(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 4, Page No: 1286-1291
July-August 2021

IJMSCR

Varied oculo-cutaneous manifestations of Neurofibromatosis 1 in the same family

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Purpose: To analyze various oculocutaneous manifestations of Neurofibromatosis 1 in same family members.
Methods: Various members of a single family diagnosed with Neurofibromatosis underwent complete systemic and ophthalmic examination including head to toe examination to look for cutaneous manifestations all over the body, slit lamp bio microscopy to look for lisch nodules, with intraocular pressure measurement to rule out glaucoma and dilated fundus examination. MRI orbit and brain was done to rule out neurological manifestation.
Results: Father aged 34yrs had multiple cafe au lait spots over the abdomen, back, a single lisch nodule on the iris and axillary freckling.
Elder daughter aged 1.5yrs had multiple cafe au lait spots over the abdomen and back; a large hyperpigmented macule was seen on the left side of the face.
Younger daughter aged 2 months presented with left eye buphthalmous and corneal edema. Intra ocular Pressure was 18 mmHg OD and 26mmhg OS and was diagnosed to have congenital glaucoma associated with NF 1
Conclusion: The severity of ocular manifestations and disease course can vary from patients, even among members of the same family, thus it is very important to take a detailed family history and screen all family members early to avoid ocular complications.

Keywords: NF1- Neurofibromatosis 1, Intraocular pressure, lisch nodules, neurofibromas, congenital glaucoma

INTRODUCTION

Neurofibromatosis, (von Recklinghausen's disease), is an autosomal dominant disease seen in 1 in 3500 births.[1] Ocular manifestations of the disease include lisch nodules, plexiform neurofibroma, optic pathway gliomas, and congenital glaucoma. It is also associated with systemic manifestations.

Lisch nodules are melanocytic hamartomas made up of mast cells, melanocytes and elongated fibroblasts.[2]

Apart from the above-mentioned ocular manifestation, patients more often present with cutaneous lesions such as café au lait spots which presents as well characterized pigmentary lesions with well-defined margins.[2]

NF-1 diagnosis is based on the presence of at least 2 of the 7 criteria which include:

1. Six or more cafe-au-lait macules over 5mm in greatest diameter in prepubertal individuals,
2. Frecklings over the axillary and inguinal area,
3. Lisch nodules over the iris,
4. Two or more neurofibromas or one plexiform neurofibroma,
5. Sphenoid dysplasia,

6. Optic glioma
7. First-degree relative of NF-1. [3]

Here we describe 3 cases of NF-1 with various ophthalmic manifestations. All of our cases met at least 3 criteria of the disease.

MATERIALS AND METHODS:

The study was conducted in a medical college teaching hospital in India. In this study 3 patients diagnosed with neurofibromatosis type 1 underwent a complete systemic and ocular examination.

On systemic examination the presence of multiple hyper pigmented spots suggestive of café au lait spots was noted in all the patients. The patients were examined for the presence of any axillary freckling or neurofibromas.

Complete ophthalmic examination was done including measuring the visual acuity along with anterior segment evaluation using slit lamp to rule out presence of lisch nodules. All patients underwent dilated fundus examination to rule out presence of retinal hamartoma or optic nerve glioma.

The patients underwent intra ocular pressure measurement by Goldman applanation tonometer for the adult patients and tonopen for the two children.

The required radiological investigations were done including MRI to rule out any schwannomas or sphenoid wing dysplasia.

Hence, we did a detailed evaluation of systemic and oculocutaneous manifestations of NF1 in 3 members of the same family.

Since 2 out of the 3 members were minors' consent regarding photography and publication was taken from the father.

CASE 1

A male patient aged 34 years who was diagnosed 12 years ago with NF-1 presented to the ophthalmology Outpatient department for an ophthalmic examination. The patient gives a history of excision of neurofibroma on the back 3 years ago.

On general physical examination, he was found to have multiple cafe au lait spots over the abdomen and the back (fig 1.a, 1.b) with axillary freckling.

On Ophthalmic examination, his vision in both eyes was 6/6. Anterior segment examination, under slit-lamp bio microscopy, the cornea was clear, pupils were round regular and reactive, Anterior chamber was normal in depth. The left eye showed the presence of a single lisch nodule on the iris.(as mentioned in table 1) Dilated fundus examination of both eyes was normal. Systemic examination was normal.

CASE 2

A 1 and half-year-old female baby was brought for Ophthalmic evaluation in view of NF-1. The father of the baby is a known case of Neurofibromatosis 1.

On general physical examination, multiple cafe au lait spots were present over the abdomen and back (fig 1.c.).

Specifically, a large hyperpigmented macule was seen on the left side of the face not crossing the midline as shown in (fig 1.d). (as mentioned in table 1).

On ocular examination, the vision of the child could not be assessed and slit-lamp bio microscopy could not be done for this patient as the child was not cooperative. Dilated fundus was unremarkable. Systemic examination was normal. With the above history, physical, and ophthalmic examination a diagnosis of NF-1 was made. The parents were counseled regarding regular follow up and ophthalmic examination.

CASE 3

A female baby aged 2 months was brought for Ophthalmic evaluation by the father with complaints of the Left eye being larger than the Right eye and swelling over the left upper eyelid since birth. Father is a diagnosed case of NF-1. The baby was delivered at term by normal vaginal delivery. The mother was diagnosed with oligohydramnios during pregnancy and was treated for the same.

On torchlight examination the left eye was notably larger than the right eye (fig 2.a), corneal edema was also present and was diagnosed as Buphthalmos. IOP was 18 mmHg OD and 26mmhg OS as measured by tono-pen. Fundoscopy revealed a cup to disc ratio of 0.7:1. Based on the above finding, a diagnosis of congenital glaucoma was made

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On general physical examination, the baby was found to have multiple cafe au lait spots present all over the body (fig 2.b). Systemic examination was normal.

Magnetic Resonance Imaging of brain showed:

Right-sided microphthalmia, right side sphenoid wing hypoplasia (fig 2.c, characteristic of NF-1), T2 hyperintense in the left cavernous sinus/parasellar region, soft tissues around the bilateral buccal and parotid spaces and in the occipital region. Radiologically diagnosed as Neurofibromas/Schwannoma.

Given the familial link, buphthalmos, congenital glaucoma, café au lait spots, sphenoid wing hypoplasia a diagnosis of NF-1 was made.

The importance of continuous ophthalmologic examination and follow up in view of various findings of NF-1 was stressed to the patient. Parents were counselled about genetic evaluation.

All the above-mentioned clinical features of all the cases have been summarized in table 1.

DISCUSSION:

Neurofibromatosis (NF) is an autosomal dominant disease affecting multiple systems in the body.NF 1 is a common phacomatosis presenting with multiple skin tumors and café au lait spots. The gene is located on the long arm of chromosome 17. [4] It is caused by mutations affecting cellular growth regulation, therefore resulting in the formation of multiple tumors in the body. [5] Ocular involvement is an important diagnostic criterion. Although lisch nodules have only diagnostic value, other ocular involvement can have grave visual prognoses like glaucoma and optic nerve gliomas.

In one of our cases, we diagnosed the child with congenital glaucoma and found out the cause to be due to NF-1 with clinical examination and family history.

It is also known that NF-1 lesions have a tendency to become malignant and it has been reported that neurofibromas can undergo malignant transformation,[6] most commonly peripheral nerve sheath tumors. Thus, before neurofibromas in other systems induce malformation and/or malignant transformation, timely surgical resection is needed. Our study represents the various clinical manifestations of NF-1 and highlights the importance of ophthalmic examination in such cases along with a detailed family history as this condition can be present in other family members as well.[7] Detection of the NF1 gene can be done prenatally but is extremely difficult due to the size of the gene. Thus, genetic counselling plays and important role in early detection of the disease.[8]

In children there is an added disadvantage as many of the clinical signs appear after a certain age. For example, café au lait spots tends to appear mostly after 1 year of age [2,9] as seen in the study conducted by Abdolrahimzadeh B et al. Primary congenital glaucoma may be the first presenting symptoms.[9] This combined with a family history of neurofibromatosis should raise a strong suspicion and warrant a regular follow up. A child suspected to have NF1 but not confirmed should be regularly followed up till 7 years of age. [9,3]

As the disease requires a lifelong follow-up for the various clinical manifestations which may arise in the different phases of life, the early diagnosis of NF-1 becomes a crucial task. A multidisciplinary approach is required to diagnose and treat these patients. [10,11] This study provides further knowledge about clinical features of patients with NF-1 which might be helpful for further understanding about the disease.

REFERENCES:

1. Gromova M, Gerinec A. Ocular manifestations of neurofibromatosis 1--m. Recklinghausen. Bratislavske Lekarske Listy. 2008 ;109(6):259.
2. Abdolrahimzadeh B, Piraino DC, Albanese G, Cruciani F, Rahimi S. Neurofibromatosis: an update of ophthalmic characteristics and applications of optical coherence tomography. *Clin Ophthalmol*. 2016; 10:851-860. Published 2016 May 13.
3. Ferner RE, Huson SM, Thomas N, et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *J Med Genet*. 2007;44(2):81-88.
4. Maurya R P, Yadav I, Singh V P, Singh M K, Kumar M, OCULO-CUTANEOUS MANIFESTATION OF NEUROFIBROMATOSIS TYPE 1: A Case Report

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5. Jett, K., Friedman, J. Clinical and genetic aspects of neurofibromatosis 1. *Genet Med* **12,** 1–11 (2010).

6. Nuri Karadurmus, Yalcin Basaran, Galip Buyukturan, Mukerrem Safali,Neurofibromatosis type 1 complicated with malignant transformation and diffuse pulmonary disease,Journal of Oncological Sciences,Volume 2, Issues 2–3,2016,Pages 84-86,ISSN 2452-3364.

7. Ghalayani P, Saberi Z, Sardari F. Neurofibromatosis type I (von Recklinghausen's disease): A family case report and literature review. *Dent Res J (Isfahan)*. 2012;9(4):483-488.

8. Terzi YK, Oguzkan-Balci S, Anlar B, Aysun S, Guran S, Ayter S. Reproductive decisions after prenatal diagnosis in neurofibromatosis type 1: importance of genetic counseling. Genet Couns. 2009;20(2):195-202. PMID: 19650418

9. Li, H., Liu, T., Chen, X. *et al.* A rare case of primary congenital glaucoma in combination with neurofibromatosis 1: a case report. *BMC*

10. *Ophthalmol* **15,** 149 (2015).

11. Hirbe, David H Gutmann,Neurofibromatosis type 1: a multidisciplinary approach to care,The Lancet Neurology,Volume 13, Issue 8,2014,Pages 834-843,ISSN 1474-4422

12. Siqveland E, Pond D. Neurofibromatosis type 1: update on a common genetic condition. Minn Med. 2009 Mar;92(3):49-52. PMID: 19400389.

TABLE 1

Number	Age	Sex	Cutaneous manifestation	Ocular manifestation	MRI
Case 1	34	M	Café au lait spots on the trunk and back	Lisch nodule	Normal
Case 2	1.5 years	F	Café au lait spot on the face not crossing the midline	Nil	Normal
Case 3	2 months	F	Café au lait spots on the trunk	Congenital glaucoma	Sphenoid wing hypoplasia
				Buphthalomos	Neurofibroma

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LEGENDS

Figure 1

1.a and 1.b -Multiple Cafe au lait spots over the abdomen and the back on case 1

1.c -Multiple Cafe au lait spots were present over the abdomen and back on case 2

1.d - Large hyperpigmented macule was seen on the left side of the face not crossing the midline of case 2

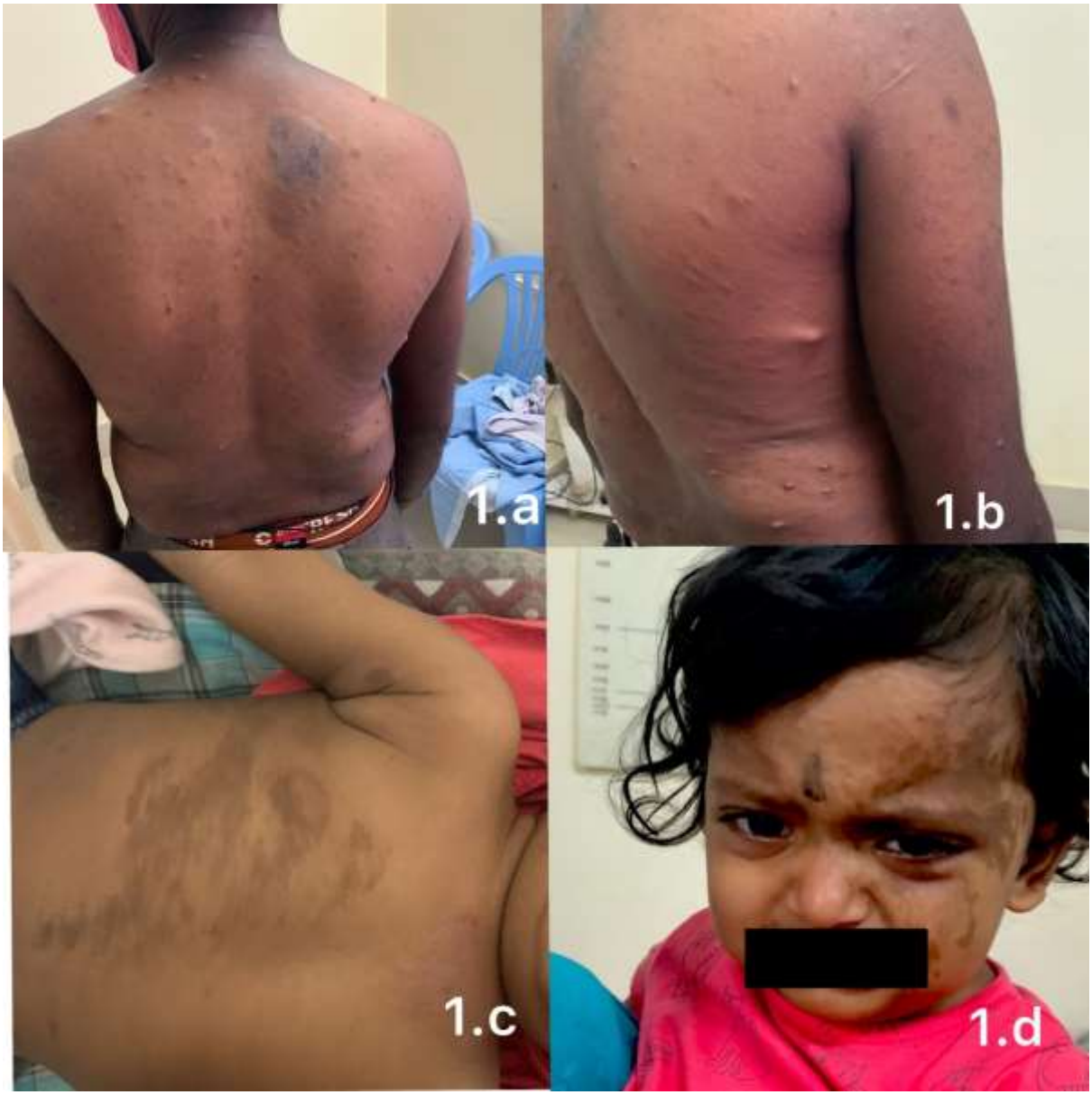

Figure 2

2.a - Left eye notably larger than the right eye of case 3

2.b – Multiple cafe au lait spots present all over the body of case 3

2.c - Right side sphenoid wing hypoplasia seen on MRI of case 3

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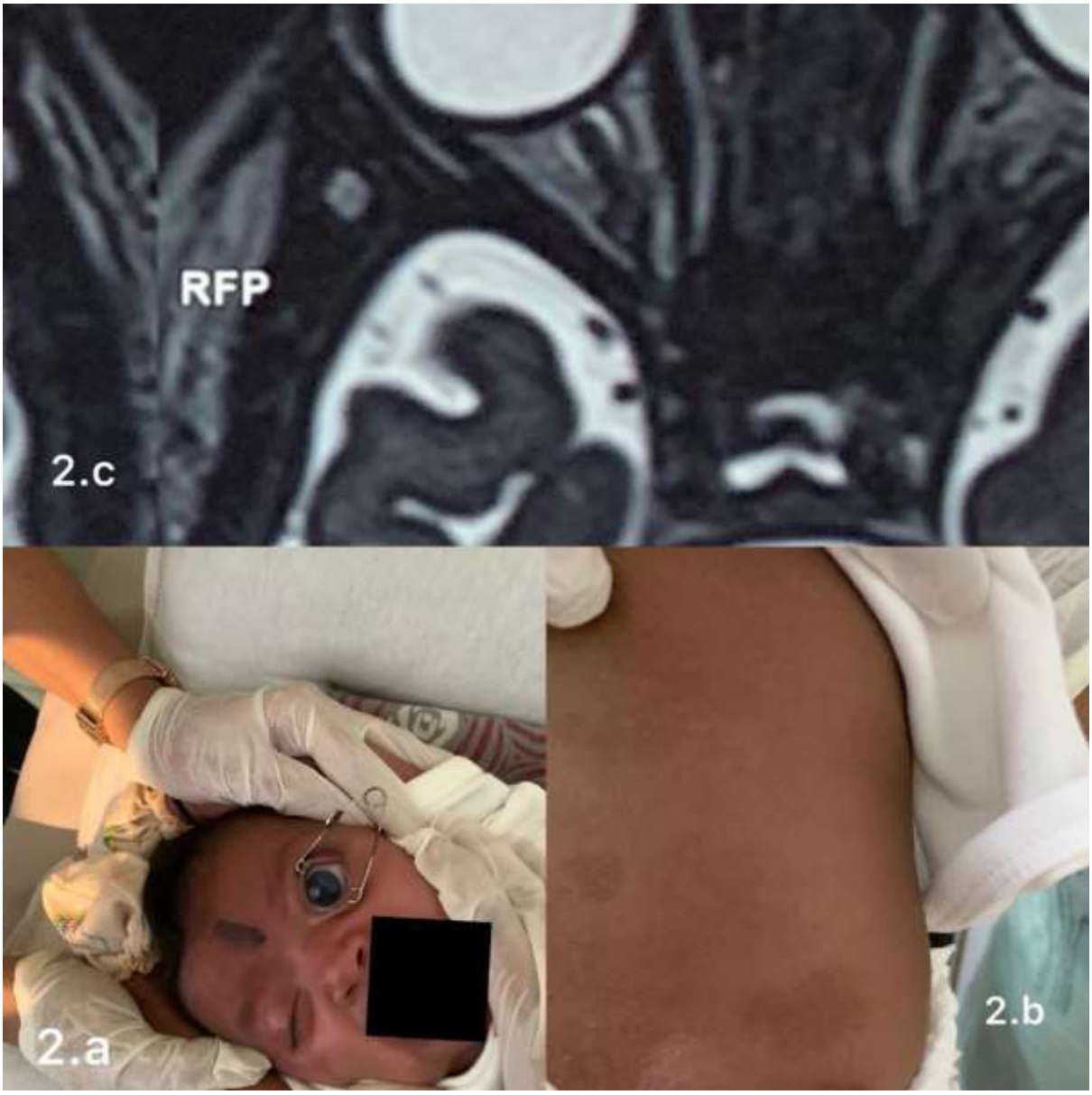

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