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FULL PAPER

Graves' ophthalmopathy: the role of diffusion-weighted imaging in detecting involvement of extraocular muscles in early period of disease

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Objective: To evaluate involvement of the extraocular muscle (EOM) using diffusion-weighted imaging (DWI), to determine whether there is correlation with conventional orbital MRI and apparent diffusion coefficient (ADC) values in patients with Graves' ophthalmopathy (GO).

Methods: 35 patients known clinically with GO and 21 healthy controls were studied. Patients were assessed with clinical activity scores. All subjects underwent conventional MRI and DWI study. Involvement of the EOM was evaluated. The patients were classified as involved or uninvolved on orbital MRI and their ADC values in DWI compared.

Results: There was significant difference in the mean ADC value of all the EOMs in patients vs controls. The ADC values of all the EOMs were higher in patients. There were

significant differences in ADC values between uninvolved muscles on conventional MRI and controls for the MR, SR and LR. There was no significant difference in ADC value between the two groups when considering the IR. ADC values of medial, lateral and superior rectus muscles were increased.

Conclusion: Increased ADC values of the EOM in patients with GO suggest that EOM damage begins at a very early stage before being detected on routine orbital MRI. The routine MRI with DWI sequence will be a useful adjunct in the selection of a group of patients most likely to benefit from early treatment.

Advances in knowledge: This study can help to evaluate the involvement of GO in early period with MRI added DWI.

Graves' ophthalmopathy (GO) is a disorder frequently associated with autoimmune thyroid diseases that involve the retro-ocular space. This disease leads to oedema and swelling resulting in proptosis and diplopia.^{1,2} It is clinically relevant in 40–50% of patients with Graves' disease and in 2–5% of patients with immune thyroiditis.³

GO is usually bilateral, but it can be asymmetric or unilateral in 15% of patients.³ The exact pathogenesis of GO remains unclear. Whatever the mechanism, ultimately, the connective tissues are extensively remodelled with the enlargement of the extraocular muscles (EOMs) and orbital adipose tissues.^{4,5} Patients with GO usually present symmetric, multiple EOM enlargement in both orbits, although asymmetric muscle involvement can occur. However, true unilateral orbital involvement is uncommon, occurring in only 6–10% of patients.⁶ The muscles most frequently affected are the medial and inferior rectus muscles.⁶

Orbital conventional MRI is required to avoid unnecessary decompression surgery in unclear or asymmetric proptosis, in suspected optic neuropathy. MRI can detect not only the presence or absence of swollen tissue but also objectively quantify the activity of inflammation.⁷ Diffusion-weighted imaging (DWI) provides qualitative and quantitative functional information concerning the microscopic movements of water at the cellular level. It allows a non-invasive characterization of microstructural changes. DWI has become a valuable imaging method in the evaluation of certain diseases such as head and neck, liver or kidney lesions.

Recently, there has been one study on evaluation of GO using MRI with DWI in literature.⁸ The goal of our study was to assess whether differences between involvement on conventional orbital MRI and apparent diffusion coefficient (ADC) values for each EOM in patients with GO compared with those in healthy controls, and to investigate effectiveness of ADC values in diagnosis of involvement of EOM.

METHODS AND MATERIALS

This study was approved by our institutional review board with patient-informed consent. 35 patients known clinically with GO were included in this study (26 females, 9 males; mean age, 40.31 ± 13.50 years). Patients had no other orbital pathologies. 21 control individuals (mean age, 38.21 ± 12.30 years) were selected who had neither thyroid disease nor ocular disease. Patients were questioned regarding symptoms of orbital condition such as orbital pain, photophobia, dryness and lacrimation. All ocular changes were graded in accordance with the Clinical Activity Score (CAS).⁹ Free thyroxine (FT4), free triiodothyronine (FT3) and thyrotropin (TSH) levels, and thyroid stimulating antibody (TSAb) activity were measured before evaluation. GO was diagnosed on the basis of the CAS. The CAS was determined by the same endocrinologist before performing orbital MRI. When the CAS was three points or over, it was defined as active GO.

Imaging techniques

We performed orbital MRI in all patients after evaluation with the CAS. There was an average 2–7 days between CAS evaluation and MRI. Having the patient close his/her eyes in the primary position minimized eye movements to prevent movement and contraction of the EOM. First, all patients underwent routine MRI protocol for routine orbital imaging including without intravenous contrast medium. MRI was performed on 1.5-T MRI system (Avanto; Siemens Healthcare, Erlangen, Germany) with a head coil. Routine orbital MRI protocol includes axial, coronal and sagittal unenhanced and enhanced T_1 weighted (T1W) [repetition time/echo time (TR/TE), 550/15 ms], axial T_2 weighted (TR/TE, 4000/90 ms) and coronal short tau inversion recovery (STIR) sequences (TR/TE, 5000/80 ms) obtained with 3-mm slice thickness, 0.2-mm interslice gap, matrix = 256×256 pixels and field of view (FOV) = 140 mm. Transverse and sagittal scans were obtained on a course parallel to the optic nerve. Coronal images were perpendicular to the mid-sagittal plane with the same parameters. The coronal plane is most frequently utilized to assess the size of the EOM, because all the rectus muscles are visualized in the same image.¹⁰ According to this study, we obtained coronal DWI images before contrast administration in the same T1W plan. For DWI, a single-shot spin echo-planar pulse sequence [TR/TE, 2500/140 ms, FOV = 230 mm, matrix size = 128×128 pixels, number of acquisitions = 2, slice thickness = 4 mm, slice number = 25 and interslice gap = 0.4 mm] was used in all subjects with two different b -values (0 and 1000 s mm^{-2}). The ADC maps were reconstructed automatically by the commercially available software and calculated in $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$.

On the enhanced T1W images, the medial rectus (MR), lateral rectus (LR) and inferior rectus (IR) muscle volumes were measured. The superior rectus muscle (SR), the superior ophthalmic vein and the levator palpebrae superioris were measured together as the superior muscle group (SMG) because of difficulties in delineating these structures from each other. SMG was only used for the purposes of calculating SR muscle volumes.

ADC measures of the EOM were obtained from the region posterior to the globe, and anterior to the point at which the muscles were indistinguishable posteriorly from tendinous

origin. In this way, the volume measurements mostly conformed to the muscle belly.¹¹ The measurement of ADC values of the SMG, MR, LR and IR was made from the thickest part of the muscle in selected coronal planes from both side muscles according to the study conducted by Bijlsma and Mourits.¹²

Two radiologists (RK, HY), blinded to the clinical history, measured the ADC values of each muscle of patients and control subjects. Multiple regions of interest were placed, and a mean was obtained from each muscle.

Additionally, the same radiologists evaluated muscle involvement on the conventional MRI sequences. The findings such as enlargement, swelling and increased signal on STIR sequence and enhancement on contrast-enhanced sequences in the muscles were investigated. A total of 70 muscles for each muscle group (in total, $n = 280$ muscles) on both sides were evaluated separately in patients. Patients with GO also were classified as all including no involvement (Group 0) and involvement (Group 1) on conventional MRI sequences and compared with the healthy control group (classified as Group 2, in total $n = 168$ muscles on both sides). Each observer also evaluated DWI images and ADC values in all subjects. Disagreement between observers was resolved through consensus. The differences in ADC values among groups were compared.

Statistical analysis

Numerical data were summarized by their means and standard deviations. Differences between means were tested using analysis of variance and Student's t -test. The relation between ADC values of the EOM and clinical data were evaluated using linear regression analysis. To compare between more than two groups, one-way analysis of variance and *post hoc* Tukey tests were used. For correlation analysis between the categorical variables, Pearson correlation (correlation coefficient) was used, and the distribution of categorical variables was tested by Pearson χ^2 test. The mean difference in p -value was considered statistically significant at the ≤ 0.05 level. All data analysis was performed with the statistical software SPSS® v. 17.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

There was no correlation between the CAS and ADC value of all EOMs. There was no significant difference in EOM volumes between the groups ($p > 0.05$).

There was significant difference in the mean ADC value of all the EOMs (IR, MR, LR and SR) in patients with GO vs healthy control. The ADC values of all the EOMs were higher in patients ($p = 0.0001$) (Figure 1). The lowest cut-off ADC value was $1459.50 \pm 4.80 \times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$ in Group 0 and $1444.45 \pm 1.10 \times 10^{-6} \text{ mm}^2 \text{ s}^{-1}$ in Group 1.

The mean ADC value of the IR and LR muscles showed a positive correlation with that of TSH ($p = 0.003$, $r = 0.252$).

A total of 70 muscles for each muscle group were evaluated depending on whether there was muscle involvement on conventional orbital MRI. The mean ADC values are shown among all groups in Table 1 and Figure 2 for a patient.

Figure 1. Coronal fat-saturated T_2 weighted (a), coronal gadolinium-enhanced T_1 weighted scan (b) and apparent diffusion coefficient (c) maps in the same plane of orbits in a patient with Graves' ophthalmopathy. The arrows in (a) and (b) indicate some of the extraocular muscle (EOM). The patient has enlargement, marked enhancement and increased apparent diffusion coefficient values of all the EOMs consistent with bilaterally symmetrical involvement. Max, maximum, Min, minimum.

Given IR, there were 66 muscles involved in a total of 70 muscles on conventional orbital MRI. ADC values showed significant difference between Groups 1 and 2 ($p < 0.001$). ADC value was higher in Group 1 than in Group 2. Although there was no significant difference, ADC values were higher in Group 0 than in Group 2.

When evaluating MR, SR and LR, there were 28 muscles involved in a total of 70 muscles on conventional orbital MRI. There was no significant difference between Groups 0 and 1 in MR and LR. There was significant difference between Groups 0 and 1 ($p = 0.001$) in SR. There was significant difference between Groups 0 and 2 in MR ($p < 0.001$), LR ($p = 0.001$) and SR ($p = 0.001$). ADC value was significantly higher in Group 0 than in Group 2 in MR, LR and SR. There was significant difference between Groups 1 and 2 in MR ($p < 0.001$), LR ($p = 0.001$) and SR ($p < 0.001$). ADC value was higher in Groups 1 (the group of muscles involved on conventional MRI) and 0 (the group of muscles uninvolved on conventional MRI) than in Group 2 (the group of healthy controls) in these muscle groups.

DISCUSSION

GO is an inflammatory autoimmune disorder of the orbit. Proptosis is caused by EOM enlargement and extraorbital fatty tissue swelling. The pathophysiology of the disease is based on a complex interplay among orbital fibroblasts, immune cells, cytokines, autoantibodies, genetics and environmental factors.¹³

The immune basis of the disease is suggested by a perivascular and diffuse infiltration of CD4 and CD8 T cells, B cells, plasma cells and macrophages.¹⁴ The EOMs are intact in early, active stages of the disease. In the later stages of the disease, the resolving inflammatory process within the muscles may leave them fibrotic and with ocular misalignment.¹⁵ GO follows a biphasic course, with a progressive or active phase lasting 6–18 months, followed by a stable or inactive phase. This pattern has been called Rundle's curve.¹⁶ Both active and inactive disease may present with enlarged muscles. EOM dysfunction is caused, early in the disease, by swelling of the muscle bodies. The increased size of EOM and extraorbital fatty tissue swelling are the hallmarks of GO.¹⁷

Imaging studies can be helpful in establishing the diagnosis of GO, because they provide objective morphological findings of the orbital structures. Based on such studies (especially MRI), it is possible to establish the degree of EOM and orbital fat enlargement, exclude coexisting orbital pathology, clarify a confusing clinical picture and perform surgical planning. Thus, imaging studies should aid the evaluation of inflammatory disease activity.

In recent years, additional investigation has focused on the utility of DWI in characterizing a number of lesions such as head and neck or orbital pathologies. Several case series and case reports have used DWI to characterize orbital pathologies.^{18–24}

Table 1. Mean apparent diffusion coefficient (ADC) values ($\times 10^{-6} \text{mm}^2 \text{s}^{-1}$) of all extraocular muscles in patients with Graves' ophthalmopathy and the healthy control group

Locations	Mean ADC values $\pm$ standard deviation		
	Group 0	Group 1	Group 2 ($n = 42$)
Inferior rectus muscle	1459.50 $\pm$ 4.8 ($n = 4$)	1444.45 $\pm$ 11 ($n = 66$)	1274.26 $\pm$ 22
Medial rectus muscle	1459.79 $\pm$ 10 ($n = 42$)	1495.86 $\pm$ 12 ($n = 28$)	1299.74 $\pm$ 12
Superior rectus muscle	1481.02 $\pm$ 9.9 ($n = 42$)	1554.11 $\pm$ 15 ($n = 28$)	1232.40 $\pm$ 6.7
Lateral rectus muscle	1462.69 $\pm$ 11 ($n = 42$)	1477.07 $\pm$ 14 ($n = 28$)	1367.88 $\pm$ 10

Group 0, uninvolved muscle group on conventional orbital MRI; Group 1, involved muscle group on conventional orbital MRI; Group 2, healthy control muscle group.

Figure 2. Coronal short tau inversion recovery MRI image (a) and apparent diffusion coefficient map (b) in a patient with Graves' ophthalmopathy (GO) showing no inflammation in the extraocular muscle (EOM) in a patient with GO. The arrows indicate the EOMs. Although there is no involvement in the EOM on orbital MRI (a), ADC image shows hyperintense signal [arrows in (b)] consistent with involvement of the EOM.

Additionally, very few MRI studies have assessed activity of GO. Strongly T_2 weighted and fat-suppressed images obtained using the turbo inversion recovery magnitude and STIR sequences have been shown to be useful in detecting EOM oedema but not useful in longstanding GO in order to detect inflammatory changes and activity follow up, possibly because GO is in inactive phase.²⁵ The signal intensity on STIR sequences has been correlated with the activity of GO.^{8,26–28} Some studies have shown that in T1W images with gadolinium, it is possible to distinguish inflammatory oedema from congestive venous outflow in burned-out disease.^{26,29}

DWI is most commonly used to identify acutely infarcted cerebral tissue, which causes a subsequent shift of water from the extracellular space into the intracellular space, an increase in the intracellular viscosity. Increased interstitial water, which is found in vasogenic oedema, demonstrates increased diffusion. ADC is related to the water content within tissues. This has been shown to correlate with inflammatory activity.⁸

Conventional single-shot echo planar imaging diffusion technique has some artefacts, such as susceptibility artefact, signal loss at the orbital apex, bands of bright signal at air-bone interfaces, anatomic distortion of the orbital structures and wavy appearance of the margin of the globe.¹⁸ Despite these limitations, an adequate image quality was obtained for evaluation on DWI sequences.

We sought to understand the pathophysiological basis of GO by performing ADC analysis of the EOM in patients with GO. EOM enlargement is associated with proptosis, increased TSH and with TRab.³⁰ We found a positive correlation with the mean ADC value of the IR and LR muscles and TSH. This finding is consistent with previous studies in which the higher TSH levels in patients are associated with enlarged EOM volumes.³¹ The mechanism whereby more severe hyperthyroidism leads to greater EOM volumes is uncertain, but we speculate that it may be related to higher levels of thyroid-orbital antigens.

Clinical activity scales, such as the CAS^{9,32} and vision, inflammation, strabismus and appearance (VISA),³³ can be very helpful in assessing disease activity. Although the combination of

MRI studies and clinical scores would improve diagnostic accuracy, the results have been conflicting. Some researchers have found no clear correlation between MRI findings and CAS indexes.^{25,28,34} However, other researchers have reported significant positive correlations.³⁵ Recently, Politi *et al*⁸ have reported that T2, post-contrast T_1 signal intensity ratios and normalized ADC of the EOM were significantly higher for the control group and correlated with muscle dysfunction and the CAS. Finally, CAS is a subjective measure the result of which is highly dependent on the examiner. We accepted the CAS as evaluating the disease activity of GO, and we found no correlation with ADC values with the CAS at the time of diagnosis. Moreover, we found ADC values were increased even in the uninvolved muscle on conventional orbital MRI. These findings suggest that regardless of the CAS score, meaning whatever stage of the disease, DWI can demonstrate EOM involvement.

We found that the mean ADC value of patients is significantly higher than that of healthy controls for all muscle groups. This difference in the ADC value suggests that extraocular muscle inflammation is more likely to be associated with an increased ADC value.

In terms of involvement on conventional MRI, there was a difference in most muscles between involved muscles and uninvolved muscles compared with control. There were significant differences in ADC values between uninvolved muscles on MRI and controls in all muscles except IR. IR was the most affected muscle group. There was no involvement on only 4 of 70 muscles (2.8%). Although, there was no significant difference, ADC value in patients uninvolved on MRI was higher than in control subjects. This result is probably owing to the small number of cases involved in MRI. Regardless of the situation of involvement, the highest ADC value was detected in MR.

Politi *et al*⁸ thought ADC values were affected by many factors such as oedema, fibrosis and infiltration of inflammatory cells and deposition of glycosaminoglycan. In accordance with this study, we speculate that an increase in ADC values in patients may be related to these factors. Additionally, our results suggested that EOM damage begins at a very early stage before being detected on routine orbital MRI. Even in patients with GO without clinical eye signs or symptoms, MRI with DWI can demonstrate the involvement of the EOM.

CONCLUSION

Although there was no involvement in EOMs, high ADC value was seen on conventional MRI in GO. DWI can prove useful in detecting involvement of the EOM in GO in the early period even before it is seen on conventional orbital MRI. The use of the DWI sequence in addition to routine MRI will be a useful adjunct in the selection of a group of patients most likely to benefit from early treatment. The determination of EOM involvement in early period by using DWI is a critical issue in the choice of treatment options and to prevent permanent changes in patients with GO. We should start treatment in patients with high ADC values regardless of the CAS score and when they do not have evidence of EOM involvement on conventional imaging.

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