Unilateral congenital glaucoma may be the earliest presenting sign of orbitofacial neurofibromatosis and intracranial lesions: a case series
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Purpose
The aim was to report a number of cases initially presenting with unilateral congenital glaucoma within the first year of life that subsequently were found to be associated with the orbitofacial variant of neurofibromatosis-1 (NF1) as well as with variable intracranial lesions.

Patients and methods
The records of 340 patients presenting with unilateral congenital glaucoma were retrospectively reviewed to identify patients who subsequently developed orbitofacial NF ipsilateral to the glaucoma or other manifestations of NF1. All clinical, radiological, or histopathological data for enucleated globes, if available, were reviewed.

Results
Seven patients were identified with a mean age at presentation of 4.3±5.4 months. They presented with unilateral buphthalmos and high intraocular pressure with subtle proptosis and/or lid swelling. The mean age at NF1 diagnosis was 23.14±18.5 months. Initial imaging reports were either read as ‘normal’ or described a lesion near the cavernous sinus (CS): CS thrombosis, clival meningioma, histiocytosis, carotid cavernous fistula, or CS hemangioma. Once the diagnosis of NF1 was made, subsequent imaging studies (computed tomography and/or MRI) showed a defect at the greater wing of sphenoid bone (all patients); neurofibroma involving the CS, orbit, and nearby intracranial and subcutaneous structures to varying degrees (all patients); and hamartomas at the level of the basal ganglia (six patients). Associated intracranial lesions were sphenoid wing meningioma, optic nerve glioma, and trigeminal schwannoma. Histopathology of two enucleated eyes showed glaucomatous changes with prominent ciliochoroidal hyperplasia in one case and a ciliary body schwannoma in another.

Conclusion
In newborns with unilateral congenital glaucoma, the differential diagnosis should include NF1. Targeted radiologic examinations may reveal diagnostic signs and decrease disease morbidity. The glaucoma surgeon may opt for earlier aggressive intervention in this potentially blinding disease.

Keywords:
cavernous sinus lesion, ciliary body schwannoma, neurofibroma, neurofibromatosis 1, orbitofacial neurofibromatosis, plexiform neurofibroma, unilateral congenital glaucoma

Introduction
Neurofibromatosis type 1 (NF1) is the most common of all phakomatoses (1:3000–4000 live births) [1,2]. It is an autosomal dominant neurecutaneous disorder known to involve multiple systems and has a potential for malignant transformation [1]. A characteristic feature of which is the neurofibromas, benign neural tumors affecting the peripheral nervous system either superficial (dermal neurofibromas) or more diffuse, involving multiple nerves (plexiform neurofibromas). They consist mainly of proliferating Schwann cells (≥80%) with fibroblasts and perineural cells [3].

A special variant of NF involving the face and orbit is known as orbitofacial neurofibromatosis (OFNF). It occurs in 1–22% of patients with NF1, manifesting the most in early childhood and resulting in progressive disfiguring tumors, and is known for its aggressive behavior with a higher growth rate than those elsewhere in the body [1].
Although glaucoma has been associated with NF1, yet rarely did it occur in very young children, and only few reports are found in the literature describing buphthalmos as the sole and earliest presentation [4–7]. Such cases have a complicated clinical course, with multiple mechanisms incorporated in the pathogenesis. Management is considered challenging and most cases have an unfavorable outcome [3–7].

In our study, we report seven cases of children presenting with unilateral buphthalmos within the first year of life who later developed classic features NF1 as well as variable types of intracranial tumors that were not detected on initial imaging. Their clinical course is described.

**Patients and methods**

The medical records of patients presenting with primary congenital glaucoma to the glaucoma clinic at our tertiary referral hospital during the period from January 2011 to December 2017 were reviewed. Patients identified to have subsequently developed a picture consistent with ipsilateral OFNF or other manifestations of NF-1 were included in our study. All clinical, radiological, and surgical data of the patients were recorded.

The following data were collected: first, patient demographics; second, clinical and radiological data; third, for glaucoma, the intraocular pressure (IOP) at presentation and at last follow-up, medications, surgery, and intraoperative gonioscopy were recorded (glaucoma was defined as an IOP ≥22 mmHg measured by Goldman applanation tonometry with optic disc cupping); and fourth, for NF1, the presence of orbitofacial involvement and laterality, the initial and subsequent imaging reports, the age at diagnosis of NF1, based on the criteria of the NIH [8], whether there were any neurosurgical procedures, and pathology reports of enucleated eyes were all noted.

Histopathological assessment of those globes was performed using standard hematoxylin and eosin stain on formalin-fixed paraffin-embedded tissue sections. Immunohistochemical staining with S-100 protein was employed to confirm the diagnosis.

Ethical approval by the Institutional Review Board was obtained for both the retrospective and prospective components of this study, and parents signed an informed consent for patients undergoing surgery. This study adhered to the tenets of the Declaration of Helsinki.

**Results**

In this retrospective cross-sectional study, 340 patients records of patients presenting with unilateral congenital glaucoma were reviewed, of whom, seven (2.06%) patients were identified with NF1 (based on NIH criteria). Four of them were females (57%). The mean age at presentation was 4.25±5.37 months. The mean age at actual diagnosis of NF1 was 23.14±18.5 months. The average time between presentation and diagnosis of NF1 was 16.75±25.2 months. The mean follow-up period was 19.29±16.47 months.

The main presenting symptom was an enlarged globe in all cases. Clinical examination revealed first, buphthalmos with or without corneal opacity (all seven cases); second, raised IOP (mean 23.7±5.09 mmHg); third, subtle proptosis of less than 2 mm difference between both eyes (five cases); fourth, upper lid swelling (causing mild ptosis) in three cases described as s-shaped in one (Fig. 1).

Initial imaging reports [including ultrasound, computed tomography (CT) and MRI] were either negative, maybe showing just an enlarged globe, swollen orbital tissue, especially extraocular muscles and retrobulbar fat, engorged orbital veins and thickened optic nerve, or described a lesion near the

**Figure 1**

Progression of lid involvement in patient 2 over time: (a) at 3 months, (b) at 8 months, and (c) at 2 years.
cavernous sinus (CS): CS thrombosis, clival meningioma (patient 1), histiocytosis (patient 2) (Fig. 3), carotid cavernous fistula (patient 3), or CS hemangioma (patient 7). The first CT of patient 1 even described a normal study result. With follow-up, clinical signs suggestive of NF1 started to be established: first, café au lait patches, in all children, varying from few spots on the back to numerous lesions on the trunk and limbs; second, plexiform neuroma of the right upper eyelid in five cases, and an extensive temporal subcutaneous neurofibroma involving the upper lid in two patients (4 and 7); and third, hemihypertrophy of the face consistent with OFNF in five cases (Fig. 2). Moreover, subsequent imaging (CT and/or MRI) revealed the classical defect at the greater wing of sphenoid bone in six cases (Fig. 3) and neurofibroma involving the CS, orbit, and nearby intracranial and subcutaneous structures to varying degrees (Fig. 4). Other intracranial tumors were sphenoid wing meningioma (patient 2), optic nerve glioma (patient 5), and trigeminal Schwannoma (patient 4). One case (patient 1) had hamartomas or what was previously described as unknown bright objects (UBOs) appearing as increased T2-w signal intensity at the level of the basal ganglia (Fig. 5).

Regarding the glaucoma, the average number of surgeries performed whether goniotomy or SST with
or without mitomycin was 1.7. The mean IOP at the last follow-up was 14.5±8.48 mmHg; however, only two cases achieved IOP control. Patient 1 received two-angle procedures and intraoperative gonioscopy revealed a narrow angle and anterior insertion of the iris, resembling angle features of PCG. Patient 6 received combination eye drops (timolol+carbonic anhydrase inhibitor), and despite advanced optic nerve damage, some useful ambulatory vision for few meters was maintained in the eye (Table 1).

In total, four (57%) enucleations were performed. The average age at enucleation was 3.9 years. Patients 2 and 7 received filtering procedures; however, the IOP continued to rise, and with advanced proptosis, globe ptosis, and optic nerve atrophy, enucleation was done for the blind painful eye at the ages of 45 and 29 months, correspondingly. In patient 3, enucleation was performed at the age of 6 years following trauma to the affected eye; the globe was hypotonous and hemophthalmic. Patient 5 had a complicated cataract, retinal detachment, and corneal opacity. His visual acuity was no light perception when a decision for enucleation was taken at the age of 3 years (Table 1).

Histopathology reports were available for two cases: the specimen examination of patient 2 showed evidence of an enlarged glaucomatous globe (deep anterior chamber, ganglionic cell layer atrophy of the retina, and an excavated optic disc). Additionally, prominent corneoscleral nerves and ciliochoroidal hyperplasia were seen. Examination of specimen of patient 3 revealed a ciliary body schwannoma. The tumor composed of spindle cells, with eosinophilic cytoplasm, indistinct cell borders, and oval nuclei. The nuclei formed nuclear palisading (i.e. Antoni A pattern) in areas and were arranged in a loose myxomatous background (Antoni B pattern) in other areas. There was also positive immunoreactivity with S–100 protein (Fig. 6).

Two of our patients required interventions for intracranial masses. Patient 2 received gamma knife treatment for a sphenoidal wing meningioma at the age of 2 years, and the tumor showed evidence of regression on postoperative imaging and remained stationary throughout follow-up. Patient 4 received two neurosurgical procedures; the first was at the age of 5 months when a petroclival mass (neurofibroma) was excised. Nine months later, she developed hydrocephaly, and a cerebrospinal fluid (CSF) shunting procedure was done. Unfortunately, she died almost a year later from chronic complications of the CSF shunting tube and extensive brain atrophy.

Detailed clinical features of all subjects are summarized in the Table 1.
### Table 1 Clinical data & investigations

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|----------|---|---|---|---|---|---|---|
| Age at glaucoma diagnosis | 3 months | 2 weeks | 1 month | 8 days | 1st year | 1st year | 1 month |
| Sex | Female | Female | Male | Female | Male | Male | Female |
| Laterality | Right | Right | Right | Left | Right | Left | Right |
| IOP at initial presentation | 24 | 24 | 28 | 30 | 22 | 14 | 24 |
| Initial diagnosis | PCG | PCG | *Sturge-weber + secondary glaucoma | PCG | PCG | PCG | PCG |
| Age at diagnosis of NF1 | 4 months | 9 months | 4.5 years | 5 months | 2.5 years | 3 years | 2 years |
| Initial imaging results | CECT: Cavernous sinus thrombosis MRI: SOL of Cavernous Sinus extending to the foramen ovale (clival meningioma) | CT: Normal MRI @ 3 months: CS and Meckel’s cave soft tissue mass with small intraorbital component. Secondary proptosis, enhancing thickened meninges along the GWS Differential diagnosis: Langerhans cell histiocytosis, metastasis (of neuroblastoma) or lymphoreticular neoplasms | CECT: carotid cavernous fistula (@ age 2.5 years) | CT @ 8 days: arachnoid cyst at the sylvian fissure, proptosis with blurring and thickening of retro-orbital fat planes | N/A | N/A | MRI @ 7 months: Right Cavernous Sinus hemangioma with intraorbital and infratemporal extension, proptosis and buphthalmos |
| Final imaging results | MRI: NF involving CS extending to foramen ovale Hamartomas at the basal ganglia Defective GWS MRI: sphenoidal wing meningioma MRI: hypoplastic GWS with a contiguous soft tissue mass (NF) MRI@ Sm: Trigeminal nerve Schwannoma involving all three divisions + Deficient GWS MRI: NF involving lateral orbital wall and cavernous sinus Thick elongated and kinked optic nerve (optic nerve glioma) Hypoplastic GWS MRI: Defective GWS CT: (at 2 years) Defective GWS |
| Clinical course | IOP 10 mmHg, 10 months after 2nd goniotomy Intraoperative gonioscopy showing narrow angle and anterior insertion of the iris resembling PCG Goniotomy at 1m SST + MMC at 6m Gamma-knife excision for sphenoidal wing meningioma (2 years) Debulking of lid mass at 2 years 3 months Optic atrophy à Enucleation (3 years 9 months) for a blind painful eye | 2 SST elsewhere at 1m and 8m NLP at presentation IOP 2 mmHg and hemophthalmos following trauma Enucleation for blind painful eye (6 years 5 months) Surgical excision of a petroclival mass (5m) (neurofibroma by pathology) CSF shunting procedure (14 months) IOP 13 mmHg on antiglaucoma treatment (20 months) Progressive hemicerebral atrophy and death (23 months) 3 previous surgeries elsewhere NLP at presentation, opaque cornea US: cataract, shallow RD, thick choroid, wide ON shadow AXL=32 mm Enucleation for blind painful eye (3 years) | SST + MMC 6M 3 debulking procedures BCVA 1.0Log MAR (SE=−6.0D) CD=0.9 IOP=14 mmHg On antiglaucoma treatment | 2 glaucoma surgeries at 1m and 5m. Enucleation elsewhere for a blind painful eye at 29 months |

24 | 45 | 7 | 20 | 5 | 34 | N/A

(Continued)
NF1 is not an uncommon disease [1,2], and glaucoma has been reported to occur in 23–50% of patients, especially in the presence of an ipsilateral OFNF [4]. However, glaucoma at birth and in early childhood has long been considered rare, with only a few case reports (describing 1 or 2 patients each) highlighting the presence of congenital glaucoma and/or buphthalmos in infancy before the establishment of NF1 diagnosis [5–7,9,10].

We report an incidence rate of 2.06% of early childhood glaucoma associated with NF1 in this cross-sectional cohort of cases under study. All seven patients initially presented with unilateral buphthalmos and congenital glaucoma. In the presence of suspicious proptosis and ptosis, CT and/or MRI imaging studies were done. Reports of imaging were initially misleading. Results ranged from normal to variable diagnoses of space-occupying lesion, mostly centered at the CS (e.g. CS thrombosis, hemangioma, carotid cavernous fistula, histiocytosis, and clival meningioma). Diagnostic delay attributed to misinterpretation of MRI scans has been previously reported in patients with NF1 with hemifacial hypertrophy but was explained by the fact that plexiform neurofibromas can resemble mesenchymal tumors and lymphangiomas [11].

Table 1 (Continued)

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|----------|---|---|---|---|---|---|---|
| Follow up (months) | N/A | Prominent corneal nerves, PAS, Iridectomy, deep AC Ciliochoroidal hyperplasia trabecular meshwork and schlemm’s canal are present. The retina shows loss of ganglionic cell layer ‘atrophy’, optic disc excavation | CB Schwannoma, Iris NV, Vitreous hemorrhage | N/A | N/A | N/A | N/A |

AC, anterior chamber; AXL, axial length; BCVA, best corrected visual acuity; CB, ciliary body; CD, cup disc ratio; CECT, contrast enhanced CT; CSF, cerebrospinal fluid; F, female; GWS, greater wing of the sphenoid; IOP, intraocular pressure; MMC, mitomycin C; NF, neurofibroma; NLP, no light perception; NV, neovascularization; ON, optic nerve; PAS, peripheral anterior synechiae; PCG, primary congenital glaucoma; RD, retinal detachment; SE, spherical equivalent; SOL, space-occupying lesion; SST, sub scleral trabeculectomy; US, ultrasound. * Diagnosis established at a private rural practice.
As other clinical features of NF1 started to emerge in our patients, namely, the appearance of café au lait patches, lid thickening, ptosis, and proptosis, a second MRI was requested, searching for other intracranial features of NF1, and all came conclusive. The predominant features were a defective greater wing of the sphenoid bone that was not present in earlier images. This challenges the hypothesis of Hunt and Plugh [12] that sphenoidal bone defects, an uncommon but a distinctive manifestation of NF1, are merely sphenoidal dysplasia resulting from a congenital mesodermal development and supports the theory put forward by Macfarlane et al. [12] that suggest it being a secondary phenomenon owing to a local vascular abnormality caused by enlargement of the ipsilateral CS, resulting in local expansion of the superior orbital fissure and progressive prolapse of the adjacent temporal pole.

Among patients with NF1, Lisch nodules occur in 50% of 5-year-old children, 75% of 15-year-old adolescents, and more than 90% of patients greater than 25 year olds. None of our patients showed the characteristic iris Lisch nodules or ectropion uveae, probably, because these are known for their late age of appearance than our cases [4].

Intraoperative gonioscopy of case 1 revealed a narrow angle and anterior insertion of the iris resembling angle features of PCG. Quaranta et al. [13] in 2004 reported similar gonioscopic findings in 69% of their patients with NF1 in the form of iris insertion anteriorization and a narrow ciliary body band. On the contrary, histopathological studies of postenucleation specimens in two of our patients (2 and 3) showed ciliochoroidal hyperplasia with retinal ganglion cell loss and ciliary body schwannoma, respectively, suggesting another mechanism for the development of glaucoma in these patients. These findings are, in part, consistent with the observations of Edward et al. [3] who studied the mechanisms of glaucoma in enucleated eyes of five patients with NF1.

Schwannomas account for 0.5–1.00% of all orbital tumors; however, a schwannoma of the uveal tract is rarely encountered; fewer than 20 cases have been reported in the literature [14–16]. To the best of our knowledge, this may be the first report of a ciliary body schwannoma in a young child with congenital glaucoma.

Glaucoma associated with NF1, in general, is known to carry a poor visual prognosis [1,3,4]. In our patients, four (57%) had enucleations for a blind painful eye (absolute glaucoma, hemophthalmos, retinal detachment in patients 2 and 7, 3, and 5, respectively). In a long-term visual outcome study conducted on 37 patients presenting with OFNF in the period between 1981 and 2009 [17], five patients had enucleations (13.5%); however, the mean presenting age in their cohort of patients was much older than ours (15 years). Moreover, in another study comprising nine patients with OFNF, three had enucleation of their blind eyes (33%) [18]. The high incidence and diversity of intracranial lesions (ICLs) in this cohort (four out of seven cases) also has not been reported before. Truly brain tumors are reported in 15–20% of children with NF1, but the majority of these tumors are gliomas involving the optic nerve or chiasm [19]. Intracranial masses required radiological and neurosurgical intervention in two of our patients (2 and 4, respectively). Patient 2 received successful gamma knife excision at the age of 2 years. Patient 4 had a surgical excision at the age of 5 months of a petroclival mass. The histopathological report confirmed the diagnosis of neurofibroma. An additional CSF shunting procedure was done at 14 months, and the patient died before her second birthday. In 2011, Evans et al. [20] reported a mortality rate among patients with NF1 in North West England to be 11%, which is comparative to our results (14.3%). However, in their study, an aggressive form of optic nerve glioma was the leading cause of death among patients less than 10 years of age.

Conclusion

Unilateral congenital glaucoma in an infant may mask a more sinister systemic disease. NF should be considered in all newborns with globe enlargement and presumed congenital glaucoma if the slightest proptosis or ptosis is suspected even in the absence of anterior segment signs. Timely imaging and follow-up imaging are essential for the early diagnosis of associated ICLs bearing in mind that an inconclusive cavernous lesion or an internal carotid lesion is a common misleading radiological sign. Appropriate management of some ICLs decreases the morbidity and may be lifesaving. The glaucoma surgeon may opt for earlier aggressive management in view of the progressive nature of this disease such as directly proceeding with valves implantation to avoid loss of vision in these patients.

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Conflicts of interest
There are no conflicts of interest.
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