

Cluster of Neurofibromatosis Cases in Remote Area of Northern Karnataka: A Case Series

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ABSTRACT

Tumours of the nerve system and skin are hallmarks of neurofibromatosis, a neurocutaneous condition. One class of inherited illnesses known as phakomatoses includes neurofibromatosis type 1 (NF1) or von Recklinghausen disease. It may show up anywhere in the body, including the skin, eyes, bones, and organs. We report a visually recorded seven cases of NF1 from same area. Every single patient had some kind of skin symptom. We describe the presence of several isolated neurofibromas, café au lait macules, axillary and inguinal freckling, neurological or cognitive dysfunction, and Lisch nodules in 100% of the eyes as ocular symptoms. Also, a rare occurrence of plexiform neuroma seen. Rare and familial presentation and similar cases in the same region, these findings collectively underscore the complex nature of the patient's medical presentation, necessitating a multidisciplinary approach to management and care.

KEYWORDS: Axillary freckling, Lisch nodules, Neuroma, Neurofibromatosis (NF)

INTRODUCTION

Neurofibromatosis, a neurocutaneous condition, is characterized by tumors affecting the nervous system and skin. [1] The majority of neurofibromatosis cases are of Neurofibromatosis Type 1 (NF1), also known as von Recklinghausen's disease, which is inherited via an autosomal dominant pattern. Each parent with an aberrant allele has a 50% chance of passing the gene to their children. Despite the high penetrance of NF1, its expression can vary widely, even among affected individuals within the same family. [2, 3]

The disease manifests with a broad spectrum of clinical features, including cutaneous, neurological, and skeletal abnormalities, making its presentation highly variable from

mild cutaneous manifestations to severe complications, including malignant tumors and significant neurological impairments. [1, 3, 4] Common features such as café-au-lait spots, axillary and inguinal freckling, Lisch nodules, and optic gliomas are frequently observed. [3] However, the extent of disease expression can vary significantly, with some patients developing more severe complications like malignant peripheral nerve sheath tumors, significant bone deformities, and cognitive impairments. [4, 5]

The cases discussed herein emphasize the challenges and complexities of NF1, underscoring the necessity for a multi-disciplinary approach to diagnosis and management. [4, 6]

CASE SERIES:

Case Report 1:

Clinical History and Examination

We present a case of a 52-year-old male with a 35-year history of painless progressive subcutaneous neurofibromas. Clinical examination revealed multiple non-tender nodules ranging from 0.5 cm to 2 cm scattered across the face, torso, limbs. Additionally, café-au-lait spots and inguinal/axillary freckling were observed. Ocular examination identified Lisch nodules in both eyes (Figure 1).

Systemic workup revealed no internal organ involvement or oral manifestations. There was no history of fever, pedal edema, abnormal sensations, or prior medication use. Psychiatric evaluation yielded unremarkable findings.

Family History: The patient's two children exhibited café-au-lait spots, suggestive of familial involvement. The patient did not exhibit any systemic organ-related issues or oral manifestations. However, his two offspring displayed café-au-lait pigmentations of varying sizes and frequencies. No



Figure 1: Image 1.a: Multiple, raised, skin-coloured nodules resembling neurofibromas on face. Image 1.b: Multiple pedunculated neurofibromas on back. Image 1.c: Pedunculated neurofibromas on chest. Image 1.d: Lisch nodules seen in right eye. Image 1.e: Lisch nodules seen in left eye.

prior fever, pedal edoema, abnormal feelings, or history of medication use were associated with the disorder. The contributing factor was the family history.

Investigations:

Slit lamp examination confirmed the presence of Lisch nodules in both eyes. Histopathology revealed non-capsulated tumors composed of spindle-shaped cells with twisted nuclei.

Treatment:

Based on the clinical presentation and histopathological confirmation, a diagnosis of Neurofibromatosis Type 1 (NF1) was established. The patient was initiated on Pirfenidone, an antifibrotic agent from the Pyridone class, administered as Tab. Fibrodone 200 mg once daily. Follow-up at the Dermatology (DVL) OPD was advised after one month.

Case Report 2:

Clinical Presentation:

It is case of a 16-year-old female who has café-au-lait spots of varying sizes and shapes since age five, while currently asymptomatic for plexiform neurofibromas. These are present on her face, neck, limbs, and trunk. Axillary and inguinal freckling were also noted, all consistent with NF1 (Figure 2). She had birth history of a single neonatal seizure.

Although systemic and oral examinations were unremarkable, the patient had mild mental retardation, characterized by difficulty with basic math and spelling.

Investigations:

Histopathology results indicate a non-capsulated tumor composed of cells with nuclei that protrude like little whips. Slit lamp examination revealed Lisch nodules in both eyes (Figure 2). Brain MRI demonstrated no intracranial abnormalities.



Figure 2: a: Café-au-lait spots prominently visible upon her neck. Image b: Café-au-lait spots prominently visible upon her Face. c: Presence of axillary and inguinal freckling. d: Café-au-lait spots adorns her limbs and trunk. e: Lisch nodules in right eye. f: Lisch nodules in left eye

The constellation of café-au-lait spots, Lisch nodules, and axillary/inguinal freckling suggests a diagnosis of Neurofibromatosis Type 1 (NF1). The presence of mild mental retardation may point to possible neurologic complication of NF1.

Case Report 3 :

An 8-year-old male presented with recurrent headaches and a history of NF1 in his two family members. Examination revealed no oral manifestations, but numerous café-au-lait spots scattered across his face, trunk, limbs and axillary frecklings (Figure 3). Ophthalmologic evaluation identified Lisch nodules in both eyes, further supporting the diagnosis. A brain MRI scan showed no abnormalities. Psychiatric assessment yielded normal results. Biopsy results are pending.

Case Report 4:

A 25-year-old baker with no relevant family history presented with multiple itchy nodules on his lower back for 6 months. He also had 3 to 4 episodes of epistaxis six months back. During physical examination, a cluster of numerous non-tender nodules was observed on the patient's back. These nodules range in size (0.5-2 cm) and consistency (soft to firm) (Figure 4). In addition, papules were present, especially in the infrascapular region.

There were no associated symptoms such as fever, pedal edema, altered sensations, nor prolonged drug intake reported. However, mild bilateral ulnar nerve thickening was



Figure 3: Image 3.a: Numerous café-au-lait spots distributed across face. Image 3.b: Café au-lait spots distributed across trunk. Image 3.c: Café au-lait spots distributed across chest. Image 3.d: Axillary freckling.

noted, suggesting potential neurological involvement.



Figure 4: Multiple Fibroic Nodules over the trunk

This constellation of findings raises the suspicion of a neurocutaneous disorder, such as neurofibromatosis, warranting further diagnostic evaluation and management.

Case Report 5:

History and Clinical Examination:

A 40-year female patient presented with a long-standing history of numerous swellings and pigmented patches on her body. She reported seeking care from multiple healthcare providers but not receiving a definitive diagnosis.

Examination: Figure 5

- Multiple plexiform neurofibromas on the back.

- Café-au-lait macules scattered throughout the body.
- Lisch nodules identified on ophthalmic evaluation.
- Brain MRI demonstrated no intracranial abnormalities.

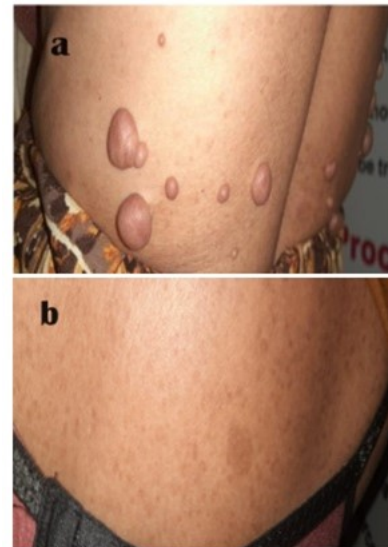


Figure 5: Image 5.a: Multiple plexiform neurofibromas on back. Image 5.b: Café au lait macules

Case Report 6:

This case report is of a 20-year-old male with an atypical presentation of neurofibromatosis. The patient presented with Pigmentation irregularities since infancy (café-au-lait macules), Axillary freckling (Figure 6) and a history of two neonatal seizures

Examination: Figure 6

- Atypical 4x4 cm plaque on the back, suspected to be a plexiform neuroma
- Lisch nodules on ophthalmologic evaluation
- Brain MRI results were inconclusive.
- Psychiatric Evaluation: Mild mental retardation and learning disabilities were identified.
- No biopsy taken.

DISCUSSION

This case series highlights the diverse clinical manifestations and complexities of Neurofibromatosis Type 1 (NF1), an autosomal dominant genetic disorder with complete penetrance marked by varied phenotypic expression, even among affected family members, although about half of the cases are sporadic. [1, 4]

Spectrum of Presentations: The six cases presented in this series demonstrate the diverse clinical manifestations



Figure 6: Image 6.a: Café au lait macules on trunk. Image 6.b: Axillary freckling. Image 6.c: Plexiform neurofibroma marked in a circle

of NF1. All cases exhibited characteristic cutaneous findings like café-au-lait macules (Cases 1-6) and axillary/inguinal freckling (Cases 1, 2, 4, 5, 6). Lisch nodules, a diagnostic ocular sign, were identified in Cases 1, 2, 3, 4, and 5. Plexiform neurofibromas, a more complex manifestation, were observed in Cases 1 and 6 (with an atypical presentation in Case 6). Cases 2 and 4 may have had potential neurological complications. Notably, none of the cases reported oral manifestations, although previous research suggests a high prevalence (up to 72%) in NF1 patients.

Previous studies have well-documented the hallmark features of NF1, including café-au-lait spots, neurofibromas, Lisch nodules, and axillary/inguinal freckling.^[1, 3, 4, 6] This case series aligns with these observations, with all cases displaying these primary symptoms. However, the variability in presentation, such as the presence of plexiform neurofibromas and neurological symptoms^[7], reflects the disease's heterogeneity, which is consistent with existing literature. Notably, the presence of Lisch nodules across multiple cases highlights their utility as a clinical marker for NF1.^[8]

The variability in symptom severity and presentation within the same family, as seen in this series, has been previously reported in NF1 literature.^[9, 10] This underscores the challenge in predicting disease progression and the need for personalized treatment approaches. The cases presented reflect a wide spectrum of clinical severity, from mild cutaneous symptoms to more complex neurological involvement.

Interestingly, none of the presented cases had oral manifestations, which contrasts with findings from other studies which often report abnormalities in the oral and maxillofacial region as common features of NF1.^[3, 11-13] The

absence of such findings in our cases may suggest a milder spectrum of disease expression or could reflect the unique phenotypic variability seen within NF1.

NF1 is known for its association with cognitive impairments,^[14] learning and social adaptation problems, and an increased risk of neurological complications such as optic and non-optic gliomas and seizures.^[1, 7, 10] The cases of the 16-year-old female and the 20-year-old male highlight these issues, showing mild mental retardation and a history of neonatal seizures. This supports the notion that NF1-related cognitive deficits and neurological manifestations can be diverse and unpredictable. NF1 follows an autosomal dominant inheritance pattern with complete penetrance but variable expressivity. Familial clustering, as seen in Case 1, Case 2, and Case 3, supports the genetic basis of NF1. The variability in clinical expression among affected family members further illustrates the influence of genetic modifiers and possibly environmental factors.^[10, 14]

The use of Pirfenidone in Case Report 1 represents a novel approach in managing cutaneous neurofibromas, given its antifibrotic properties. While traditional management has focused on symptomatic relief and surgical removal of problematic tumors, recent studies^[15-17] are exploring pharmacological interventions to address the fibrotic component of neurofibromas. This case suggests potential benefits and warrants further investigation into antifibrotic therapies in NF1 management.

Establishing a diagnosis of NF1 relies mainly on both clinical and histopathological examinations, particularly in low-resource settings. The clustering of cases reported in this study from north Karnataka highlights the potential for increased prevalence in specific geographical areas. By combining various specialties and ongoing monitoring, we can provide the best possible care for individuals living with NF1.

CONCLUSION

This case series reinforces the well-established complexity of Neurofibromatosis Type 1 (NF1). While all cases presented with classic features like café-au-lait macules and Lisch nodules, the variability in severity and additional manifestations like plexiform neurofibromas and potential neurological complications highlights the unpredictable nature of the disease. The absence of oral manifestations in this series compared to previous research further emphasizes the significant phenotypic variability within NF1. These findings underscore the need for personalized treatment approaches and ongoing monitoring for potential complications.

Furthermore, the observed clustering of cases in this study suggests potential geographic variations in NF1 prevalence. Additionally, the use of Pirfenidone in one case demonstrates the exploration of novel therapeutic avenues targeting the underlying fibrotic component of neurofibromas. Future research should focus on understanding the

reasons behind phenotypic variability, exploring potential environmental influences, and investigating the efficacy of pharmacological interventions like Pirfenidone for managing NF1 manifestations. By combining expertise from various specialties and implementing long-term monitoring protocols, we can strive to improve the overall care and well-being of individuals living with NF1.

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