CLINICAL STUDY

Congenital unilateral buphthalmos in Walker–Warburg syndrome: a clinicopathological study

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Abstract

Background and purpose **Walker–Warburg syndrome is a congenital autosomal recessive oculocerebral disorder characterised by hydrocephalus, brain agyria, microphthalmos and retinal dysplasia with or without meningoencephalocele. We describe an unusual finding of congenital unilateral glaucoma and buphthalmos in one eye and microphthalmos in the fellow eye of two neonates with Walker–Warburg syndrome.**
Patients **Two neonates with Walker–Warburg syndrome and unusual findings of buphthalmos in one eye and a microphthalmic fellow eye are presented.**
Results **Histological examination of the buphthalmic eyes revealed the presence of mesenchymal tissue in the anterior angle covered by endothelium. No anterior chamber angle was identified in the microphthalmic fellow eye and the iris was adherent to the corneal periphery.**
Conclusions **Congenital buphthalmos may also appear in Walker–Warburg syndrome. The buphthalmos may result from later embryonal ocular developmental arrest than that of the microphthalmic eye.**

Key words Buphthalmos, Congenital glaucoma, Microphthalmos, Walker–Warburg syndrome

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Received: 10 March 1999
Accepted without revision: 9 July 1999

Walker–Warburg syndrome is a rare autosomal recessive oculocerebral disorder characterised by hydrocephalus, agyria of the brain, microphthalmos and retinal dysplasia with or without encephalocele.[1–3] Patients with this syndrome have intrauterine growth retardation, myopathy and elevated plasma muscle enzyme levels. The disorder is mapped to locus 9q31. Brain biopsy demonstrates type II lissencephaly and cerebellar malformation. Death often occurs during the neonatal period, while survivors are severely mentally retarded.

The ocular findings of this syndrome are Peters' anomaly, cataract, retinal dysplasia, and colobomas of the iris, the choroid and retina. The most common external ocular sign is unilateral or bilateral microphthalmos,[4] which is considered a reliable sign in the prenatal diagnosis of Walker–Warburg syndrome by ultrasound. We describe two neonates with Walker–Warburg syndrome who were born with unilateral congenital glaucoma and buphthalmos, and discuss the possible embryonal maldevelopment causing these findings.

Case reports

Of three neonates with Walker–Warburg syndrome seen at our facility in the last 10 years, two had buphthalmos in one eye and microphthalmos in the fellow eye. The third had microphthalmos in one eye with a normal-sized fellow eye.

Patient 1

A full-term white male infant (birth weight 3450 g) was born as the third child to first-cousin white parents. In the seventh month of gestation, ultrasound revealed a meningoencephalocele equal in size to the head protruding through a large defect in the occipital bone. The parents refused an abortion. At birth, the diagnosis of meningoencephalocele was confirmed. In addition, microphthalmos was found in the right eye and buphthalmos in the fellow eye. The intraocular pressure measured by Schiotz tonometer in the buphthalmic eye was 30 mmHg. The left cornea, 12 × 11 mm in diameter, was hazy and oedematous with Descemet's breaks. The anterior chamber was deep and the iris appeared normal. No significant pathological findings were observed in the fundus. The right cornea measured 5 × 6 mm. It was opaque and no structure could be seen behind it. The intraocular pressure measured by Schiotz tonometer was 10 mmHg. The infant died from respiratory arrest 8 days later and an autopsy was performed. No history of similar findings in other family members was obtained.

Eye (1999) 13, 778–780

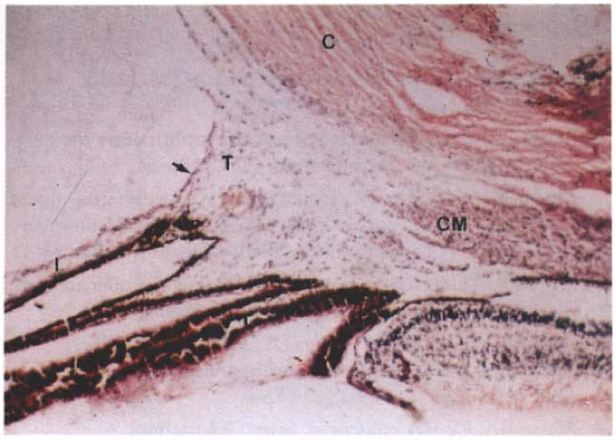

Fig. 1. *Patient 1. A section through the angle of the left buphthalmic eye demonstrating extension of the corneal endothelium (arrow) over the trabecular meshwork (T) and iris (I). The iris is inserted anteriorly obstructing the scleral spur. C, cornea; CM, ciliary muscle (H&E, ×100).*

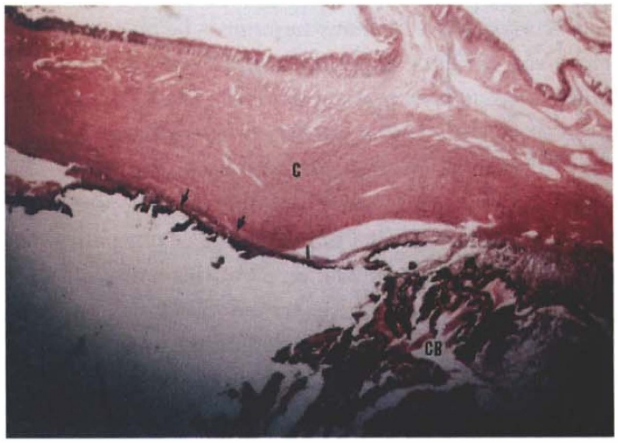

Fig. 2. *Patient 1. Histological micrograph of the anterior segment of the right microphthalmic eye showing an atrophic iris and iridocorneal adhesions (arrows) causing obliteration of the anterior chamber and the angle. C, cornea; I, iris; CB, ciliary body; R, dysplastic retina (H&E, ×100).*

Pathological features

Brain agyria, aqueductal stenosis, hydrocephalus and thick cerebral and cerebellar cortex with disorganisation of the cortical layers were found.

The left buphthalmic globe measured 21 × 21 × 22 mm and the cornea 12 × 11 mm. The pupil was 3 mm in diameter. The cornea was protuberant with a ground-glass appearance. The vitreous was liquefied and the attached retina was pale with poor vascularisation. Microscopic examination revealed a globular cornea with hypercellular stroma. The iris inserted into the anterior trabecular meshwork with underdevelopment of the scleral spur. The iris stroma was extremely hypoplastic and was covered by corneal endothelium extending over the trabecular meshwork (Fig. 1).

The right microphthalmic globe measured 12 × 12 × 12 mm. The hypoplastic optic nerve was 6 mm in length. The conjunctiva was thickened and the cornea was opaque. The anterior chamber was obliterated by hypoplastic iris. A funnel-shaped retinal detachment was disclosed. Microscopic examination of the cornea revealed thickened corneal epithelium and hypercellular stroma with condensation of collagen lamellae. Thin Descemet's membrane with dropout of endothelial cells was noted. The anterior chamber was obliterated by embryonal tissue and no chamber angle was identified (Fig. 2). Peripheral iridocorneal adhesions were found. The ciliary body was displaced anteriorly towards the iris and the ciliary epithelium was detached and adhered to the detached dysplastic retina. The optic nerve showed total loss of nerve fibre bundles.

Patient 2

A second white premature neonate was born after 28 weeks of gestation to first-cousin parents and died 10 days later. He had meningoencephalocele, hydrocephalus and microphthalmos of the right eye and buphthalmos of the left eye. The intraocular pressure was 10 mmHg in the microphthalmic eye and 26 mmHg in the buphthalmic eye. The right globe had an axial length of 16 mm and the corneal diameter was 7 × 6 mm. The left globe had an axial length of 21 mm and the corneal diameter was 11 × 11.5 mm. Both corneas were clear, without evidence of Descemet's breaks. The irides appeared normal, but the anterior chamber of the right microphthalmic eye appeared shallower than that of the left eye and the angle was obliterated by poorly differentiated embryonal tissue. The left anterior chamber angle was identified but was covered with corneal endothelium.

Discussion

Our centre is the only tertiary referral centre for a population of 200 000. During 10 years we have observed three neonates with Walker–Warburg syndrome. Therefore, we estimate the prevalence of this disorder as 0.15 per 100 000 per year. This rate may be higher than in other populations due to a higher incidence of consanguineous marriage in our region.

The usual external ocular manifestation of Walker–Warburg syndrome is microphthalmos.[4,5] This may be unilateral or bilateral and appears in 38–62% of neonates with this syndrome.[6] This finding, along with Peters' anomaly, narrow angle, cataract, primary hyperplastic vitreous, iris and chorioretinal colobomas, retinal non-attachment and the most common ophthalmic manifestation of retinal dysplasia, indicates an early developmental arrest, probably at the fifth gestational week. At this stage, the optic vesicle has been formed and closure of the optic tube commences;[7] the anterior chamber angle is unformed.[5] We presume that in neonates with Walker–Warburg syndrome, the microphthalmic eye has a developmental arrest at this stage. Since aqueous humour does not form well at this stage, the eye remains microphthalmic.

Aqueous humour formation starts in the middle of the fourth gestational month, when tight junctions around the corneal endothelial cell apices are formed.[8] Differentiation over this stage allows maintenance of a

clear cornea while aqueous humour is being formed. However, since the angle is still lined with endothelial lining,[9] the outflow may be minimal. Thus, developmental arrest at the fifth to seventh months may result in increased intraocular pressure causing congenital buphthalmos. We assume that the rare occurrence of congenital buphthalmos in our patients is the result of developmental arrest at this embryonic stage. The attached retina in the buphthalmic eyes further supports the assumption that the anterior chamber angle malformation occurred at a later embryonal stage, since retinal non-attachment is a common finding up to the eighth week of gestation.

Congenital glaucoma has been described in two anecdotal cases of Walker–Warburg syndrome without describing whether they had buphthalmos at birth and without histological description of their angle.[5,10] In contrast to these few cases, the usual finding was microphthalmos, described in most of the case reports and in 10 of 16 patients with Walker–Warburg syndrome in one case series.[5]

Microphthalmos with retinal detachment and other cerebral malformations have been considered by some to be reliable prenatal ultrasonic diagnostic criteria of Walker–Warburg syndrome.[11,12] Since, in rare cases, buphthalmos may present at birth in Walker–Warburg patients, the interpretation of prenatal ultrasonic findings should be done with caution.

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