Magnetic resonance imaging findings of age-related distance esotropia

in Japanese patients with high myopia

Running title: Magnetic resonance imaging of distance esotropia with high myopia

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Abstract

Purpose: This study aimed to investigate the characteristics of the extraocular muscles and the orbital connective tissue pulleys in Japanese patients with age-related distance esotropia (ARDE) and high myopia using magnetic resonance imaging (MRI).

Methods: This was a retrospective case-series study. High-resolution coronal MRI scans of 12 orbits were obtained in 6 patients with ARDE and high myopia (age range: 51–69 years). We analyzed the images to determine the positions of the rectus muscle pulleys relative to the center of the globe, the integrity of the lateral rectus-superior rectus muscle (LR-SR) band, and the LR angle (the angle between the major axis of the LR and the vertical plane).

Results: The distance esotropia ranged from 4–25 Δ, and 3 cases exhibited vertical deviations. The mean (±standard deviation [SD]) axial length was 28.5 (±1.6) mm. The mean positions of the medial rectus muscle pulley and LR pulley were 1.3 mm inferior and 1.4 mm inferior, respectively, to those seen in the normal control group in our previous study (P=0.002 and P=0.05, respectively). All 12 orbits had abnormal elongated LR-SR bands, and 8 orbits (67%) displayed ruptured LR-SR bands. The LR angle (mean±SD; 18.8°±8.5°) increased significantly with the inferior displacement of the LR pulley (R²=0.77, P=0.0002).
Conclusions: Inferior displacement of the LR pulley and abnormal LR-SR bands were seen in Japanese ARDE patients with high myopia, as was found in ARDE patients without high myopia. The LR angle might be useful for judging the degree of LR pulley displacement.

(249/250 words)
Keywords: age-related distance esotropia; esotropia; high myopia; orbital pulley; sagging eye syndrome (within 4–6 words)
Age-related distance esotropia (ARDE) that progresses slowly in the absence of an underlying neurological disease is an increasingly recognized type of adult strabismus. This form of strabismus is called divergence paralysis esotropia [1] or to use the currently accepted term, ARDE [2–5]. Several hypotheses have been proposed concerning the etiology of this condition. The possible causes include an age-related reduction in the elasticity of the medial rectus muscles (MR) [6]; a gradual aging-associated reduction in the divergence amplitude with normal ocular motility [7]; and tonic adduction due to convergence at near fixation, leading to shortening of the MR, which can result in esodeviation at distance [8].

Demer et al. [1, 9] described a phenomenon in which degenerative orbital connective tissue caused pulley displacement in patients with ARDE, and they referred to it as sagging eye syndrome (SES). Furthermore, they suggested that bilateral symmetrical inferior sagging of the lateral rectus muscles (LR) reduces the bilateral abducting forces in ARDE patients, whereas asymmetrical sagging results in cyclovertical strabismus. Tan and Demer [10] also reported ARDE occurring in patients with high myopia.

This study aimed to investigate the characteristics of the extraocular muscles and the orbital connective tissue pulleys in Japanese patients with ARDE and high myopia, and to compare the results of the current study with those of previous studies.
Methods

We reviewed the cases of patients with ARDE and high myopia who had undergone high-resolution orbital magnetic resonance imaging (MRI) during medical examinations of strabismus conducted between 2002 and 2015 at Okayama University Hospital, Okayama Saiseikai General Hospital, or Ibara Municipal Hospital. This retrospective case-series study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review boards of Okayama University Hospital, Okayama Saiseikai General Hospital, and Ibara Municipal Hospital for collaborative research. Twelve eyes of 6 patients with ARDE and high myopia (axial length: ≥27 mm or refractive error: ≥−8.00 diopters for at least one eye) were included (Table 1). In each case, the main initial symptom was binocular diplopia at distance. Demer et al. reported the following clinical definition of SES (which includes ARDE) [1, 9–10]: orthophoria or asymptomatic esophoria of ≤10Δ at 33 cm with symptomatic distance esotropia with or without vertical deviation, but without abduction deficits. In this study, patients with symptomatic esophoria/tropia of ≤10Δ at 33 cm with or without vertical deviation were included when it was confirmed that their diplopia had developed gradually, based on their medical history. All of the ARDE patients were confirmed to exhibit clinically normal abduction and horizontal saccades. The exclusion criteria were as follows: a history of trauma, cerebrovascular disorders, central nervous system disorders, superior oblique palsy, abducens palsy, thyroid eye disease, myasthenia gravis, or other obvious causes of binocular diplopia or heterotopia. Patients whose MRI scans showed obvious globe dislocation from...
the muscle cone (heavy eye syndrome) were also excluded.

Complete clinical examinations were performed in each case, including best-corrected visual acuity, refractive error, axial length, and motility examinations. Ocular misalignment was measured not only for the primary gaze position, but also for the lateral gaze positions at distance (5 m) and near (0.3 m), using the alternate prism cover test. The ocular axial length was obtained using an ultrasonic ocular axial length measurement apparatus (Optical Biometer OA-1000, Tomey Corporation, Nagoya, Japan). Ocular torsion was measured using a Maddox rod or a major amblyoscope.

High-resolution orbital T1-weighted MRI was performed using a 3T MRI scanner (Signa Excite 3.0T, GE HealthCare, Milwaukee, WI, USA) with a head coil [11]. Multiple contiguous quasi-coronal MRI scans that ran perpendicular to the long axis of the orbit (slice thickness: 3 mm) were obtained with a 256 × 256 matrix over a 12-cm square field of view in the target-controlled central gaze. These scans were used to analyze the positions of the rectus muscle pulleys. An axial localizer scan with a slice thickness of 3 mm was performed using the same matrix over a 12-cm square field of view. During the imaging, the subjects were told to fixate on small targets after their heads had been stabilized in the supine position using headbands. Within the scanner, a circular target (diameter: 2 cm) was placed in front of the subjective central position of the scanned eye (the other eye was covered). Three-dimensional fast imaging employing steady-state acquisition (FIESTA), with a 224 × 224 matrix over a 16-cm square field of view, a 0.8-mm slice thickness, a repetition time of 4.8 ms, and an echo time
of 2.3 ms (3T MR scanner, Signa Excite 3.0T), was performed to detect any abnormalities of the brainstem/ocular motor nerves, the globe, or the orbit because FIESTA has a high spatial resolution and produces high-contrast images. It was confirmed that none of the patients had any abnormalities of the brainstem, ocular motor nerves, or orbit.

The positions of the rectus muscle pulleys were analyzed using a normalized, oculocentric coordinate system, which was based on their horizontal and vertical coordinates relative to the center of the globe at position “0,” as described by Clark and Demer [12]. The nasal positions of the rectus muscle pulleys were indicated by their positive and temporal positions using negative horizontal coordinates relative to the center of the globe, and the superior positions of the rectus muscle pulleys were indicated by their positive and inferior positions using negative vertical coordinates.

Qualitative morphological evaluations of the subjects’ LR-superior rectus muscle (SR) bands were performed using quasi-coronal T1-weighted MRI scans [1, 9]. The LR-SR band was considered to be elongated or displaced (Figure 1a) if it did not retain its normal structure along the sclera of the eyeball (Figure 1d) [1, 9, 10, 13]. It was considered to have “ruptured” if it did not appear to be continuous on serial images (Figures 1b and c). No morphological evaluation of LR-SR band thickness was performed because objective evaluations of LR-SR band thickness would have been difficult due to the quality of the images. However, the frequency of LR-SR band abnormalities among the ARDE patients was examined.
The angles of the LR and SR relative to reference lines were measured using the coronal slice in which the LR-SR band was observed most clearly (Figure 2). An ellipse that exhibited the best fit to the cross-sectional area of the LR or SR was obtained [1]. The length of the major axis of the best fitting ellipse was computed. The angle (degrees) between the major axis of the LR and a line running parallel to the y-axis of the image; i.e., the vertical, was measured to obtain the LR angle (“angle a” in Figure 2). The angle between the major axis of the SR and a line running parallel to the x-axis of the image (the horizontal) gave the SR angle (“angle b” in Figure 2). The left orbital image was analyzed after it had been flipped horizontally.

We compared the data regarding the rectus muscle pulley positions, LR and SR angles, and SR-LR displacement angle with those obtained in previous studies [1, 10]. We also analyzed the correlations among the axial length, rectus muscle pulley positions, and LR and SR in the ARDE patients using regression analysis. All statistical analyses were performed using JMP 8.0® (SAS Institute, Inc.). Image J (https://imagej.nih.gov/ij/) was employed to analyze the rectus muscle pulley positions and LR and SR angles.

Results

Clinical characteristics

The clinical findings of 12 eyes of 6 ARDE patients are presented in Table 1. The patients’ distance esotropia ranged (median) from 4–25 Δ (16 Δ), and 3 patients showed vertical deviations of 4–5 Δ. Three males and 3
females were included (age range: from 51 to 69 years; mean age: 62±7.6 years). The ARDE patients’ mean (±SD) axial length was 28.5 (±1.6) mm (right: 28.4 (±1.6) mm, left: 28.6 (±1.6) mm). Their logMAR visual acuity ranged from -0.18 to -0.70 (median: -0.04). The mean (±SD, range) spherical equivalent refractive error was -12.6 (±10) diopters (range: from -21 to -6 diopters).

Rectus muscle pulley positions

The mean (±SD) positions of the rectus muscle pulleys relative to the center of the globe are indicated in Table 2. In the ARDE patients, the mean position of the MR pulley was located 1.3 mm inferior to that seen in the normal controls [14] (Welch's t test, P=0.002). Similarly, the mean position of the LR pulley in the ARDE patients was located 1.4 mm inferior to that seen in the controls (P=0.05). The nasal displacement of the MR pulley increased significantly with the axial length (R²=0.38, P=0.03) (Figure 3). No significant correlation was found between axial length and other pulley positional parameters.

LR-SR band

All 12 of the examined orbits had abnormal LR-SR bands, which exhibited elongation or displacement. Four of the 12 orbits (33%) had continuous LR-SR bands (Figure 2a). Eight LR-SR bands (67%) were discontinuous or ruptured (Figures 2b and 2c).
LR and SR angles

The mean (±SD, range) LR and SR angles of the 12 eyes were 18.8° (±8.5°, 7.9°–33.3°) and 13.2° (±8.0°, 0.3°–26.1°), respectively. The LR angle significantly increased with inferior displacement of the LR (R²=0.77, P=0.0002) (Figure 4) and inferior rectus (IR) pulleys (R²=0.36, P=0.04) (Figure 5). There were no significant correlations between the SR angle and the vertical positions of the rectus muscle pulleys. Furthermore, no significant correlation was found between the LR or SR angle and axial length.

Discussion

In the present study, inferior displacement of the horizontal rectus muscle pulleys was seen in Japanese patients with ARDE and high myopia (in comparison with the positions of these structures in the normal controls) (Table 2). Inferior displacement of the LR and MR pulleys has been reported to occur in ARDE patients without high myopia [1], which agrees with the findings of the current study. However, it was also reported that significant inferior displacement of the LR and MR pulleys was not seen in SES patients with high myopia [10]. Furthermore, in the current study it was demonstrated that the nasal displacement of the MR pulley increased with axial length. Therefore, the orbital connective tissue pulleys of patients with distance esotropia and high
myopia might be affected by the mechanical stress caused by globes with long axial lengths, in addition to the influence of aging. A further investigation of these issues involving a large number of cases is required in future.

The frequency of ruptured LR-SR bands was 67% in the current study. A previous study reported that ruptured LR-SR bands were seen in 64% of cases of distance esotropia involving patients with SES who did not exhibit high myopia, and 91% of cases of cyclovertical strabismus involving patients with SES who did not exhibit high myopia, whereas no such rupturing was seen in older or young controls [1]. However, in another study 90% of elderly subjects without strabismus displayed continuous LR-SR bands on imaging examinations [15]. These reports seem to indicate that the frequency of ruptured LR-SR bands is higher among ARDE patients (with or without high myopia) than among older controls.

The mean LR angle in the current study was 18.8±8.5°, which was between the 22.4±5.6° value seen in ARDE patients without high myopia and the 17.6±7.2° value noted in older controls in a previous study [1]. The present study was the first to measure the SR angle. Unfortunately, no meaningful results regarding the mean LR or SR angle were obtained.

Based on the relationships between the increase in the LR angle and inferior displacement of the LR pulley or IR pulley, we suggest that the destruction of the rectus muscle pulley array due to elongation or rupturing of the LR-SR band might cause tilting of the superior part of the LR and inferior displacement of the LR pulley (Figures 4 and 5). During image reading, the LR-SR band is often difficult to identify, and inferior displacement
of the LR is often evaluated qualitatively. On the other hand, it is easier to evaluate tilting of the LR. Therefore, the LR angle might be a useful parameter for judging the degree of the inferior displacement of the LR pulley. The limitations of the current study include the small number of examined cases and the fact that the normal controls were from multiple ethnic backgrounds and varied markedly in age [14].

In conclusion, in Japanese patients with ARDE and high myopia inferior displacement of the LR pulley and abnormal LR-SR bands were detected, as has been reported for ARDE patients without high myopia. The LR angle might be a useful parameter for judging the degree of LR pulley displacement. An observational study of many cases involving long-term follow-up is needed to investigate the characteristics and progression of ARDE with high myopia because the current study only examined a small number of cases.

Acknowledgments:

Compliance with ethical standards

Conflicts of interest

Fumio Shiraga received grants from Santen Pharmaceutical and Alcon Pharmaceutical. The sponsors had no control over the interpretations, writing, or publication of this study. The other authors declare that they have no conflicts of interest.
All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the ethics committee of Okayama University Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This study’s approval number is K1507-021.

Informed consent was obtained from all participants included in this study.

References


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Figure legends

Fig. 1 Quasi-coronal T1 and T2-weighted magnetic resonance images of the orbits

a In the right orbit of patient 4, a moderately elongated lateral rectus-superior rectus muscle (LR-SR) band (arrow) was observed on T1-weighted magnetic resonance imaging (MRI). b The right orbit of patient 1 exhibited a ruptured LR-SR band together with marked downward displacement of the LR and medial rectus muscle (MR) pulleys on T1-weighted MRI. c In the left orbit of patient 6, a profoundly ruptured LR-SR band and a sagging LR were observed on T1-weighted MRI. The superior part of the LR was tilted laterally, and the temporal part of the SR was displaced superiorly. d T2-weighted MRI demonstrated that the LR-SR band (arrow) retained a normal structure along the sclera of the eyeball in the left orbit of a 46-year-old male with traumatic strabismus and non-high myopia [13]. LR-SR band: lateral rectus-superior rectus muscle band, LR: lateral rectus muscle, MR: medial rectus muscle, SR: superior rectus muscle

Fig. 2 The left orbital image of Figure 1c was analyzed after it had been flipped horizontally
The superior part of the lateral rectus muscle (LR) was tilted laterally, and the temporal part of the superior rectus muscle (SR) was displaced superiorly. **a** The LR angle (degrees) between the major axis of the LR and a line running parallel to the vertical is shown. **b** The SR angle between the major axis of the SR and a line running parallel to the horizontal is shown.

**Fig. 3** Linear regression analysis detected a weak correlation between the horizontal displacement of the medial rectus muscle pulley and axial length.

**Fig. 4** Linear regression analysis revealed a significant correlation between the lateral rectus angle and the vertical displacement of the lateral rectus muscle pulley.

**Fig. 5** Linear regression analysis revealed a weak correlation between the lateral rectus angle and the vertical displacement of the inferior rectus muscle pulley.