・Clinical Research・

Difference of anterior and posterior orbital development in patients with congenital microphthalmia: a retrospective cohort study from China

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Abstract
● **AIM:** To evaluate volume differences between anterior and posterior orbit and demographic characteristics of Chinese patients with congenital microphthalmia.

● **METHODS:** A retrospective cohort study, involving 169 unilateral congenital microphthalmia patients aged between 1 and 57 years old was conducted. Three-dimensional images of the orbit were generated from past CT scans, and digital orbital volume comprehensive measurement was done. The measured data included orbital volume (OBV), posterior orbital volume (POV), orbital width (OBW), orbital height (OBH), orbital depth (OBD), and posterior orbital area ratio.

● **RESULTS:** Significant differences were observed among OBV, POV, OBW, OBH, and OBD of the affected and unaffected eyes in different age-based groups (all $P<0.001$). Among them, OBH had the greatest different. The mean microphthalmic to contralateral ratio (MCR) of OBV, POV, OBW, and OBH continuously increased from 1 to 3 years old, whereas the MCR of POV decreased from 3 to 17 years old. The MCR of OBD was not found to be correlated to age. There was no significant difference between OBV, POV, OBW, and OBH in ages from 13 years old to adulthood (all $P>0.05$). The difference in posterior orbital area ratio between the affected and unaffected groups was not statistically significant ($P>0.05$).

● **CONCLUSION:** OBH is maximally affected, whereas OBD is minimally affected by microphthalmia. Posterior orbital retardation began 2y prior to orbital retardation and occurred at 3 years old in the affected eye, suggesting that intervention therapy should be done before the age of 4.

● **KEYWORDS:** orbital measurement; congenital microphthalmia; tomography, spiral computed
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INTRODUCTION

Congenital microphthalmia is a genetic disorder, causing abnormal facial and ocular development, and leads to severe visual impairment and hemifacial deformity[1]. In the United Kingdom, the annual incidence was 10.0 cases per 100 000 births in 1999 and 10.8 cases in 2011, whereas in China, it was 9 cases per 100 000 births[2-3]. In our previous study, the asymmetry in orbital development in Chinese children was evaluated and intervention therapy was suggested before 3 years of age[4]. However, in some patients, posterior orbit development was different, resulting in the displacement of the implant. Therefore, the assessment of posterior orbital volume can be essential in the evaluation and further reconstruction of the implant. Different from the previous congenital microphthalmia reports, our sample was expanded also including adults, the total number of cases increased, and it focused on the posterior characteristics of the development of the human orbit. The purpose of this study is to investigate the effect of posterior orbital volume in the development of microphthalmia, standardize posterior orbital measurement using computed tomography (CT) scan and provide valuable quantitative and qualitative information towards a more effective management and treatment of the disorder.

SUBJECTS AND METHODS

Ethical Approval The retrospective clinical study adhered to the tenets of the Declaration of Helsinki and was consistent with good clinical practices and local regulatory requirements. Written informed consent was obtained from all adult

Table 1 Orbital volume, posterior orbital volume, orbital width, orbital height, and orbital depth in AE and UE groups

Group	*n*	Male	Orbital volume (cm³)		Posterior orbital volume (cm³)		Orbital width (mm)		Orbital Height (mm)		Orbital depth (mm)	
			AE	UE	AE	UE	AE	UE	AE	UE	AE	UE
A	42	18	10.43±2.83	13.55±2.72	7.14±2.10	9.11±1.94	26.32±2.44	29.27±2.09	26.19±3.12	30.16±2.51	32.93±3.53	34.09±3.59
B	20	14	13.12±2.64	16.15±1.74	9.02±1.59	11.13±1.69	28.44±2.65	31.38±2.14	28.67±2.79	32.83±2.51	36.44±3.85	37.40±3.03
C	18	9	13.77±1.94	16.53±1.79	9.36±1.62	11.11±1.24	29.53±1.95	31.70±1.76	30.58±2.80	33.80±2.28	38.15±1.86	38.97±2.03
D	15	7	14.16±2.88	17.39±1.80	9.51±1.54	11.42±1.08	30.47±2.76	32.28±1.38	30.61±4.07	33.97±1.71	37.90±2.97	39.26±2.64
E	6	3	16.23±1.83	18.85±1.52	10.80±0.88	13.16±1.98	31.21±2.11	33.60±1.30	32.20±2.79	34.80±1.55	40.23±2.35	40.63±2.02
F	16	8	15.10±2.77	18.42±3.28	10.20±1.85	12.67±2.40	31.66±2.75	33.75±1.87	31.63±2.65	34.70±1.60	39.34±3.33	40.92±2.88
G	11	6	16.96±3.80	21.03±3.66	11.47±2.84	14.59±2.64	31.99±2.49	35.26±1.61	31.64±2.08	35.59±2.05	41.30±2.79	42.44±2.94
H	9	5	15.86±3.37	20.33±3.65	10.92±2.44	14.28±2.67	31.46±3.22	35.35±2.52	31.18±2.24	35.68±1.87	41.24±3.35	42.68±4.15
I	32	13	17.38±2.61	20.81±2.38	12.01±2.01	14.21±2.09	32.28±3.10	35.56±2.12	32.24±3.66	35.80±2.63	42.69±2.99	44.16±3.51

AE: Affected eye; UE: Unaffected eye.

participants or children's parents, and the protocols were reviewed and approved by Beijing Tongren Hospital, Capital Medical University.

Patients Included This clinical retrospective cohort study included 169 patients whom were diagnosed with congenital microphthalmia between January 2007 and January 2020. Those patients already received CT scan of the orbit before study enrollment. Study data were collected before any treatment. Inclusion criteria: 1) clinically confirmed unilateral congenital microphthalmia, with an axis length <18 mm or orbital volume <2/3 of the age-specific norm; 2) age ≥1-year-old; 3) CT scan of the orbit has been performed before study enrollment; study data were collected before any treatment.

Patients Excluded 1) Congenital craniofacial malformations; 2) Eyelid surgery intervention; 3) Orbital surgery intervention.

Age-based Groups and Gender Patients were divided into 9 groups based on age and development of the human orbit as follows: group A (patients who aged ≥1 and <2 years old), group B (≥2 and <3 years old), group C (≥3 and <4 years old), group D (≥4 and <5 years old), group E (≥5 and <6 years old), group F (≥6 and <9 years old), group G (≥9 and <13 years old), group H (≥13 and <18 years old) and group I (≥18 years old). Genders in 9 groups was shown in Table 1.

Measurement Orbital Pathlines The edge of anterior orbit was defined using dacryon, ectoconchion, junction of superior rim and inferior rim. The ectoconchion was the junction of the zygomaticofrontal suture and the curved surface of orbital aditus. The dacryon was the junction of the lacrimal bone, the frontal bone, and the frontal tuber of the maxillary bone. The posterior pathlines were the lateral rim of the optic canal (Figure 1). The horizontal baseline between bilateral ectoconchion-ectoconchion was employed to define anterior orbit and posterior orbit (Figure 2).

CT Examination and Parameters Each patient was scanned with a Brilliance 64-channel orbital multi-detector CT scanner (Philips Medical Systems Inc., Cleveland, OH, USA) with the orbitomeatal line as baseline. Scanning parameters for adults were voltage of 120 kV, tube current of 250 mA, 16×0.625 mm detector collimation, with a pitch of 0.563. Images were reconstructed on a 512×512 pixel matrix at a thickness of 0.67 mm. To minimize the radiation exposure in children, we adhered to the as low as reasonably achievable principle by adjusting the parameters, such as peak kilo-voltage and tube current to lower level (100 kV, 93.8 mA), and limiting the scans to the orbital region[5].

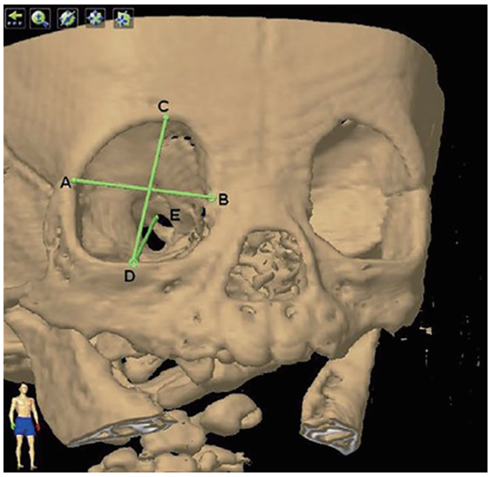

Figure 1 Pathlines A: Ectoconchion; B: Dacryon; C, D: The junction of the superior rim and the inferior rim; E: The lateral rim of the optic canal.

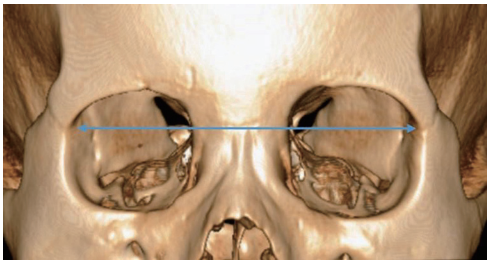

Figure 2 The bilateral transition mark of ectoconchion.

Orbital Volume and Edge Length Measurement The bony orbit was outlined in each slice of axial CT scans. The anterior border of the orbit was defined as the line drawn between the inner aspects of the orbital rim on each side. At the level of medial canthi, the line was drawn between the lateral rim and the anterior lacrimal crest. The posterior border was a line that enclosed the foramens and fissures of the orbit (Figure 1). The volume of orbit, using 70 to 80 layers of horizontal CT slices, was calculated in orbital three-dimensional (3D) reconstruction, in which 3D volume rendering was implemented. The volume of posterior orbit, using the marker of bilateral ectoconchion connection as the anterior boundary and the lateral rim of the optic canal as the posterior boundary in 3D reconstruction. The edge length measurement including orbital width, orbital height and orbital depth. The Digital Imaging and Communications in Medicine images were imported to syngo Multi-Modality Workplace (Syngo-MMWP, ver.VE36A; Siemens Medical Solutions, Forchheim, Germany), which generated 3D images of the orbit and enabled digital orbital volume measurement (Figure 3). Orbital volume, posterior orbital volume, orbital width, orbital height, and orbital depth were subsequently measured[4]. The data were completed by 2 independent physicians and averaged. If the error exceeded 5%, it needed to be re-measured.

Microphthalmic/contralateral ratio (MCR, %) was defined as the ratio of the orbital variables of microphthalmic eye to the contralateral unaffected eye, including MCR of orbital volume, MCR of orbital width, MCR of orbital height, and MCR of orbital depth[6].

Orbital Area Measurement Position the plane on the horizontal cross-sections of the CT scan with the maker of ectoconchion. Use bilateral ectoconchion connection, lateral rim of the optic canal, and frontal nasal to calibrate the boundary. The area of two-dimensional orbital cross-section was measured using Image J software (ver. 1.4; National Institutes of Health, Bethesda, MD, USA). The posterior orbital area ratio was equal to posterior orbital area divided by orbital area.

Statistical Analysis Statistical analysis was conducted using SPSS software (ver. 19.0; IBM, Armonk, NY, USA). Comparisons of orbital volume, posterior volume, orbital width, orbital height, orbital depth, and posterior orbital area ratio were made between the affected and unaffected orbits of 169 patients. Comparisons of orbital volume, edge length, and area ratio were made with a paired samples *t*-test. Comparisons between groups were made with an independent samples *t*-test. Inter-observer reliability of orbital volume and edge length were analyzed using intraclass correlation coefficients (ICC) based on the 95% confidence interval (CI) for absolute agreement. Two-sided $P<0.05$ was considered statistically significant.

RESULTS

A total of 169 patients, 83 males and 86 females, with a mean age of 8.2±9.5y (range, 1 to 57), diagnosed with congenital microphthalmia, were enrolled in the study. Group A had 42 patients, 18 males and 24 females, group B had 20 patients, 14 males and 6 females, group C had 18 patients, 9 males and 9 females, group D had 15 patients, 7 males and 8 females, group E had 6 patients, 3 males and 3 females, group F had 16 patients, 8 males and 8 females, group G had 11 patients, 6 males and 5 females, group H had 9 patients, 5 males and 4 females, group I had 32 patients, 13 males and 19 females.

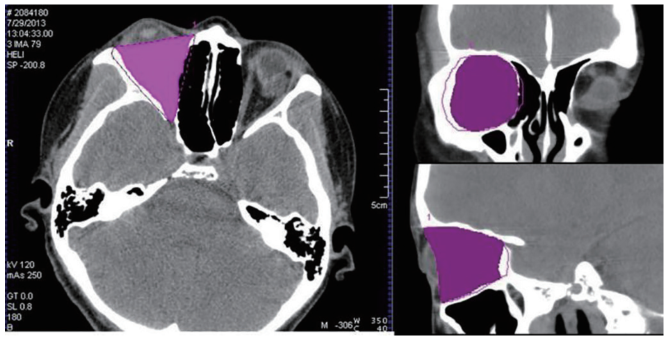

Figure 3 Syngo Multi-Modality Workplace volume measurement.

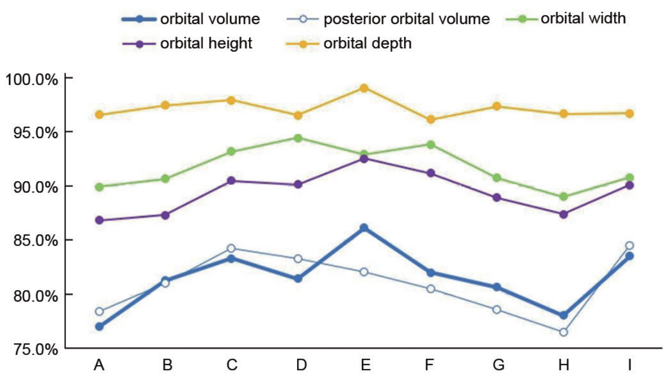

Figure 4 The mean microphthalmic to contralateral ratio of orbital volume, posterior volume, width, height, and depth for 9 age groups.

Comparing Measured Data The mean orbital volume, posterior orbital volume, orbital width, orbital height, and orbital depth in the 169 affected and unaffected eyes are presented in Table 1. Significant differences were observed between the affected and unaffected groups in all 5 parameters. A paired samples *t*-test unveiled that there was a significant difference between the affected and unaffected groups in orbital volume (t=22.574, P<0.001), posterior orbital volume (t=15.936, P<0.001), orbital width (t=22.278, P<0.001), orbital height (t=26.189, P<0.001) and orbital depth (t=11.888, P<0.001).

MCR of Orbital Volume and Edge Length The mean MCR of orbital volume, posterior orbital volume, orbital width, orbital height, and orbital depth in the 9 different age groups are displayed in Figure 4.

The following four parameters increased with age (groups A to C): mean MCR of orbital volume (77.0% to 83.3%), mean

Table 2 Posterior orbital area ratio in horizontal cross-sections of CT scan Mean±SD

Age group	A	B	C	D	E	F	G	H	I
n	42	20	18	15	6	16	11	9	32
AE	0.83±0.04	0.85±0.06	0.84±0.04	0.83±0.05	0.86±0.05	0.83±0.03	0.82±0.05	0.83±0.05	0.84±0.06
UE	0.82±0.04	0.84±0.06	0.83±0.04	0.84±0.04	0.84±0.03	0.84±0.03	0.82±0.03	0.82±0.04	0.84±0.05

AE: Affected eye; UE: Unaffected eye.

MCR of posterior orbital volume (78.4% to 84.2%), mean MCR of orbital width (89.9% to 93.1%), and mean MCR of orbital height (86.8% to 90.5%). The mean MCR of posterior orbital volume decreased from group C to group H (84.2% to 76.5%). Among all MCR-based parameters, the mean MCR of orbital depth did not appear to correlate with age (96.1% to 97.9%).

For age groups H and I (>13 years old), where changes were less evident, an independent samples *t*-test was carried out for the different anatomical parameters. The analysis revealed that there was no significant difference between groups H and I for the following parameters: orbital volume of the affected eyes (t=1.452, P=0.154) and unaffected eyes (t=0.484, P=0.631), posterior orbital volume of the affected eyes (t=1.301, P=0.201) and unaffected eyes (t=0.093, P=0.926), orbital width of the affected eyes (t=0.808, P=0.422) and unaffected eyes (t=0.150, P=0.882), orbital height of the affected eyes (t=1.042, P=0.302) and unaffected eyes (t=0.247, P=0.806), orbital depth of the affected eyes (t=1.585, P=0.118) and unaffected eyes (t=1.360, P=0.179).

Comparisons of Posterior Orbital Area Ratio No statistically significant difference was noted between the affected and unaffected groups for posterior orbital area ratio in horizontal cross-sections of CT, and mean variance ranged from 0.82 to 0.85 in all 9 groups. A paired sample *t*-test revealed that there was no significant difference between the affected and unaffected groups in posterior orbital area ratio (t=1.522, P=0.130; Table 2).

Inter-Observer Reliability For orbital volume, Inter-observer reliability was excellent (ICC=0.881, 95%CI, 0.821-0.922; P<0.05) for two observers. For edge length, inter-observer reliability was excellent (ICC=0.906, 95%CI, 0.855-0.949; P<0.05) for two observers.

DISCUSSION

We found that orbital height was maximally affected, whereas orbital depth was minimally affected by microphthalmia. Posterior orbital retardation began 2y prior to orbital retardation and occurred at 3 years old in the affected eye. The results above may be considered for further intervention.

This retrospective, large-sample, cohort study was conducted in China in both children and adults with congenital microphthalmia; our past study was limited to 38 children with congenital microphthalmia who aged 0-6 years old[4]. The present study has a broader age span, more detailed group data, and involved a great number of cases in each group compared with a previous Asian study[7]. The study focused on the changes of posterior orbital volume with age. The subject sex aspect was not taken into account in the study, since previous studies showed no correlation between sex and orbital volume in children[7-9].

At present, ophthalmologists can employ different diagnostic examinations (*e.g.*, CT scan, magnetic resonance imaging (MRI), B-scan ultrasonography, and 3D facial scanning) to collect orbital data and evaluate orbital spatial information. However, to date, no standardized and reproducible orbital volume measurement has been reported[10]. Therefore, the present research aimed to investigate the development of the orbit using a retrospective, large-sample, cohort study. We employed the CT scan as the main diagnostic method for the following reasons: First, it could provide massive clinical clues and excellent image quality for bone landmarks. Second, accurate and repeatable measurements could be conducted using the syngo Multi-Modality Workplace to generate 3D images. Third, we strictly adhered to the as low as reasonably achievable principle, and the experiment was not performed more than once in every 2y. Finally, CT scan can be easily implemented, it is widely used and more cost effective than most alternatives such as MRI.

Growth and Development of the Orbit We found that orbital development in the affected eye increased slower than in the unaffected eye, and the affected volume was retarded in the age of 5-17 years old. Additionally, a comparison between age groups H and I for the unaffected eye revealed that orbital development nearly stopped at the age of 13-18.

As shown in Table 1, orbital volume steadily increased in the unaffected eyes. Among them, group A (≥1 and <2 years old) had the fastest growth, and the groups G, H and I (≥9 years old) grew slowly, which showed that the development at the age of 5 to 7 years old could develop to nearly 85%-90% of the adult volume[4,7-8]. However, there was no significant difference between groups H and I, indicating that orbital development practically stopped after the age of 13 years old. In group I, the mean volume of the unaffected orbital was 20.81±2.38 cm^3, similar to the 21.0 cm^3 found in previous study conducted in Hong Kong[7].

In the affected eye, similarly to the unaffected eye, group A showed the fastest growth, while slower growth was observed in the higher age groups (Table 1). Orbital volume in the affected eyes compared to a previous study in healthy subjects between 1 and 6 years old, showed that that the affected orbit was significantly retarded compared to the unaffected side[8].

Previous studies used the mean MCR of orbital volume to compare differences in orbit development, which could be a valuable tool to better understand the underlying mechanism[8,11]. As shown in Figure 4, the mean MCR of orbital volume increased noticeably from age group A to age group B (77.0% to 83.3%); the increase of the MCR indicated a rapid natural development of the affected orbit during 1-3 years old without any intervention[7-8]. After a fluctuation in the age of 3-5 years old, the mean MCR slowly decreased in the age of 5-17 years old, suggesting a persistent aplasia of the affected eyeball, and a rapid growth of the facial cranium of the unaffected orbit[9,12]. However, the mean MCR of all parameters increased in the 13-18 years old group. This seemingly contradicting increase could be attributed to late formal diagnosis in cases of mild microphthalmia, due to various socioeconomical factors.

For congenital microphthalmia, reduced orbit volume was the primary criterion for determine microphthalmia and evaluate interventions; the difference in the volume between affected and unaffected eye may reflect the decrease of volume in the affected orbit[4,13-14]. Orbital development is multi-factor process, and it is mainly affected by the growth and development of facial cranium, pneumatized paranasal sinuses, and tissues in the orbit[9,12,15]. The size of the eyeball or even hydrogel may stimulate orbital growth. Moreover, the presence and development of the eyeball is also critical for the development of the orbit and extraocular muscles[4]. Other factors, such as growth hormones, sex hormones, and thyroid hormones are of great importance as well[8].

In the case of anophthalmia, a study showed that the mean MCR of orbital volume increased from 71.3% to 85.4% after intervention at a mean age of 48mo[16]. In another congenital microphthalmia study, the mean MCR of orbital volume was found to be 79.3%, 87.6%, 94.3%, and 89.8% before surgery and at years 1, 2, and 3 after surgery, respectively[6]. In our study, the corresponding rate was 77.0%, 81.2%, 83.3%, and 81.4%, respectively.

Posterior Orbital Development and Retardation We found that the posterior orbital volume of the affected side showed significant retardation at ages 3 to 17 and required active intervention. The volume of the anterior orbital of the affected side increased significantly at ages 4 to 5y, following normal craniofacial development.

Bone density and pressure-bearing capacity is different between posterior and anterior orbital and, therefore, their development should be investigated separately, since they may exhibit different properties and characteristics[17].

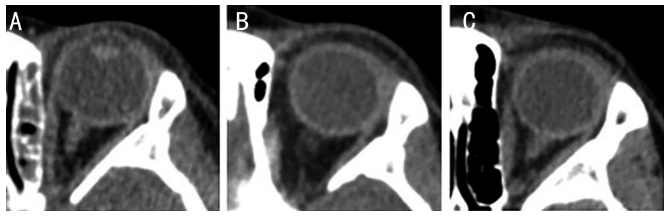

Figure 5 Orbital tracking and bone development of the same patient at 2 (A), 4 (B) and 6 (C) years old.

In our study, posterior orbital volume increased steadily with age in both the affected and unaffected eyes (Table 1). As in the case of orbital volume, the fastest posterior orbital volume growth was noted at the age of 1 to 3 years old, while no growth was reported at the other age groups. Therefore, we analyzed the mean MCR of posterior orbital volume.

The mean MCR of posterior orbital increased in the 1-3 years old group (78.4% to 84.2%), and subsequently declined in the 3-17 years old group. In contrast, the mean MCR of orbital volume increased significantly in the 4-5 years old group. The affected volume of anterior orbit increased by an average of 0.78 cm^3 indicating that the anterior orbit follows the same trend as the skull during this period[9,12]. However, from age 6 to 17, the skull showed a lower growth rate[7,9]. The decrease in the mean MCR of posterior orbital volume was due to an average increase of 1.74 cm^3 in the unaffected volume of posterior obit in the age of 4-5 years old, while the affected side increased only 1.29 cm^3. Therefore, while skull and anterior orbit tend to grow steadily, the decline of the mean MCR of posterior orbital volume unveiled that there was a serious delay in the posterior orbital volume growth, requiring further attention and intervention.

It needs to be noted that in our study there was a patient who received several CT scans in a local clinic, and it was unveiled that the unaffected eyeball, due to the narrowness of the posterior orbit, was closer to the orbital rim at the age of 2, 4, and 6 years old (Figure 5). The latter could explain how the eyeball expanded the posterior orbit volume and affected the relative position of eyeball.

According to the anterior and posterior orbital development observed in our sample, anterior orbital intervention could be performed at the age of 1-3 years old; during this period, intervention was mainly focused on palpebral fissure and conjunctival sac development. At the age of 3 or 4 years old, active external interventions, *e.g.* hydrogel implant, can be more effective[11,16,18].

Analysis of Orbital Edge Length and Posterior Area Ratio We found that orbital height had the largest difference between affected and unaffected eyes. Compared to the unaffected orbit, orbital height of the affected orbit increased more rapidly in the 1-3 years old group and showed a retardation between 5 and 17 years old. Similarly, orbital width of the affected orbit increased in the 1-3 years old group and decreased between 6 and 17 years old. However, the mean MCR of orbital depth was not affected by the age of the individuals.

Although orbital width, height, and depth increased with age in both the affected and unaffected eye, the values declined significantly in the affected group compared with those in the unaffected group (Table 1). Regarding the MCR of edge length, we made the following observations (Figure 4): First, in the age group of 1 to 3 years old, the mean MCR of the affected eye increased with the width (89.9%-93.1%) and height (86.8%-90.5%) of the orbit; this means that the width and height of the orbit caused a rapid growth on the eye, especially for ages 2 to 3 years old. Furthermore, a slight decline of the mean MCR of the orbital height for ages 5 to 17 years old, and the mean MCR of orbital width for ages 6 to 17 years old was observed. Additionally, microphthalmia had a minor influence on depth of orbit, consistent with previous findings[4]. Finally, the curve of the mean MCR of orbital depth from age group H to age group I (Figure 4) was still stable while orbital volume, posterior orbital volume, orbital height and width increased from 13 years old to adulthood, indicating that the orbital depth was never affected by the size of the eyeball[19].

In a previous study, we demonstrated that the reduction in orbital volume was due to a reduction in the cross-sectional area[4]. If the difference in the mean MCR of the orbital depth was not large between age groups, then the increase in orbital volume could simply consider orbital width and height as well. From the 5 parameters studied in the affect and unaffected eye, orbital height had the highest paired sample *t*-test value (t=26.189), and had the lower curve of the mean MCR (Figure 4). Therefore, orbital height was the anatomical parameter with the most consistent difference between the affected and unaffected eye. A possible explanation for this difference in orbital height can be that the supporting effect of the eyeball works against gravity to some extent.

In the horizontal section, ectoconchion was used as a landmark in the horizontal cross-section to evaluate posterior orbital area ratio. As seen in Table 2, the difference of the posterior orbital area ratio for the different age groups was not significant, suggesting that the proportion of posterior orbital area ratio had little change horizontally for all age groups. Hence, the difference in the development of posterior volume in the affected and unaffected groups did not project to a two-dimensional level (X-axis and Y-axis), rather than the height (Z axis). Therefore, anterior orbital volume was more sensitive in orbital height than the posterior orbital volume. This also explained the apparent change in appearance after anterior intervention.

In summary, orbital volume, height and width gradually increased with age in the affected and unaffected eye, with the effect being more pronounced between the age of 1 to 3 years old. From 4 to 5 years old, anterior orbit continued to develop following the craniofacial development; in the absence of external stimulation (hemisphere or prosthesis), microphthalmia caused a retardation of orbital development until adulthood. The posterior orbital volume of the unaffected eye increased rapidly from 3 years old to adulthood. Therefore, the mean MCR of posterior orbital volume decreased at the same period as seen in Figure 4. Orbital height was the most sensitive parameter and orbital depth was the least sensitive criterion correlated to microphthalmia. Comparison of orbital volume and edge length between groups H and I indicated that the development of orbital volume was nearly completed at the age 13.

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