



# A rare case of neurofibromatosis type I with unilateral congenital ectropion uveae and glaucoma

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## ABSTRACT

**Purpose:** Neurofibromatosis Type I (NF-1) is a neurocutaneous disease affecting the skin, eye and peripheral nervous system. Congenital glaucoma is a rare association, but can be a prelude to the diagnosis of NF-1 later in life. We report this unusual association in a child and discuss the possible underlying pathophysiologic mechanisms.

**Observations:** A nine year old female child on treatment for glaucoma in the right eye was referred to us for definitive management. Her ocular evaluation was remarkable for reduced visual acuity, megalocornea with buphthalmos, congenital ectropionuveae, Lisch nodules and glaucomatous optic neuropathy in the right eye. Systemic evaluation revealed café-au-lait spots on the chest and back. A diagnosis of Neurofibromatosis Type I with congenital ectropion uveae and glaucoma was arrived at and neuroimaging failed to detect any optic pathway gliomas. In view of advanced glaucomatous neuropathy, a conservative therapy was recommended.

**Conclusion and importance:** Unilateral congenital glaucomas with ectropion uveae are likely to be associated with NF-1. These children should be monitored closely for glaucoma progression and may require neurological evaluation including imaging studies to exclude optic pathway gliomas.

## 1. Introduction

Neurofibromatosis 1 (NF-1, Von Recklinghausen disease) is a neurocutaneous disease, with an approximate incidence of 1/3500 births.<sup>1</sup> Diagnosis of NF-1 is based on having 2 or more of the well established criteria (Table 1) described by the National Institute of Health.<sup>2</sup>

Congenital glaucoma is a rare association in NF-1, with the most common proposed mechanism being failure of normal development of the anterior chamber angle. Grant and Walton<sup>3</sup> have emphasized that multiple mechanisms are responsible for the development of congenital glaucoma. They found only 1 case associated with NF-1, among 300 patients with all types of childhood glaucoma examined over a period of 6 years in their report. We report a child with unilateral congenital ectropion uveae and glaucoma, characterized by presence of café-au-lait macules and Lisch nodules fulfilling the minimal criteria essential for the diagnosis of NF-1.

## 2. Case report

A 9-year-old girl presented to us with proptosis and painless defective vision in right eye (RE) since birth (Fig. 1). She was the second child, born of non-consanguineous marriage with an uneventful natal

and perinatal history. She was diagnosed to have glaucoma in RE and was on fixed-dose combination of Brimonidine + Brinzolamide and Travoprost + Timolol eye drops in both eyes (BE) for the last four years. Her mother was unable to recall details of previous treatment and baseline investigations were not available. On general examination, the child had multiple (> 10) light brown macules of varying sizes ranging from 2mm to 40mm with smooth margins distributed over the chest and back, suggestive of café-au-lait spots (Fig. 2).

Ocular evaluation revealed a visual acuity of counting fingers close to face in RE and 20/20 in the left eye (LE). Anterior segment evaluation of the RE was remarkable for buphthalmos, scleral thinning, megalocornea with a horizontal corneal diameter of 16 mm, ectropion uveae (Fig. 3) and relative afferent pupillary defect. While Lisch nodules (Fig. 4) were noted in BE, there was no evidence of Haabs' striae in either eye. Intraocular pressure by Goldman Applanation tonometer was 16 and 12 mmHg in RE and LE respectively. Central corneal thickness was 548  $\mu$  in RE and 559  $\mu$  in the LE. Gonioscopic evaluation of the RE revealed intermittent peripheral anterior synechiae with 3+ pigmentation (Fig. 5), obscuring much of the details of the angle structures. Posterior pole evaluation of RE revealed glaucomatous optic neuropathy with a cup to disc ratio of 0.9. The axial length of RE and LE respectively were 29.71 mm and 22.06 mm. B Scan Ultrasonography

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**Table 1**  
Diagnostic criteria for Neurofibromatosis type 1.

1	Six or more café-au-lait macules with a diameter > 5 mm in pre-pubescent individuals and > 15 mm in post-pubescent individuals.
2	Two or more neurofibromas of any type or one plexiform neurofibroma
3	Freckling in the axillary or inguinal regions
4	Optic nerve glioma
5	Two or more iris Lisch nodules
6	A distinctive osseous lesion (e.g., sphenoid wing dysplasia, long bone cortical thinning with or without pseudoarthrosis)
7	A first degree relative with neurofibromatosis type 1

was within normal limits. Ultrasound Biomicroscopy was not feasible due to inadequate cooperation from the child. The anterior and posterior segment examination of LE was within normal limits with wide open angles till ciliary body band on Gonioscopy. Retinal Nerve fiber layer thickness measurements by Optical Coherence Tomography (OCT) was within normal limits in LE, while that of RE was poorly reliable due to artifacts. Magnetic Resonance Imaging (MRI) of the brain and orbits were within normal limits with no evidence of optic pathway gliomas.

The child was diagnosed to have NF-1 and congenital glaucoma associated with congenital ectropion uveae in RE. As per the Childhood Glaucoma Research Network (CGRN)<sup>4</sup> classification, the child was assigned “Glaucoma associated with non-acquired systemic disease/syndrome” category. The clinical evaluation of LE was within normal limits, except for the finding of Lisch nodules. There was no evidence of glaucomatous optic disc damage or retinal nerve fiber layer abnormalities on OCT suggestive of glaucoma. The glaucoma medications were

discontinued in LE. Owing to potentially poor visual outcome in RE, no further intervention other than continuing maximal medical therapy was suggested. A month subsequent to the initial visit, IOP by applanation was 16 mm Hg in each eye.

**3. Discussion**

NF-1 can have various ophthalmic manifestations including Lisch nodules, optic nerve gliomas, neurofibromas of eyelid, conjunctiva and orbit. It is predominantly inherited as an autosomal dominant trait, but about 50% of NF-1 can have spontaneous mutations.<sup>5</sup> We examined the parents and her young sibling and did not find any ocular or systemic abnormality suggestive of neurofibromatosis. In the absence of clinical signs of NF-1, the risk of the parent of having another child with NF-1 is said to be less than 1%.<sup>6</sup>

Although one has well-defined criteria for the diagnosis of NF-1, diagnosis is a challenge in infants and children as many of these markers manifest later in life. Various mechanisms proposed to cause glaucoma in NF-1 include direct infiltration of the anterior chamber angle by neurofibromas, secondary angle closure resulting from neurofibromas of the ciliary body and choroid, fibrovascularization leading to synechial angle closure with neovascular glaucoma and developmental abnormalities of the anterior chamber angle.<sup>7</sup>

Findings in our child is largely in agreement with the observations by Edward et al.,<sup>7</sup> who concluded that ectropion uveae in NF-1- associated glaucoma is secondary to endothelialization with varying degrees of closure of the anterior chamber angle and is commonly associated with severe pediatric glaucoma. Endothelialization secondary to angle closure from diffuse neurofibromas of the choroid and ciliary



**Fig. 1.** Profile picture of the patient showing proptosis in the right eye.



Fig. 2. Multiple café-au-lait spots in back, as indicated by white arrow heads

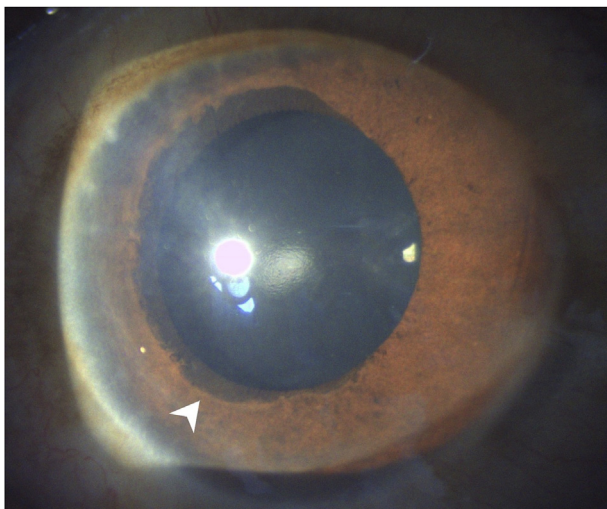


Fig. 3. Megalocornea with ectropion uveae in the right eye (white arrow heads)

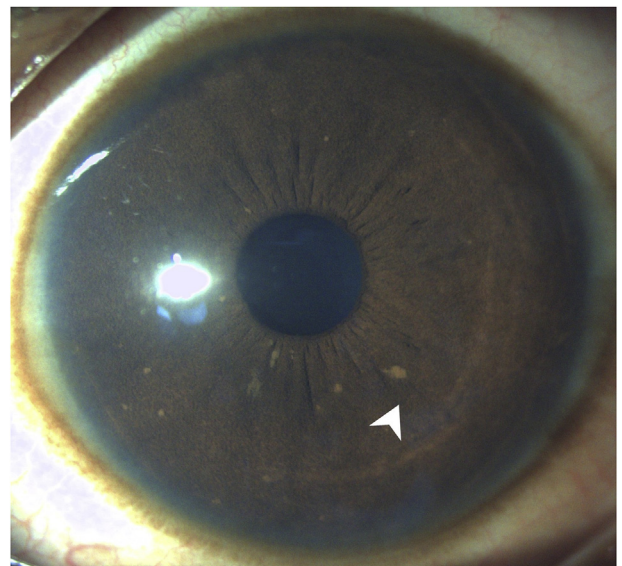


Fig. 4. Left eye showing yellow-white Lisch nodules (white arrow heads)

body<sup>8</sup> have also been suggested based on a study of enucleated specimen of a buphthalmic eye with NF-1. We could not detect choroidal neurofibromas based on normal ultrasonographic study in our child, while involvement of the ciliary body cannot be excluded since ultrasound biomicroscopy was not possible. We did not observe plexiform

neurofibromatosis or lid thickening in this child, though its presence is often accompanied by ipsilateral glaucoma<sup>3</sup> and the association of ectropion uveae with orbitofacial involvement<sup>9</sup> usually results in most

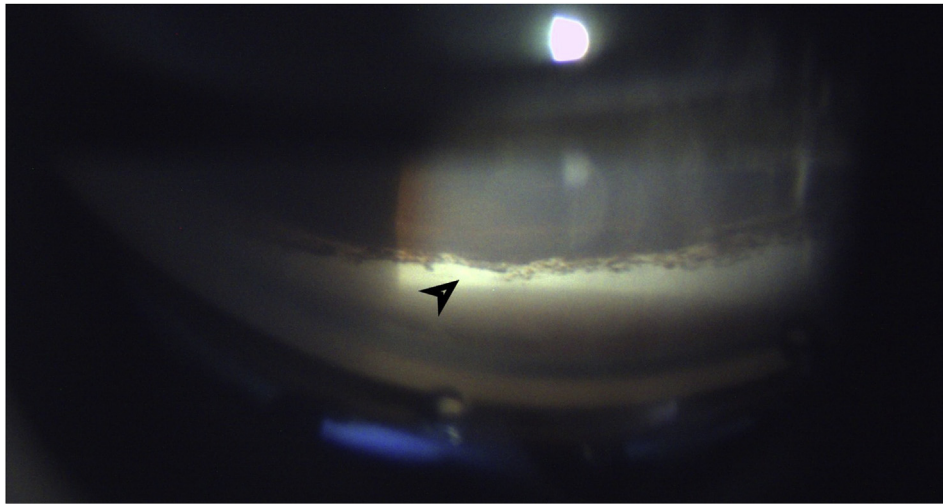


Fig. 5. Gonioscopy showing patchy peripheral synechiae with irregular pigmentation in the right eye (black arrow head)

severe form of glaucoma.

Children presenting with congenital glaucoma warrant careful systemic evaluation to exclude associated systemic disorders, as in this child. Finding of congenital ectropion uveae should alert the examining ophthalmologist to evaluate closely for detection of Lisch nodules on the iris, careful dermatological evaluation for café-au-lait spots, and imaging to detect optic pathway gliomas early for appropriate management to preserve vision. Optic nerve pathway gliomas are Grade 1 astrocytomas, present in 15–20% of children with NF-1 before eight years of age.<sup>10</sup> Though older children have a significantly less risk of gliomas, it is recommended to annually evaluate every child with NF-1 until 18 years. Owing to visual loss from severe glaucoma or less commonly optic nerve pathway gliomas, all children with NF-1 require periodical evaluation with a multi-disciplinary approach.<sup>11</sup>

Prompt diagnosis of NF-1 early in life is crucial to detect glaucoma early for appropriate management with angle surgeries or glaucoma drainage implants in refractory cases. Although management of glaucoma in NF-1 is similar to that of primary congenital glaucoma, response to therapy appears more refractory and NF-1 associated glaucomas carry worse prognosis with a third of patients requiring enucleation or evisceration as reported by Morales et al.<sup>12</sup> Given the poor visual outcome owing to glaucomatous optic neuropathy in this child and higher risk of complications like choroidal hemorrhage due to incisional surgeries, we advocated continuing medical therapy for management of glaucoma.

Our case represents a young girl with unilateral ectropion uveae and congenital glaucoma resulting from angle endothelialization in NF-1, without evidence of optic pathway gliomas. Both congenital glaucoma and optic nerve gliomas can cause significant visual loss if not detected early, treatment as appropriate instituted and periodically evaluated for progression. Diagnosis of gliomas are often challenging in the presence of glaucomatous optic nerve atrophy, since optic nerve function tests like colour vision or visual field evaluation are not possible due to visual loss. Progressive congenital glaucoma refractory to therapy may also result in significant enlargement of the globe with pseudo proptosis, which can be mistaken for progressive gliomas as in the child presented. Periodic monitoring with neuroimaging is essential when progressive visual disturbance or proptosis is noted.

#### 4. Conclusion

Neurofibromatosis is a clinically heterogenous disease requiring multidisciplinary care. The knowledge of this association of NF-1 in congenital glaucoma will enable the treating ophthalmologist to better communicate with the parents regarding the need for continuous

neurological follow up, in addition to glaucoma monitoring. Complete systemic examination is mandatory in any child with congenital glaucoma.

#### Patient consent

The patient's parent consented to publication of the case in writing, as the child is minor.

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#### Authorship

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

#### Declaration of competing interest

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#### References

1. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. *J Am Acad Dermatol*. 2009;61:1–14.
2. Stumpf D, Alksne J, Annegers J. Neurofibromatosis. Conference statement. National institutes of Health consensus development conference. *Arch Neurol*. 1988;45:575–578.
3. Grant WM, Walton DS. Distinctive gonioscopic findings in glaucoma due to neurofibromatosis. *Arch Ophthalmol*. 1968;79:127–134.
4. Beck A, Chang TC, Freedman S. Section 1: definition, classification, differential diagnosis. In: Weinreb RN, Grajewski A, Papadopoulos M, Grigg J, Freedman S, eds. *World Glaucoma Association Consensus Series-9: Childhood Glaucoma*. Amsterdam, The Netherlands: Kugler Publications; 2013:3–10.
5. Thavikulwat AT, Edward DP, AlDarrab A, Vajaranant TS. Pathophysiology and management of glaucoma associated with phakomatoses. *J Neurosci Res*. 2018;97:57–69.
6. Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, Evans DG. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet*. 2007;44:81–88.
7. Edward DP, Morales J, Bouhenni RA, et al. Congenital ectropion uvea and mechanisms of glaucoma in neurofibromatosis type 1: new insights. *Ophthalmology*. 2012;119(7):1485–1494.
8. Brownstein S, Little JM. Ocular neurofibromatosis. *Ophthalmology*.

- 1983;90(12):1595–1599.
9. Ritch R, Forbes M, Hetherington Jr J, Harrison R, Podos SM. Congenital ectropion uveae with glaucoma. *Ophthalmology*. 1984;91(4):26–31.
  10. Listernick R, Ferner RE, Liu GT, Gutmann DH. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. *Ann Neurol*. 2007;61(3):189–198.
  11. Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. *Lancet Neurol*. 2014;13(8):834–843.
  12. Morales J, Chaudhry IA, Bosley TM. Glaucoma and globe enlargement associated with neurofibromatosis type 1. *Ophthalmology*. 2009;116(9):1725–1730.