid therapy, but they never demonstrated that patients whose CAS was 3 points or less was inactive GO [11]. In their report, 10 of 13 patients whose CAS was 3 points or less were responders to immunosuppressive therapy [2]. This result also meant that CAS alone could not detect active GO adequately. In our series, as shown in Table 2, if CAS was over 1 point, 35 of 40 patients (87.5%) were active GO by orbital MR imaging. Even if CAS was 0 point, 2 of 8 patients (25%) were active GO by orbital MR imaging. Furthermore, as shown in Fig. 3, maxT2RT and meanT2RT of CAS 1 or 2 group was sig-

nificantly higher than those of CAS 0 group. These results suggest that orbital MR imaging could detect active GO more sensitively than CAS.

As shown in the results, 20 of 35 patients, whose CAS was negative and maxT2RT was positive, showed significant improvement after treatment, except for ophthalmic parameters. We considered that there was the possibility of the improvement of ophthalmic parameters during longtime follow-up, because we evaluated ophthalmic parameters within one week after treatment. Although the date is not shown, 15 of 35 patients, positive for both CAS and maxT2RT, also showed significant improvement after treatment. These results indicated that CAS alone could not detect active GO sufficiently, and that orbital MR imaging could predict the response to ivGC more accurately than CAS alone.

However, when we evaluate our results, we have to consider racial differences, since it is well known that there are racial differences in clinical manifestations of GO [18-20]. The difference of orbital structure may influence the cut-off value of CAS, which indicates active GO by orbital MR imaging. Even if the same inflammation of EOM was detected by orbital MR imaging, Caucasians who tend to have more sculptured facial features, such as deep set eyes and prominent nose, may have different CAS when compared to Asians with less sculptured facial features. Therefore, at least in Japanese population, whose facial features are less sculptured, even if only one parameter of CAS is positive, we should assess the disease activity of GO by orbital MR imaging.

There have been some criticisms that MR imaging is not suitable for the assessment of Graves' ophthalmopathy due to the cost of the procedure. We fail to see the logic behind this sentiment. The cost of orbital MR imaging in Japan is the government-fixed price of 17500 yen for the first time in a month and 11200 yen thereafter until the next month. 70% of this price is covered by public health insurance and the patient pays 30% (5250 yen or 3360 yen) at the counter. The fact that proper medical care is prohibitively priced in other parts of the world has no relevance to the clinical utility of a medical procedure. Vast segments of the world's population still cannot afford basic antibiotics. That does not subtract from the importance of delivering antibiotics to them or the value of antibiotics in medical care. On the other hand, there are some legitimate concerns about orbital MR imaging in daily examination. One of the problems is the reproducibility of T2 relaxation times and area SUM. Another problem is the dependence of T2 relaxation times on specific MR imaging equipment. It is necessary to improve the reproducibility of T2 relaxation times and areaSUM and to develop a common scale to evaluate orbital tissue, even if MR imaging equipment is different between institutions.

In conclusion, our result demonstrated that orbital MR imaging combined with CAS can detect active GO more sensitively than CAS alone, and that orbital MR imaging with CAS can also predict the response to ivGC for GO more accurately than CAS alone. In addition, even if only one parameter of CAS is positive, further examination with orbital MR imaging is advised.

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