Classification of microphthalmos and coloboma

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Abstract

A new classification of microphthalmos and coloboma is proposed to bring order to the complexity of clinical and aetiological heterogeneity of these conditions.

A phenotypic classification is presented which may help the clinician to give a systematic description of the anomalies. The phenotype does not predict the aetiology but a systematic description of ocular and systemic anomalies improves syndrome identification. There are two major classes, total and partial microphthalmos, and a subclassification which follows the embryology of the anomalies.

The aetiological classification consists of three classes: (1) genetic (monogenic and chromosomal), (2) prenatally acquired (teratological agents and intrauterine deformations), and (3) associations. Genetic disorders give rise to malformations; prenatally acquired anomalies are disruptions or deformations.

The aetiological classification can be applied to other congenital birth defects and improves counselling of families. Recurrence risks vary considerably between the classes.

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Microphthalmos and coloboma are common malformations. Microphthalmos is found in between 1.2 and 1.8 per 10 000 births in white populations and colobomata in 0.7 per 10 000 births.¹²

Anophthalmos is extreme microphthalmos and clinical conditions with anophthalmos are therefore equivalent to conditions with microphthalmos.³ Congenital cystic eye is a malformation resulting from a failure of invagination of the optic vesicle, and should therefore be classified with cases of microphthalmos. Colobomata of the uvea are often associated with microphthalmos and a classification of microphthalmos should therefore also include coloboma. Microphthalmic eyes usually have microcornea, so microcornea should be included in a discussion of microphthalmos.

The eye derives from three embryological germ layers: the neuroectoderm which gives rise to the optic vesicle, the neural crest cells which migrate to the anterior chamber of the developing eye, and the ectoderm from which the lens placode is derived. Neuroectodermal and mesodermal cells participate in the closure of the optic fissure.³ This multiple embryological derivation explains the variability of the phenotype and the aetiological heterogeneity of congenital ocular defects.

Phenotypic classification

A structured assessment of congenital defects is necessary in the clinical delineation of syndromes and associations. A phenotypic classification is helpful in systematic recording of all pathological manifestations; the anomalies observed may also suggest the initial embryological error, or the time during pregnancy when development took an abnormal course.

MICROCORNEA

The mean horizontal diameter of the neonatal cornea is 9.8 mm,⁴ with a range of 9.0 to 10.5 mm. The average vertical diameter of the adult cornea is 10.6 mm, and the horizontal is 11.75 mm.³ The true diameter of the cornea is difficult to measure if the limbus is indistinct and in these cases transillumination of the globe will show the ciliary ring.

Microcornea may occur as an isolated anomaly or associated with other ocular disorders; in each case it may be associated with systemic anomalies. Microcornea without foreshortened axial length has been described in the oculodentodigital syndrome,⁵ but microcornea usually appears in eyes in which both the anterior and posterior axial lengths are short.⁶ It may also happen that patients have microcornea associated with aniridia,⁷ or other anterior segment malformations, and a normal sized posterior segment; further, microcornea can be present with posterior macrophthalmos.⁸ Axial length measurements by ultrasonographic A scans are therefore advisable in patients with microcornea. If there are anterior chamber malformations, glaucoma is a risk. In microcornea, the corneal power is increased, probably because of a small radius of curvature. In severe microcornea, however, Weiss *et al*⁸ found a decrease in corneal power because in very small corneae the curvature of the cornea approximates that of the sclera.

MICROPTHALMOS

The size of the globe can be measured ultrasonographically, by computerised tomographic scans (CT scans), or by magnetic resonance imaging (MRI). Fetal ultrasonograms of the eye can be obtained both transabdominally⁹ and by a transvaginal procedure in the transverse section.¹⁰ Normal values for fetal axial length¹¹ and for the growth of the fetal orbit⁹ are available; in hereditary cases, microphthalmos may be diagnosed prenatally by expert ultrasonography.¹⁰ The length of the neonatal eye is presented in table 1.⁴ There is a close correlation between the weight of the neonate and its axial eye length.

The growth of the eye is fast during the first three years¹⁸; the adult size is reached at

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Table 1 Axial length of the neonatal eye (modified from Blomdahl³).

	Larsen ¹²⁻¹⁴	Gernet ¹⁵	Luycks ¹⁶	Grignolo and Rivara ¹⁷	Blomdahl ³
Anterior chamber	2.4	2.9	2.6	—	2.6
Lens	3.9	3.4	3.7	—	3.6
Vitreous	10.4	—	10.8	—	10.4
Total axial length	—	17.2	17.6	17.0	16.6
No of eyes	90	70	104	36	28

around 13 years, when the outer sagittal diameter is 24 mm, the inner sagittal 22 mm, the anteroposterior 25 mm, and the transverse 24 mm.^{3 19}

Microphthalmos is assessed when the axial diameter, adjusted for age, is below the 95th centile. In adults, microphthalmos is identified in eyes with an axial length of less than 18.5 mm.^{18 19} The phenotype of patients with microphthalmos and coloboma is highly variable, but can be classified as shown in tables 2 and 3.

I. Total microphthalmos is where both anterior and posterior segments are foreshortened. The most serious type of microphthalmos is (A) *congenital cystic eye* which is the condition that follows if the optic vesicle fails to invaginate. In these cases there is no trace of the globe^{20 21}; the cyst has a tendency to increase in size and should be removed at an early age in order to place a conformer which may expand the orbit.²²

(B) *Anophthalmos* is the clinical term for extreme microphthalmos where ocular structures can be found only by serial histopathological sections.

(C) *Simple microphthalmos* without other major malformations is termed nanophthal-

mos. In these cases the eyes are usually deeply set in the orbit, refraction is high hypermetropic, and the cornea is small. Both the anterior and posterior segments of the eye are foreshortened, the relative lens volume is increased, and there is sclerochoroidal thickening.^{23 24}

(D) *Microphthalmos with other ocular malformations* is common. (1) Microphthalmos with congenital cataract is known in both rodents²⁵ and man, for example, in the sporadic Hallermann-Streiff syndrome,²⁶ and the X linked Nance-Horan syndrome.²⁷ (2) The chamber angle may be deficiently developed and there may be anterior synechiae. This has been seen in rodents treated with teratogens²⁸ and in human families, for example, in an Indian sibship with microphthalmos, sclerocornea, anterior chamber ‘dysgenesis’, and congenital cataract.²⁹ There may be defects of the posterior layers of the cornea and the cornea may be cloudy. This has been observed, for example, in a sister and brother with microphthalmos, microcornea, and sclerocornea associated with fine sparse hair, a narrow nasal bridge, protruding, cupped ears, and a short upper lip.³⁰ (3) Colobomata of the uvea (a) are often present in microphthalmic eyes. They may be of varying size and may involve or spare the iris; minor manifestations can be seen by transillumination. There may only be a small notch in the pupil signalling a very small coloboma. A retinochoroidal coloboma may be so small that only a small change in the colour of the retinal pigment epithelium discloses its presence, or, in contrast, it may involve all the structures between the optic nerve and the ciliary body. The macula is often involved. The optic nerve may be part of a coloboma (b) of the posterior pole.

The colobomatous part may become staphylomatous and sometimes the coloboma forms a cystic lesion in microphthalmic eyes (c). This cyst may press the eye forwards in the orbit in which case it is difficult to assess that the eye is, in fact, too small; CT scans are useful for this evaluation.^{31 32}

(E) *Microphthalmos with multiple ocular malformations*, that is, malformations deriving from different embryological germ layers are also found; examples are Delleman syndrome (the oculocerebrocutaneous syndrome),³³ and the osteoporosis-pseudoglioma syndrome.³⁴

II. In *partial microphthalmos*, the anterior chamber and the cornea may be of normal size even if the posterior segment is small.³⁵ Posterior segment microphthalmos is seen, for instance, in patients with high hypermetropia.^{18 36} In some patients the anterior chamber is small while the posterior compartment is of normal size³⁷ or larger than normal.³⁸

Coloboma means mutilation; it indicates that a portion of the eye is lacking. Colobomata of the posterior segment of the uvea of both adult and fetal eyes can be visualised with ultrasonography, MRI, or CT scan even if the optic media are cloudy.³⁹⁻⁴¹

The term ‘coloboma’ is used for three types of malformations, typical, atypical, and macular. Typical colobomata are situated inferonasally at the site of the optic fissure, whereas

Table 2 Phenotypic classification of microphthalmos.

I Total microphthalmos
(A) Congenital cystic eye
(B) Apparent anophthalmos
(C) Simple microphthalmos
(D) Microphthalmos with intraocular malformations
(1) Congenital cataract
(2) Anterior chamber malformations
(3) Coloboma
(a) Coloboma of the uvea
(b) Coloboma of the optic nerve
(c) Cystic coloboma
(E) Multiple ocular malformations
II Partial microphthalmos
(A) Anterior segment microphthalmos
(B) Posterior segment microphthalmos

Table 3 Phenotypic classification of coloboma.

I Typical
(A) Coloboma of the iris
(a) Complete (keyhole)
(b) Partial
(1) Peripheral
(2) Notch in the pupil
(3) Pigment epithelium defect
(4) Heterochromia of the iris
(B) Coloboma of the ciliary body
(C) Coloboma of the choroid
(1) (a) Partial (b) Complete
(2) (a) With (b) Without macular involvement
(3) (a) Cystic (b) Non-cystic
(D) Coloboma of the optic nerve
(1) Typical
(a) Cystic (b) Non-cystic
(2) Special
(a) Pits of the optic nerve
(b) Pedler coloboma
(c) Morning glory
(d) Optic disc hypoplasia
II Atypical
Coloboma outside the optic fissure
III Macular ‘coloboma’

atypical colobomata may be situated at any other site. The development of the latter is not clear, but it is not related to closure of the optic fissure. Macular 'coloboma' is the name given to a heterogeneous group of anomalies characterised by a pigmented malformation in the macula. They are not embryological coloboma. Only typical coloboma will be discussed (table 3).

Most previous classifications of colobomata have been aetiological,^{42,43} but there are surveys of coloboma in which the classification is partly phenotypic and partly aetiological.⁴⁴ Since the phenotype does not predict the aetiology, it is more logical to keep the two types of classification apart, as in the survey of Pagon.⁴⁵

Colobomata appear as coloboma of the iris, the lens, the ciliary body, the choroid, the optic nerve, or as staphylomatous colobomata or microphthalmos with cyst, or in combinations (table 3). Special cases of coloboma comprise pits of the optic disc, Pedler coloboma, the morning glory malformation, and optic nerve hypoplasia.

Pits are non-hereditary crater-like depressions of the nerve head, first described by Wiethe⁴⁶; the majority of them are situated at the temporal side of the disc. In contrast to typical colobomata, pits are not associated with systemic malformations. Pits have, however, been described in colobomatous eyes.⁴⁷⁻⁴⁹

In Pedler coloboma⁵⁰ the scleral canal is abnormally wide and filled with loose connective tissue. There is an epipapillary mass consisting of buckling of the overlying retina which gives the impression of a tumour.^{3,51} Muscle fibres are present in the wall and the disc can be seen pulsating synchronously with respiration.^{44,51,52}

The morning glory malformation is also an excessive deepening of the optic nervehead. A tuft of glial and vascular tissue projects into the vitreous, and the retinal vessels are seen at the margin of the depression. Optic nerve hypoplasia is considered by some to represent a type of coloboma because it has occasionally been described in patients in whom the other eye had a coloboma⁴³ or microphthalmos with

cyst.⁴¹ The embryological pathology of pits, Pedler coloboma, and morning glory malformations have not been definitively explained. Some authors believe that pits, Pedler coloboma, and morning glory optic nerves are defects of closure of the optic fissure.^{3,43,47,53} However, Mann⁵⁴ and Brown *et al*⁵⁵ were undecided as to the pathogenesis, and Manchot,⁵⁶ on the basis of a histopathological examination of a case of the morning glory syndrome, proposed that it was a mesodermal lesion and not a coloboma. The embryology of optic nerve hypoplasia is undoubtedly heterogeneous.

Aetiological classification

The correlation between phenotype and aetiology is poor in most congenital defects and also where microphthalmos is concerned. The clinician, therefore, needs a structured approach to the identification of an aetiology and this is where a classification is helpful. An aetiological classification of microphthalmos is shown in fig 1. There are three classes: (1) genetic (monogenic and chromosomal), (2) prenatally acquired (teratogenic disruptive causes and deformations), and (3) associations.

GENETIC DISORDERS

There are more than 100 genetic traits with microphthalmos and coloboma. There are approximately 50 different autosomal dominant syndromes, 67 autosomal recessive syndromes with these malformations are known at present, and there are 16 X linked syndromes with microphthalmos and coloboma.⁵⁷ Mitochondrial mutations or deletions have not, so far, been described as a cause of microphthalmos. The disorders which arise from genetic anomalies are termed malformations.^{26,58} In some disorders ocular malformations are isolated signs, for instance, autosomal dominant coloboma-microphthalmos,⁵⁹ but it is much more common that systemic features are part of the symptomatology. The associated features may involve the brain, as in holoprosencephaly,⁶⁰ skin, as in focal dermal hypoplasia,⁶¹ internal organs, as in Meckel's disease,⁶² or the extremities, as in the oculodentodigital syndrome.⁵

The importance of chromosomal disorders in ophthalmology was realised very early.^{63,64} Deletions and translocations of almost all chromosomes may present with microphthalmos or coloboma.⁶⁵ The most common ones are trisomies 13 and 18, del(18p), del(13q), and del(4p),⁶⁶ but microphthalmos or coloboma in mentally handicapped patients with two minor malformations should always raise the suspicion of a chromosomal aberration.

PRENATALLY ACQUIRED MICROPTHALMOS AND COLOBOMA

The term prenatally acquired indicates that the embryo or fetus had a normal genetic background but that the intrauterine environment resulted in disruptions or deformation.^{26,58} *Disruptive microphthalmos* has been

Figure 1 Aetiological classification of microphthalmos. The three major classes, genetic, prenatally acquired, and unknown aetiology, are subdivided into malformations and syndromes, disruptions, deformations, and associations. The final classes consist of identified disorders.

described as a consequence of maternal ingestion of teratogens, among them alcohol,⁶⁷ thalidomide,^{68,69} and isotretinoic acid.⁷⁰ Maternal diabetes and maternal rubella are the best known diseases which may delay the normal growth of the eye.⁷¹ In a singular case, it was postulated that during amniocentesis the needle had perforated the eye of a fetus.⁷²

Deformations of the fetal eye have been observed in cases with microphthalmos where a large choristoma compressed the developing eye,^{73,74} and in patients who had an encephalocele which compressed the orbit.⁷⁵ Oblique facial clefts are supposed to derive from the swallowing of amniotic bands. When a band traverses the fetal eye, microphthalmos or even clinical anophthalmos may occur.^{76,77} Colobomata have also been described in eyes in which choristomas or mesodermal tissue were present in the line of closure of the optic fissure,⁴⁴ but it is impossible to know if the coloboma preceded the abnormal tissue or was caused by it.

ASSOCIATIONS

Associations are non-random concurrences of several particular, but variable, minor malformations which are not pathogenetically related, or which are not known to have the same principal aetiology.²⁶ Lubinsky⁷⁸ thought that they were "derivatives of causally non-specific disruptive events acting on developmental fields". In other words, associations may be the result of teratogens which act at a certain time on a certain area in a person who responds in a certain way. Associations, therefore, would represent embryological relationships and timing, not specific causes.

Microphthalmos and coloboma resulting from associations represent only a minority of

cases. These anomalies are often, but not always, present in the CHARGE association and may be seen in the VATER association.⁷⁹⁻⁸¹

Discussion

The object of a phenotypic classification is to identify clinical syndromes or associations. The phenotypic classification of microphthalmos and coloboma predicts neither the genotype nor an agent which may have caused the malformations. In bygone years, microphthalmos was classified into 'pure', 'colobomatous', and 'complicated' microphthalmos.^{19,82} The first two classes referred to the ocular morphology; in contrast, the third referred to the presence of systemic anomalies and not to specific ocular features. The phenotypic classification presented here is concerned with the ocular features only. The phenotypic classes are not nosological entities, but the phenotype of the ocular malformations together with the systemic signs may often lead to the identification of a recognised syndrome.

The phenotypic classification does not attempt to split anophthalmos, congenital cystic eye, microphthalmos, and coloboma into different aetiological classes. These congenital anomalies may have the same aetiology in some cases, as seen, for example, in fig 2,⁸³ where they all appeared in a single family. In contrast, there are more than 150 different causes of microphthalmos and coloboma. This underlines the necessity of an aetiological classification.

The aetiological classification gives a systematic approach to the possible causes of the congenital anomalies. It makes distinctions between malformations, disruptions, and deformations. The clinician will often be able to differentiate between these, although there are sometimes overlaps. The embryology of the eye is so well known that anomalies can usually be delineated into those which are caused by genetic factors changing embryological growth and differentiation (malformations), and environmental factors which do not comply with embryological barriers (disruptions and deformations).

The present aetiological classification is not restricted to microphthalmos and coloboma, but is of general application in syndromology. Almost all congenital anomalies can be systematically delineated into genetic (monogenic, mitochondrial, chromosomal) or prenatally acquired disorders. Recurrence risks obviously vary considerably between the classes.

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Autosomal recessive
anophthalmos-microphthalmos-coloboma syndrome

Figure 2 A rare consanguineous Arab family showing that the phenotype in the autosomal recessive microphthalmos sequence may present congenital cystic eye, anophthalmos, microphthalmos, and coloboma. Some affected family members were mentally retarded, others were mentally healthy.

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