Choroidal Neurofibromatosis With Congenital Iris Ectropion and Buphthalmos: Relationship and Significance

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ABSTRACT
We report a case of unilateral buphthalmos in neurofibromatosis-1 without the other classical characteristics of the François syndrome (triad of unilateral buphthalmos, homolateral eyelid plexiform neuroma, and homolateral facial hemihypertrophy) and emphasize the difficulties in early diagnosis. The painful buphthalmic right eye was enucleated at the age of 13 months. Histopathology demonstrated diffuse choroidal neurofibromatosis in association with congenital iris ectropion syndrome. Cutaneous manifestations of neurofibromatosis subsequently developed in the patient and stigmata of the disease were later identified in other asymptomatic family members.

INTRODUCTION
Von Recklinghausen's disease, or peripheral neurofibromatosis (NF-1), is a well recognized autosomal dominant phakomatosis that exhibits great variability in its clinical manifestations. The primary defect involves maldevelopment of the neuroectoderm and its neural crest derivatives, although all features are not clearly neuroectodermal in origin. Ocular complications frequently do not appear until late childhood or adulthood, and congenital glaucoma, when present, is commonly associated with a poor prognosis. The present report describes a child who presented in the neonatal period with progressive unilateral congenital glaucoma of uncertain etiology until the enucleated globe demonstrated features of ocular neurofibromatosis including features which would explain the development of intractable glaucoma.

CASE REPORT
A 4-week-old boy presented to the hospital with a diagnosis of congenital unilateral glaucoma and buphthalmos. Unilateral corneal haze was noted shortly after birth. He was the product of a full-term normal delivery and the youngest of three siblings, all of whom were healthy. There was no family history of glaucoma or neurofibromatosis.

Examination under anesthetic at the age of 4 weeks demonstrated diffuse right corneal edema and mild ectropion uvea. The horizontal corneal diameters were 12.5 mm and 11.0 mm in the right and left eyes respectively, while the intraocular pressures using a Perkins hand-held tonometer were 30 mm Hg and 15 mm Hg respectively. The right optic disc was deeply cupped and the left was normal. Gonioscopic examination revealed a very anterior insertion of the right iris. A goniectomy was performed from the 5 o'clock to 7:30 o'clock positions in the right eye. Despite normal intraocular pressure recordings (15 to 18 mm Hg), the horizontal corneal diameter increased to 15 mm over the next 6 months and there was increasing axial anisometropia but the cupped disc did not noticeably deteriorate.

At the age of 8 months, the intraocular pressure again exceeded 30 mm Hg and was associated with marked corneal haze. Two further goniectomies failed to reduce the intraocular pressure. At 13 months, the child was hospitalized for enucleation of his unsightly (corneal diameter 16.5 mm; axial length 33.0 mm), blind, buphthalmic right eye. The enucleation had to be expedited because 1 week prior to the scheduled date the child developed a painful, total hyphema. The etiology of the hyphema was uncertain, but accidental trauma could not be ruled out.

The child, who is 23 months old, has been attending the pediatric clinic since the age of 8 months with a large head circumference which was presumed to be familial, as his father's was more than 2 cm above the 98th percentile. He was first noted to have cafe au lait patches on his trunk and axillary freckling at the age of 17 months, which continue to increase in size and number. A computerized tomographic brain scan was unremarkable apart from the absent globe. On review of the family, both the mother and one of the two older children had similar previously undiagnosed manifestations of cutaneous neurofibromatosis.

PATHOLOGIC FINDINGS
Macroscopic Examination
The specimen consisted of a right globe with an axial length of 33 mm and 3 mm of attached optic nerve. The clear cornea was 16 mm in diameter. The globe was sectioned horizontally. The anterior chamber angle appeared to be open and the anterior chamber was filled with blood. The lens was correctly situated. The pars plicata appeared stretched and attenuated. The retina appeared rather darkly pigmented, the choroid was slightly thickened, and the optic disc was deeply cupped (Fig 1).

Microscope Findings
The corneal epithelium, Bowman's membrane, and stroma were normal. Descemet's membrane was of normal thickness and the corneal endothelial cells were unremarkable. The anterior chamber was filled with a fresh hematoma. The anterior chamber angle was open throughout, but Schwalbe's line, the scleral spur, trabecular meshwork, and
canal of Schlemm were absent. The corneal endothelium was contiguous through the chamber angle and onto the anterior iris. The iris insertion was anterior, and the surface of the iris appeared stretched. The iris stroma was markedly hypercellular and contained numerous spindle cells, some of which contained melanin. Ectropion uvea was noted (Fig 2).

The lens was unremarkable. The somewhat atrophic pars plicata of the ciliary body was stretched and displaced anteriorly and the ciliary muscle was absent. Proliferating and focally pigmented spindle cells extended from the iris through the ciliary body and into the choroid, where they formed a layer up to 0.60 mm thick in the posterior choroid. The retina was unremarkable. The optic disc was deeply cupped (3 mm). The sclera was stretched, being only 0.80 mm thick at its thinnest point. The posterior episclera contained a plexiform area of nerves surrounded by proliferating spindle cells (Fig 3).

Electron microscopy of the anterior chamber angle showed smooth muscle and neural tissue, seemingly from the translocated ciliary muscle, but no trabecular meshwork elements. Scanning electron microscopy demonstrated endothelial overgrowth of the angle.

The histopathologic appearances of the right globe were those of diffuse neurofibromatosis affecting the iris, ciliary body, choroid, and posterior episclera, associated with anterior segment dysgenesis (congenital iris ectropion syndrome) and secondary glaucoma with buphthalmos. There was no demonstrable cause for the hyphema.

DISCUSSION

Von Recklinghausen's neurofibromatosis is a common inherited disorder caused by a gene mutation on chromosome 17. The primary defect is related to a disorder of neural crest derived cells (melanocytes, Schwann, and chromaffin cells). It is associated with a variety of benign and malignant tumors throughout the body. The complications that present to the ophthalmologist are all uncommon and occur in approximately 5% of cases although ophthalmic manifestations of neurofibromatosis occur in greater than 90% of people over 6 years old.

Reports of congenital glaucoma in newborns secondary to neurofibromatosis are very rare. Ipsilateral eyelid neurofibromata and/or facial hemihypertrophy are present in the majority of these cases. Our case is more unusual in that no other stigmata of neurofibromatosis were detected at presentation with the exception of congenital ectropion uvea, and there was no available suggestive family history. Fieman and Yakovae found that 43% of 46 children with neurofibromatosis manifested physical signs at birth, and 63% had physical signs by 1 year of age. Our patient had no cutaneous stigmata of neurofibromatosis initially, but he had developed multiple cafe au lait spots by the age of 17 months. Lisch nodules, which occur in 92% of adult cases, were not present, but they are considered uncommon in children less than 6 years old, and Walton has commented on their absence in eyes with associated congenital glaucoma.

Many mechanisms have been postulated for the development of glaucoma in neurofibromatosis, but the most tenable relate to developmental or mechanical abnormalities. Early reports suggested that choroidal involvement by neurofibromatosis was present characteristically in cases with glaucoma. However, choroidal lesions were the second most common ophthalmic manifestation of neurofibromatosis in two recent studies, occurring in 51% of 77 patients and in 35% of 51 patients respectively. There were no reported cases of glaucoma amongst these 128 patients. One must, therefore, assume that there is a wide spectrum of choroidal involvement and that choroidal lesions alone do not appear to be a significant risk factor. In our case, there was diffuse choroidal and ciliary body involvement in addition to gross angle hypoplasia (Fig 2), congenital ectropion uvea, and patchy endothelialization of a smooth cryptless iris surface—features which are consistent with the congenital iris ectropion syndrome.
It is possible that it is primarily patients with diffuse and severe choroidal involvement who are more likely to have significant ciliary body involvement, angle dysgenesis, congenital or acquired ectropion uvea, and early onset glaucoma. To our knowledge, there are no longitudinal studies which relate the development of glaucoma to the location and extent of intraocular pathology.

As with other regional overgrowth disorders, ocular hypertension may not be the sole etiological factor in the genesis of megalophthalmos. This possibility has received little attention, even though cases of buphthalmos with normal intraocular pressures have been described. Hoyt and Billson supported this concept when they described a case of neurofibromatosis with progressive unilateral buphthalmos and facial hemihypertrophy. They considered the enlarging corneal diameter to be out of proportion to the intraocular pressures recorded and suggested that ocular hyperplasia may play a more significant contributory role in the genesis of buphthalmos in this disorder than had been reported hitherto.

We were also surprised by the progressive globe enlargement in our patient even during periods of apparently normal intraocular pressure recordings. This could suggest that other factors in addition to a suprathreshold intraocular pressure contributed to megalophthalmos in our patient. Elevated nerve growth factor, mast cell, and nerve growth-stimulating activity occur in neurofibromatosis, while Schwann cells have been shown to have many nerve growth factor receptor sites. The significance of these findings, which may reflect neural overgrowth or alternatively may predispose to the formation of neural tumors, is unclear. Hence, nerve or other tissue growth factors may play a role in neurofibromatosis-induced buphthalmos, as plexiform neurofibromas which are largely composed of Schwann cells can, as in this case, involve the ciliary body and choroid.

Many clinicians have perceived that patients with choroidal neurofibromatosis have a poor visual prognosis, but recent studies do not support this view. However, if there is associated ectropion uvea, this should alert the examiner to the possibility of a neurocraniopathy, angle abnormalities, and early onset glaucoma. Similarly, the simultaneous occurrence of congenital iris ectropion syndrome is further evidence for the incorporation of the former in the spectrum of neural crest-derived anterior segment dysgenesis syndromes. We now consider that any infant with congenital unilateral glaucoma of uncertain etiology requires follow-up physical examinations which should ideally include inspection of asymptomatic family members for associated hereditary disorders such as neurofibromatosis.

REFERENCES