American Journal of Ophthalmology Case Reports 25 (2022) 101345

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Progressive ectropion uveae and secondary angle-closure glaucoma in type 1 neurofibromatosis

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ARTICLE INFO

Keywords:
Ectropion uveae
Neurofibromatosis type 1
Glaucoma

ABSTRACT

Purpose: To present a case of progressive ectropion uveae and secondary angle-closure glaucoma in association with type 1 neurofibromatosis (NF-1).
Observation: An 11-year-old-Hispanic-male with a known history of NF-1 who was followed for the ocular manifestations of NF-1 developed an irregular pupil and ectropion uveae in the right eye at the age of 3 years that gradually increased in severity. The area of ectropion uveae increased in size and extended superiorly with concurrent superior synechial angle closure and intraocular pressure (IOP) elevation. The patient subsequently developed chronic angle-closure glaucoma that could not be controlled with medical therapy. He underwent successful implantation of an aqueous drainage device which resulted in excellent intraocular pressure reduction.
Conclusions and Importance: Ectropion uveae can be progressive and lead to the development of extensive angle closure in patients with NF-1. Despite the low incidence of glaucoma in patients with NF-1, the presence of ectropion uveae in this condition necessitates careful observation of the anterior segment, including the anterior chamber angle and close monitoring of the IOP.

1. Introduction

NF-1 is a relatively rare autosomal dominant disorder of the neuroectoderm affecting 1 in 2500 to 3500 people worldwide, which results in the development of hamartomas, particularly of the skin, eyes, and nervous system.[1,2] The syndrome primarily affects tissue derived from the neural crest, particularly sensory nerves, Schwann cells, and melanocytes. The eye and the ocular adnexa are frequently involved in patients with NF-1.[2] Glaucoma associated with NF-1 is not common, occurring in 1%–2% of NF-1 patients.[2]

The mechanisms underlying IOP elevation in the setting of NF-1 are multifactorial and may include (1) neurofibromatous infiltration of the anterior chamber angle with or without formation of peripheral anterior synechiae (PAS); (2) anterior segment neovascularization; (3) ectropion uveae; and (4) non-pupillary block angle closure due to pushing forward of the iris as a result of neurofibromatous thickening of choroid and ciliary body.[3]

Ectropion uveae refers to the presence of iris pigment epithelial cells on the anterior iris surface with distortion of the iris and irregularity of the pupil due to dragging of the posterior epithelial cell layer onto the anterior iris. The mechanisms by which the anatomical changes of ectropion uveae occur in NF-1 are uncertain; however, some investigators have classified it as congenital ectropion uvea (CEU).[2,4,5] The temporal characteristics of ectropion uveae in NF-1 are not well established and could be progressive or static. Herein, we present a case of progressive ectropion uveae and the development of advanced angle-closure glaucoma in a patient with NF-1.

2. Case report

The patient is an 11-year-old-Hispanic-male who was referred to our center at the age of 3 years for evaluation and management of NF-1. At the time of initial presentation, examination was remarkable for multiple café au lait spots on the back and axilla, s-shaped swelling and ptosis of the right upper eyelid, normal extraocular movements, and slight proptosis of the right eye. Best spectacle corrected visual acuity was 20/50 in the right eye and 20/20 in the left eye with a cycloplegic refraction of −4.00 + 0.75 X 90 in the right eye and +0.50 sphere in the left eye. Intraocular pressure (IOP) was 16 mmHg in both eyes. Slit lamp biomicroscopy disclosed five Lisch iris nodules on the surface of each iris

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https://doi.org/10.1016/j.ajoc.2022.101345
Received 14 August 2021; Received in revised form 20 January 2022; Accepted 21 January 2022
Available online 2 February 2022

and slight irregularity of the right pupil. Posterior segment biomicroscopy disclosed cup-to-disc ratios of 0.4 and 0.3 in the right and left eye, respectively.

Magnetic resonance imaging of the orbit was consistent with sphenoid wing dysplasia and right orbital plexiform neurofibroma. Accordingly, the patient was closely followed for ocular complications of NF-1 and underwent surgery to debulk the upper eyelid neurofibroma that extended into the orbit.

At baseline subtle superior irregularity and hyperpigmentation of the pupil was observed. During follow-up, iris hyperpigmentation was noted to gradually extend toward the anterior chamber angle. The ectropion uvea was further documented as progressively increasing in size contemporaneously with increasing IOP. IOP elevation of the right eye was first noted 3 years after initial presentation, at the age of 6 years, at which time it was 28 mmHg, concurrent with the development of ectropion uveae.

Initial ocular hypotensive medical therapy reduced the IOP to 17–19 mmHg. Starting at age 9 years, the IOP increased to 35 mmHg in the right eye despite maximum medical therapy.

Due to inadequate IOP control, the patient was referred for tube shunt surgery. Preoperative indentation gonioscopy of the right eye disclosed a flat, anterior insertion of the iris with no visible angle structures superiorly and ectropion uveae extending clockwise, from 8 to 4 o'clock (Fig. 1). The inferior angle was open. There was 2+ pigmentation of the inferior trabecular meshwork.

Since the angle was completely closed superiorly, a Baerveldt glaucoma implant (BGI 101–350) was placed in the inferonasal quadrant with a human donor scleral patch allograft with the tube in the anterior chamber, and the use of a temporary a 4–0 Prolene intraluminal stent suture with an 8-0 Vicryl ligature. There were no intraoperative or postoperative complications. During 29 months of post-operative follow-up the IOP has remained in the 11–18 mmHg range on the fixed combination of dorzolamide and timolol, with one outlier measurement of 24 mmHg attributed to medication non-adherence.

Specular microscopy obtained soon after tube shunt surgery demonstrated decreased endothelial density, increased polymegathism and polymorphism in the right eye (Fig. 2).

3. Discussion

Patients with NF-1 are at increased risk of developing glaucoma with a prevalence of 1–2% in childhood.[2] Ipsilateral congenital glaucoma is present in 23–50% of NF-1 patients with eyelid plexiform neurofibromas.[2,3,6] Various mechanisms for IOP elevation have been implicated including infiltration of the anterior chamber angle by neurofibroma cells, PAS formation in association with ectropion uveae, and other angle abnormalities such as the presence of an anterior and flat iris insertion, abundant iris processes, or increased pigmentation of the angle.[3,6,8,9]

The exact mechanism of ectropion uvea in NF-1 is not clear. Several investigators have classified it as congenital ectropion uvea.[2,4,5] However, except for one reported case,[10] CEU is a nonprogressive condition and not associated with the development of peripheral anterior synechiae.[11] Conversely, ectropion uvea in the setting of NF-1 is characterized by a similar biomicroscopic iris appearance in association with the presence of PAS.

Our patient had subtle ectropion uveae at the age of 3 years, which increased in severity by the age of 10 years. This significant change in size indicates a dynamic pathophysiologic mechanism.

The presence of endothelial cell overgrowth in NF-1 was first described by Brownstein and Little in 1983.[12] They reported a 4.5-month-old-male who initially was diagnosed and managed for primary congenital glaucoma, but five years later developed an eyelid plexiform neurofibroma along with other signs of NF-1, including ectropion uveae.[12] They attributed the iris endothelialization to chronic angle closure that resulted from a massive neurofibroma of the ciliary body.

In a histopathologic study of five eyes of five patients with NF-1 and unilateral glaucoma, Edward, et al. demonstrated histologic evidence of ectropion uveae and corneal endothelial cell overgrowth in all cases.[7] In a gene expression assay performed on one case, they showed that endothelial cell proliferation was associated with loss of neurofibromin (the *NF1* gene product) and elevated mitogen-activated protein kinase (MAPK) gene expression in those corneal endothelial cells.[7] The authors postulated ectropion uveae occurs as a result of corneal endothelial cell proliferation and angle invasion, similar to what occurs in iridocorneal endothelial syndrome. In the reported cases, however, most eyes also had apparent neurofibroma involvement and forward displacement of the ciliary body which may be an alternate mechanism to explain PAS formation and IOP elevation.

We used specular microscopy to evaluate the corneal endothelium. While we found dysmorphic endothelium in the affected eye of our patient (Fig. 2), a limitation of this study is the fact that specular microscopy was performed just under 2 months after implantation of an aqueous drainage device. The tube, however, was implanted inferiorly while the superior cornea was imaged. Additionally, the abnormal findings could be secondary to high IOP and chronic use of glaucoma medications, although the fact that these changes are mainly limited to

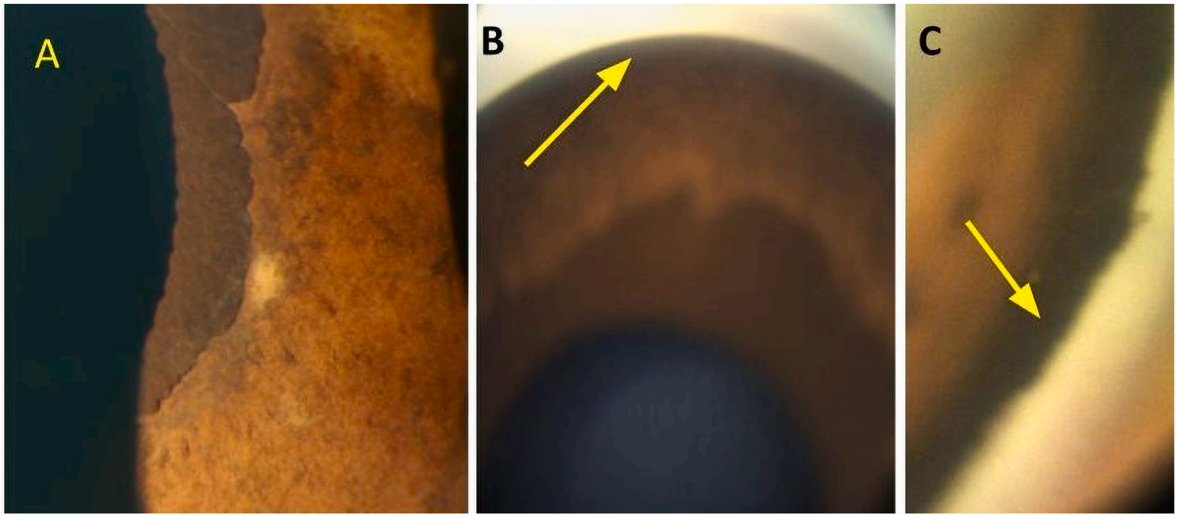

Fig. 1. A. Ectropion uveae and lisch nodule **B**. Closed angle superiorly **C**. Hyperpigmented open angle nasally and inferiorly.

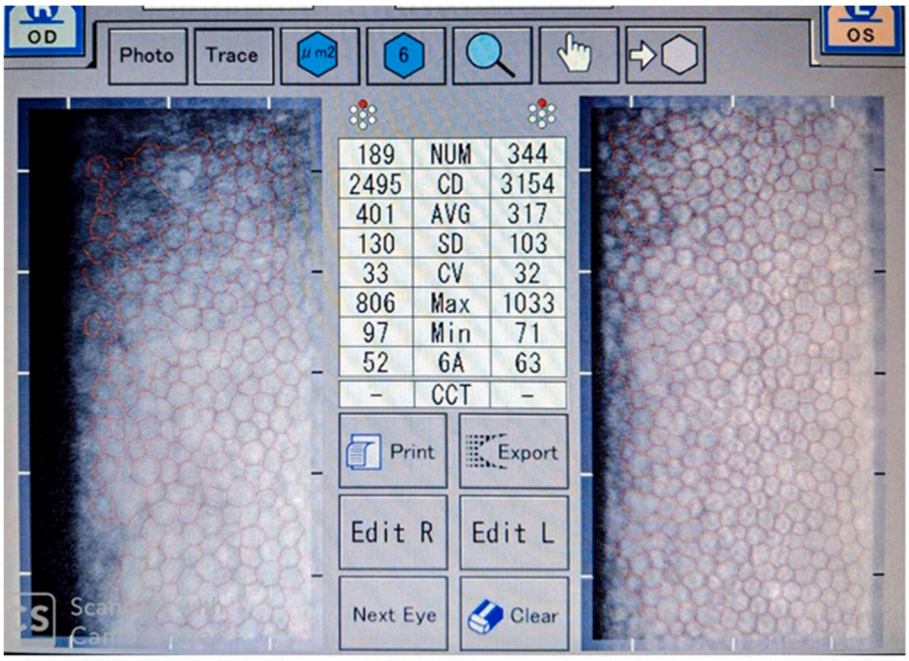

Fig. 2. Specular microscopy of the superior corneal endothelium demonstrates decreased endothelial density, increased polymegathism and polymorphism in the right eye. Imaging was performed 50 days after tube shunt surgery.

the superior cornea makes these alternative explanations less likely.

The anatomic causes of glaucoma in these eyes seem to be multifactorial and it is unclear what role the angle endothelialization plays in the severity of the IOP elevation. The progressive nature of ectropion uveae in our case is consistent with prior reports[7,12] and supports the previously proposed pathophysiology of ectropion uveae in NF-1.[7] Endothelialization of the anterior chamber angle in NF-1 results in ectropion uveae, ectopic pupil, angle closure, Descemetization of the iridocorneal angle, and iris atrophy.

Glaucoma is shown to have a poor prognosis in NF-1 cases with ectropion uveae. Over time, ocular hypotensive medical therapy is likely to fail due to extensive angle closure.[3,6,7] The use of microinvasive glaucoma surgeries is also limited due to the angle abnormalities in this condition, which makes trabeculectomy or glaucoma tube shunt surgery the preferred surgical choices. The severity and extent of iris pigment hyperplasia affect the surgical approach. In our case, the superior angle was completely obliterated so we implanted the drainage device in the inferonasal quadrant. Although inferior and superior glaucoma drainage devices have similar efficacy, the inferior quadrant tubes are more likely to become exposed,[13] which necessitates delicate tissue handling and complete tube coverage with a patch graft. We prefer scleral allografts in children due to their persistence over time. In this patient, inferior eyelid coverage was judged sufficient for safe implantation of the device inferiorly.

In conclusion, we report a case of progressive ectropion uveae and advanced secondary angle-closure glaucoma in a patient with NF-1. The occurrence of progressive ectropion uveae is consistent with the presence of ongoing changes in the anterior chamber due to corneal endothelial cell proliferation. IOP elevation associated with angle closure in NF-1 that fails to respond to medical therapy can be managed successfully with aqueous drainage device surgery.

Consent to publish the case report was obtained from the patient's father in writing. In addition, this report does not contain any personal information that could lead to the identification of the patient.

Funding

Supported by an unrestricted grant from Research to Prevent Blindness, NY, NY.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

HE: None. JLZ: None. APT: Consultant to Ivantis, Sandoz, and Zeiss.

Acknowledgements

None.

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