**European Ophthalmic Pathology Society**
**63rd Annual Meeting**
**Basel, June 11th –14th, 2025**

**Member's Name: Tero Kivelä, MD, FEBO**

Department of Ophthalmology
University of Helsinki and Helsinki University Hospital
Zaidankatu 2, PL 225
FI-00029 HUS, Helsinki, Finland

1 section, MH24-40273

# UNDIAGNOSED GANGLIONEUROMA IN AN EYE WITH CONGENITAL GLAUCOMA, ASSOCIATED WITH NEUROFIBROMATOSIS TYPE 1

## Case Report

A girl was born on gestational week 34+5 days to healthy parents after an uneventful pregnancy. Because the mother was 36 and the father 44 years old, a placental biopsy to exclude chromosomal abnormalities was taken and was found to be normal. Her Apgar points were low at 5-7-8, she had hypocalcaemia, dysmorphic features like slanting eyebrows and small jaw, and her right eye was larger than the left one. Echography of the brain was normal. Café-au-lait spots were found on her belly, feet, and arm.

An ophthalmologist detected a cloudy right cornea, high IOP of 35 mmHg, compared with 20 mmHg in the left, and hypoplastic optic disks. Trabeculectomy was performed at age 5 months, failed, was repeated, failed again, and was followed by glaucoma shunt implantation.

Her growth was retarded with rump length 3 SD and body weight 2 SD below average. Metabolic disease was suspected because of elevated urine ethyl malonate levels and a mitochondrial disease because plasma carnitine levels were elevated. MRI revealed in a 20 x 13 x 10 mm cavernous sinus tumour connected with the orbit through an enlarged superior orbital fissure. It was associated with a dysplastic sphenoid bone and multiple focal areas of high signal intensity, a.k.a. unidentified bright objects (UBO).

Whole genome sequencing found two defects: heterozygotic *de novo* pathogenic p.(Glu104del) indel and p.(Arg380Trp) missense *ACADS* variant, causing short chain fatty acid acetyl coenzyme-A deficiency, and heterozygotic *de novo* p.(Leu1153Metfs*4) frameshift *NF1*variant, confirming neurofibromatosis type 1.

She walked at age 2 years 1 month. Her right eye was progressively proptotic by age 2 years 11 months. MRI showed a diffuse tumour that filled the superior, lateral and medial orbit, extended to the intracranial space through the optic canal and the superior orbital fissure, and enlarged the bony orbit. The choroid was diffusely thick, especially posteriorly, and the uveal ring had high signal intensity by MRI.

She developed lagophthalmos upon sleep. Trametinib, which inhibits MEK1 and MEK2, was started to shrink the tumour, but the parents soon declined it for fear of side effects. Debulking orbital surgery was performed instead, resecting a 20 x 15 x 6 mm block of neurofibroma. The IOP remained high at 23-31 mmHg with medication. She developed corneal erosion, opacification, and deep stromal neovascularisation. Proptosis returned, and the largely blind eye was enucleated and the orbital tumor resected at age 6.5 years.

## Ophthalmic Pathology

The right eye measured 20 mm in diameter and 30 mm in length. Corneal diameter was 14 mm, and eyelid groove was 5 mm behind the limbus. The horizontally bisected globe appeared normal, except for elongated pars plana and thickened choroid, especially posteriorly.

The cornea was 945 µm thick. Its epithelium was hyper- and metaplastic. Almost half of the corneal thickness was of richly vascularized lamellar collagenous scar with CD34-immunonegative fibroblasts over a CD34-immunopositive corneal stroma. The cornea covered by the upper eyelid had no scar, but no Bowman layer was seen, and deep neovascular vessels were present. The anterior corneal stroma was remarkable for presence of isolated thick nerves. Descemet's membrane had some guttata like excrescences.

The chamber angle on both sides was closed by synechiae. A fibrous retrocorneal membrane grew over the peripheral cornea. The endothelial cells had migrated over the anterior surface of the iris, depositing Descemet-like material.

The stroma of the iris and ciliary body were also remarkable for the presence of large nerves and many nerve endings, as highlighted with antibodies to neurofilaments, synaptophysin, and calcineurin.

The choroid was diffusely thick, increasing from 265 µm at ora serrata to 315 µm at equator and 735 µm in posterior pole. It contained abundant ganglion cells dispersed individually or arranged in clusters from which nerve fibres emerged. Myriad nerve endings were present throughout the uvea in a way normally seen only in the ciliary muscle. The posterior choroid was unusually vascular with large veins in its anterior third. Antibodies to S100 showed many melanocytes and Schwann cells, some of the latter stained also for GFAP.

Despite the long-standing glaucoma, the retina had retained quite many ganglion cells as highlighted with antibodies to NEUN. The radial glial cells were in a reactive state as evidenced by immunopositivity to GFAP.

The main histopathologic diagnosis was *congenital glaucoma* associated with *diffuse ganglioneuroma of the choroid associated with neurofibromatosis 1*. Additionally, a secondary retrocorneal membrane with proliferation of endothelial cells over the iris was present, as well as a superficial corneal fibrovascular scar with deep neovascularisation from corneal exposure.

## Comment

Ganglioneuroma as an entity was first reported by Wilhelm Loretz, a German physician, in 1870.[1] However, the first intraocular ganglioneuromas in the English literature were published as late as in 1965 by Wolter, Bryson & McGee[2] in an adult with bilateral juvenile glaucoma without proptosis or signs of neurofibromatosis, and in 1983 by Woog *et al*.[3] associated with glaucoma and neurofibromatosis without proptosis. The early history of both patients remained unknown.

More recently, 7 case reports of choroidal ganglioneuroma associated with neurofibromatosis have been published from 2006 to 2022. These share the following features: congenitally large eye,[4-7] ipsilateral congenital glaucoma,[4-6,9] proptosis and downward globe displacement,[6,7,9] ipsilateral sphenoid wing hypo- or dysplasia,[4,6,7,9] usually a palpebral[4,8,9] or an orbitocranial neurofibroma,[6,7,9] and a thickened choroid by MRI or US.[5,6,7,9] The ganglioneuroma was first noted by histopathology after evisceration[4,9] or enucleation.[5-7,9]

Although diffuse neurofibromas also can thicken the choroid in neurofibromatosis, the combination of an orbitocranial neurofibroma with congenital glaucoma and proptosis seems to be a typical triad.

A recent EOPS presentation dealt with ganglioneuroma. Thaung (EOPS2017-24) described a 55-year-old woman who developed a choroidal melanoma in her amblyopic eye. In addition, the posterior choroid was diffusely thickened by spindle cells intermixed with ganglion cells and melanocytes. It appeared to correspond to a pigmented nevus-like lesion that had been seen in the fundus separate from the melanoma. Immunopositivity for neurofilaments was only very focal. She did not meet the current diagnostic criteria of neurofibromatosis. The final diagnosis was *isolated ganglioneuroma*.

The following year van Ginderdeuren (EOPS2018-06) described a 70-year-old man with an amblyopic painful eye. A huge choroidal amelanotic tumor and total retinal detachment were present. The neoplastic spindle and epithelioid cells were MelanA negative but positive for neuroendocrine markers synaptophysin and chromogranin. Metastases developed 3 years later, eventually also in the contralateral eye. The diagnosis was *choroidal paraganglioma*, which is another neural crest derived tumour distinct from ganglioneuroma.

Ganglioneuromas have been thought to arise early in life as tumour-like proliferations of choroidal ganglion cells and related neuroectodermal elements, apparently often already during foetal growth. The abnormal development of the uvea appears to interfere with the development of the iridocorneal angle, leading typically to congenital glaucoma and buphthalmos.

However, all choroidal ganglioneuromas are not associated with neurofibromatosis. DeParis *et al*.[10] reported a 5-year-old girl with unilateral congenital glaucoma associated with diffuse thickening of the iris and choroid. The entire uveal tract contained neoplastic spindle cells admixed with ganglion cells, which was diagnostic of uveal ganglioneuroma. No evidence of neurofibromatosis was detected. Instead, targeted next-generation sequencing revealed a germline nonsense *PTEN* mutation, accompanied by loss of heterozygosity in the tumor. The diagnosis was *Cowden syndrome* (OMIM 158350) in which diverse hamartomas can occur and risk of cancer is increased. It belongs to the PTEN hamartoma tumor syndrome (PHTS) spectrum. Jiang *et al*.[11-12] thereafter reported a 6-year-old boy with high IOP and bilateral ganglioneuroma associated with retinal detachments diagnosed by a biopsy, and a *de novo* germline pathogenic frameshift PTEN variant.

Whether caused by NF1 or PTEN, diffuse choroidal ganglioneuroma appears to cause a hyperintense uveal ring in MRI images, as well as early-onset glaucoma.

## References


1. Loretz W. Ein Fall von gangliosen Neurom (Ganglion). *Virchows Arch Path Anat* 1870; 49: 435-41.
2. Wolter JR *et al*. Ganglioneuromelanocytosis of the choroid. *Arch Ophthalmol* 1965; 74: 353-6.
3. Woog JJ, *et al.* Choroidal ganglioneuroma in neurofibromatosis. *Graefe's Arch Clin Exp Ophthalmol* 1983; 220: 25-31.
4. Shome D, *et al*. Choroidal ganglioneuroma in a patient with neurofibromatosis type 1: a case report. *Eye* 2006; 20: 1449-50.
5. Ishijima K, *et al*. Intraocular neovascularization associated with choroidal ganglioneuroma in neurofibromatosis type 1. *Eur J Ophthalmol* 2011; 21: 837-40.
6. Mbagwu M, *et al*. Unsuspected ganglioneuroma of the choroid diagnosed after enucleation. *Ocul Oncol Pathol* 2016; 2: 48–50.
7. Goyal S, *et al*. Choroidal ganglioneuroma and orbital plexiform neurofibroma presenting as buphthalmos in an infant with neurofibromatosis type 1. *Ophthal Plast Reconstr Surg* 2016; 32: e87-9.
8. Ozgun G, *et al*. Co-occurrence of choroidal pigmented ganglioneuroma and plexiform neurofibroma in a patient with neurofibromatosis 1. *Kaohsiung J Med Sci* 2014; 30: e215-6.
9. Gupta H, Kandalkar B. Choroidal ganglioneuromas in Francois variant neurofibromatosis-1: a rare retinoblastoma mimic. *Indian J Ophthalm*ol 2022; 70: 2602-4.
10. DeParis SW, *et al*. Uveal ganglioneuroma due to germline *PTEN* mutation (Cowden syndrome) presenting as unilateral infantile glaucoma. Ocul *Oncol Pathol* 2017; 3: 122–8.
11. Jiang Z, *et al*. New *PTEN* mutation identified in a patient with rare bilateral choroidal ganglioneuroma. *BMC Ophthalmology* 2020; 20: 487.
12. Jiang Z, *et al*. Multimodal imaging features of bilateral choroidal ganglioneuroma. *J Ophthalmol* 2020; 2020: 6231269.