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Von Recklinghausen Disease (Nf-1) – Different Ocular Presentation

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Abstract
Von Recklinghausen disease (NF-1) - is a disorder that primarily affects cell growth in neural tissues. Neurofibromatosis 1 is an autosomal dominant disorder involving multiple systems involving benign tumors of nerves and skin along with bone deformities and ocular manifestations.
Here we present two cases of NF-1 with different ocular presentation.
***Case 1**. A 11 years old male child presented to OPD with swelling over right forearm measuring 4 × 5 cm and cafe-au-lait spots throughout the body . On slit lamp examination patient was found to have small multiple hypopigmented lesions over the iris suggestive of Lisch Nodule in both eyes. The diagnosis of NF-1 was made according to the presence of two or more diagnostic criteria of the National Institute of Health Consensus Development Conference.*
***Case 2**. A 12 year old male child presented to ophthalmology opd with RE mechanical ptosis due to protruding mass suggestive of neurofibroma which was rubbery, soft, and immobile on palpation measuring 3 x 5 cm, and was markedly visible within the blepharon. And multiple Lisch nodules present in both eyes. Multiple cafe-au-lait spots and axillary freckeling was also present . CT scan imaging confirmed the presence of a peripherally enhanced mass involving the right orbital blepharon as a result of significant neurocutaneous expansion causing downward displacement of the orbit.*
Since the patients with NF-1 can present with ophthalmic complaints, the ophthalmic evaluation is an essential part of examination. Proper diagnosis and treatment require the understanding about the myriad of manifestations of NF-1.

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I. Introduction

Neurocutaneous pathologies typically arise during embryonic development as congenital disorders of neuroectodermal or mesodermal origin. They present as abnormalities of the, nervous system, skin and eye [1]. Two forms of this genetic disorder may be delineated: neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2). Neurofibromatosis type 1 (NF1) or von Recklinghausen's neurofibromatosis is one of the most common autosomal dominant disease [2,3] with a prevalence between 1/2000 and 1/3500 [4,5]. NF1 additionally carries with it a vast spectrum of clinical presentations, which mainly consist of neurofibromas, macules, cafe-au-lait spots, and optic gliomas [6], whereas a hallmark of NF2 is the manifestation of bilateral vestibular schwannomas. Neither NF1 nor NF2 demonstrates a predilection to any particular sex or ethnic group, but NF1 has a higher incidence overall. NF2, in contrast to NF1, is associated with such a high tumor burden that it may result in reduced life expectancy of the afflicted [7].

In the realm of ophthalmology, the most pertinent of physical manifestations include the following ocular signs: plexiform and conjunctival neurofibromas, corneal stromal nerve hypertrophy (lignes grise), iris hamartoma (Lisch nodules), early-onset cataracts, glaucoma, patchy choroidal appearance due to choroidal nodules, corkscrewing of retinal vasculature/retinal hamartomas, and optic nerve gliomas causing proptosis/strabismus [8]. Hence, ophthalmic intervention is a much-desired therapy for many patients for a variety of reasons: plexiform and conjunctival neurofibromas can both cause eye-lid mechanical ptosis resulting in impaired vision and facial disfigurement, the former of which is observed in this report, early-onset cataracts may result in vision loss, and congenital glaucoma may progress to cause buphthalmos - ultimately leading to loss of the eye itself.

CASE 1. A 11 years old male child presented to OPD of Opthalmology Department, GMC, kota, Rajasthan, India with complain of muddy discoloration and irritation in both eyes. His uncorrected visual acuity was 6/6 in both eyes. On slit lamp examination patient was found to have small multiple hypopigmented lesions over the iris suggestive of Lisch Nodule in both eyes. Fundus examination did not reveal any abnormality.

Extraocular movements were unaffected in both eyes, and intraocular pressure (IOP) was unremarkable in both eyes.. Both preauricular, as well as submandibular lymph nodes, were palpated; no enlargement was detected. Lisch nodule with multiple hyper-pigmented skin lesions prompted us to rule out a neurocutaneous syndrome. Therefore, patient was referred to the paediatric department for further evaluation. On Paediatric evaluation, patient was found to have multiple pigmented flat lesions of 2mm to >5mm in size suggestive of cafe-au-lait spots over the front and back side of the trunk and over the lower extremity. A swelling was present in right forearm measuring 4 × 5, on Ultrasound Multiple well defined variable sized oval lesion and minimal internal vascularity in axilla suggestive of neurofibroma. Systemic inquiry yielded no significant findings such as a loss of appetite, weight loss, lethargy, bone pain.

No neurological deficit was noted. MRI brain showed hyper intensity involving bilateral Globus pallidus, bilateral thalamus and bilateral crus of midbrain suggestive of focal abnormal signal intensity based on paediatric, ophthalmological and neurological examination, the diagnosis of Von recklinghausen disease (NF-1) was made. He is the only child of his parents and family history was insignificant for such lesions.

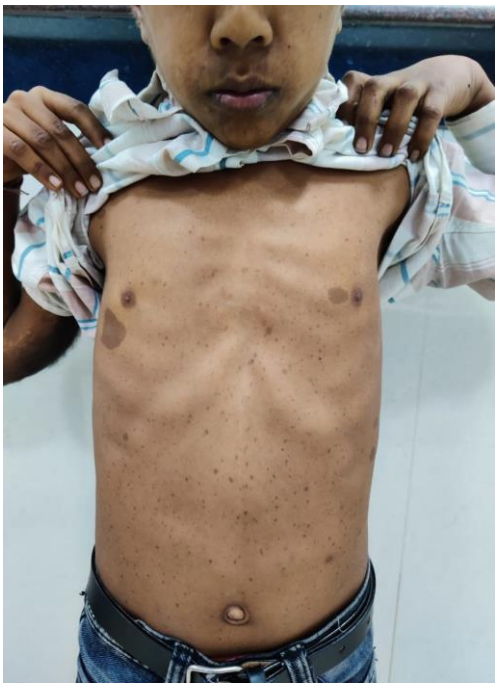

Figure : Multiple Café-au-lait spots all over Chest and abdomen

Figure : Multiple Café-au-lait spots all over Back

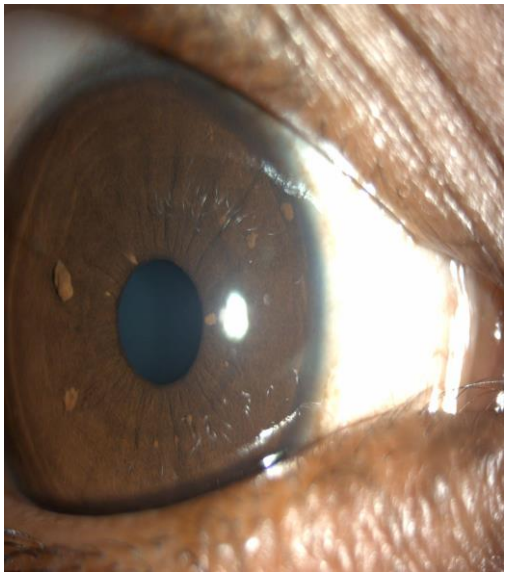

Figure – showing Right Eye multiple Lisch Nodules

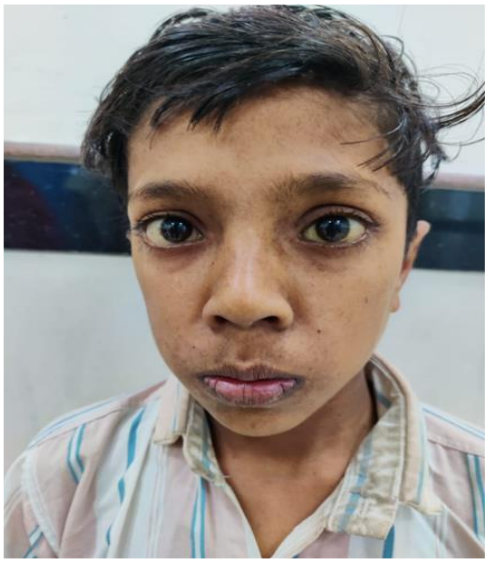

Figure : Eyelids and Perioribital area is normal in both eyes(no neurofibroma)

CASE 2. A 12 year old male child, resident of baran presented to the OPD of Opthalmology Department, GMC, kota , Rajasthan, India with complain of drooping of right eye upperlid which was painless since 4-4.5 years. He also complain of painless diminution of vision of Right eye since 2 years which was progressive in nature. He denied any history of trauma, emesis, nausea or fever.

The disease started in childhood with the appearance of multiple hyperpigmented macules. On systemic inquiry revealed generalized freckling and various sized café-au-lait spots throughout the body since birth which confirm the diagnosis of NF1.

On ocular examination, Right Eye mechanical ptosis due to protruding mass was prominent. No thrill was noted in right eye, the large mass was rubbery, soft, and immobile on palpation measuring 3 x 5 cm, and was markedly visible within the blepharon. Transillumination was negative.

On palpation, the left eye and blepharon provided no significant findings with no mass and no thrill noted. Anterior segment examination of the left eye was unremarkable with no sign of chemosis, edematous cornea, dilation, or tortuous conjunctival vessels.

Slit-lamp Examination of Right Eye anterior segment shows iris hamartomas or multiple Lisch nodules on Iris.

Best corrected visual acuity in Right Eye was 6/36 and in Left Eye was 6/6

Pupillary reflexes were normal with no relative afferent pupillary defect in both eyes . Posterior segment examination was clear in both eyes with no disc/macular edema or other abnormalities. Extraocular movements were normal in both eyes. Intraocular pressure (IOP) was unremarkable in both eyes.

Both preauricular, as well as submandibular lymph nodes, were palpated; no enlargement was detected.

CT scan imaging confirmed the presence of a peripherally enhanced mass involving the right orbital blepharon as a result of significant neurocutaneous expansion causing downward displacement of the orbit.

Figure : Multiple Café-au-lait spots all over face and neck with Mechanical Ptosis RE upperlid.

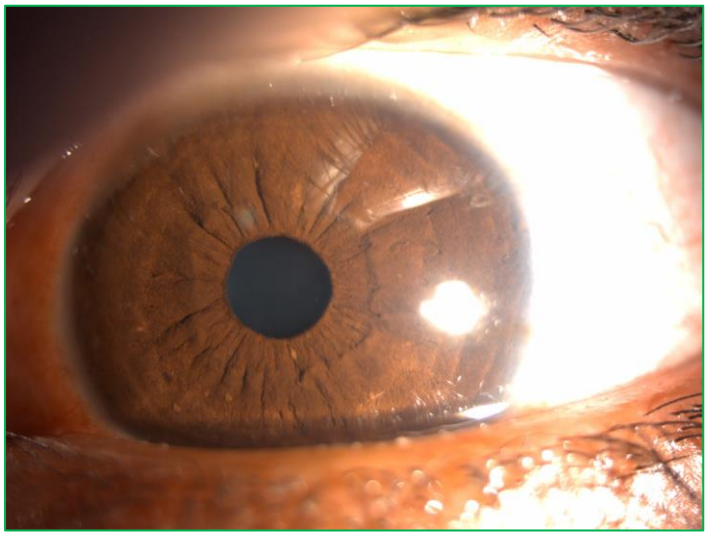

Figure: Right Eye Slit Lamp Examination revealed Multiple Lisch nodules on iris

II. Discussion

The characteristic neurofibromas in NF1 are outgrowths that can be classified as any of the three types: cutaneous, subcutaneous, or plexiform [8]. Cutaneous type growths are only a few millimeters in length and mostly non-tender. Subcutaneous neurofibromas, on the other hand, are tender to manipulation and measure approximately 3 to 4 centimeters. Notably, both cutaneous and subcutaneous neurofibromas are non-specific for NF1. In such cases, the diagnosis must be carefully decided based on the presence of other signs and symptoms. This is in contrast to plexiform neurofibromas, which have the greatest tendency to transform into malignant peripheral nerve sheath tumors (MPNST), including malignant schwannoma, neurofibrosarcoma, and neurogenic sarcoma; they may also have the potential to cause significant hemifacial hypertrophy [9]

Fortunately, recent advances in laser therapy have the potential to provide desirable outcomes for patients afflicted with NF1 without invasive procedures. An example of such recent innovations includes that of a free-hand carbon dioxide (CO2) laser. In some cases, plexiform neurofibromas may be inoperable, leaving patients with few options for treatment. In fact, until very recently, there were no approved therapies for inoperable plexiform lesions. The first of such therapies included the development and subsequent approval of Koselugo (selumetinib) by the United States Food and Drug Administration (USFDA) in 2020. This drug is a mitogen-activated kinase kinase (MEK) inhibitor used for the purpose of inhibiting the overactivation of RAS proteins, which occurs as a result of dysfunctional neurofibromin in NF1 patients [10].

III. Conclusion

Since the patients with NF-1 can present with ophthalmic complaints, the ophthalmic evaluation is an essential part of examination. Proper diagnosis and treatment require the understanding about the myriad of manifestations of NF-1. Case 2, 12 year old child was managed surgically to resolve mechanical ptosis. This approach allowed for recovery of the patient's comfort by way of restoring his ability to open and close the eye with relative ease. There is also potential for improvement in overall visual acuity. Even lisch nodules can help us to reach the diagnosis for NF1 as in case 1. As an ophthalmologist we can help to reach diagnosis of deadly systemic disease on time and can save lifes.

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