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Case Report

Neurofibromatosis-1 - A Review

Dr Deepti Parmar[1], Dr Kalpana Sharma[2], Dr Sumeet Sud[3], Dr Rajni[4]

[1]M. S. Ophthalmology, Medical Officer, Regional Hospital Solan.
[2]M. S. Ophthalmology, Medical Officer, Civil Hospital Theog
[3]M.S Ophthalmology, B. M. O. Specialist, Regional Hospital Solan.
[4]M. D. Dermatology, Medical Officer, Regional Hospital Solan.

Corresponding Author: Dr Kalpana Sharma

ABSTRACT

Neurofibromatosis type 1 or Von Recklinghausen's disease is a genetic disorder characterized by the development of multiple benign tumors of nerves and skin (neurofibromas) and areas of abnormal pigmentation of the skin. We report a case of 19 years old female with NF-1. This article reviews various clinico-pathological aspects of the disease and lays on the importance of multidisciplinary approach involving detailed clinical examination as there may be involvement of other organs also.

Key words: Neurofibromatosis type 1, NF-1, Von Recklinghausen's disease, genetic disorder.

INTRODUCTION

Neurofibromatosis is characterized by neuroectodermal tumors arising within multiple organs. Inheritance in neurofibromatosis is autosomal dominant. Neurofibromatosis has two types neurofibromatosis type 1 and neurofibromatosis type 2. Neurofibromatosis type I (NF-1) is the most common type of the disease accounting 90% of the cases. Neurofibromatosis was first described by Friedrich Daniel Von Recklinghausen in 1882. [1]

CASE REPORT

A 19-years-old female presented with history of multiple hyper pigmented skin macules. The disease started in childhood. On examination multiple café-au-lait spots with diameter >1.5 cm were seen on left arm and right leg. (Figure 1) Axillary freckling was also present. Neurofibromas were seen on right arm. (Figure 2) On ocular examination visual acuity in both eyes was 6/6, pupillary reaction was normal. Intraocular pressure was 16 mm of hg in right eye and 18 mm of hg in left eye. On slit-lamp examination there were multiple yellow to brown pigmented iris nodules superiorly in the right eye, consistent with Lisch nodules. (Figure 3) The iris of the left eye was normal. Posterior segment examination was normal. General physical examination and systemic examination of patient was within normal limits. There was no history of similar complaints in the family. 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.

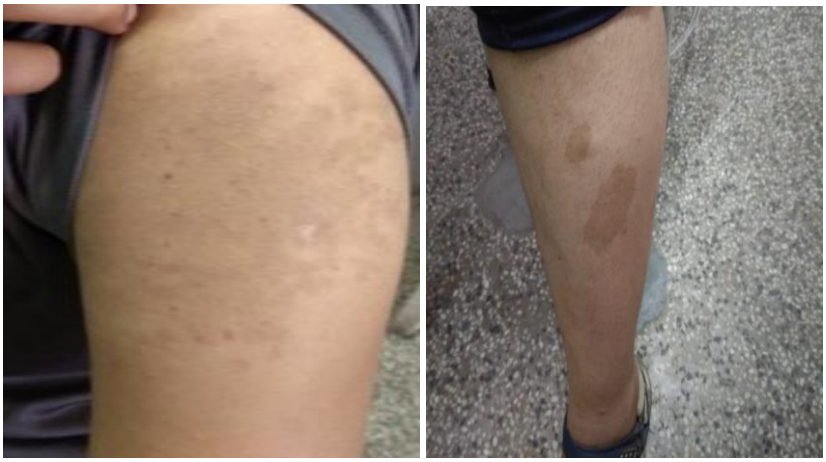

Figure 1-café au-lait spot in left arm and right leg.

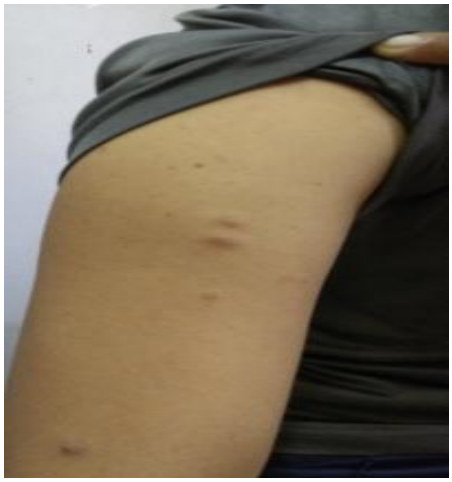

Figure 2-neurofibromas, subcutaneous nodules in right arm.

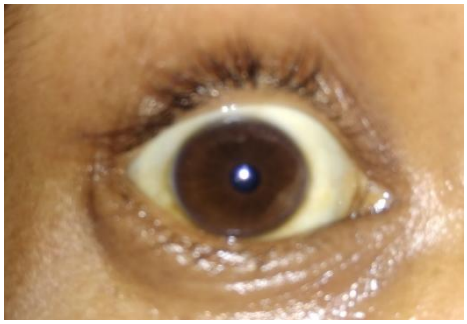

Figure 3-lisch nodules superiorly in right eye

DISCUSSION

Neurofibromatosis (NF-1) has a prevalence of between 1 per 3000 [2] and 1 per 5000 [3] live births. It has no sex or racial predilection. NF1 is caused by mutations that affect the *NF1* gene located at the 17q11.2 chromosome. This gene is tumor suppressor and its mutations leads to an increase in cell proliferation and development of tumors. The pathological changes behind it begin in the embryonic period, prior to formation of the neural crest. There is positive family history in 50% of NF1 patients of the disease. The rest of the patients represent spontaneous mutations. There are four forms of neurofibromatosis:

1.	Von Recklinghausen's neurofibromatosis or neurofibromatosis type 1(NF-1) or peripheral neurofibromatosis
2.	Bilateral acoustic neurofibromatosis or neurofibromatosis type 2 (NF-2) or central neurofibromatosis
3.	Segmental neurofibromatosis
4.	Cutaneous neurofibromatosis

Riccardi [4] suggested the presence of three additional forms: type 3 (mixed), type 4 (variant) and type 5 (late-onset). The most common type (NF-1) accounting for 90% of cases, is characterized by multiple cafe-au-lait spots and the occurrence of neurofibromas along peripheral nerves. Café-au-lait spots are hyperpigmented macule that may vary in color from light to dark brown. These lesions usually appear during the first years of life or are present at birth. Café au-lait spots are composed of epidermal melanocytes with giant pigment granules (macromelanosomes) within the cytoplasm and are of neural crest origin. They are not pathognomonic of neurofibromatosis, having been reported in association with several other conditions and in patients not affected by the condition. [5]

Cutaneous neurofibromas are soft, flesh- or lilac-pink coloured tumours, sessile or dome-shaped, sometimes pedunculated,

and most numerous on the trunk and limbs. They arise from peripheral nerve sheaths. There are two major types of neurofibromas discrete or localized and plexiform neurofibroma. Neurofibromas are found mostly on the skin. Nevertheless, many organs may be involved, including the stomach, intestines, kidney, bladder, larynx, and heart. In the head and neck region, the most commonly affected sites are the scalp, cheek, neck, and oral cavity. Other clinical features include Lisch's nodules (melanocytic pigmented iris hamartomas) and oral lesions. Lisch nodules are variable in size and have a smooth, dome-shaped configuration. [6] Lisch nodules may also be seen in the trabecular meshwork. [7] Possible complications in childhood include the development of an optic glioma, endocrine disturbances and involvement of the lower urinary tract. The children may also present with learning disabilities. Plexiform neurofibromas occur in about one third of NF-1 cases, most commonly on the trunk and less often on the limbs, head and neck. They are benign and rarely symptomatic, but they can cause significant cosmetic and visual problems if the orbit is involved. The cranial nerves most commonly involved in plexiform neurofibromas are the fifth, ninth and tenth nerves. Plexiform neurofibromas of the orbit tend to originate from the orbital branches of the trigeminal nerve. They often affect the upper eyelid, causing a characteristic sinusoidal deformity of the lid margin. [8] The tumor is soft and feels like a bag of worms; the resultant displacement of the globe or ptosis can result in amblyopia in children. Plexiform neuromas of the orbit are associated with congenital absence of the sphenoid or enlargement of the sella turcica.

According to the National Institute of Health Consensus Development conference, [9] at least two of the following criteria must be present to make the diagnosis of NF-1:

1.	Five or more cafe-au-lait spots larger than 5 mm in diameter in prepubertal patients; six or more cafe-au-lait spots larger than 15 mm in diameter in postpubertal patients.
2.	Two or more neurofibromas of any type, or one plexiform neurofibroma
3.	Axillary or inguinal freckling
4.	Optic glioma
5.	Two or more Lisch's nodules (iris hamartomas visualized on slit lamp examination)
6.	A distinctive osseous lesion (pseudoarthrosis of the tibia or sphenoid wing dysplasia)
7.	A first-degree relative diagnosed with NF-1 in accordance with the above criteria

CONCLUSION

NF1 is a multisystem disorder requiring multiple disciplinary approach involving physician and geneticist. The patient described here is a case of NF-1. In such cases, a detailed patient investigation is required, because of the possibility for generalized involvement of other organs. The complete clinical and genealogic analysis is important for the determination of the genetic risk and prognosis for the relatives of these patients. The treatment of such kind of patient is surgical achieving cosmetic improvement which may be only palliative.

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