

Neurofibromatosis 1: A family case series

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ABSTRACT

Neurofibromatosis type 1 (NF1) or Von Recklinghausen disease comes under a group of multisystem hereditary syndromes called phakomatoses. It presents with skin, ophthalmic, bony, and systemic manifestations. We present a photographically well-documented case series of NF in a family ($n=3$). Skin manifestations were present in all the patients. The ophthalmic manifestations were Lisch nodules (100% of eyes), subcutaneous neurofibroma of eyelids (33% of eyes), mechanical ptosis (33% of eyes), and mechanical ectropion (16.5% of eyes). We report the rare occurrence of multiple solitary neurofibromas causing mechanical ptosis and mechanical ectropion.

Keywords: Familial, hereditary, Lisch nodules, mechanical ectropion, mechanical ptosis, neurofibroma, Von Recklinghausen disease

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal-dominant neurocutaneous syndrome that impacts several organ systems, including the eye. The ocular manifestations of NF1 include iris Lisch nodules, optic pathway gliomas, eyelid or orbit plexiform neurofibroma, glaucoma, and rarely, retinal hamartomas.^[1] The primary care physicians require a basic knowledge of NF1 to identify the disorder. It is essential for them to know the classic signs of the disease and know the indications of referral to specialists. The present study examines a case series of three members of a family—father, son, and daughter—who presented with various manifestations of NF1.

Case Description

Case 1

A 65-year-old hypertensive male presented with multiple nodules on the eyelids [Figure 1a and b] since childhood.

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The General Physical Examination (GPE) revealed multiple painless subcutaneous neurofibromas in the face, trunk, and extremities. One large plexiform neurofibroma (elephantiasis nodosa) was on the left lateral side of the head [Figure 1c]. Multiple cafe au lait spots were present on the limbs and trunk. Axillary and inguinal freckling were also present. The ocular examination revealed left upper lid mechanical ptosis and lower lid mechanical ectropion due to neurofibromas. The Both eyes oculus uterque (OU) showed multiple Lisch nodules and atrophic patches on the irides [Figure 1d], pseudophakia with Posterior Capsular Opacification (PCO) present in OU, Best corrected visual acuity (BCVA) 0.6 logMar, and 0.9 logMar in Right eye oculus dexter (OD) and Left eye oculus sinister (OS), respectively.

Case 2

A 23-year-old son presented with multiple subcutaneous neurofibromas that were present on the limbs, trunk, and face [Figure 2a and b], multiple cafe au lait spots of various sizes, and shapes present on the neck [Figure 2c], abdomen, and thigh. The ocular examination revealed no other abnormality except for multiple Lisch nodules [Figure 2d]. A large subcutaneous mass was present in the gluteal region for which debulking

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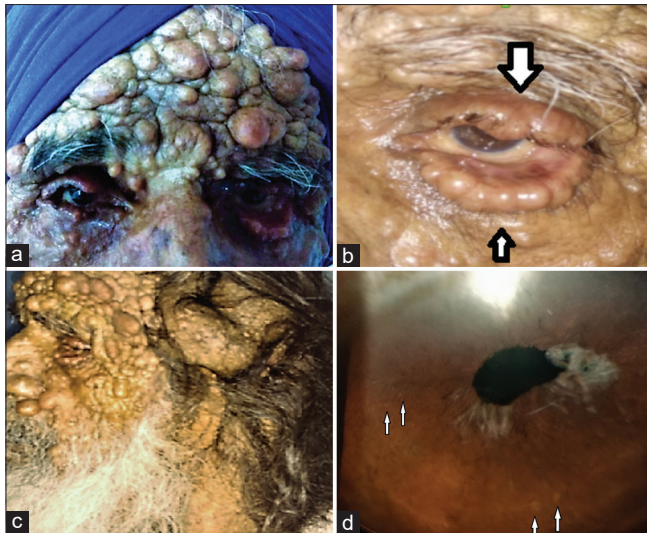


Figure 1: (a) Multiple neurofibromas on the face. (b) Multiple neurofibromas on the eyelid causing upper lid mechanical ptosis and lower lid mechanical ectropion. (c) Plexiform neurofibroma on the side of the scalp. (d) Several Lisch nodules on the iris

surgery was performed [Figure 2e]. The biopsy report revealed a cellular tumor in the deep dermis. The tumor cells were oval- to spindle-shaped with a scant amount of cytoplasm [Figure 2f]. No increased mitotic activity/necrosis was seen. These features were suggestive of neurofibroma. Axillary and inguinal freckling were also present.

Case 3

An 18-year-old daughter presented with multiple small painless neurofibromas over the limbs and trunk [Figure 3a–c]. She did not have any plexiform neurofibroma. Multiple café-au-lait spots were seen all over the trunk, face, and limbs. The ocular examination revealed multiple Lisch nodules [Figure 3d] over the iris. No other ocular abnormality was found. The fundus examination was normal.

Discussion

NF was first described by Von Recklinghausen in 1882.^[2] NF1 is an autosomal-dominant disorder. It affects about 1 in 2,500–3,500 people worldwide.^[3] In our case series, the two patients fulfill five and one patient fulfills four criteria given by the National Institutes of Health (NIH) in 1988 for the diagnosis of NF.^[4]

Lisch nodules are the commonest ophthalmic manifestation of NF1. They begin to develop in early childhood and are present in almost all adults with the disease.^[5] In our case series, bilateral Lisch nodules were present in 100% of the patients.

Café-au-lait spots and freckles on the skin are frequently seen in NF1 patients. Freckling is found in approximately 80% of the patients under the age of 6 and 90% of the adults over 30 years.^[6]

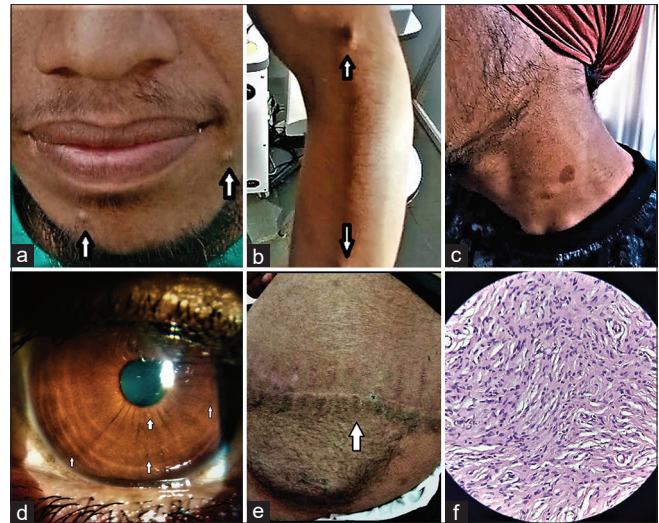


Figure 2: (a, b) Multiple neurofibromas on the face and forearm. (c) Café-au-lait spot on the neck. (d) Multiple Lisch nodules on the iris. (e) Surgical scar of the debulking surgery performed on the buttock. (f) Histopathology using HE staining revealed oval- to spindle-shaped cells with a scant amount of cytoplasm suggesting neurofibroma

In our case series, these skin manifestations were found in 100% of the patients.

Neurofibromas, found in almost all NF1 patients over 30 years, are generally located over the trunk, with 20% seen in the head and neck regions.^[6] Neurofibromas are divided into cutaneous, subcutaneous, and plexiform neurofibromas. The plexiform neurofibromas are the largest and are observed in 25–30% of the cases.^[7,8] In our case series, plexiform neurofibromas were found in two (on the lateral side of the scalp in the father and on the gluteal region in the son) of the three patients.

Neurofibroma of the eyelids leading to mechanical ptosis and mechanical ectropion occurred in one case. Plexiform neurofibroma has been reported in the literature causing mechanical ptosis. However, in our case series, one patient had multiple solitary neurofibromas on the upper eyelids bilaterally leading to mechanical ptosis in both eyes. The vertical palpebral fissure height in the right eye was 7 mm and the left eye was 9 mm. This patient also had grade 3 mechanical ectropion of the lower lid with visible lower fornix in the left eye due to multiple neurofibromas on the lower lid.^[8] In a study conducted by Lee *et al.*,^[9] 3 out of 33 patients had mechanical ptosis secondary to multiple solitary neurofibromas, and one out of the 33 patients had mechanical ectropion due to nodular neurofibromas.

This is the first ophthalmic family case series to the best of our knowledge and we have photographically documented all the findings including the histopathology of neurofibroma. We also report the rare occurrence of multiple solitary neurofibromas causing mechanical ptosis and mechanical ectropion. There is only one such study reported by Lee *et al* on this finding earlier.^[9] In our case series, neurofibromas were present in

Table 1: Percentage of various manifestations of NF in the family

Findings	Father	Son	Daughter	Percentage
Café-au-lait spots	Present	Present	Present	100%
Axillary and inguinal freckling	Present	Present	Present	100%
Cutaneous solitary neurofibroma	Present	Present	Present	100%
Cutaneous plexiform neurofibroma	Present	Present	Absent	66%
Lisch nodules	Present	Present	Present	100%
Subcutaneous neurofibroma of the eyelids	Present	Absent	Absent	33%
Mechanical ptosis	Present	Absent	Absent	33%
Mechanical ectropion	Present, only left eye	Absent	Absent	16.5%
Systemic hypertension	Present	Absent	Absent	33%

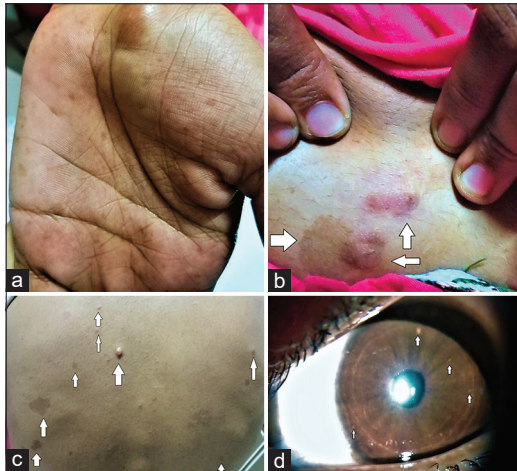


Figure 3: (a) Multiple neurofibroma and café-au-lait spots on the palmar aspect of the hand. (b) and (c) Multiple neurofibromas and café-au-lait spots on the trunk. (d) Multiple Lisch nodules on the iris

100% of the patients [Table 1], thus, corroborating the virtually complete penetrance rate in NF1 and variable expressivity. This is important from the primary care perspective when a classic case of NF1 approaches a primary care physician. It becomes important not only to diagnose a case with typical findings but also prompt referral to the specialties like ophthalmology, orthopedic, neurology, and dermatology for the better management of the patient and preventing life-threatening and sight-threatening complications. The primary care of the patient also includes routine check-ups of patients 6–12 months in case of children, and annually in adults. The routine examinations should include skin, neurologic, vision, and blood pressure evaluations. In this way, a comprehensive approach can be developed. Once a specialist opinion is done, the patients can be followed up by the primary care physicians for routine medical care and documentation of new findings. It is also important to do the screening of family members and genetic and family counseling of the patient. The patients can also be taught about the important signs of the disease like a sudden rise in blood pressure, decrease in vision, pain or progression of scoliosis and back deformities, and the rapid growth of mass anywhere in the body.^[10] Hence, primary care provides an essential role in the routine care and follow-up of NF1 patients.

Conclusion

In conclusion, NF1 presents with various ophthalmic manifestations of which Lisch nodules are the most common. It is an autosomal-dominant hereditary disease and it can lead to life-threatening and sight-threatening complications, which if diagnosed early, can be prevented. So, it is very important to know the classical findings of NF patients and to diagnose them early and prompt referral of patients to specific specialties. The key home message from this study is that a patient of NF1 should be examined comprehensively and primary care physicians and family physicians play a very important role in the routine care and counseling of NF1 patients and their families.

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Conflicts of interest

There are no conflicts of interest.

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