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Original Article

Clinical Parameters Reflecting Globe/orbit Volume Imbalances in Japanese Acquired Esotropia Patients with High Myopia but without Abduction Limitations

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In high myopia, eye dislocation due to increased globe volume or tight orbital volume causes acquired esotropia. GOR (globe/orbit volume ratio), an indicator of the degree of progression of this pathology, was investigated the relationships among easily obtained clinical parameters. In this retrospective study, 20 eyes from 10 acquired esotropia patients with high myopia but without abduction limitations were examined. The mean age of the patients was 63.7 ± 8.2 years (mean ± standard deviation). Volumes were measured on the three-dimensional fast imaging employing steady-state acquisition magnetic resonance imaging images using the volume-measurement function. Correlations between GOR and the displacement angle of the globe (DA), axial length (AL), and equatorial diameter (ED) were investigated. Mean DA, AL, ED, and GOR values were 107.5 ± 8.5°, 28.86 ± 1.92 mm, 25.00 ± 1.16 mm, and 0.36 ± 0.05, respectively. Only AL was correlated with GOR ($p < 0.0001$, $R^2 = 0.6649$); DA ($p = 0.30$, $R^2 = 0.0633$) and ED ($p = 0.91$, $R^2 = 0.0008$) were not. AL was the only clinically available parameter to indicate globe/orbit volume imbalances in acquired esotropia with high myopia but without abduction limitation. AL may be important for the clinical assessment of the progression of this pathology.

Key words: acquired esotropia, high myopia (high myopes), globe volume, magnetic resonance imaging, limitation of abduction

Acquired progressive esotropia associated with high myopia is caused by dislocation of the posterior part of the eye from the muscle cone due to an increase in globe volume [1,2]. Such dislocation is correlated by the axial length (AL) of the eye, which is an indicator of the degree of progression of myopia. In this condition, the eye dislocates between the superior rectus muscle (SR) and the lateral rectus muscle (LR), thereby restricting supraduction and abduction of the eye [1-3]. In describing this pathology, it would seem that the displacement angle (DA; the angle between the line connecting the center of SR to the center of the globe and the line between the center of LR and the center of the globe) increases as AL increases; however, there is a report that AL does not correlate with DA in acquired esotropia associated with high myopia [3]. This suggests that other pathologies may be involved.

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To assess the degree of progression of acquired esotropia associated with high myopia, previous studies have used all factors: the angle of strabismus, the degree of eye movement restriction, AL, and DA [1-4]. This may indicate that it is difficult to describe the progression of acquired esotropia associated with high myopia.

In acquired esotropia associated with high myopia, the eye becomes dislocated when the globe volume increases or when the orbit volume tightens. A study using clinically measurable findings found that in acquired esotropia associated with high myopia, when limited to divergence insufficiency esotropia, this pathology is caused by an imbalance between AL and orbital length [4]. However, neither AL nor orbital length represents the actual volume. Ideally, parameters that use the actual volume of the eye or orbit should be used to evaluate this pathology. The globe/orbit volume ratio (GOR) is considered an appropriate indicator of acquired esotropia associated with high myopia due to globe/orbit volume imbalances. There are currently no reports of studies using the GOR in clinical practice, most likely because of the time and effort required to measure it.

On the other hand, the downward displacement of LR pulley has been reported in elderly individuals complicated by acquired distance esotropia and/or vertical strabismus without abduction limitations [5-7]. Such downward displacement of the LR pulley is known as sagging eye syndrome (SES) caused by age-related sagging and rupturing of connective tissue, regardless of the presence or absence of high myopia. In our previous study [8], the downward displacement of the LR pulley, which is found in SES, was also observed in Japanese age-related acquired distance esotropia patients with high myopia in the absence of globe displacement from the muscle cone.

In considering the pathology of acquired esotropia associated with high myopia, it is necessary to consider the combination of several pathologies. The pathology of acquired esotropia associated with high myopia may include highly myopic esotropia due to globe/orbit volume imbalances [2,4] and distance esotropia due to the downward deviation of LR; DA would also increase [7,8]. It remains unclear whether DA is useful for assessing globe/orbit volume imbalances in patients with acquired esotropia associated with high myopia but without abduction limitations or globe displacement.

The GOR can be measured by magnetic resonance imaging (MRI) using 3D images but is difficult to measure in general clinical practice. Therefore, easily obtained clinical parameters related to globe/orbit volume imbalances, namely DA, AL (longitudinal diameter), and equatorial diameter (ED), even in outpatient clinics, were investigated in the present study in order to identify those that strongly correlate with GOR in acquired esotropia patients with high myopia but without abduction limitations.

Subjects and Methods

This retrospective study was conducted according to a protocol approved by the Institutional Review Boards of Okayama University Hospital, Okayama Saiseikai General Hospital, and Ibara Municipal Hospital for collaborative research (K1507-021). Each subject gave informed consent. The study protocol adhered to the Declaration of Helsinki. Among strabismus patients with high myopia (an AL of ≥ 26 mm or a refractive error of ≥ -6.0 D in at least one eye) who consulted Okayama University Hospital or collaborating hospitals between January 2002 and July 2018, 10 patients (20 eyes) (including previously reported cases 1-6 [8]) who 1) had acquired esotropia, including esotropia complicated by vertical strabismus but without abduction limitations, 2) had a primary complaint of diplopia, and 3) had undergone head and orbital MRI (3T) were selected for the present study. The clinical records and laboratory test results of the patients were reviewed. Patients with nonacquired strabismus, strabismus fixus, a history of strabismus surgery, peripheral or nuclear oculomotor palsy, trochlear nerve palsy, divergence paralysis, or orbital disease were excluded. Ophthalmological tests, including corrected vision, refraction, AL, and ocular motion tests, were performed. Subjects were considered to exhibit normal abduction when the temporal corneal limbus reached the lateral canthus. The alternate prism cover test was performed to measure strabismus at a distance (5 m) and closer (0.3 m), and AL was measured using an optical coherence tomography-based biometer (Optical Biometer OA-1000, Tomey Corporation, Nagoya, Japan).

MRI was performed using a Signa Excite 3T scanner (GE Healthcare) [8,10]. The conditions for T1 quasi-coronal imaging were as follows: matrix: 256×256, field of view: 12 cm, slice thickness: 3 mm, repetition time (TR): 750 ms, and echo time (TE): 11.1 ms. The conditions for T1 axial imaging were as follows: matrix: 256×256, field of view: 12 cm, slice thickness: 3 mm, TR: 550 ms, and TE: 11.1 ms. During imaging, the subjects were told to fixate on small targets, while their heads were 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 while the other eye was covered. The three-dimensional fast imaging employing steady-state acquisition (3D-FIESTA) was conducted under the following conditions: matrix: 224×224, field of view: 16 cm, slice thickness: 0.8 mm, TR: 4.8 ms, and TE: 2.3 ms [8].

The methods for ocular and orbital volume measurements were as follows. Ocular and orbital volumes were measured using the volume measurement function of Advantage Workstation 4.2 (GE Healthcare) on 3D-FIESTA MRI images, each of which was reformatted to produce a thickness of 2 mm by tracing the globe along the sclera and cornea and by tracing the orbit along the orbital wall and the line connecting the zygomatic and lacrimal bones (black broken lines) [9] (Fig. 1). The left orbital images of a 64-year-old man were not traced because of poor quality. Nineteen globe volumes and 19 orbital volumes were obtained from the 10 patients. GOR (*i.e.*, the globe volume divided by the orbital volume) was used to measure globe/orbit volume imbalances (Fig. 2).

Using ImageJ 1.52a (Wayne Rasband, National Institutes of Health, Bethesda, MD, USA), the angle between the line connecting the area centroids of the SR and the globe and the line connecting the area centroids of the LR and the globe was measured on a quasi-coronal T1 imaging cross section located 6 mm anterior to the junction between the optic nerve and the globe as DA [7] (Fig. 3). ED (φ) was calculated from the maximum globe area (S), which was measured on cross-sectional quasi-coronal T1 images using ImageJ, according to the following formula:

$$\varphi = 2 \times \sqrt{S/\pi}$$

The conditions used to measure ED were assumed to be the same as those used to measure AL because the subjects fixated on small targets in front of the subjective central position of the scanned eye while the other eye was covered during imaging. Therefore, theoretically it was assumed that images were obtained perpendicular to the axis of the scanned eye. The cross section of a globe with high myopia is not always a circle.

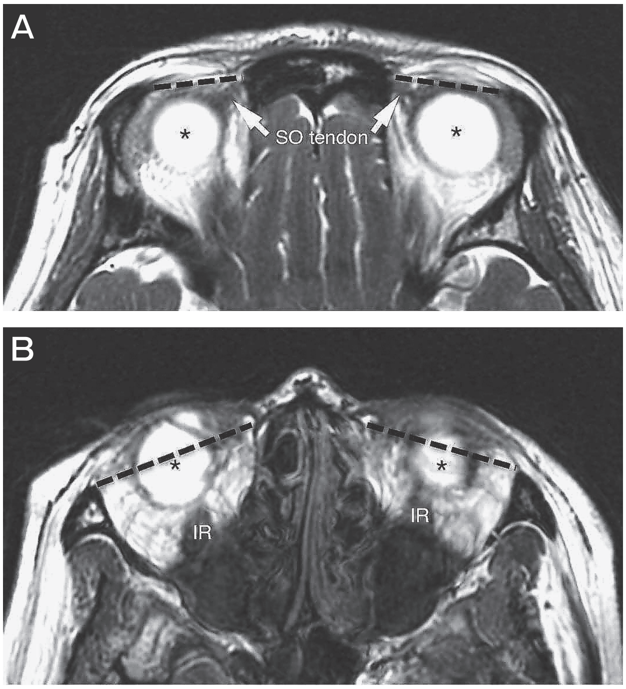

Fig. 1 Reformatted axial images of a 49-year-old female with high myopia. On each image, the orbital margins were traced, as was the line between the zygomatic and lacrimal bones (black broken lines). In addition, the margins of the globe were traced with increased intensity (*). **A**. At the upper level, the superior oblique (SO) tendons (white arrows) were examined. **B**. At the lower level, the inferior rectus (IR) muscles were examined.

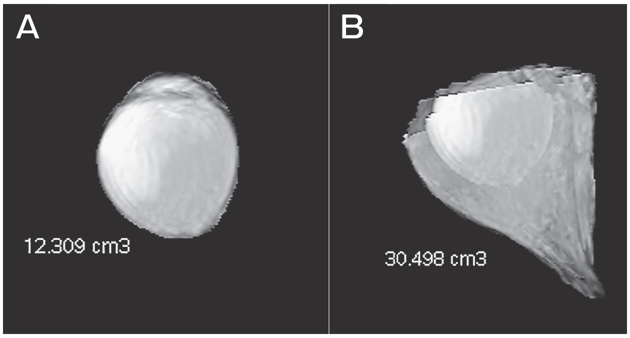

Fig. 2 3D images of the globe (**A**) and orbit (**B**) obtained in a 41-year-old male with high myopia. Volume measurements were obtained using the volumetry function of Advantage workstation 4.2 (GE Healthcare), and the results obtained are shown on the monitor. The globe/orbit volume ratio was calculated by dividing the globe volume by the orbital volume.

However, a method in which the maximum globe area is calculated on the assumption that the cross section is a perfect circle and the diameter is calculated as ED was considered to be more reproducible than ellipse approximations by measuring the major and minor axes, because the errors caused by the measurer and measurement location were small.

The relationships among DA, AL, ED, globe volume, and GOR were analyzed statistically to identify parameters that closely reflect GOR. All statistical analyses were performed using EZR [11].

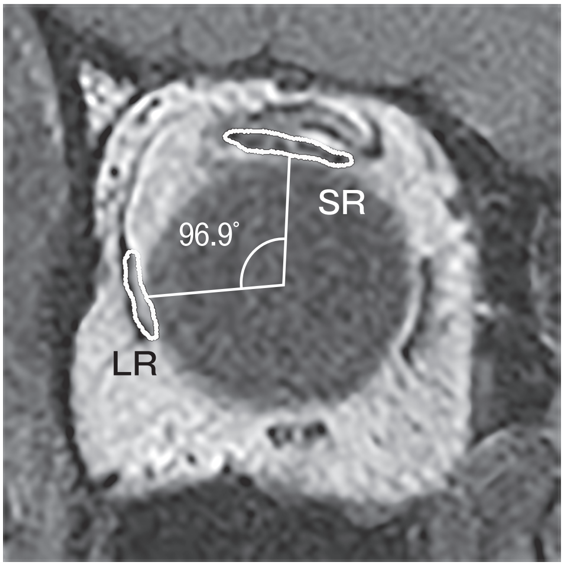

Fig. 3 Case 4, a 54-year-old female. The angle between the lines connecting the area centroids of the superior rectus muscle (SR), globe, and lateral rectus muscle (LR) in a cross-section 6 mm anterior to the junction of the optic nerve and globe on quasi-coronal T1 imaging of orbital magnetic resonance imaging was measured as the displacement angle using ImageJ.

Results

The subjects were 4 males and 6 females who were examined 0.1 to 10 years (median: 4 years) after initially noticing that they had diplopia. They had esotropia with a horizontal angle of $4\Delta-20\Delta$ during far visual fixation accompanied by a vertical deviation of $\leq 6\Delta$. Their mean age (mean±standard deviation) was 63.7 ± 8.2 years (range: 51-75 years), and the mean DA, AL, and ED were $107.5\pm 8.5°$, 28.86 ± 1.92 mm, and 25.00 ± 1.16 mm, respectively. Mean globe volume, orbit volume, and GOR were 9.43 ± 1.05 cm^3, 26.61 ± 2.85 cm^3, and 0.36 ± 0.05, respectively.

Although DA did not correlate with globe volume ($p=0.12$), GOR ($p=0.30$), or AL ($p=0.45$), it did correlate with ED ($p=0.005$) (according to Pearson's product-moment correlation coefficient) (Table 1, Fig. 4). Correlations were also observed between AL and globe volume ($p=0.004$), between AL and GOR ($p<0.0001$, Fig. 5A), and between ED and globe volume ($p=0.0004$). No correlation was observed between AL and ED ($p=0.61$) or between ED and GOR ($p=0.91$, Fig. 5B).

Discussion

Based on the results (Table 1), AL was confirmed as the parameter that reflected only GOR in highly myopic eyes with acquired esotropia but without abduction limitations. DA was also confirmed as an inappropriate

Table 1 Statistics correlations results by Pearson's product-moment correlation

		Globe volume	Globe/orbit volume ratio	Equatorial diameter	Axial length
Displacement angle	R^2	0.1348	0.0633	0.3658	0.0317
	p-value	0.12	0.30	***0.005***	0.45
Axal length	R^2	0.3916	0.6649	0.015	
	p-value	***0.004***	<***0.0001***	0.61	
Equatorial diameter	R^2	0.5258	0.0008		
	p-value	***0.0004***	0.91		

R^2, coefficient of determination.

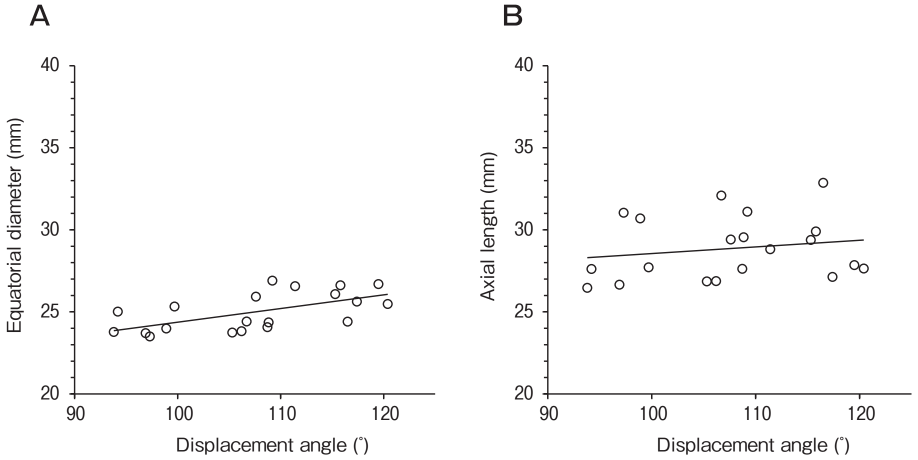

Fig. 4 A, Relationship between the displacement angle and equatorial diameter of the globe. Relationships were examined using Pearson's product-moment correlation coefficient. $p = 0.005$, $R^2 = 0.3658$, $y = 0.0831x + 16.061$.
B, Relationship between displacement angle and axial length. $p = 0.45$, $R^2 = 0.0317$, $y = 0.0404x + 24.515$.

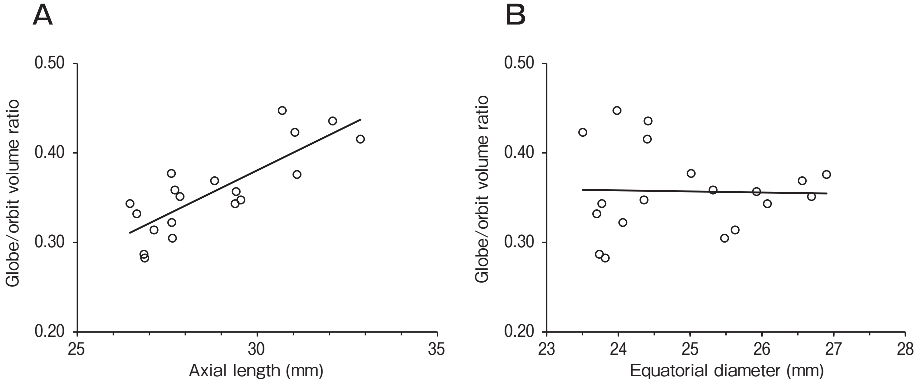

Fig. 5 A, Relationship between the axial length and globe/orbit volume ratio. Relationships were examined using Pearson's product-moment correlation coefficient. $p < 0.0001$, $R^2 = 0.6649$, $y = 0.0197x - 0.2109$.
B, Relationship between the equatorial diameter of the globe and globe/orbit volume ratio. $p = 0.91$, $R^2 = 0.0008$, $y = -0.0012x + 0.3875$.

parameter for globe/orbit imbalances. The result showing that DA did not correlate with GOR may be explained by the method used to calculate DA [7]. DA increases if there is a downward displacement in LR; therefore, it increases, even in the absence of marked axial elongation, if LR is inferiorly displaced, as is observed in age-associated pulley degeneration (Fig. 6A) [5, 6]. Even if the GOR is large, DA does not increase if there is no marked nasal displacement of SR or downward displacement of LR (Fig. 6B). A possible reason for the correlation between DA and ED is that the simultaneous expansion of the globe toward the equatorial region triggers the downward displacement of LR, and the downward displacement of LR might cause an increase in DA, even in the absence of posterior globe prolapse (Fig. 6C).

Even though both AL and ED were correlated with globe volume, AL was positively corelated with GOR but not with ED (Table 1, Fig. 5). This suggests that an increase in ED does not affect GOR because the orbital volume increases along with the increase in globe volume, but the reason why the orbital volume increases in response to an increase in ED is unknown.

The mean orbital volume in the present study (26.61 ± 2.85 cm^3) was close to the normal orbit volume (26.78 ± 4.04 cm^3) reported by Nishida *et al.* [9] in an analysis of MRI images. Therefore, changes in the globe volume may affect GOR.

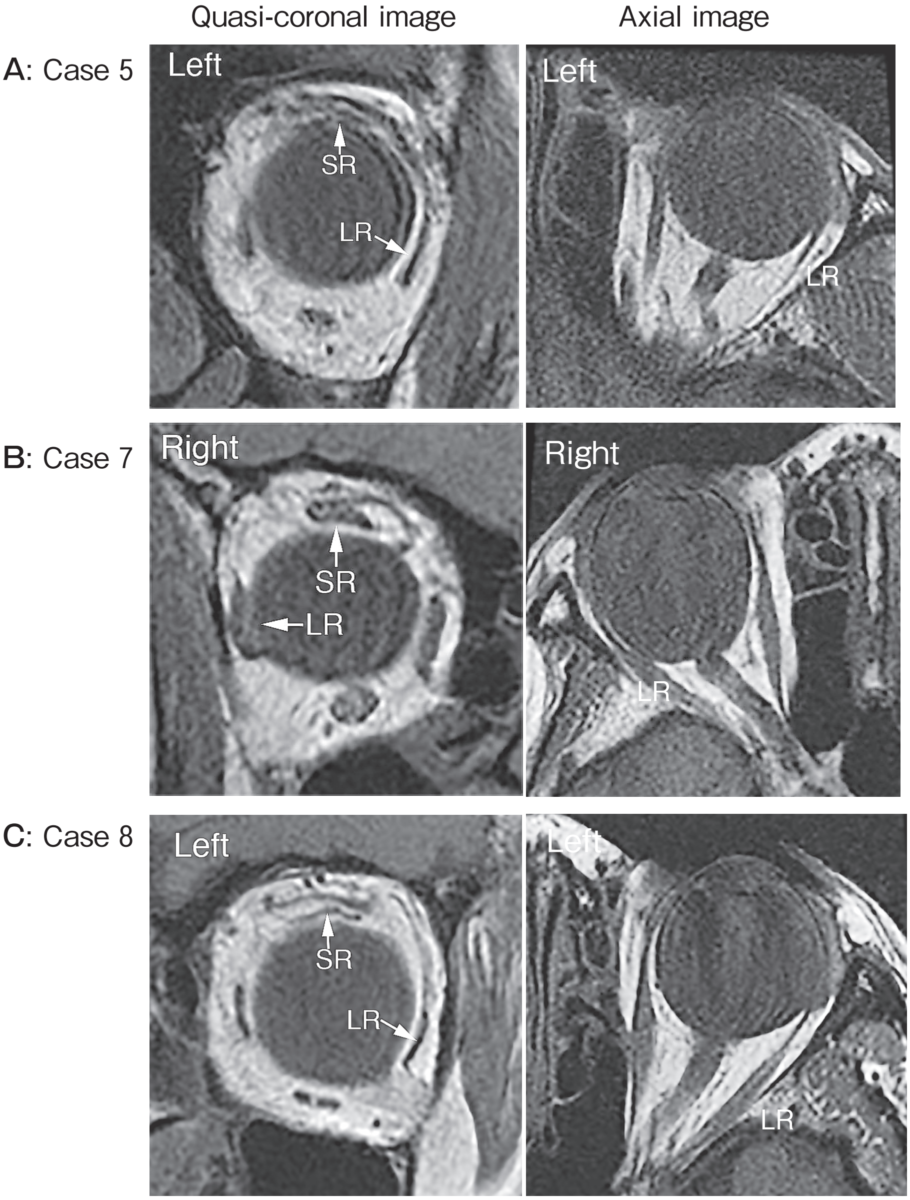

Fig. 6 Upper low (**A**): Case 5, a 69-year-old male. Displacement angle of the globe (DA): 120.4°, globe/orbit volume ratio (GOR): 0.305, axial length (AL): 27.64 mm, equatorial diameter (ED): 25.48 mm. lateral rectus muscle (LR). superior rectus muscle (SR). Middle low (**B**): Case 7, a 75-year-old female. DA: 106. 7°, GOR: 0.436, AL: 32.09 mm, ED: 24.41 mm.
In Case 7 compared to Case 5, DA was smaller while axial elongation and staphyloma were more prominent and GOR was larger. In the coronal section, connective tissue was present between the globe and LR in Case 5, whereas no clear connective tissue was observed in Case 7 between the globe and LR, and the globe was considered to be in direct contact with the LR.
Lower low (**C**): Case 8, a 74-year-old female. DA: 119. 5°, GOR: 0.351, AL: 27.85 mm, ED: 26.69 mm.
In Case 8 compared to Case 5, the space of orbital connective tissue between the lower aspect of the globe and inferior orbital wall was smaller, and GOR was larger. AL and DA were similar to those in Case 5.

In a previous study that compared acquired progressive esotropia with globe displacement from the muscle cone associated with elongation of the ocular axis accompanying abduction and supraduction disorders (esotropia fixus [1, 2, 12], heavy eye syndrome (HES) [7]) and SES accompanying high myopia [7], a significant difference was observed in DA but no marked difference was observed in AL (Table 2). Another study found that DA and AL did not correlate in high myopic strabismus [3]. DA did not correlate with AL or globe volume (Table 1) in the present study. Therefore, factors other than AL may be involved in the pathogenesis of HES.

As a limitation of the present study, both of each patient's eyes were used as independent data because of the small number of patients. It is generally inappropriate to use the right and left eyes of a subject as independent data; only one eye should be selected.

In summary, AL was the only clinical parameter to indicate globe/orbit volume imbalances in patients with acquired esotropia with high myopia but without abduction limitation; DA did not. AL may be import-

Table 2 Comparison of age, axial length, and displacement angle in patients with late onset esotropia with high myopia among the current and previous studies

	Current study (2019)	Yamaguchi [2] (2010) Highly myopic strabismus	Kohmoto [4] (2011) Divergence insufficiency type	Nakano [3] (2014) Highly myopic strabismus	Tan [7] (2015) HES vs SES*
Age (years-old) (Mean ± SD)	63.7 ± 8.2	63.8 ± 8.3	58.9 ± 8.6	65.5 ± 17.9	HES: 63 ± 12 SES: 62 ± 8
Axial length (mm) (Mean ± SD)	28.86 ± 1.92	31.9 ± 2.1 (High-myopia: 29.5 ± 2.1)	27.6 ± 1.6 (High-myopia without diplopia: 27.6 ± 1.3)	28.9 ± 2.03	HES: 32 ± 5 SES: 32 ± 6
Displacement angel (°) (Mean ± SD)	107.5 ± 8.5	179.9 ± 30.8 (High-myopia: 105.2 ± 8.4)	112.9 ± 9.7 (High-myopia without diplopia: 99.2 ± 2.8)	132 ± 14.0	HES: 121 ± 7 SES: 104 ± 11

*HES, Heavy eye syndrome; SES, Sagging eye syndrome. **SD, standard deviation.

ant for the clinical assessment of the progression of this pathology. DA should not be used in the evaluation of this disease. An observational study involving a large number of cases is needed to investigate this issue further because the present study was retrospective and examined only a small number of cases.

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