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Changes of optic nerve head morphology in high myopia

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高度近视的视盘形态学改变

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摘要

目的:分析高度近视(HM)患者中年龄、眼轴(AL)及等效球镜(SE)与视盘形态学特征的相关性。

方法:对 HM 患者的临床资料进行回顾性研究,并根据年龄、AL 及 SE 对患者进行了分组。按照年龄分组为:年龄 Age1 组(<20 岁)、Age2 组(20-29 岁)和 Age3 组(≥30 岁)。按照 SE 分组为:SE1 组(-9 D≤SE<-6 D)、SE2 组(-12 D≤SE<-9 D)和 SE3(SE<-12 D)。按照 AL 分组为:AL1 组(<26 mm)、AL2 组(26 mm≤AL<27 mm)、AL3 组(27 mm≤AL<28 mm)和 AL4 组(AL≥28 mm)。探讨不同年龄、AL、SE 对视盘形态学参数的影响及其相关性。

结果:本研究共分析了 188 例 HM 患者的 188 只右眼(男 65 例,女 123 例),平均年龄为 25.00±6.44 岁。不同年龄组别患者视盘形态学相关参数变化小,差异无统计学意义(均 $P>0.05$)。视盘倾斜指数和视盘旋转角度与年龄、AL 及 SE 均无相关性。然而,视盘-中心凹距离(DFD)、α 角、视盘最大直径(LD)、视盘最小直径(SD)及视盘面积与 AL 及 SE 均呈显著相关(DFD: r=0.195, 0.221; α 角: r=-0.242, -0.266; LD: r=0.319, 0.295; SD: r=0.274, 0.225; 视盘面积: 0.310, 0.265; all $P<0.01$),但与年龄无显著相关性($P>0.05$)。在 HM 患者中,当 AL 超过 28 mm 时,α 角度显著减小,而 DFD 显著增大。

结论:DFD 和 α 角度可作为评估 HM 患者中视盘形态变化的指标。HM 患者中视盘形态变化的主要原因与 AL 及 SE 的增加有关,而非年龄因素。

关键词:高度近视;视盘;形态学;眼轴

Abstract

• AIM: To analyze the correlation of age, axial length (AL) and spherical equivalent (SE) with the morphology of optic nerve head (ONH) in high myopia (HM) patients.

• METHODS: In this retrospective study, the medical records of HM patients were reviewed, and were classified based on age, AL, and SE. Participants were stratified into three age subgroups: Age1 (<20 y), Age2 (20-29 y), and Age3 (≥30 y). For SE, participants were classified into three subgroups: SE1 (-9 D≤SE<-6 D), SE2 (-12 D≤SE<-9 D), and SE3 (SE<-12 D). AL was further divided into four groups: AL1 (<26 mm), AL2 (26≤AL<27 mm), AL3 (27≤AL<28 mm), and AL4 (AL≥28 mm). The effects of different ages, AL, and SE on optic disc morphological parameters and their correlations were investigated.

• RESULTS: Totally 188 right eyes from 188 HM patients (65 males and 123 females) with mean age of 25.00±6.44 y were analyzed. No significant difference was observed in morphological data of ONH among the age groups (all $P>0.05$). The ONH tilt index and ONH rotation angle had no correlation with the age, AL, and SE. However, the optic disc-fovea distance (DFD), angle α, largest diameter (LD), short diameter (SD), and ONH area were significantly correlated with AL and SE (DFD: r=0.195, 0.221; angle α: r=-0.242, -0.266; LD: r=0.319, 0.295; SD: r=0.274, 0.225; ONH area: 0.310, 0.265; all $P<0.01$) but not with age ($P>0.05$). In HM, as the AL grew larger than 28 mm, the angle α was smaller and the DFD was larger significantly.

• CONCLUSION: The DFD and angle α can be used as evaluation indicators for the changes of ONH morphology in HM patients. The main cause of morphology change may be related to AL and SE increase rather than age.

• KEYWORDS: high myopia; optic nerve head; morphology; axial length

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INTRODUCTION

Myopia is the most prevalent correctable visual impairment worldwide. The prevalence of myopia, especially the prevalence of high myopia (HM) is continuously increasing[1]. In clinic, it has been observed that the development of HM is often accompanied by changes in the optic nerve head (ONH) morphology, including relative position and size of ONH, ONH tilt and rotation, atrophy of the peripapillary tissue[2-3]. HM is generally characterized by the axial length (AL) elongation with the dilation and thinning of the eyeball wall[4]. Due to the AL increase, degenerative structural changes start exhibiting in the retina, especially at the posterior pole of the retina. In this study, we used fundus photography to detect the ONH morphology for HM. We compared morphology parameters at different ages, spherical equivalent (SE), and AL. Further, we assessed the correlation between morphology parameters with these factors to screen out the related and predictable indicators of HM related degenerative changes.

PARTICIPANTS AND METHODS

Ethical Approval The study adhered to the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Hospital, China. Informed consent was waived because of the retrospective and anonymous nature of this study.

Participants From May 2023 to June 2024, the medical records of consecutive patients with HM in the Refractive Department were reviewed. Comprehensive examinations including slit-lamp biomicroscope, intraocular pressure (IOP), AL (IOL Master 700; Carl Zeiss Meditec, Germany), ultra-widefield fundus imaging (Optos; Daytona P200T, Nikon, Japan) and diopter were assessed.

Inclusion criteria: 1) SE<-6.00 D; 2) IOP≤21 mmHg. In addition, patients were excluded from the study if they had hypertension, diabetes, systemic connective tissue disorder, any other ophthalmic disease (such as cataract, glaucoma, macular hole, retinal hole, retinal haemorrhage *etc.*), history of ophthalmic trauma and surgery. Totally 188 patients were enrolled in the retrospective study. Participants were stratified into three age subgroups: Age1 (<20 y), Age2 (20-29 y), and Age3 (≥30 y). For SE, participants were classified into three subgroups: SE1 (-9 D≤SE<-6 D), SE2 (-12 D≤SE<-9 D), and SE3 (SE<-12 D). AL was further divided into four groups: AL1 (<26 mm), AL2 (26≤AL<27 mm), AL3 (27≤AL<28 mm), and AL4 (AL≥28 mm). The effects of different ages, AL, and SE on optic disc morphological parameters and their correlations were investigated.

Parameters from Optos We used Optos ultra-widefield imaging camera for digital photography of the retinal fundus, and the images were exported into the Image-Pro Plus (version 6.0) to measure the morphology of ONH. Such as disc-fovea distance (DFD), angle α, largest diameter (LD), short diameter (SD), ONH area, tilt index and rotation angle. The measurement unit of ONH were expressed as the total number of pixels using the Image-Pro Plus. Optic DFD defined as the distance between the macular central fovea to the center of ONH. The definitions of tilt and rotation were explained before[5]. Briefly, the tilt was quantified by the tilt index, defined as the ratio between LD and SD of ONH. ONH was considered as tilted when the tilt index was above 1.3. The rotation was defined as the angle between the long axis and the vertical meridian of ONH. The vertical meridian was defined as a vertical line that passed through the centre of ONH and at 90° from the horizontal line, which connects the fovea and the centre of ONH. The ONH was considered as rotated when the rotation angle was more significant than 15°. The angle α between retinal temporal arterial vascular arcades was measured from the centre of ONH with 250 pixels' radius[6] (Figure 1).

Statistical Analysis SPSS22.0 software was used for the statistical analysis. Wherever the data had the normal distribution, it was presented as mean±standard deviation. However, variance analysis was used for difference analysis among the multiple groups, and the least significant difference (LSD) test was applied for paired comparison within groups. Wherever the data could not meet the normal distribution, it was represented as median (upper quartile, lower quartile). The Mann-Whitney U was used for difference analysis between the two groups, however the Kruaskal-willis was applied for difference analysis among multiple groups, and paired comparison within the group was used for corrected P value. Spearman correlation test was used for bivariate correlation analysis, where the correlation coefficient r was used to express the correlation between the two variables. The P value of <0.05 was considered to be statistically significant.

RESULTS

Demographic Data In total, 188 HM patients (188 right eyes, 65 males and 123 females) with mean age of 25.00±6.44 y that met the inclusion and exclusion criteria were analyzed. The mean SE was -9.75±2.72 D and the mean AL was 27.19±1.47 mm (Table 1).

ONH Morphology Data in Different Age Groups The ONH morphology parameters in Age1, Age2, and Age3 groups were not significantly different (all P>0.05; Table 2).

ONH Morphology Data in Different AL Groups The DFD of AL4 group was significantly larger (P<0.05) than AL2 group. The angle α of AL4 group was significantly smaller (P<0.05) than AL1 and AL2 groups. However, as the AL grew larger than 28 mm, the angle α was smaller and the DFD was larger. The LD in AL4 group was significantly larger than AL1 and AL2 groups (P<0.05). Although, there was no significant difference in the SD in AL1, AL2, AL3, and AL4 groups (P>0.05). The ONH area in AL4 group was significantly larger than AL1 and AL2 groups (P<0.05). With the increment in AL, the SD showed no significant changes. But as AL greater than 28 mm, the LD and ONH area was increased. The differences in tilt index, tilt ratio, rotation angle, and rotation ratio were not statistically significant in different AL groups (Table 3).

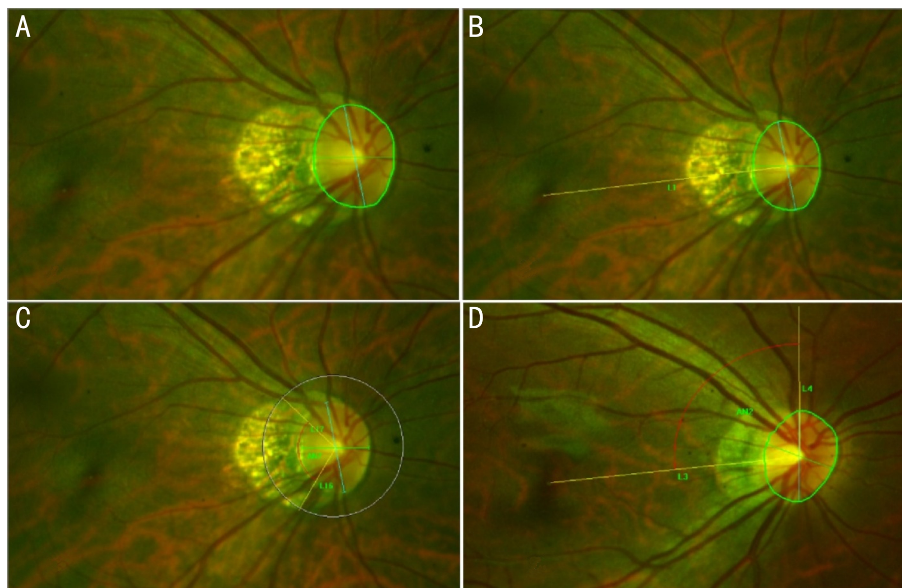

Figure 1　Parameters by Optos　A: The area of optic nerve head; B: Optic disc-fovea distance; C: The angle α; D: Rotation angle. L3: The line connecting the fovea and the center of the optic disc; L4: The line of longest diameter; L17: The line connecting the intersection of the superior temporal retinal arterial vascular arcades with the center of the optic disc; L16: The line connecting the intersection of the inferior temporal retinal arterial vascular arcades with the center of the optic disc; AN2: The angle between the largest diameter and the line connecting the fovea and the center of the optic disc; AN7: The angle between temporal retinal arterial vascular arcades was measured from the center of the optic disc with a 250-pixel radius.

Table 1　Clinical characteristics of the patients

Parameters	Value	Min	Max
Gender (male/female)	65/123	NA	NA
Age ($\bar{x}\pm s$, y)	25.00±6.44	17	47
AL ($\bar{x}\pm s$, mm)	27.19±1.47	24.42	32.43
SE ($\bar{x}\pm s$, D)	-9.75±2.72	-6.25	-20.75

AL: Axial length; SE: Spherical equivalent; NA: Not applicable.

Table 2　ONH morphology data in different age groups　　$\bar{x}\pm s$

Parameters	Age1 (n=38)	Age2(n=112)	Age3 (n=38)	F/H	P
DFD	432.54±24.93	432.72±30.45	441.97±30.18	1.519	0.222
Angle α (°)	120.36±18.17	121.44±22.74	115.59±19.45	1.078	0.342
LD	165.17±26.82	158.9±20.38	161.81±28.71	1.045	0.354
SD	133.38±20.66	124.99±18.29	126.73±28.29	2.239	0.109
ONH area	17828.74±5474.67	15894.87±4170.16	16756.24±6892.03	2.127	0.122
Tilt index	1.24±0.12	1.28±0.14	1.3±0.18	1.473	0.232
Tilt ratio (%)	31.6	37.5	42.1	0.909[f]	0.635
Rotation angle (°)	36±26.31	32.29±24.21	28.41±22.51	0.926	0.398
Rotation ratio (%)	71.1	72.3	68.4	0.212[f]	0.899

DFD: Disc-fovea distance; LD: Largest diameter; SD: Short diameter; ONH: Optic nerve head. [f]Variance analysis.

ONH Morphology Data in Different SE Groups　The DFD of SE3 group was significantly larger than SE1 and SE2 group (P<0.05). The angle α of SE3 group was significantly smaller than SE1 and SE2 groups (P<0.05). With the increase of the SE, especially when the SE was greater than -12 D, the DFD became larger with the smaller angle α. The LD in SE2 and SE3 groups were significantly larger than SE1 group (P<0.01). The SD in SE3 group was also significantly larger than SE1 group (P<0.05). The ONH area in SE3 group was significantly larger than SE1 group (P<0.01). With the increase of SE (especially when the SE was greater than -12 D), the LD, SD, and ONH area also became larger. The differences in tilt index, tilt ratio, rotation angle, and rotation ratio were not statistically significant in different SE groups (Table 4).

Correlation Analysis　The ONH morphology parameters did not have significant correlation with age (all P>0.05). However the DFD, LD, SD, and ONH area had a significant positive correlation with AL and SE, whereas the angle α had a significant negative correlation with AL and SE (DFD: r = 0.195, 0.221; LD: r=0.319, 0.295; SD: r=0.274, 0.225; ONH area: 0.310, 0.265; angle α: r=-0.242, -0.266; all P<0.01; Table 5).

Table 3 ONH morphology data in different AL groups $\bar{x}\pm s$

Parameters	AL1 (n=35)	AL2 (n=61)	AL3 (n=40)	AL4 (n=52)	F/H	P
DFD	432.42±24.31	428.52±27.09	433.21±29.87	444.11±33.17[b]	2.836	<0.05
Angle α (°)	124.63±22.91	124.23±20.86	120.33±24.39	111.8±15.39[a,b]	4.138	<0.01
LD	153.62±22.01	157.24±20.35	162.88±25.32	168.06±25.27[a,b]	3.406	<0.05
SD	120.88±18.87	124.94±14.94	128.08±23.28	132.85±26.01	2.564	0.056
ONH area	15085.91±4405.17	15723.62±3814.96	16849.15±5912.62	17948.85±5924.63[a,b]	2.885	<0.05
Tilt index	1.28±0.13	1.27±0.14	1.28±0.12	1.29±0.17	0.235	0.872
Tilt ratio (%)	40	29.5	47.5	36.5	3.487[f]	0.322
Rotation angle (°)	35.21±23.65	30.99±24.39	32.61±26.94	31.49±23.02	0.244	0.865
Rotation ratio (%)	77.1	70.5	65.0	73.1	1.459[f]	0.692

[a]P<0.05 Compared with AL1 group; [b]P<0.05 Compared with AL2 group. AL: Axial length; ONH: Optic nerve head; DFD: Disc-fovea distance; LD: Largest diameter; SD: Short diameter. [f]Variance analysis.

Table 4 ONH morphology data in different SE groups $\bar{x}\pm s$

Parameters	SE1 (n=93)	SE2 (n=64)	SE3 (n=31)	F/H	P
DFD	430.61±22.7	434.12±32.11	447.28±38.04[a,b]	3.847	<0.05
Angle α (°)	123.33±19.41	119.99±25.31	110.26±13.7[a,b]	4.552	<0.05
LD	154.63±17.84	163.95±25.35[a]	172.54±29.54[a]	8.137	<0.01
SD	124.28±16.07	127.13±20.79	135.14±32.04[a]	3.105	<0.05
ONH area	15459.06±3745.22	16761.69±5296.17	18839.13±7245.79[a]	5.480	<0.01
Tilt index	1.25±0.12	1.3±0.15	1.31±0.19	2.956	0.055
Tilt ratio (%)	32.3	40.6	45.2	2.134[f]	0.344
Rotation angle (°)	31.99±23.43	31.38±26.89	34.86±21.73	0.223	0.800
Rotation ratio (%)	72.0	64.1	83.9	4.055[f]	0.132

[a]P<0.05 Compared with SE1 group; [b]P<0.05 Compared with SE2 group. SE: Spherical equivalent; DFD: Disc-fovea distance; LD: Largest diameter; SD: Short diameter; ONH: Optic nerve head. [f]Variance analysis.

Table 5 Correlation between ONH morphology data with age, AL, and SE

Parameters	Age		AL		SE	
	r	P	r	P	r	P
DFD	0.017	0.816	0.195	<0.01	0.221	<0.01
Angle α (°)	-0.016	0.831	-0.242	<0.01	-0.266	<0.001
LD	-0.031	0.674	0.319	<0.001	0.295	<0.001
SD	-0.092	0.208	0.274	<0.001	0.225	<0.01
ONH area	-0.055	0.454	0.310	<0.001	0.265	<0.001
Tilt index	0.142	0.053	0.034	0.646	0.091	0.216
Rotation angle (°)	-0.082	0.261	-0.009	0.904	<0.01	0.939

AL: Axial length; SE: Spherical equivalent; DFD: Disc-fovea distance; LD: Largest diameter; SD: Short diameter; ONH: Optic nerve head.

DISCUSSION

In this study, we analyzed the morphology parameters of ONH in HM and found that the DFD, LD, SD, and ONH area was larger, while the angle α was smaller as the AL extension.

The ONH is a conspicuous structure in which the optic nerve and retinal vessels enter or exit the eyeball. In HM, as the AL grows, the posterior pole of the eyeball expands which causes the ONH and the scleral tube to pull by forces in different directions, and creates a series of characteristic morphological changes, such as ONH tilt and rotation, optic cup shallowness, irregular disc edges, peripapillary atrophy. In HM, the ONH often appears as a vertical ellipse, raised at nasal side with a flat temporal side connected with the myopic arc, and blurred boundary. Previous studies have shown that change in the shape of the ONH may be related with the age, race, eyeball size, refractive status, and other factors[7]. In the current study, we measured various parameters related to the ONH morphology and explored the relationship of age, AL, SE with the changes occurring in the morphological structure of ONH. This study would help us assess the risk factors of HM while monitoring the progress of myopia.

DFD is a description of the relative positional relationship between the ONH with the macula, which is important for describing the posterior pole extension of the fundus. In this study, we found that DFD had no correlation with age, which is in concurrence with the previous report[8]. Previous studies have confirmed a positive correlation between DFD and diopter[9-10]. Meanwhile, in our study, DFD had a significant positive correlation with SE and AL. Histological studies revealed the relationship between DFD and AL, which can be

explained by the expansion of the posterior segment of eyeball[11]. Axial myopia mainly shows due to the expansion of the posterior segment of the eye, which expands from the equator to the posterior pole. In line with the previous studies, our data also depicts that DFD can be used as a characteristic reference index for morphological changes occurring at the posterior pole in HM.

Our study showed that the angle α decreased significantly with the increase in AL and SE. Fledelius and Goldschmidt *et al*[12] found that the vessel angle was smaller than that of emmetropia, and kept on decreasing during the 38-year follow-up period in HM. Liang *et al*[13] also reported that the vessel angle decreased as the AL increased. Collectively, these results suggest that the angle α can be used as a characteristic index of the morphological changes of the HM, and can also used as an important reference for the displacement of the ONH to the nasal side[3]. However, currently the measurement of DFD and the angle α rely on other software tools, which brings inconvenience while the clinical evaluation. We anticipate that relevant fundus examination instruments can automatically identify and measure these parameters in the future.

We observed that the LD, the SD, and ONH area were positively correlated with SE and AL. Moreover, the range of LD change was large, while the range of SD change was relatively smaller, suggesting that the ONH has a tendency to be oval. Previous studies have shown that the shape of ONH is related to SE, also in myopia, eyeball dilation is mainly concentrated in the posterior pole, including the ONH[14-15]. Wang *et al*[16] reported that eyes with HM had a larger disc size compared with those contralateral low myopia eyes. Liu *et al*[17] observed that the ONH area was only related to SE, but not with AL or age. Previous study has shown insignificant correlation between the size of ONH and SE in childhood[18]. After the diopter correction for the magnification effect, the correlation between the two was significantly decreased; on the other hand, for axial HM, the correlation between the size of ONH and the AL was significantly increased. Although a large amount of data proved that the size of ONH is related to AL, however the prevalence of ONH tilt in HM, the two-dimensional image presented by fundus photography cannot depict true representation of the ONH. The relationship between the change of ONH size and HM needs further study to prove their correlation.

The tilt and rotation of the ONH arise due to the changes in angle at which the optic nerve enters the scleral tube. It is a common fundus manifestation in HM[19], though the incidence is not prevalent in the general population[20]. Several studies have shown that ONH tilt and rotation had a significant positive correlation with SE and AL[9,21]. A cross-sectional study of highly myopic eyes[19] reported that the elderly, female, and long AL are the risk factors for ONH tilt and rotation. Kim *et al*[22] also demonstrated that ONH tilt and atrophy are the characteristic changes of temporal sclera stretching. However, our study has observed that the ONH tilt and rotation had no significant correlation with age, AL, or SE. As our research objects were HM, ONH tilt and rotation might have occurred during the early stage of myopia, although the complete distinction of ONH tilt and rotation by either congenital or acquired is practically not feasible[23]. And, the age distribution of the subjects was biased in the range between 17 and 47 y, the causality of the age-related conclusion cannot be confirmed. ONH tilt may also occur due to the congenital dysplasia in HM, as it is difficult to develop progressive ONH tilt before the appearance of posterior scleral staphyloma involving the ONH[24]. Therefore, clarifying the relationship between HM and ONH tilt and rotation requires a large sample size and long-term prospective study.

The study had certain limitations. First, since the current investigation is a retrospective study, the longitudinal data were unavailable, leaving the conclusion's causality unclear. Then, the age distribution of the subjects was biased in the range between 17 and 47 y, the causality of the age-related conclusion cannot be confirmed. Subsequently, it might not reflect the true representative of the entire population with HM. This study did not conduct intra-or inter-rater reliability assessments, which may raise concerns about data reliability. However, the data were automatically collected with Image-Pro Plus to minimize the influence of subjective factors by evaluators. Finally, the tilted optic disc was measured in two dimensions, which might not exactly present the shapes of the three-dimensional optic disc. Hence, developing a three-dimensional method for measuring the tilt ratio is very important.

In patients with HM, the ONH tilt and rotation had no significant correlation with age, AL, or SE. However, as SE and AL increase, the relative position and size of ONH will change significantly, especially the DFD, angle α, and ONH area and LD. However, the prevalence of ONH deformation in HM, the two-dimensional image presented by fundus photography cannot depict true representation of the ONH. DFD and angle α can be used as the evaluation indicators for the changes occurring in the ONH morphology in HM. Overall, ophthalmologists and myopia patients should pay more attention to axial elongation, not just only to the change in diopter.

Conflicts of Interest: Tang WQ, None; Nie F, None; Luo YL, None.

Authors' Contributions: Tang WQ designed the research study; Tang WQ wrote the paper; Tang WQ and Nie F analyzed and interpreted the data; Tang WQ and Nie F contributed to critical revision of the article; Tang WQ and Luo YL obtained and provided administrative, technical, or logistic support. All authors approved the manuscript.

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