Research Article

Clinical Features and Visual Outcome in Microphthalmos

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Abstract: Many previous studies have reported the prevalence of microphthalmos in live births. These patients invariably present with poor vision. However, their quality of life can be improved by improving the remaining functional vision.This study was planned with an aim to estimate the prevalence of microphthalmos in a tertiary eye care setting in an Indian population. Clinical features and visual improvement after refractive correction in these patients were also analyzed. Data analysis of 22 patients (38 eyes) of microphthalmos was done. This included history, clinical examination, refraction, corneal diameter and axial length measurements, cataract extraction with lens implantation, whenever indicated, and systemic evaluation. The main outcome variable in this study was improvement in visual acuity following spectacle correction. The prevalence of microphthalmos was found to be 2.6 per 10,000 patients seen. The average axial length and average corneal diameter were found least in complicated microphthalmos. Refraction could be performed in 24 eyes of 14 patients. Eighty three per cent of eyes (20 out of 24 eyes) noticed visual improvement after correction. Microphthalmos is a relatively rare ocular anomaly. It presents with various clinical features the most common being poor vision, nystagmus, and cosmetic disfigurement. Complicated microphthalmos is the most severe form of microphthalmos. Correction of refractive errors results in reasonably satisfactory improvement in vision.

Keywords: Microphthalmos; coloboma; visual acuity; refractive error; corneal diameter; axial length.

INTRODUCTION

Microphthalmos is a developmental anomaly wherein the axial length of the globe is two standard deviations below the mean for age [1]. The standard mean axial length of the eye in neonates is 17 mm, while that in adults is 23.8 mm. It was suggested that microphthalmos should be diagnosed when the axial diameter, adjusted for age, was less than the 95th centile or in adults the axial length less than 18.5 mm [1, 2]. Taking the corneal diameter and axial length both into consideration the International Clearinghouse for Birth Defects Monitoring Systems defined this condition as having the corneal diameter of less than 10 mm and the antero-posterior diameter of the globe of less than 20 mm [3].

The eye develops fast during the first three years and the adult size is reached around 13 years of age [2]. Microphthalmos may present either unilaterally or bilaterally; the latter can be symmetrical or asymmetrical. It can occur as an isolated anomaly or may be associated with other ocular anomalies, most common being microcornea, and coloboma of uveal tract. Sometimes it may co-exist with an orbital cyst or teratoma that presents as lower lid bulging [4, 5]. Moreover, it may be seen as a localized ocular abnormality or as a part of well-defined syndrome.

Duke-Elder and Wybar classified microphthalmos into three categories: simple, colobomatous, and complicated [2]. In *simple microphthalmos* the eye is structurally normal except that its average axial length is significantly less than that of the normal eye. In spite of normal appearance, some of these eyes have poor visual acuity due to hypoplasia of the macula, cystoid macular edema, and uveal effusion [6]. Nanophthalmos is a subtype of simple microphthalmos characterized by microcornea, hypermetropia of around 8 D and an axial length of less than 18 mm.

Colobomatous microphthalmos invariably has coloboma of the uveal tract. Non-closure of embryonic fissure results in typical coloboma and is marked by a defect in the iris, the ciliary body, the choroid and the retina [2]. Occasionally, it may also involve the optic nerve head. The iris coloboma can develop even after closure of the fissure.

Complicated microphthalmos is usually associated with systemic anomalies and malformations of the eye. It can involve both anterior and posterior segments of the eye [7]. It usually presents with microcornea, corneal opacities, anomalies of the angle

of anterior chamber, congenital glaucoma, congenital cataract, persistent hyperplastic primary vitreous and retinal detachment [8].

Severe visual impairment is encountered in microphthalmic eyes owing to anomalies of anterior and posterior segments. Microphthalmos adversely affects the patient's appearance and may affect a child's psychological and social development. The treatment is, therefore, aimed at improving the vision and cosmetic look [9].

We embarked on this study to document the prevalence, clinical features and visual improvement after refractive correction in patients with microphthalmos in the ophthalmic outpatients department of our institution.

MATERIALS AND METHODS

All the patients who visited the Department of Ophthalmology of a tertiary care center from January 2009 to December 2013, were studied. Patients with anophthalmos, a congenital complete absence of the eyeball, were excluded from the study. The study adhered to the tenets of Declaration of Helsinki and was approved by the institutional review board.

A comprehensive history was taken from each patient. The examination included recording of vision, cycloplegic refraction, anterior segment slit-lamp examination and dilated fundus examination. The horizontal and vertical white-to-white corneal diameters and axial length were measured using Castroviejo calipers and A-scan ultrasonography (USG), respectively. Although the diagnosis of microphthalmos was made clinically, the corneal diameter and axial length measurements helped to support it (as per the International Clearinghouse for Birth Defects Monitoring Systems criteria) [3]. B-scan USG was needed to confirm the diagnosis in some patients. All associated ocular findings were also documented.

The general examination was done by a physician to look for systemic anomalies.

Three patients had cataract and they underwent cataract extraction with posterior chamber intraocular lens (IOL) implantation after thorough ocular and systemic examinations and repeated biometry for calculation of IOL power.

Snellen visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) scores for data analysis. Statistical package for the social sciences (SPSS) version 16.0 software was used to analyze the data. Kruskal Wallis test was performed to see the difference in mean values across the three groups. Wilcoxon signed rank test was performed to see the improvement in logMAR visual acuity after the spectacle correction.

RESULTS

During a four year period a total of 109,599 patients (53 % male, 47 % female) were examined and out of them 29 had microphthalmos. The prevalence of this relatively rare congenital ocular anomaly was found to be approximately 2.6 per 10,000 patients in the present study. Seven patients were lost to follow-up and, therefore, not included in the subsequent analysis.

The age of presentation of patients ranged from 2 months to 65 years, with the median age of 9.5 years. Out of 22 microphthalmic patients, 10 (45 %) were males and 12 (55%) females. There was no history of consanguinity or family history of congenital ocular abnormality in any patient.

The common complaints at presentation were poor vision in the affected eye, small size of eyeball (Fig. 1A), cystic swelling in place of normal eyeball (Fig. 1B), nystagmus, coloboma of iris (Fig. 1C) and unsightly appearance of the eye. The older patients presented with gradual progressive diminution of vision due to refractive change or lenticular opacity (Fig. 1D). Three patients out of 22 (14 %) came for the correction of ocular deviation.

Microphthalmos was unilateral in six (27%) cases and bilateral in 16(73%). Colobomatous microphthalmos was found in eight (36%) cases, complicated in 11 (50%) and simple microphthalmos in three (14%). None of our cases presented with nanophthalmos.

The corneal diameter could be measured in 34 (89.5 %) eyes only. In four eyes of two patients indistinguishable limbal anatomy prohibited the measurement. Microcornea was present in all cases of microphthalmos with mean corneal diameter of 8.7 ± 1.7 mm (range 4.2 to 10.3 mm). Difference between the mean values of the corneal diameter was significantly different in simple, colobomatous and complicated groups, with maximum in simple microphthalmos and least in complicated (Table 1).

Axial length measurement of the eyeball was done for patients older than five years of age (15 eyes of 9 patients). Two out of 22 patients needed B-scan USG (Fig. 2) for orbital and posterior segment evaluation, and confirmation of antero-posterior diameter of eyeball.

The mean axial length was 17.4±1.5 mm (range 13.4 to 19.2 mm). Alike corneal diameter, the mean axial length significantly differed in all three groups and was maximum in simple microphthalmos and least in complicated (Table 1).

Visual acuity (in logMAR) at presentation was similar in the three groups. Refraction could be performed in 24 eyes of 14(64%) out of 22 patients. Out of eight patients in whom refraction could not be performed, four patients refused, two patients had dense corneal opacities while mental retardation and congenital cataract prohibited the refraction in one patient each.

There was significant visual improvement after spectacle correction in all the three groups (Table 1). The visual improvement after spectacle correction was observed in 20 (83 %) eyes while in four patients the vision remained unchanged. Out of the four eyes that did not show improvement on refraction, two were of a patient with complicated microphthalmos with nystagmus and multiple dense stromal corneal opacities. One out of the three patients, who underwent cataract surgery with IOL implantation,did not show visual improvementdue to severe visual deprivation amblyopia. The patient was informed about the visual prognosis before the surgery but opted for the procedure for cosmetic improvement. Extensive retinochoroidalcoloboma involving the posterior pole and optic disk was responsible for no visual gain in the last patient.

When we compared the percentage improvement in visual acuity in all the three groups it was observed that simple microphthalmos had highest percentage improvement whereas it was lowest in complicated microphthalmos (Table1).

Spearman correlation test was performed to see the association of corneal diameter and axial length with percentage improvement in visual acuity.We found that axial length was not significantly associated with percentage improvement in visual acuity (r=0.499, p=0.082) whereas average corneal diameter was significantly associated with percentage improvement in visual acuity (r=0.582, p = 0.005).
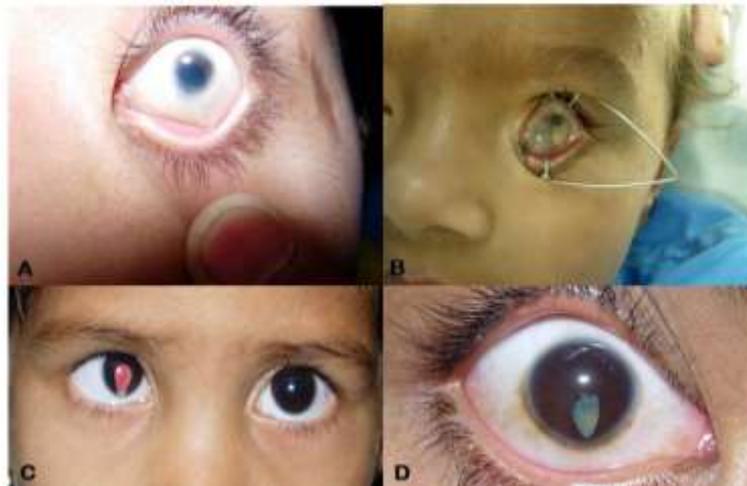

Fig. 1: Different clinical presentations of microphthalmos (A): microphthalmic LE, (B) orbital cyst pushing the microphthalmic eye up, (C) iris coloboma RE through which red reflex is seen, (D) colobomatous microphthalmos with cataract RE
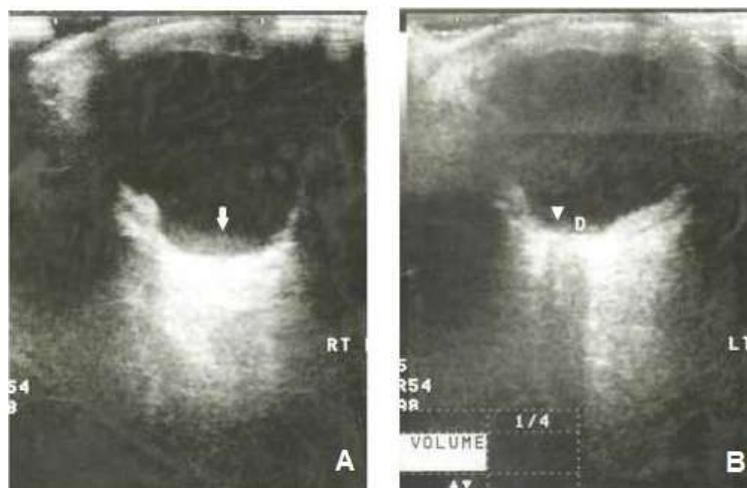

Fig. 2 : USG B-scan showing (A) retinochoroidalcoloboma (arrow) implicating the optic disc in right eye, (B) localized depression (arrow head) in front of optic nerve shadow (optic disc coloboma) in left eye of same patient

Table 1: Clinical parameters in different types of microphthalmos

Type of Microphthalmos	Mean axial length (in mm)	Mean corneal diameter (in mm)	LogMAR VA at presentation	Log MAR VA after correction	Percentage improvement in logMAR VA	p value*
Simple	18.57±0.87	10.04±0.20	1.80±0.81	0.90±0.22	43.22±19.64[#$]	0.043
Colobomatous	17.88±0.72	8.88±1.65	1.81±0.80	1.11±0.78	38.63±22.31[$†]	0.018
Complicated	15.72±1.65	8.08±1.79	1.42±0.28	1.21±0.36	16.01±9.57[†#]	0.014
Total	17.49±1.51	8.70±1.70	1.65±0.64	1.12±0.54	30.42±20.69	<0.0001
p value	0.011	0.003	0.504	0.351	0.015	

* p value between logMAR VA at presentation and after correction of 14 patients in which refraction was done; VA = Visual acuity; #$: p value of simple vs. colobomatousmicrophthalmos = 0.034; $†: p value of colobomatous vs. complicated microphthalmos = 1.000; †#: p value of complicated vs. simple microphthalmos = 0.045

DISCUSSION
Demography

Microphthalmos is reported to be one of the major causes of congenital visual impairment and blindness in India [10-13]. A prospective study conducted in Punduchery found 10 cases of microphthalmos in 12797 births, of which 12337 were live births and 460 stillborn [14]. The prevalence of microphthalmos in the present hospital based study was found to be approximately 2.6 per 10000 patients. This is much higher than reported from other countries in studies done in birth cohorts. A prevalence of anophthalmos/microphthalmos of 1.5 per 10000 births had been recorded from three large registers of congenital malformations from Central-East France, Sweden, and California [15].In Scotland the prevalence of microphthalmia was reported to be 1.9 per 10000 [16].Another study showed the birth prevalence of upto 2 per 10000 [17].A recent Chinese study conducted on 3573 healthy full-term newborns had reported 0.03 % perinatal prevalence of microphthalmos [18].

Laterality

Seventy-three per cent of microphthalmic patients showed bilateral ocular involvement in the current study. This is contrary to the earlier studies where unilateral presentation was more commonly encountered [19-21].In a study on 17 patients of microphthalmos all showed unilateral pathology except one [17]. Tucker *et al*. also found 70 % of microphthalmic patients with a normal fellow eye [22]. Being a tertiary eye hospital with referrals from both primary and secondary care levels, patients with microphthalmos with severe visual impairment and disability were referred mainly for expert opinion and reassurance. This could be a plausible explanation for high prevalence of bilateral cases in our series.

Gender

Forty-five percent patients (10 out of 22) were males and fifty-five percent (12 out of 22) females in our study. Almost equal sex distribution supports the view of other authors that gender is not a risk factor for the disease [19, 20].

Etiology

Microphthalmos can be caused by environmental, heritable, and unknown factors. Environmental factors include exposure to perinatal infections (rubella, syphilis, toxoplasmosis, varicella, cytomegalo virus), fever, exposure to X-rays and thalidomide, and misuse of alcohol and solvents during pregnancy[2,9]. Consanguinity, maternal age over 40 years, maternal vitamin A deficiency, multiple births and premature low-birth weight babies are other risk factors for microphthalmos [11, 19, 20].

Several genetic factors are known to cause microphthalmos [9]. Chromosomal duplications, deletions and translocations have been implicated in microphthalmia, and are typically associated with characteristic syndromes. Of monogenic causes, SOX2 and microphthalmia-associated transcription factor (MIFT) genes are identified as the major causative gene for microphthalmos [9, 23]. SOX2 *de novo* heterozygous loss-of-function point mutations have been shown to account for 10–20% of severe bilateral microphthalmos. Mutations of OTX2 genes result in a wide range of ocular disorders from anophthalmos and microphthalmos to retinal defects. Central nervous system malformations and mental retardation are common in patients with OTX2 mutations [24]. RAX, located on chromosome 18q21.32, is linked to about 2% of inherited microphthalmia [25]. Similarly, CHX10 mutations (chromosome 14q24.3) account for about 2% of isolated microphthalmia [26]; mutations in both genes characteristically present with recessively inherited phenotypes. Fares-Taie *et al*. and Aldahmesh *et al*. recently showed that the mutation in ALDH1A3 genes are also responsible for microphthalmia [27, 28]. Transitory expression of mutant ALDH1A3 open reading frames showed that missense mutations reduce the formation of retinoic acid which is important for the normal development of eye.

Pathogenesis

Simple microphthalmos may occur due to decreased size of the embryonic optic cup, altered proteoglycans in the vitreous, low intraocular pressure and abnormal growth factor production while inadequate production of secondary vitreous may cause complex microphthalmos [29,3 0]. Guthoff *et al*. proposed that microphthalmia with cyst results from

failure of optic fissure to close [30]. However, the exact pathogenesis of microphthalmos is still uncertain [9].

Types of microphthalmos

Microphthalmos can be classified in different ways; on the basis of possible etiology, on severity of reduction of axial length, or associated malformations. Warburg studied cases of microphthalmos extensively and suggested a classification based on etiology [31]. He divided the etiology of microphthalmos into three major groups: genetic, prenatally acquired due to ingestion of teratogens by mother, and unknown etiology. However, this classification does not differentiate microphthalmos, anophthalmos, congenital cystic eye, and coloboma into different etiological groups. The Duke-Elder and Wybar classification is simple and clinically practical but it does not throw light on the probable etiology [2]. Simple and colobomatousmicrophthalmos refer to ocular morphological abnormalities whereas complicated or complex microphthalmos usually indicates the presence of severe ocular malformations or systemic abnormality. Hence, this classification helps to plan strategies for management of the anomaly. Simple and colobomatousmicrophthalmos patients require refractive correction and an optical aid. They have to be followed closely as they are susceptible to develop ocular complications like angle closure glaucoma or retinal detachment. Complicated microphthalmos needs a multidisciplinary and more meticulous management approach.

Microcornea

Microcornea is usually present in microphthalmia, therefore, corneal measurements become essential in all cases. The normal average vertical diameter of the adult cornea is 10.6 mm and the horizontal 11.75 mm [32]. The severity of microcornea correlates with the severity of microphthalmos and poor visual prognosis. A study by Elder et al showed that 81% of microphthalmic eyes with a corneal diameter of 5 mm or less at birth had a visual acuity of no perception of light [33].

In the present study we observed that the corneal diameter among the three types of microphthalmoswas least in complicated microphthalmos. Moreover, the average corneal diameter was found to be more a more sensitive indicator of severity of microphthalmos than the axial length.

Axial length

The diagnosis of microphthalmos is based on clinical examination, and measurement of axial length of the eyeball complement it. Ultrasonography is most commonly used to determine the length of globe in microphthalmic eyes [9]. A-scan ultrasonography is usually employed for the axial length measurement, and

B-scan USG to evaluate the size and associated ocular malformations. Transvaginal USG helps in detecting in-utero microphthalmia at about 12 weeks of intrauterine life [34]. More recently, optical biometry (IOLMaster from Carl Zeiss Meditec, Jena, Germany and Lenstar, Haag-Streit AG, Koeniz, Switzerland), based on the principle of partial coherence interferometry, is employed for measuring the axial length of eyeball. It gives a quick, contact-free, highly precise, reproducible and observer independent measurements as compared to ultrasound biometry [35-37]. Nonetheless, optical biometry performs poorly in the presence of media opacities, poor fixation, high refractive errors (> 6 diopters) and in uncooperative patients [38, 39]. Therefore, it is less suited in cases of microphthalmos due to the presence of nystagmus, corneal or lenticular opacities and high ametropia.

In nine out of 22 (41 %) patients the axial length could be measured in our series. The average axial length (and the corneal diameter)recorded was least in complicated microphthalmos suggesting that it is the most severe form of microphthalmos.It is difficult to do ocular measurements and refraction in such small disfigured eyes. Poor co-operation of these visually disabled children and presence of nystagmus make the task even more problematic. Moreover, reluctance and disinterest shown by both parents and patients also play a major role and add to the difficulty. Shah *et al.* in their study could measure ocular axial length in less than one-third (30.3 %) of the children with microphthalmos [40].

Visual acuity and Refractive errors

The aim of therapy in microphthalmia is to maximize the existing vision. Hence, it is pertinent to refract these eyes [9]. Pal *et al.* and Hornby *et al.* reported that spectacle correction helps to improve vision in micropthalmos [41,42]. All microphthalmic eyes had poor presenting visual acuity ranging from 0.8 to 3 logMAR (Snellen equivalent 6/36 to perception of light) in this study. Refraction was not possible in sizable number of cases due to the reasons already mentioned. Eighty three per cent of the refracted eyes showed improvement in vision in the current study with a maximum percentage improvement in logMAR visual acuity of 66.7% (Snellen equivalent from perception of light to 6/24). Thesubjective improvement in the residual vision, nonetheless, was found to be quite satisfying for the patients as it helped them in navigation and daily chores. All the patients preferred using the prescribed glasses. Furthermore, thisfunctional improvement in vision was really rewarding for these patients as it madethem less dependent on others thereby improvingtheir quality of life.

We encountered both myopia and hypermetropia in our cases of microphthalmos. A similar observation was reported by Pal and coworkers

as well [41]. Hypermetropic refractive error in microphthalmos is because of reduced curvature of cornea while the shape of cornea and crystalline lens is responsible for myopic refractive error [1, 2]. Moreover, increased refractive index of the lens due to nuclear sclerosis might also have contributed to myopia in our series.

Associated systemic anomalies

There are multiple syndromes associated with microphthalmos [31].The frequency of association led to sub-classification of microphthalmos into syndromic and non-syndromic groups. Children with bilateral disease had a two to seven times higher odds of having systemic involvement than unilaterally affected children [40]. Tucker et al noted associated systemic diseases in 20.6% (seven out of 34) patients of microphthalmos [22]. However, the systemic association is more common and strong in anophthalmos (50%) than microphthalmos (17.6%) [17].

Seven out of 22 (31.8 %) patients in this study had associated systemic anomalies like cleft lip, cleft palate, dental deformity, syndactyly, hearing loss and mental retardation, the commonest being orofacial malformations. Interestingly, six out of these seven (85.7 %) patients had bilateral microphthalmos.

Surgical rehabilitation

In a prospective study in 21 microphthalmic infants with bilateral congenital cataract, good visual outcomes were obtained after early surgical intervention [43]. However, in some patients postoperative complications such as glaucoma, posterior synechiae, and visual axis obscuration were encountered. In another study, the results of phacoemulsification were evaluated in eight eyes with nanophthalmos; the procedure was converted to extracapsular cataract surgery in two eyes because of uncontrolled shallowing of the anterior chamber. Postoperative complications included iritis with posterior synechia, choroidal hemorrhage, posterior capsule opacification, glaucoma, and retinal detachment [44]. Microphthalmic eyes are considered as surgically difficult and extra precaution and care should be taken during intraoperative and postoperative periods. We managed our three cataract cases with small incision cataract surgery with posterior chamber IOL implantation without any peroperative and postoperative complications.

Prosthetic management

A small sized globe gives reasonable natural stimulation for orbitofacial growth and development. Moreover, it provides a better cosmetic look than artificial stimulation with external conformers and internal implants [45]. The orbital cyst associated with microphthalmos plays an important role in socket expansion and results in good cosmetic outcome in almost all cases [46]. In the present study, as most of the patients had some vision and all orbital cavities

contained a microphthalmic globe, they were managed conservatively without orbital expansion.

There are some limitations of our study. It was a hospital based study; however, to calculate the exact prevalence of microphthalmos, studies comprising larger sample size from the general population are recommended. We have not compared the effect of laterality on improvement in visual acuity and genetic etiology of the disease was not studied.

CONCLUSION

In conclusion, microphthalmos is a rare congenital ocular growth abnormality that causes profound diminution of vision due to structural and functional defects. Out of the three types, complicated microphthalmos is the most severe form. A sincere attempt to improve vision by refraction in these patients is strongly recommended. The average corneal diameter is a more sensitive marker for determining the percentage improvement in visual acuity than the axial length. Cataract surgery with IOL implantation can also help restore some useful vision in selected patients.

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