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Ocular Findings in Neurofibromatosis

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Abstract

Neurofibromatosis (NF) is an inherited disease affecting multiple systems in the body. The eye is frequently affected in neurofibromatosis, and therefore ocular manifestations play a major role in the diagnosis of NF. This chapter aims to explore the spectrum of ocular manifestations found in neurofibromatosis highlighting the importance of ophthalmic exam in these patients. It will describe various intraocular manifestations involving the iris, lens, and retina. It will be focusing on glaucoma and the pathogenesis behind it in this group of patients. Moreover, periorbital and orbital involvement such as skin neurofibromas and optic nerve gliomas will be discussed along with some of their histopathological findings.

Keywords: neurofibromatosis, glaucoma, cataract, retinal hamartoma, Lisch nodules, choroid, optic nerve, glioma, plexiform neurofibroma, diffuse neurofibroma

1. Introduction

Neurofibromatosis (NF) is an inherited disease affecting multiple systems in the body. It is caused by a genetic mutation affecting cellular growth regulation, therefore resulting in disrupted pathways and formation of multiple tumors in the body. Ocular involvement is an important part of the disease as it may be required for the diagnosis. Although some manifestations are only of diagnostic value such as Lisch nodules, other ocular involvement can be vision threatening like glaucoma and optic nerve gliomas. Therefore, this chapter aims to explore how this disease can affect various structures of the eye and some histopathological changes that may be seen in some.

2. Types of neurofibromatosis

Neurofibromatosis is caused by a gene mutation affecting a tumor suppressor protein resulting in uncontrolled proliferation of neural cells that can involve various parts of the body such as nerves, skin, and eyes. It is classified into two types based on the location of the mutated gene. Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen disease, is caused by a mutation in the gene NF-1 located on chromosome 17. This leads to a dysfunctional tumor suppressor protein known as neurofibromin. As a result, NF-1 manifests as multiple benign tumors in the body such as plexiform neurofibromas, Lisch nodules, and optic nerve gliomas.

Six or more café au lait macules (greatest diameter of >5 mm in prepubertal individuals and > 15 mm in postpubertal individuals)
Two or more neurofibromas of any type or one plexiform neurofibroma
Axillary or inguinal freckling.
Optic glioma
Two or more Lisch nodules (iris hamartomas)
A distinctive osseous lesion (sphenoid dysplasia or tibial pseudarthrosis)
A first degree relative with NF1

Table 1.
Diagnostic criteria for NF1 (two or more must be present).

NF-1 is inherited as autosomal dominant trait but may be sporadic in about 50% of the cases [1]. Ophthalmic manifestations are of diagnostic value in NF. **Table 1** shows the criteria that are used for the diagnosis of NF-1 [2]. Three out of the total seven may involve ocular structures. Therefore, an individual may be diagnosed with NF-1 solely on his ophthalmic exam.

Neurofibromatosis type 2 (NF-2) is caused by a chromosome 22 mutation in the gene encoding for the protein merlin or schwannomin, which is also a tumor suppressor protein. Dysregulation of this gene results in overproduction of Schwann cells. Therefore, the most prominent feature of this disease is bilateral vestibular schwannomas occurring in almost 90% of the patients. It may also affect different structures in the body causing tumors such as optic meningiomas and gliomas. Similar to NF-1, it is inherited in autosomal dominant fashion but may be sporadic [2].

Clinical presentation of both diseases may overlap as they both affect cellular growth of neural tissue. This chapter will be discussing ocular manifestations that are seen in NF highlighting the importance of ophthalmic examination in these patients.

3. Intraocular manifestations

3.1 Iris

Various intraocular conditions have been described in NF, most commonly, iris hamartomas. Iris hamartomas is a hallmark feature in NF-1 and is therefore considered one of the diagnostic criteria. Histologically, Lisch nodules have been described to be a collection of spindle cells that are melanocytic in origin [3]. They usually occur during childhood and increase in size and number with aging. They are typically seen under slit-lamp examination; are described as round elevated nodules within the iris, measuring around 2–3 mm in size; and are brown to yellow in color (**Figure 1**). Lisch nodules are typically bilateral; however, unilateral nodules have been reported previously in some types of NF [4].

3.2 Glaucoma

Glaucoma has been found to occur in about 1 in 300 NF-1 patients [5]. Patients with orbito-facial involvement have been linked to higher rates of glaucoma at 23–50% [6–8]. It was also found that patients with eyelid plexiform neurofibromas have ipsilateral globe enlargement up to 36 mm axial length [6]. Although glaucoma



Figure 1.
Slit-lamp photo of an iris showing Lisch nodules in a patient diagnosed with neurofibromatosis.

in NF is not common, it has been studied due to the visual burden it may cause. Various mechanisms have been described in the pathogenesis of glaucoma in these patients. The most commonly described mechanism is the presence of neurofibromas in the angle causing aqueous outflow obstruction [6]. Other suggested processes include secondary angle closure due to the anterior displacement of the peripheral iris by an abnormally thickened ciliary body or developmental anomalies in the angle [7].

Moreover, congenital ectropion uvea has been linked to refractory glaucoma in patients with NF. Histologically, endothelialization of the anterior chamber angle has been observed in these eyes. It has been hypothesized that loss of the NF gene and therefore RAS–RAF–ERK–MAPK pathway activation may be the cause of endothelial overgrowth in these patients [9]. It is difficult to link one mechanism causing glaucoma in NF as most cases are probably multifactorial as described above.

3.3 Lens

Lens opacities are of importance in NF-2 as they may be the first sign to suggest the diagnosis during childhood [10]. NF-2 typically causes posterior subcapsular cataract or cortical cataract and occurs in 60–80% of patients with the disease [10, 11].

3.4 Retina and choroid

Retinal astrocytic hamartomas are benign tumors that usually affect the optic nerve. They clinically resemble a small white mulberry and are mostly linked to tuberous sclerosis but have been reported in NF patients as well. Rarely, those lesions may extend to the peripheral retina and cause devastating complications such as neovascular glaucoma and retinal detachment. Other retinal lesions described in NF patients include combined hamartoma of the retina and retinal pigment epithelium (CHR-RPE) and retinal capillary hemangiomas [12–14].

In the past, choroidal involvement was thought to be uncommon in NF patients as it was difficult to visualize subtle changes with fundus examination and conventional angiography. However, with the development of new diagnostic technologies such as optical coherence tomography (OCT), choroidal changes have been found to reach up to 100% of NF patients [15]. Uveal neurofibromatosis has been also demonstrated histopathologically within the choroid (**Figure 2**) [9].

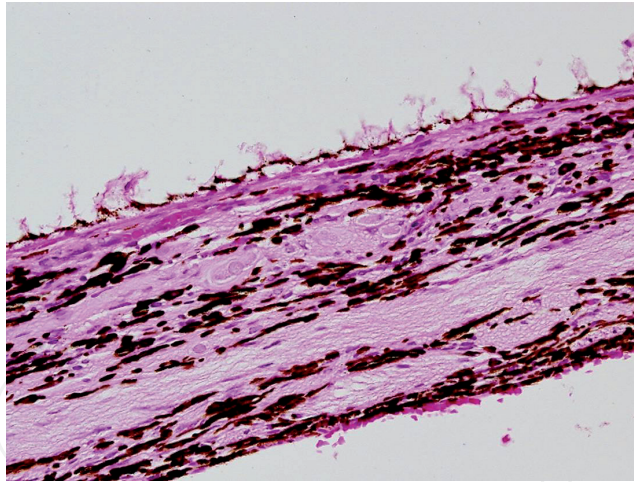


Figure 2.
The choroid in a neurofibroma patient with spindle and ganglion cells (original magnification X400 hematoxylin and eosin).

4. Periocular and orbital manifestations

4.1 Optic pathway glioma

Optic pathway gliomas are low-grade tumors which are classified as WHO grade I pilocytic astrocytomas. They usually occur early in childhood in around 5–25% of NF patients [15]. Although benign, these tumors can cause significant visual loss due to the direct compression of the optic nerve. They may arise anywhere along the optic pathway from the optic nerve to the chiasm and radiation. When those tumors involve the orbit, they may cause unilateral proptosis, strabismus, and decreased vision. Due to the nature of these tumors and the catastrophic consequences they may have, annual screening for all NF patients less than 10 years of age and then every 2 years until the age of 18 years is recommended [16].

4.2 Orbital-periorbital plexiform neurofibroma (OPPN)

One of the most characteristic findings in NF-1 patients and a hallmark of the disease is plexiform neurofibroma. It is a congenital tumor usually unilateral involving the eyelid, orbit, and periorbital area. It starts early in childhood with rapid growth that slows down after puberty. OPPN affects approximately 10% of patients with NF-1, and it carries a risk for malignant transformation in about 10%. It is considered a benign tumor of peripheral nerves with spindle cell proliferation and wavy filamentous pattern of growth (**Figures 3 and 4**). Histologically, they may be composed of mixed diffuse and plexiform types (**Figure 5**) with proliferation of Schwann cells, fibroblasts, and mast cells. Plexiform neurofibromas are similar but are encapsulated with the proliferations being surrounded by perineurium (**Figure 6**). Plexiform neurofibromas are of clinical significance as they are often described clinically as a “bag of worms” and can grow to form bulging masses that can be quite disfiguring to a patient leading to social embarrassment. They usually cause mechanical ptosis when involving the upper eyelid (**Figure 7**), which may lead to amblyopia in children. Further progression to orbital and periorbital areas lead to proptosis, strabismus, and displacement of the globe. Rarely, plexiform neurofibromas may also involve the conjunctiva of the eye. Sphenoid wing dysplasia can be found in patients with OPPN affecting the same side and usually present with proptosis and pulsatile exophthalmos. Plexiform neurofibroma is a highly recurrent tumor, especially in orbito-facial area and in younger patients [17–19].

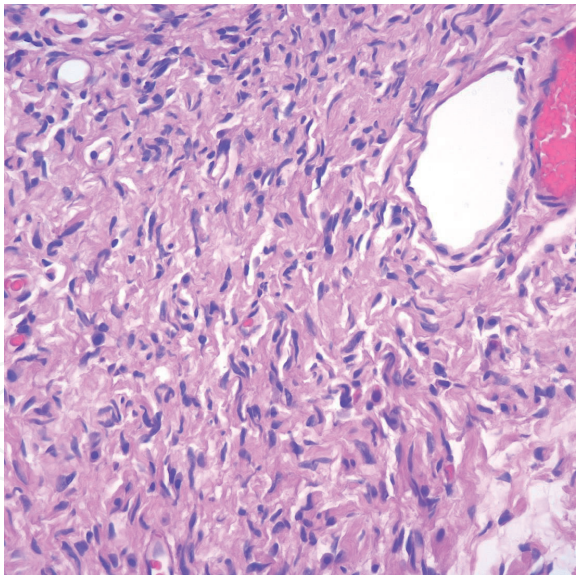


Figure 3.
Neurofibroma of the diffuse type with spindle cell proliferation (original magnification X400 hematoxylin and eosin).

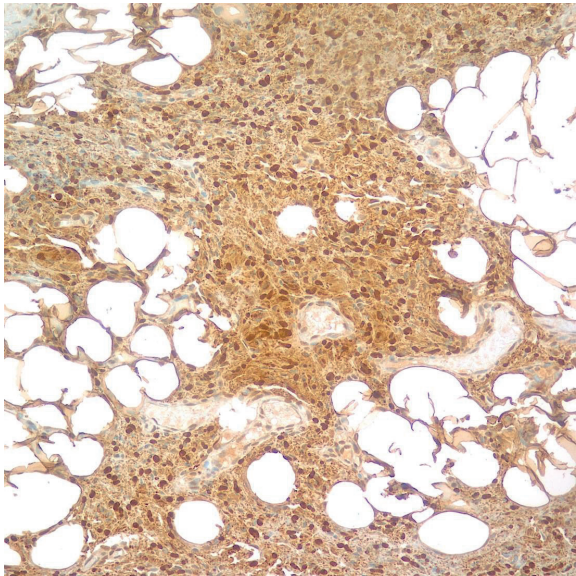


Figure 4.
The same diffuse type of neurofibroma with spindle cells expressing s-100 staining (original magnification X200 S-100).

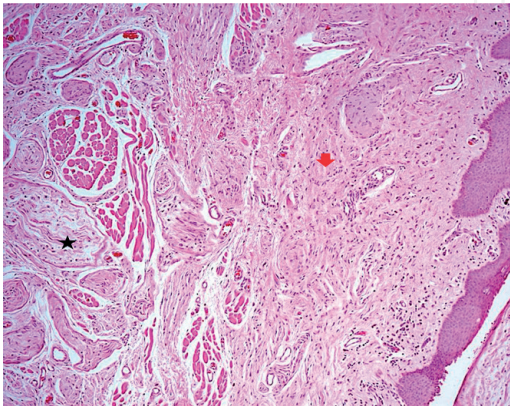


Figure 5.
Mixed plexiform (black star) and diffuse (red arrowhead) neurofibromatosis (original magnification X100 hematoxylin and eosin).

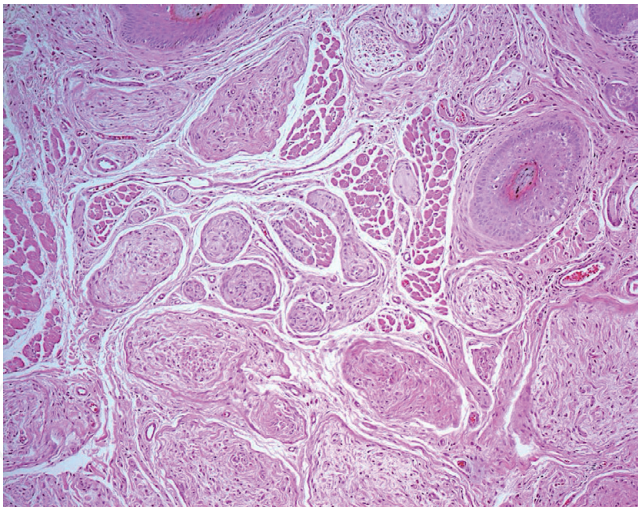


Figure 6.
An area of typical plexiform neurofibroma (original magnification X100 hematoxylin and eosin).



Figure 7.
A child with a plexiform neurofibroma of the right upper eyelid causing significant ptosis that affects the visual axis.

5. Imaging

A high-resolution magnetic resonance imaging (MRI) with and without contrast of the brain and orbits should be performed in all NF-suspected patients to confirm the diagnosis and to monitor for the progression. CT scan should be avoided if possible, because of its radiation and the risk of malignant transformation of neurofibroma [19].

6. Management

Patients with NF need a multidisciplinary team of pediatric ophthalmology, neuro-ophthalmology, oculoplastic surgeon, neuro-oncology, and genetics. All children diagnosed with NF should have regular ophthalmological examinations every 6 months until the age of visual maturation (7 years) to detect and treat amblyopia, glaucoma, or strabismus. Also, serial MRI might be needed. The frequency of examination and imaging should be tailored according to the patient needs and disease progression. Early diagnosis and management of ophthalmic related issues are important and usually treated by supportive methods.

In children, surgical interventions for neurofibroma and its related strabismus should be reserved for severe cosmesis and visually threatening conditions because of its highly recurrent nature. Adults with neurofibroma usually need an aggressive and definitive surgical approach to prevent recurrence with the possibility of

several surgeries. The most common indications for surgical debulking are cosmetic, decreased vision, progressive involvement of a vital structure, and functional deficits. Any significant increase in the growth rate of neurofibroma that is unusual for the patient age should be worrisome for malignant transformation [19].

7. Conclusion

In conclusion, neurofibromatosis can affect the eye and ocular adnexa in various ways. It is of importance to recognize ocular involvement in such patients in order to help earlier diagnosis of treatable conditions that can be vision-threatening.

Conflict of interest

The authors declare no conflict of interest.

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