Ocular Findings in a New Heritable Syndrome of Brain, Eye, and Urogenital Abnormalities

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We studied the clinical and histopathologic ocular findings in four related males with a newly recognized syndrome consisting of microphthalmos, microencephaly, mental retardation, agenesis of the corpus callosum, hypospadius, and cryptorchidism with X-linked recessive inheritance. The ocular abnormalities include microphthalmos, corneal pan­nus and hypoplasia, cataracts, uveal hypoplasia, retinal dysplasia, optic nerve hypoplasia, and congenital blepharoptosis. In case 4, a female twin who died in utero (at 15 weeks' gestation) showed none of the ocular abnormalities.

MICROPHTHALMOS is commonly divided into three varieties: (1) pure, or nanophthalmos, in which the only defect is the small size; (2) colobomatous, in which the small size is secondary to improper closure of the embryonic cleft and in which cyst formation is common; and (3) complicated, in which the small globe coexists with a variety of other ocular abnormalities. According to Duke-Elder, 1 in the complicated type the microphthalmos is not the primary defect but is "secondary to the individual deformities." These deformities may include corneal opacity, correctopia, aniridia, cataract, persistent hyperplastic primary vitreous, and retinal dysplasia, but not coloboma.2,3

Hereditary microphthalmos has a variety of inheritance patterns; the X-linked form is the most unusual.4 In most reported cases of X-linked, complicated microphthalmos, the globes are not truly congenital­ly small but rather represent atrophy bulbii associated with Norrie's disease.5

Case reports

Case 1
This boy (II-2) was born in 1951 and died at the age of 6 years of bronchopneumonia. He was the product of a full-term, uneventful pregnancy and normal delivery. Because of severe retardation he was institutionalized when he was 2 years old. Physical examination by a pediatrician in 1953 showed no light perception bilaterally, blepharoptosis, aniridia, and a "gray vascular membrane" covering the corneas. At autopsy the eyes were noted to be microphthalmic with the corneas obscured by "white fibrous scar tissue." The optic nerves were hypoplastic. Systemic malformations included microcephaly, absence of the corpus callosum, clubbed feet, and hypospadius.

Case 2
This boy (III-2), the nephew of Patient 1, was born in 1975 after a full-term pregnancy and normal delivery. He died of apnea at the age of 26 days. At autopsy he was noted to have bilateral microphthalmos with corneal pannus obscuring the pupils. Iris tissue was seen only in the inferior quadrant, the eyelids were poorly developed, and the optic nerves could not be identified. Additional deformities included hydrocephalus, extreme microencephaly, dysmorphic facies, hypospadius, and an undescended left testicle.

Case 3
This 5-year-old boy (III-3), the younger brother of Patient 2, was examined in 1983 for reported microphthalmos. Physical examination showed general underdevelopment, severe microcephaly, and profound retardation (Fig. 2). He also had spastic quadriplegia, hypospadius, undescended testicles, and fusion of the third and fourth toes.
A computed tomographic scan performed when he was 2 years old demonstrated enlarged ventricles and absence of the corpus callosum. Karyotype testing with G banding showed 46 X,Y with no abnormalities. Serum and urine electrolytes were normal.

On ocular examination the eyelids were blepharoptotic and thickened with tissue that had a fatty consistency on palpation. There was no evidence of levator palpebrae superioris muscle function. The parents said that the eyelids "had covered the eyes since birth."

When the eyelid was elevated by the examiner, the globes were noted to be microphthalmic and deep-set (Fig. 3). Jerk nystagmus was present but motility examination showed a normal range of motion. The pupils could not be evaluated because of a white, fibrovascular membrane covering the corneas bilaterally. The horizontal corneal diameters were 4 mm. A faint blue hue observed behind the corneal membrane probably represented iris. The lens could not be evaluated. The conjunctiva and sclera were unremarkable.

Slit-lamp examination and direct ophthalmoscopy were unsuccessful because of the patient's lack of cooperation. Intraocular pressures were normal to palpation.

Ultrasonography confirmed bilateral microphthalmos. In the one eye measured, the anterior-posterior diameter was 11.25 mm. The lens was present and no abnormalities of the posterior pole were apparent.

Case 4

This fetus (III-6), the child of the younger sister of Patient 1, at 22 weeks' gestation was delivered after prostaglandin induction. The mother (II-4) had been examined by an obstetrician at 16 weeks of gestation during this, her third pregnancy, for a suspected ovarian mass. Her first pregnancy had resulted in the birth of a normal, healthy boy and her second had been electively terminated. Ultrasonography at 16 weeks' gestation showed a benign ovarian cyst along with an intrauterine twin pregnancy. Real-time ultrasonography showed that the female twin had died at a fetal age of approximately 15 weeks. Amniocentesis at this time showed normal 46 X,X and 46 X,Y karyotypes. Repeat ultrasonography at 22

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Fig. 1 (Duker and associates). Pedigree of the affected family. Solid and open squares, affected and unaffected males; circles with solid centers, female carriers; circle with open center, possible female carrier; slash; elective abortion. III-7, female twin of Patient 4 (III-6); she died in utero at 15 weeks' gestation.

Fig. 2 (Duker and associates). Case 3. Note microcephaly and blepharoptosis.

Fig. 3 (Duker and associates). Case 3. Magnified view of the right eye.
weeks verified that the surviving male fetus had microcephaly and the pregnancy was electively terminated. There had been no history of prenatal drug ingestion, radiation exposure, or maternal infection.

At autopsy the male fetus was 175 mm in length, consistent with a fetal age of 22 weeks (5.5 months). The head was microcephalic. The facies was dysmorphic with a short forehead, flat occiput, beak-shaped nose, and long philtrum. The arms were flexed and the third and fourth toes overlapped bilaterally. The heart was enlarged, the liver and pancreas demonstrated interstitial fibrosis, and the testes were undescended. Karyotype testing with G banding and fragile X determination both showed no abnormality.

The left globe and attached orbital tissue measured 10 × 9 mm. The right globe was 6 × 6 mm (normal size for the eye of a 175-mm fetus is 10 × 10 mm). On gross examination the right eye had a clouded cornea with a shallow anterior chamber. The angle appeared to be closed. The lens was cataractous and the iris was hypoplastic. Many retinal folds were present and the optic nerve extended into the vitreous chamber.

Histopathologic examination showed that the cornea was grossly abnormal (Fig. 4). Bowman's layer, normally visible by light microscopy at 5 months' gestation, was not observed. The stroma was hypercellular and completely disorganized with no appar-

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Fig. 4 (Duker and associates). Case 4. Photomicrograph of the right eye (hematoxylin and eosin, × 10).

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Fig. 5 (Duker and associates). Case 4. Left, Magnified view of the cornea, eyelid, and lens. Note the corneal pannus (hematoxylin and eosin, × 20). Right, Normal cornea from an unaffected 22-week-old fetus (hematoxylin and eosin, × 40).
ent lamellar architecture. The endothelium was hypoplastic and Descemet’s membrane, which should be well formed by this stage, was not present. Vascular pannus was noted throughout the anterior stroma (Fig. 5).

The anterior chamber was shallow and the angle structures were immature. Schlemm’s canal, normally formed by the fifth gestational month, was not seen. The iris was hypoplastic. The lens was cataractous with posterior migration of epithelial cells and Morgagnian globules. The tunica vasculosa lentis was noted posterior to the lens. The optic nerve was severely hypoplastic and pulled forward into the vitreous cavity. The choroid was underdeveloped. The retina was folded and dysplastic. Three-layer rosette formation was noted but no photoreceptors could be detected by light microscopy (Fig. 6).

The eyelids were completely fused with no intercalating epithelium marking the palpebral fissure. Normally at this stage the eyelids are nearly separated with only a thin wisp of epithelium fusing upper eyelid to lower.

The left eye showed similar findings except that the lens epithelium was three or more layers in thickness all around the cortex (Fig. 7) and the fibrovascular corneal pannus was present only in the perilimbal area.

The female twin showed none of the ocular abnormalities of the male fetus. The only abnormalities noted on autopsy were severe autolysis secondary to death and a small ventricular septal defect.

Discussion

The systemic abnormalities of this X-linked recessive syndrome include microphthalmos, microencephaly, mental retardation, agenesis of the corpus callosum, hypospadias, and cryptorchidism. The microphthalmos is of the complicated variety; the associated ocular deformities are corneal clouding with fibrovascular pannus formation and dysgenesis of the stroma, cataract, uveal hypoplasia, retinal dysplasia, optic nerve hypoplasia, and congenital blepharoptosis.

An examination of the pedigree (Fig. 1) supports the interpretation that this syndrome is inherited as an X-linked recessive trait in this family. We believe, therefore, that both of the sisters (II-1 and II-4) who bore affected sons are heterozygous carriers for the disease.

A number of inherited as well as sporadic, congenital disorders share similar phenotypic presentations with this syndrome. Trisomy 13 includes microphthalmos, cataracts, retinal dysplasia, mental retardation, and dysmorphic facies, but its lack of...
male sex predilection along with the obvious karyotypic abnormalities make it distinct. Cockayne's syndrome includes microphthalmos, mental retardation, and corneal changes, but the deformities are progressive in the manner of progeria and its inheritance is autosomal recessive. The syndrome described by Jarmas and associates\(^\text{12}\) that features microcephaly, mental retardation, microphthalmos, and falciform retinal folds does not include corneal abnormalities and is inherited in an autosomal recessive fashion. Initially described by Pena and Shokeir,\(^\text{13}\) the cerebro-oculo-facio-skeletal syndrome includes malformations similar to those described here. These include microcephaly, retardation, microphthalmos, cataracts, and dysmorphic facies. These patients, however, typically have renal abnormalities, skeletal deformities, and a history of parental consanguinity implying autosomal recessive inheritance.\(^\text{13,14}\) An X-linked recessive form of microphthalmos, retardation, and urogenital deformities was first described by Lenz in 1955. The Lenz syndrome, however, lacks the corneal, uveal, and eyelid abnormalities noted in the syndrome we described.\(^\text{14}\) The correct diagnosis of a child with microphthalmos is not only of academic importance but has clinical implications because of genetic counseling.

**References**