Analysis of Axial Length in Young Patients with Marfan Syndrome and Bilateral Ectopia Lentis by Z-Scores

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Keywords

Axial length · Z-score · Marfan syndrome · Ectopia lentis

Abstract

Introduction: Marfan syndrome (MFS) is characterized by ectopia lentis (EL) and elongated axial length (AL). The characteristics of AL in young patients with MFS and bilateral EL before the lens surgery are not fully understood. **Methods:** This study reviewed MFS patients under 20 years old with bilateral EL from January 2015 to October 2020. The Z-scores were introduced in terms of the number of standard deviations from the mean of age-matched normative data. Using Z-scores, the distribution of AL and influence factors were evaluated. The correlations between AL and other biometrics were analyzed. **Results:** We reviewed 183 patients and enrolled both eyes. The mean age was 8.44 ± 4.69 years. About 36% of the patients were children under 6 years old. The median AL increased from 23.16 mm under 5 years old to 26.20 mm in the 16–20 age group, and when plotted, the trend presented a logarithmic curvature ($R^2 = 0.145$, $p < 0.001$). The median Z-AL score was 1.24. One-third of eyes

had Z-score < 0 . About 20% of the patients had AL difference over 1 mm between the right and left eyes, and the right one had longer Z-AL scores ($p = 0.013$). The eye complicated with megalocornea (10, 7.04%) had larger Z-AL scores (4.72 ± 3.51 vs. 1.10 ± 2.25 , $p = 0.002$). A positive correlation was found between Z-AL and Z-corneal curvature radius ($r = 0.265$, $p < 0.001$). **Conclusion:** Young patients with bilateral EL but small AL should not be excluded from MFS without systematic examination. The age-adjusted Z-score will facilitate further study of the individual variations in AL across different ages.

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Introduction

As an important component of the ocular refractive media, a normal crystalline lens is critical to the development of the visual system. Ectopia lentis (EL) refers to the dislocation of the lens from its physiological position, which may cause refractive errors of varying severity, poor visual acuity, and amblyopia in young patients [1]. The major etiology of congenital EL is Marfan syndrome (MFS, OMIM 154700), the prevalence of which ranges

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Fig. 1. Age distribution of MFS patients with bilateral EL. Subdivided groups were marked by different colors: <5 years old (yellow), 6–8 years old (gray), 9–11 years old (blue), 12–15 years old (cyan), and 16–20 years old (purple). The number of eyes (*n*) in each group was labeled. EL, ectopia lentis; MFS, Marfan syndrome.

from 4.6 to 6.5 per 100,000 [2–4]. MFS is an autosomal dominant hereditary disease caused by fibrillin-1 (*FBN1*) gene mutations [5]; fibrillin-1 is the main constituent of the microfilaments, which are the key structural components of the ciliary zonules [6]. Mutations of *FBN1* result in the impaired suspension of the crystalline lens in its anatomic position [7]. In addition to EL, the eyes of patients with MFS are characterized by long axial length (AL), low corneal curvatures, severe astigmatism, and dense myopia [8].

Refractive and biometric characteristics of patients with MFS have been reported [9–13]; however, most studies have used a relatively small sample size without control groups. To our knowledge, few investigations have examined the distribution of AL and the correlations between AL and other biometrics before lens surgery in young MFS patients with bilateral EL. In this retrospective study of a relatively large group of patients, we aimed to investigate the overall status of axial development in MFS patients younger than 20 years old and the relationships between AL and patient demographics, including age, sex, family history, and comorbidities. We introduced the age-adjusted Z-scores by using external controls to analyze the correlations of AL development with the corneal curvature radius (CCR), AL/CCR ratio, and white-to-white horizontal corneal diameter (WTW). Our results provide a useful reference for the precise planning

of surgical interventions for young MFS patients with bilateral EL.

Methods

Patient Eligibility

The study was approved by the Human Research Ethics Committee of the Eye & ENT Hospital of Fudan University (ChiCTR2000039132) and carried out in accordance with the Declaration of Helsinki. Informed consent in written form was obtained from all patients and the patients' guardians for those under 18 years old. The inclusion criteria were as follows: (1) patients diagnosed as having MFS or possible MFS according to the Ghent-2 nosology [14], (2) patients under 20 years old (because they are defined as “young individuals” in Ghent-2 nosology, who have different diagnostic criteria), and (3) patients with bilateral EL under slit-lamp examination during complete pupillary dilation. Patients with the following features were excluded from the study: (1) lens dislocated into the anterior chamber or vitreous body; (2) a history of traumatic lens dislocation; (3) pre-existing ocular comorbidities, such as congenital cataract, retinal tears, retinal detachment, corneal ectasia, or glaucoma; and (4) the presence of other connective tissue diseases. Both eyes were selected because we found a significant difference in the AL between the 2 eyes of each participant by the paired *t* test ($p = 0.013$). The recorded patients' ages were the ages at the examination.

Ophthalmic Examinations

The participants were examined by board-certified ophthalmologists, and their medical and family histories were evaluated.

Fig. 2. Differences in AL among MFS patients with bilateral EL of various ages. **a** The violin graph showed the distribution of AL in different age subgroups. *** $p < 0.001$ (Kruskal-Wallis test). **b** Scatterplot of AL by patients' ages and fitted logarithmic curve. The shaded area demonstrated the 95% CI. AL, axial length; EL, ectopia lentis; MFS, Marfan syndrome.

All patients were examined for EL by slit-lamp examination under complete pupillary dilation. Bilateral EL was defined as the displacement of the lens from its normal position in both eyes. The AL, CCR, WTW, and corneal astigmatism were measured using partial coherence interferometry (IOLMaster 500 and 700; Carl Zeiss Meditec AG, Jena, Germany). Five valid AL readings and 3 readings of both CCR and WTW were taken.

Z-Score Calculation

The AL and other ocular biometrics were compared to age-matched normative data published in the literature that were cross-sectional, epidemiological investigations of the Chinese population. The Z-score of AL (Z-AL) was calculated using the following formula: $Z\text{-AL} = (\text{measured AL} - \text{normative AL}) / \text{normative standard deviation (SD)}$. The Z-score describes the position of a raw value in terms of its distance from the mean when measured in SD units. For example, a Z-score ≥ 2.0 corresponds to a measurement ≥ 2.0 SD above normal. For patients of 4–18 years of age, the AL, CCR, and WTW were compared with normative measurement data in the Shandong Children Eye Study [15–17]. For those over 18 years old, the measurements for 18-year-old children in the same study were employed as reference data. For 3-year-old patients, the Shanghai Pudong Eye Study was used as the reference [18] (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517384). Because of a lack of normative measurements for 2-year-olds in the Chinese population, the Z-score was not analyzed in 1 patient (2 eyes). The Z-scores for other biometric parameters, such as Z-CCR and Z-WTW, were calculated similarly.

Statistical Analysis

Continuous variables were described in mean $\pm$ SD or median and interquartile range. Categorical variables were described in counts or proportions as appropriate. The distributions for age and ocular biometric parameters were tested for normality with the Kolmogorov-Smirnov test. The one-way analysis of variance or Kruskal-Wallis test was used, as appropriate, to compare the AL among different age groups. For independent samples, the t test or Wilcoxon test was used to analyze differences in the AL among patients with different factors, including gender, family history, and comorbidities. And, the paired t test or paired Wilcoxon test was used to evaluate the difference in AL between the left and right eye. A logarithmic correlation between AL and age was calculated for MFS patients. Correlations between the Z-score of AL and Z-scores of other biometric variables were analyzed using Spearman's correlation. All analyses were 2-tailed, and the statistical significance was set as a p value of < 0.05 . Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Demographics

The ocular biometric parameters of 183 MFS patients under 20 years old with bilateral EL were collated. Both eyes were enrolled. All participants were Chinese and

Fig. 3. Differences in the Z-AL score of MFS patients with bilateral EL of different ages. **a** The violin graph showed the distribution of Z-AL scores in different age subgroups. ns, $p > 0.05$ (Kruskal-Wallis test). **b** Proportions of Z-AL scores in different age groups. AL, axial length; EL, ectopia lentis; MFS, Marfan syndrome.

55.49% were male. The age distribution of the participants is shown in Figure 1, and the mean age was 8.44 ± 4.69 years (range, 2–20 years). Patients under 6 years old constituted the highest proportion: 36.07% of the total participants. The number of patients decreased with the advancing age group. Subjects were further stratified by age considering the characteristic of AL growth in normal children: ≤ 5 , 6–8, 9–11, 12–15, and 16–20 years old.

The AL Distribution

The AL increased as the patients aged. The distribution of AL did not present a Gaussian distribution ($p < 0.001$). The skewness was 0.970, and the kurtosis was 0.685. The overall median AL was 23.97 mm (p_{25} , 22.71; p_{75} , 25.81). The median AL and interquartile range in different age groups are shown in Figure 2a. There was a significant difference in the AL among the age subgroups ($p < 0.001$), and the trend in AL increase shown in the scatterplot followed a logarithmic curve ($R^2 = 0.145$, $p < 0.001$) (Fig. 2b). Considerable variation in AL was observed among patients of the same age.

The Z-AL Score Distribution

The Z-AL did not increase as the patients aged. The Z-AL scores did not follow a Gaussian distribution ($p < 0.001$). The skewness was 0.973, and the kurtosis was 0.255. The overall median Z-AL was 1.24 mm (p_{25} , -0.22; p_{75} , 3.41). The median AL and interquartile range in different age groups are shown in Figure 3a. The age difference was successfully adjusted by the Z-AL score because there were no statistical differences in the Z-AL score among the different age groups ($p = 0.531$). The distribution of AL within the same age group was well represented by the Z-score (Fig. 3b). The proportion of the Z-AL score shared a similar pattern among the age subgroups. A considerable variation in Z-AL was observed. In all the age groups, about 30% of patients had a Z-AL score < 0 , and extremely long AL (Z-AL score ≥ 3) was observed in approximately 30% of patients (Fig. 3b).

Relationship between Z-AL Score with Different Factors

To further explore the factors influencing the AL of the participants, we analyzed the relationships among AL or Z-AL score and laterality, sex, and family history (Table 1).

Table 1. Comparison of the AL and Z-AL between different factors according to age groups

Factor	Z-AL score		
	eyes, <i>n</i>	mean $\pm$ SD	<i>p</i> value
<i>Laterality</i>			
Right	182	1.85 $\pm$ 2.72	0.013
Left	182	1.62 $\pm$ 2.64	
<i>Sex</i>			
Male	202	1.86 $\pm$ 2.76	0.267
Female	162	1.59 $\pm$ 2.58	
<i>Family history (MFS)</i>			
Positive	144	1.70 $\pm$ 2.56	0.907
Negative	220	1.77 $\pm$ 2.76	
<i>Microspherophakia</i>			
Positive	20	2.53 $\pm$ 2.64	0.145
Negative	346	1.69 $\pm$ 2.68	
<i>Megalocornea</i>			
Positive	10	4.72 $\pm$ 3.51	0.002
Negative	132	1.10 $\pm$ 2.25	

p values < 0.05 are highlighted in bold (laterality, paired Wilcoxon test) (gender, family history, and comorbidities, Wilcoxon test). AL, axial length; MFS, Marfan syndrome; SD, standard deviation.

The right eyes had slightly but significantly larger Z-AL scores than the left ones (1.85 $\pm$ 2.72 vs. 1.62 $\pm$ 2.64, *p* = 0.013). The scatterplot showed a considerable axial difference (Δ AL = AL of the right eye – AL of the left eye) between the right and left eyes (Fig. 4a). About one-fifth of patients had the absolute value of Δ AL over 1 mm, and a longer AL in the right eye was observed in 101 patients (55.19%) (Fig. 4b). Males seemed to have longer AL, but the difference was not significant (*p* = 0.267). There was no difference between patients with or without a family history of MFS (*p* = 0.907). In the 20 eyes (10.87%) with microspherophakia, the AL appeared to be larger, but the difference was not statistically significant (*p* = 0.145). Of the 142 eyes (38.80%) with qualified WTW measurements, megalocornea (WTW $\geq$ 13) was found in 10 (7.04%). MFS eyes complicated by megalocornea had larger Z-AL scores (4.72 $\pm$ 3.51 vs. 1.10 $\pm$ 2.25, *p* = 0.002).

Correlation between AL with Biometry Parameters as Z-Scores

Z-AL scores were plotted against Z-CCR, Z-WTW, AL/CCR ratio, and corneal astigmatism. There was a positive correlation between Z-AL and Z-CCR (*r* = 0.265, *p* < 0.001)

(Fig. 5a) and a positive correlation between Z-AL and AL/CCR ratio (*r* = 0.762, *p* < 0.001) (Fig. 5b). No correlation was found between Z-AL and Z-WTW (*r* = 0.052, *p* = 0.537) (Fig. 5c). A mild but significant correlation was observed between Z-AL and AST (*r* = 0.151, *p* = 0.004) (Fig. 5d).

Discussion

About 60% of patients with MFS have EL, which is usually bilateral, progressive, and has a superior direction [8]. The implantation of an intraocular lens (IOL) plays a crucial part in the postoperative visual rehabilitation of children. The AL is the most important factor affecting the accuracy of IOL power, and a 1-mm error of measurement can induce an approximate 2.5-D refractive error [19]. Previous investigations have shown the AL in the eyes of patients with EL is different from that in normal eyes [20]. However, there have been few studies of the characteristics of the AL in young MFS patients before lens surgery. In this study, we recruited 183 MFS patients with bilateral EL to investigate the distribution and influence factors of AL in the developing age. The age-adjusted Z-score is a powerful tool to study the influencing factors and the correlation between AL and other biometrics.

Here, we present the distribution of AL in MFS patients with bilateral EL at a relatively young age. Similar to the results for the normative cohort [21], there was a positive correlation between AL and age in the current study. A logarithmic correlation between AL and age was found in congenital cataract patients [22]. AL increases dramatically in the first 2 years of life and then grows at a slower rate until adulthood [22]. The AL growth trend for patients in the current study also presented a logarithmic curvature. However, because of the limited number of patients under 3 years old, the high growth rate normally seen in the early stage of the logarithmic curve is absent in this study. Previous studies found that EL can manifest at an early age: EL is recognized at age 0 in 38% of patients with neonatal MFS [23], and 12.5% of MFS patients show EL before 3 years of age [8]. The prevalence might have been underestimated because of the difficulties for young patients expressing themselves and poor cooperation under ophthalmic examination. The distribution of AL among MFS patients under 3 years old is uncertain and warrants further study.

The Z-score has been used by cardiologists to adjust for body surface area when measuring aortic sinus diameters in various individuals [24], and new Z-scores have

Fig. 4. Analysis of AL difference of the right and left eyes of MFS patients with bilateral EL. **a** Scatterplot of AL in the right (AL-OD) and left (AL-OS) eyes. The difference of AL (Δ AL) was manifested in different colors. Δ AL over 4.0 mm or below -4.0 mm was marked in dark. **b** Distribution of the difference of AL (Δ AL = AL-OD - AL-OS). AL, axial length; EL, ectopia lentis; MFS, Marfan syndrome.

been developed to normalize age, sex, height, and weight [25]. A Z-score ≥ 2.0 (≥ 3.0 for patients under 20 years old) is a major criterion in the diagnosis of MFS [14]. However, the age-adjusted Z-score introduced in the current study was not intended to assist in making a diagnosis based on ocular biometrics, which has been excluded from the 2010 Ghent-2 criteria due to uncertain specificity [14]. In this study, the Z-scores successfully normalized the age differences in AL and other parameters by comparing age-matched published normative values.

The distribution of AL across the age groups was well represented by the Z-score. The median AL was 1.24 SD from the normative mean measurement. About 30% of eyes had relatively long AL (Z-AL score ≥ 3) and the largest had a Z-score of 10.68. A long AL has been proven to be a risk factor for retinal detachment [26] and open-angle glaucoma [27] in the eyes of MFS patients. Thus, patients with longer AL should have more intensive ophthalmic exams, especially when they have a visual complaint. Although a long AL has been recognized as an ocular manifestation of MFS, our study showed that about 30% of the eyes had a short AL (Z-AL score < 0), and the proportion was similar among the different age groups. Thus, young patients with bilateral EL but small

AL should not be simply diagnosed as having idiopathic EL without considering the systematic features. Since the manifestations of MFS can be atypical at a young age [28], a genetic test or careful follow-up is strongly recommended.

Considerable variation was observed among those of the same age, indicating that the development of the AL in MFS patients is associated with multiple factors in addition to age. However, the sex and family history of MFS were not associated with differences in AL. One possible explanation for the AL variations is the allelic heterogeneity of *FBN1* mutations. More than 3,000 mutations of *FBN1* are known today [29], but only 14.20% of the mutations are recurrent [30]. The misfolded fibrillin-1 and the disorganized elastin in the scleral stroma could lead to stretching of the sclera through the 2 physiological functions of fibrillin-1 (structure component or TGF- β signaling mediator) and by different underlying genetic mechanisms (haploinsufficiency or dominant-negative effect) [30]. In addition, the heterogeneity of *FBN1* mutations could lead to various degrees of EL, which accelerates globe growth via defocus or deprivation. Further genotypic-phenotypic analyses are required to understand the variations in AL and severity of EL. The Z-score will be

Fig. 5. Scatterplots showing correlations (Spearman's correlation) between the Z-AL score and Z-CCR score (**a**), AL/CCR ratio (**b**), Z-WTW score (**c**), and corneal astigmatism (**d**) in MFS patients with bilateral EL. AL, axial length; CCR, corneal curvature radius; MFS, Marfan syndrome; WTW, white-to-white horizontal corneal diameter; EL, ectopia lentis.

helpful when analyzing *FBN1* mutations and ocular phenotypes in young patients of different ages. However, a considerable AL difference is observed in bilateral eyes of the same patient. About 20% of patients had AL differences over 1 mm between the bilateral eyes, and the greatest difference is 7 mm, indicating that environmental factors and epigenetic factors may contribute to the difference. The aniso-axial length can lead to anisometropia and challenge the choice of IOL power. The AL of the right eyes was significantly longer than the left ones, probably because of dextrorhuality and right dominance of eyes [31]. However, further studies are warranted to test this hypothesis.

A previous study described the ocular biometrics of MFS eyes based on age stratification [32]. Although AL is an important indicator of eyeball development, the

relationships between AL and other biometric parameters have been scarcely reported in MFS patients. Correlations among AL and other biometrics were analyzed in the form of the age-adjusted Z-scores, and a positive correlation was found between AL and CCR. The decreasing power of the cornea appears to play an emmetropizing role in response to increasing AL; however, this compensatory capacity reportedly reaches its limit at an AL/CCR ratio of 3 [33]. In the linear regression model used in the current study, the AL/CCR ratio exceeded 3 when the Z-AL score was above 2.16. However, the correlation between AL and preoperative spherical equivalent was not studied because the displaced and deformed lens can affect the total refractive power. Nevertheless, we hypothesized that in the postoperative eyes with centered and stabilized IOL positions, a long-term myopic shift is

expected in the developing eyes when the Z-AL exceeds 2.16. Therefore, the selection of IOL power deserves more careful consideration in those patients to achieve the refractive target. Microspherophakia and megalocornea are sometimes found in eyes of MFS patients [34, 35]. To the best of our knowledge, the prevalence of these 2 comorbidities in MFS patients with bilateral EL has never been reported. Our study indicated that approximately 10% of eyes of MFS patients were complicated by microspherophakia, the AL of which seemed to be greater than that of normal eyes but not to a statistically significant degree. Megalocornea was found in around 7% of MFS eyes. Although WTW measurements did not change proportionally with AL growth, MFS eyes complicated by megalocornea had significantly larger AL on average. Previous studies have shown that there was higher corneal astigmatism in the eyes of MFS patients [36, 37]. Additionally, we found that patients with smaller AL generally had higher corneal astigmatism. Thus, residual astigmatism from the cornea after lens aspiration and IOL implantation, especially in MFS eyes with smaller AL, is a challenge for postoperative visual rehabilitation.

The results of this study must be assessed within the context of its limitations. First, the data are not a complete representation of MFS patients and only relate to surgical patients with bilateral EL, which prevented us from detecting differences in eyes with unilateral EL or without EL. Second, the external controls used in our study were school-based, cross-sectional studies of young Chinese individuals from a large sample size. The conclusions should be viewed with caution for other ethnic populations. Third, adult patients were excluded from the current study, as AL was shown to be stable in adults (>30 years old) with MFS during a 10-year follow-up [38]. The cross-sectional nature of our study also limited our ability to track changes in AL data over time. Despite these limitations, the results of this study describe the overall distribution of AL in the eyes of MFS patients with bilateral EL and cover a relatively young patient group compared to the available literature.

Conclusion

The mean AL of MFS was found to be longer than the age-matched controls, especially in the eyes complicated by megalocornea. But one-third of patients still had an AL below the normative average. The considerable

individual variation indicates that young patients with bilateral EL but small AL should not be excluded from MFS diagnoses without systematic examinations. The Z-scores normalized the age difference in AL and other parameters by comparing age-matched published normative values, and this technique facilitates the further study of the influence factors of AL in young patients of different ages. A full understanding of the AL will be helpful for surgical planning and complication monitoring.

Statement of Ethics

The study was approved by the Human Research Ethics Committee of the Eye & ENT Hospital of Fudan University (ChiCTR2000039132) and carried out in accordance with the Declaration of Helsinki. Informed consent in written form was obtained from all patients and the patients' guardians for those under 18 years old.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Z.-X.C. and J.-H.C. were involved in study design, data collection, and manuscript preparation. M.Z. and J.-L.Z. participated in data acquisition. M.D. and T.-H.C. critically reviewed the manuscript. Y.-H.J. and Y.-X.J. supervised the project. All the authors have read and approved the final manuscript.

Data Availability Statement

The datasets generated and/or analyzed during the present study are not publicly available (obtained from Eye & ENT Hospital, of Fudan University, Shanghai repository), but are available from the corresponding author upon reasonable request.

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