

Research

## Mucocutaneous Manifestations of Neurofibromatosis Type-1: A Clinical Profile of 51 Indian Patients

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**Key Words:** neurofibromatosis type-1, mucocutaneous, neurofibroma, *café-au-lait* macules

### Abstract

**Introduction:** Neurofibromatosis (NF) is an autosomal dominant neuro-cutaneous disorder. Eight subtypes of the disease have been proposed till date; neurofibromatosis type -1 (NF1) being the commonest variety.

**Objective:** Objective of our present study had been to review the prevalence and patterns of muco-cutaneous manifestations amongst patients of NF-1, in a population from eastern India.

**Methods:** This was a clinical, observational, cross sectional study.

**Results:** A total of 51 patients were evaluated. The mean age of the patients was 22.6 years with a male-to-female ratio of 0.7. Positive family history in first-degree relatives was found in 18 (35.3%) patients. Forty-nine patients (96.1%) had neurofibromas including 8 (15.7%) patients of plexiform neurofibromas. All of our patients had *café-au-lait* macules (CALM) and freckling was present in 49 (96.1%) patients. Other associated features in our patients were vitiligo (3, 5.9%), hairy nevus unrelated to plexiform neurofibroma (2, 3.92%), verrucous epidermal nevus (1, 2%), and lichen amyloidosis (1, 1.96%). Macroglossia was found in 2 (3.9%) patients and palatal papules in 2 (3.9%) patients. Nail dystrophy was found in only one patient. More than 2 *Lisch* nodules were found in 45 (88.3%) patients. Mental retardation was found in 5 (9.8%) patients and learning disabilities were noted in 15 (29.4%) patients.

**Conclusion:** Most of our observations were in conformity with the prevailing data. However, a little more prevalence of CALM and freckles were noted. Positive family history and prevalence of plexiform neurofibromas and axillary freckling were less frequently seen. The occurrence of freckles exclusively on face and the association of vitiligo with NF-1 were notable features.

### Introduction

Neurofibromatosis (NF) is an autosomal dominant neuro-cutaneous disorder, probably of neural crest origin, that affects all 3 germinal layers, thereby having the potential to involve any organ system [1]. Eight subtypes of the disease have been proposed till date; neurofibromatosis type-1 (NF1) be-

ing the commonest variety. *Friedrich Von Recklinghausen* first described the classical features of the disease and pointed out the origin of the skin tumor from peripheral nerves. NF-1 is characterized by a number of distinct and often diagnostic mucocutaneous and neurological abnormalities. The objective of our present study had been to review the prevalence and patterns of muco-



**Figure 1.** Multiple neurofibromas and a *café-au-lait* macule on the back of a woman



**Figure 2.** Plexiform neurofibromas and freckling of hands

cutaneous manifestations amongst patients of NF-1, in a population from eastern India. Lack of any formal study on this aspect particularly from this part of the world led us to undertake the present work.

### Materials and Methods

This was a clinical, observational, cross sectional study on mucocutaneous manifestations of NF-1. The total duration of the study was three years. Consecutive patients fulfilling the National Institute of Health (NIH) Consensus Development Conference on neurofibromatosis criteria for the diagnosis of NF-1, attending the dermatology outpatient department of a tertiary care hospital of eastern India were included in the present study.

As a definitive diagnosis of NF1 cannot be made in children below the age of 4 years by using the NIH criteria, we have excluded the patients below the age of 4 years.

A detailed history was taken and thorough clinical examination was performed. Ocular examination and evaluation of mental status were also done in every patient. Relevant investigations including radiological evaluation of skeleton and imaging of brain were done in appropriate cases.

All data were recorded in a pretested, semi-structured schedule and statistically analyzed.

**Table 1.** Distribution of Mucocutaneous Manifestations of NF-1 (n=51)

Features	n	(%)
<i>Café-au-lait</i> macule	51	(100)
Neurofibroma	49	(96.1)
Freckling	49	(96.1)
Vitiligo	3	(5.9)
Hairy nevus	2	(3.9)
Macroglossia	2	(3.9)
Palatal papules	2	(3.9)
Verrucous epidermal nevus	1	(2)
Lichen amyloidosis	1	(2)

### Results

A total of 51 patients were evaluated (**Table 1**). The mean age of the patients was 22.6 years. Out of the 51 patients, 30 (58.8%) were females and 21 (41.2%) were males, with a male-to-female ratio of 0.7. Positive family history in first-degree relatives was found in 18 (35.3%) patients. Forty-nine patients (96.1%) had neurofibromas including 8(15.7%) patients of plexiform neurofibromas over different body parts. Twenty-five patients (49%) had 1-20 neurofibromas, 9 (17.7%) had 21-40 neurofibromas, and 15 (29.4%) had more than 40 neurofibromas (**Figure 1**). Two (3.9%) patients of plexiform neurofibromas (**Figure 2**) had no other lesions of neurofibroma. Two (3.9%) patients did not have any clinically apparent neurofibroma, but fulfilled the diagnostic criteria of NF. All of our patients had *café-au-lait* macules (CALM) (**Figure 3**) of varying sizes ranging from 0.5 cm-13 cm in diameter. Freckling (**Figure 4**) was present in 49 (96.1%) patients and was most commonly (24, 47.1%) generalized in distribution. It was restricted to axillary areas in 18 (35.3%), both axillary and groin areas in 3 (5.9%), only inguinal areas in 3 (5.9%), and one patient had only facial freckling.

Other associated features in our patients were vitiligo (3, 5.9%), hairy nevus unrelated to plexiform neurofibroma (2, 3.9%), verrucous epidermal nevus (1, 2%), and lichen amyloidosis (1, 2%). Macroglossia was found in 2 (3.9%) patients and palatal papules in 2 (3.9%) patients. Nail dystrophy was found in only one patient. More than 2 *Lisch* nodules were found in 45 (88.3%) patients. Mental retardation was found in 5 (9.8%) patients and learning disabilities



**Figure 3.** Café-au-lait macules and neurofibromas on chest



**Figure 4.** Axillary freckling in a woman

were noted in 15 (29.4%) patients. Bony deformities were found in 9 (17.7%) patients of whom kyphoscoliosis was the commonest presentation found in 5 (9.8%) patients. Other bony lesions found were pectus carinatum (2, 3.9%), genu valgum (1, 2%), and widening and forward bending of tibia (1, 2%).

**Discussion**

Although NF-1 has an autosomal dominant mode of inheritance, approximately half of the index cases do not have a family history and are believed to arise from new mutations [2]. The NF-1 gene is located on chromosome number 17 and the loss of function of neurofibromin, the protein product of the non-mutated gene, results in increased mitogenic signaling leading to Ras-mediated uncontrolled cell growth and development of tumors [3]. This however cannot explain the non-tumor manifestations of NF-1. The sporadic occurrences, which constitute 30-50% cases, probably arise from germ cell (usually paternal) mutations [4]. In our series, a positive family history was found in only 35% of the patients pointing towards a high incidence of sporadic cases. In our study population there was a slight female preponderance (M: F= 0.7). Predominant female affection (M: F=0.71) was also reported in other studies [5].

CALMs, which are the first sign of NF-1, signify collection of heavily pigmented melanocytes of neural crest origin in the epidermis [2]. The lesions increase in size during the first decade, majority being less

than or equal to 10 cm in greatest dimension but the size may vary from 0.5-50 cm [6]. Ninety-five percent of patients of NF-1 have CALM by the time they reach the adulthood [4]. In our series, occurrence of CALM was universal.

Neurofibromas are benign nerve sheath tumors appearing as discrete swellings arising from peripheral nerves [2]. On the other hand, plexiform neurofibromas are diffuse, elongated fibromas coursing along the nerves. Neurofibromas ranging in number from 1 to more than forty were observed in 49 (96.1%) patients of our series including 8 patients (15.7%) of plexiform neurofibroma. Two patients of our series had only plexiform neurofibromas, a finding rarely reported in the literature [7]. Incidence of plexiform neurofibroma varies between 17-30% in different series [4, 8, 9]. The lifetime risk of progression to malignant peripheral nerve sheath tumor is about 10%, predominantly from preexisting plexiform neurofibromas [3]. None were seen in our series though.

Freckling localized or generalized, an important diagnostic cutaneous finding, was seen in 49 (96.1%) cases in the present series. Most of our patients (24, 47.1%) had generalized freckling. Freckling, localized exclusively to the axillae, was seen in only 18 (35.3%) patients, which is in sharp contrast to the findings (70-8%) documented in the existing literature [2, 6]. As intertriginous freckling are not related to sun exposure

these are considered as pathognomonic of NF-1. One of our patients had only facial freckling, which is probably a new association of the disease.

Generalized pruritus as a presenting symptom was seen in 9 (17.7%) patients of our present series and could be explained by the increased number of mast cells in NF [2].

Oral lesions in the form of papillomatous tumors of palate, buccal mucosa, tongue and lips are seen in 5-10% of the patients [6]. We came across 2 cases (3.92%) of palatal papules. In addition, there were 2 (3.9%) patients who had macroglossia. Macroglossia, described in NF-1 is usually unilateral; however in our patients the macroglossia was diffuse. We did not come across a single case of pseudoatrophic hypopigmented macules mentioned in the literature [2]. Hairy nevus unrelated to plexiform neurofibroma, was seen in 2 patients but is unlikely to be of significance. In our series the prevalence of vitiligo in NF-1 patients was 5.9% that is clearly higher than the worldwide prevalence of vitiligo (1%). Two or more *Lisch* nodules were detected in 45 (88.2%) cases in the present study. However their incidence was much lower (73%) in one Indian series [10].

Thus, most of our observations were in conformity with the prevailing data. However, a little more prevalence of CALM and freckles were noted. Less frequent occurrence was noted pertaining to family history, plexiform neurofibromas, and axillary freckling. The occurrence of freckles exclusively on face and the association of vitiligo with NF-1 have not been described in the existing literature.

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