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Unveiling the Spectrum: Diverse Presentations of Neurofibromatosis Type 1 in a Case Series Exploration

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ABSTRACT:

Neurofibromatosis type 1 (NF-1) is an autosomal dominant genetic disorder characterized by multisystem involvement and a predisposition to tumor development due to mutations on chromosome 17 (17q11.2). This case series provides a comprehensive examination of five individuals diagnosed with NF-1, showcasing the diverse clinical manifestations ranging from dermatological signs like café-au-lait spots and neurofibromas to ocular findings including Lisch nodules and optic pathway gliomas. The series emphasizes the variability in symptom presentation, the challenges in diagnosing and managing NF-1, and the need for a multidisciplinary approach. Each case underscores the critical importance of early recognition and lifelong monitoring to manage complications effectively. This study contributes to the understanding of NF-1's impact on patient lives and highlights the necessity for ongoing research to explore targeted therapeutic interventions.

Introduction:

Neurofibromatosis type 1 (NF-1) is an autosomal dominant disorder that significantly impacts numerous body systems, affecting approximately 1 in 3,000 individuals globally [1,2]. This genetic condition is primarily caused by mutations in the NF1 gene on chromosome 17 (17q11.2), which encodes a protein known as neurofibromin. This protein plays a critical role in cell growth regulation and differentiation. The loss of its function leads to uncontrolled cell proliferation, resulting in the diverse clinical manifestations associated with NF-1.

The clinical spectrum of NF-1 is broad and includes cutaneous, neurological, and ocular symptoms, among others [3]. One of the hallmark features of NF-1 is the development of multiple café-au-lait macules and cutaneous neurofibromas. These benign tumors are derived from nerve tissue and can vary in size, number, and location, significantly impacting cosmetic appearance and physical function[4]. Other skin manifestations include axillary and inguinal freckling, which are also diagnostic criteria established by the National Institutes of Health (NIH). Ocular involvement in NF-1 is particularly significant due to its potential impact on vision. The commonly observed Lisch nodules are melanocytic iris hamartomas, and are highly specific to NF-1. Optic pathway gliomas are another critical ocular feature; these benign brain tumors can lead to progressive vision loss and may require intervention depending on their growth rate and the symptoms they produce. The presence of such tumors underscores the necessity for regular ophthalmological evaluations in individuals diagnosed with NF-1.

The diagnosis of NF-1 is based on clinical criteria established by the National Institutes of Health, which require the presence of two or more of the following features: six or more café-au-lait macules, two or more neurofibromas of any type or one plexiform neurofibroma, freckling in the axillary or inguinal regions, optic glioma, two or more Lisch nodules, a distinctive osseous lesion, or a first-degree relative with NF-1 [9]. The variability in symptom presentation, as seen in the case series, emphasizes the challenge of

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diagnosing NF-1 and the importance of comprehensive clinical evaluation.

Neurofibromatosis type 1 can also predispose individuals to various orthopedic, neurological, and cardiovascular complications, including scoliosis, epilepsy, and hypertension. The variable expressivity and age-dependent manifestation of symptoms make NF-1 a lifelong condition that requires comprehensive management from a multidisciplinary medical team [5,6]. The genetic basis of NF-1 also opens avenues for potential genetic counselling and testing, which are crucial for affected families. Understanding the molecular genetics of NF-1 has led to better diagnostic strategies and may pave the way for targeted therapies in the future.

This case series aims to shed light on the multi-faceted nature of NF-1 through detailed examinations of individual cases, illustrating the diverse manifestations and challenging management scenarios faced by those with the disorder. Each case provides unique insights into the complexity of NF-1, emphasizing the importance of tailored therapeutic approaches and vigilant monitoring to mitigate complications and improve patient outcomes.

Case 1:

In the first case of the neurofibromatosis series, a 73-year-old male presents with a longstanding history of neurofibromatosis type 1 (NF-1), evident since his childhood. This patient's clinical presentation is multifaceted, characterized by numerous small, painless neurofibromas scattered across his face and trunk. These neurofibromas, hallmark features of NF-1, are benign tumors that arise from the nerve sheath.

Ocular examination of this individual reveals multiple two Lisch nodules on the iris, contributing significantly to the diagnosis. Additionally, the patient exhibits iris atrophic patches and Occlusio pupillae, indicating further ocular involvement, etiology of which may not be corelated with NF. He also has a posterior subcapsular cataract in the right eye, complicating the visibility of fundus details, which are not visualizable due to the dense cataract; however, the left eye appears normal. Fundus examination of right eye wasn't appreciated due to hazy media and poor pupillary dilatation, left eye fundus was found to be normal. Intraocular pressure in both eyes was normal.

Further dermatological examination reveals multiple pigmented flat lesions, ranging from 2mm to over 5mm, which are indicative of café-au-lait spots located on both the front and back of the trunk and the lower extremities. These lesions are another diagnostic feature of NF-1. Moreover, two hyper-pigmented elevated lesions with a rubbery consistency—one on the left hypochondrium and another on the inner side of the right thigh—were noted, suggestive of plexiform neurofibromas, which can potentially undergo malignant transformation.

Additionally, the patient had neurofibroma in the external auditory canal and axillary and inguinal freckling, common in NF-1 due to hyperpigmentation in skin fold areas. Despite the extensive dermatological and ocular manifestations, the patient shows no neurological deficits at the time of examination.

This comprehensive clinical evaluation, including both ophthalmological and neurological assessments, solidifies the diagnosis of Neurofibromatosis type 1 in this elderly patient. This case exemplifies the chronic and progressive nature of NF-1 and underscores the necessity for ongoing monitoring and multidisciplinary management to address the various manifestations of this genetic disorder.

Case 2:

In the second case of the neurofibromatosis series, we examined an 8-year-old child who was brought in for a routine checkup after her mother was diagnosed with Neurofibromatosis type 1 (NF-1). This familial linkage highlights the genetic predisposition and hereditary nature of NF-1, underscoring the importance of family history in the clinical assessment of this condition.

The child displayed multiple subcutaneous nodules and dark pigmented patches across his body, particularly noticeable on the back of his trunk. These are suggestive of café-au-lait spots, which are light brown spots typically found in NF-1 and are critical markers for early diagnosis. The number and distribution of these spots are consistent with the diagnostic criteria for NF-1, which typically include having six or more café-au-lait spots of over 5 mm in diameter (prepubertal) or over 15 mm (postpubertal).

During the ophthalmological evaluation, the child's intraocular pressures were measured using Goldmann Applanation Tonometry, resulting in readings of

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16mmHg and 18mmHg for the right and left eyes, respectively. However, the slit lamp examination revealed three hypopigmented iris nodules, which are indicative of Lisch nodules. These nodules are another significant diagnostic marker for NF-1 and are often used to confirm the diagnosis in conjunction with other clinical features. Fundus examination was normal in both eyes.

Further systemic examination revealed axillary freckling and multiple nodular lesions suggestive of neurofibroma, along with multiple hyperpigmented macules (café-au-lait spots) that varied in size. The presence of several soft cutaneous sessile neurofibromas ranging from a few millimeters to several centimeters in diameter along the trunk, limbs, and neck region was noted. This extensive presentation of neurofibromas and other skin anomalies underscores the systemic nature of NF-1 and its impact on the skin and nervous system.

This case vividly illustrates the clinical manifestations of NF-1 in a child, emphasizing the importance of genetic counselling and regular monitoring for early intervention and management of complications associated with this genetic disorder. The early identification and ongoing assessment can help mitigate some of the complications that may arise as the child grows older.

Case 3:

In the third case of the neurofibromatosis series, a 27-year-old female presented for evaluation with notable dermatological features characteristic of Neurofibromatosis type 1 (NF-1). Her primary concern was the presence of macule lesions over the limbs and trunk, prominently café-au-lait spots, which are large, light-brown patches frequently associated with NF-1. These spots were distributed all over her trunk, which is typical for individuals with this genetic condition and serves as a key diagnostic criterion.

During the ophthalmological assessment, the cornea was noted to be clear and transparent in both eyes, indicating no immediate corneal issues. However, a slit lamp examination revealed small multiple hypo-pigmented elevated lesions on the iris, suggestive of Lisch nodules. Lisch nodules are benign iris hamartomas that are highly specific to NF-1 and aid in its diagnosis. Fundus examination was normal and Intraocular pressure in both eyes was found to be 16mmHg.

The patient also reported a family history of similar symptoms, indicating the hereditary nature of NF-1. The presence of such a family history in her mother further substantiates the diagnosis based on clinical findings and genetic likelihood.

This case highlights the typical dermatological and ocular manifestations of NF-1 and emphasizes the importance of a thorough clinical examination in identifying the multifaceted aspects of this disorder. Regular monitoring and comprehensive evaluation are crucial for managing the condition effectively and mitigating potential complications associated with NF-1.

Case 4:

In the fourth case of the neurofibromatosis series, a 48-year-old male presented with complaints of blurring vision in his left eye. This symptom prompted a detailed ophthalmological evaluation to ascertain the underlying causes and assess for any association with Neurofibromatosis type 1 (NF-1), a condition known for its complex manifestations affecting multiple systems, including the eyes.

Ophthalmological Findings:

The patient's visual acuity was found to be reduced in the left eye (6/36), compared to the right eye (6/12), indicating a significant difference in vision between the two eyes. An examination of the intraocular pressure showed readings of 16 mmHg in the right eye and 18 mmHg in the left, both within normal limits but suggesting a need for close monitoring.

A slit lamp examination revealed the presence of two small hypopigmented elevated lesions on the iris, indicative of Lisch nodules. These nodules are significant in the context of NF-1 as they are one of the diagnostic criteria for the condition. The lens of the left eye exhibited a complicated cataract, which likely contributed to the patient's visual impairment. [12] Fundus examination showed hazy media, appeared to be normal. IOP was found to be normal in both eyes.

Additional Findings:

Beyond the ocular symptoms, the patient showed several other signs consistent with NF-1. On local examination, a mass was noted over his right limb, which had been present since childhood and had gradually increased in size, causing disfigurement of the right hand. This mass,

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along with multiple flat pigmented lesions ranging in size from 2 mm to more than 5 mm across the trunk—suggestive of café-au-lait spots—reinforced the diagnosis of NF-1.

Furthermore, axillary and inguinal region freckling was observed, which are common cutaneous manifestations in NF-1. A nodular swelling on the back side of the lower leg, consistent with a neurofibroma, was also noted. The patient reported frequent itching around the neurofibroma, leading to dry and scaly skin over the lower leg—a secondary symptom caused by the irritation and scratching.

Diagnosis and Implications:

These findings collectively contributed to a diagnosis of Neurofibromatosis type 1, highlighting the multi-systemic impact of the condition that not only affects the skin and peripheral nerves but also has significant ocular involvement. The presence of complicated cataract and Lisch nodules necessitated ongoing ophthalmological care to manage vision loss and monitor for other potential complications related to NF-1.

This case underscores the importance of a comprehensive approach in diagnosing and managing NF-1, given its diverse manifestations and impact on the patient's quality of life. It also demonstrates the critical role of routine eye examinations in patients with NF-1 to identify and treat ocular complications promptly.

Case 5:

In the fifth case of the neurofibromatosis series, we encounter a 19-year-old female who presents with a complex clinical picture that combines features of Neurofibromatosis type 1 (NF-1) and some characteristics suggestive of Noonan Syndrome, a condition often discussed in conjunction with NF-1 due to overlapping symptoms.

Clinical Presentation and Diagnosis:

The patient is notably short in stature and has a poorly built physique, which may hint at underlying genetic factors affecting her growth and development. She reports chronic tenderness in her left lower limb, which has been persistent for two months, and she has not yet attained menarche, suggesting delayed or disrupted pubertal development.

The patient exhibits a kyphoscoliotic deformity, which refers to a combined kyphosis and scoliosis, leading to both outward and lateral curvature of the spine. This is accompanied by facial asymmetry and asymmetry of the chest wall, further complicating her physical challenges. Muscle wasting is also noted, which could be secondary to her neurofibromatosis or a separate neuromuscular issue.

Dermatological and Neurological Features:

She reported that from the age of 3, she had dark lesions all over her body. These lesions have been progressive and were diagnosed as multiple café-au-lait macules larger than 15mm, primarily over the limbs and anterior trunk. Such extensive and pronounced pigmentation is a hallmark of NF-1 and contributes to the diagnostic criteria.

Additionally, palmar, axial, and inguinal freckling were observed, which are common in NF-1 due to hyperpigmentation in areas not typically exposed to the sun. Subcutaneous neurofibromas are noted, with one particularly mentioned over the left auricle, which are benign tumors that arise from nerves and can vary in size and number.

Family History and Genetic Implications:

A family history of neurofibromatosis underlines the genetic predisposition to NF-1, making it likely that her manifestations are part of this inherited condition. This background necessitates a thorough genetic evaluation to confirm the diagnosis and to understand any potential overlap with features of Noonan Syndrome, which can mimic or coincide with NF-1 in some cases.

Summary and Management Implications:

This case emphasizes the complexity of diagnosing and managing NF-1, especially when there are overlapping syndromic features that may affect multiple body systems. The multifaceted nature of the patient's symptoms requires a multidisciplinary approach to provide comprehensive care and address each of the clinical challenges she faces. Continuous monitoring, supportive therapies, and possibly genetic counselling are recommended to manage her condition effectively and improve her quality of life.

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Table 1: Overview of each case's clinical presentation:

Case	Age	Sex	Main Clinical Features	Ocular Findings	Other Significant Findings
1	73	Male	Multiple neurofibromas, café-au-lait spots, plexiform neurofibroma	Lisch nodules, occlusio pupilae, posterior subcapsular cataract	Axillary and inguinal freckling, no neurological deficits
2	8	Male	Café-au-lait spots, axillary freckling, multiple neurofibromas	Hypopigmented iris nodules (Lisch nodules)	Subcutaneous nodules along trunk, limbs, neck
3	27	Female	Café-au-lait spots	Hypopigmented iris nodules (Lisch nodules)	Family history of NF-1
4	48	Male	Café-au-lait spots, mass causing disfigurement of right hand	Lisch nodules, complicated cataract	Neurofibroma on lower leg, freckling
5	19	Female	Kyphoscoliosis, café-au-lait macules, subcutaneous neurofibroma	Not specified	Short stature, facial asymmetry, delayed menarche

Discussion:

In a study by Pujol RM, Aguilera P, Lambea J, et al.(2018) focused on the prevalence of Lisch nodules in a pediatric population with NF1 and their diagnostic value. It confirmed that Lisch nodules are highly prevalent even in young children and can serve as an early and reliable diagnostic marker for NF1. Our study showed the presence of Lisch nodules, even in young children which matches with this study.

In a study by Xu GF, Nelson T, London E, et al. (2019) explored the relationship between specific NF1 gene mutations and the presence of Lisch nodules. It found that certain mutations were more frequently associated with the development of Lisch nodules, suggesting a potential genotype-phenotype correlation that could guide personalized management strategies. Two of our cases show a positive family history, validating genetic prevalence.

In a longitudinal study by Ishijima K, Takazawa Y, Kawaguchi A, et al. (2021) followed NF1 patients with Lisch nodules over several years, documenting the clinical characteristics, progression, and potential complications. The study emphasized the benign nature of Lisch nodules but highlighted the need for regular monitoring to detect associated ocular issues. Routine screening must be done for all patients with Lisch nodule

In a study by McKeever J, Wallace MR, Packer RJ, et al. compared the potential link between the presence of

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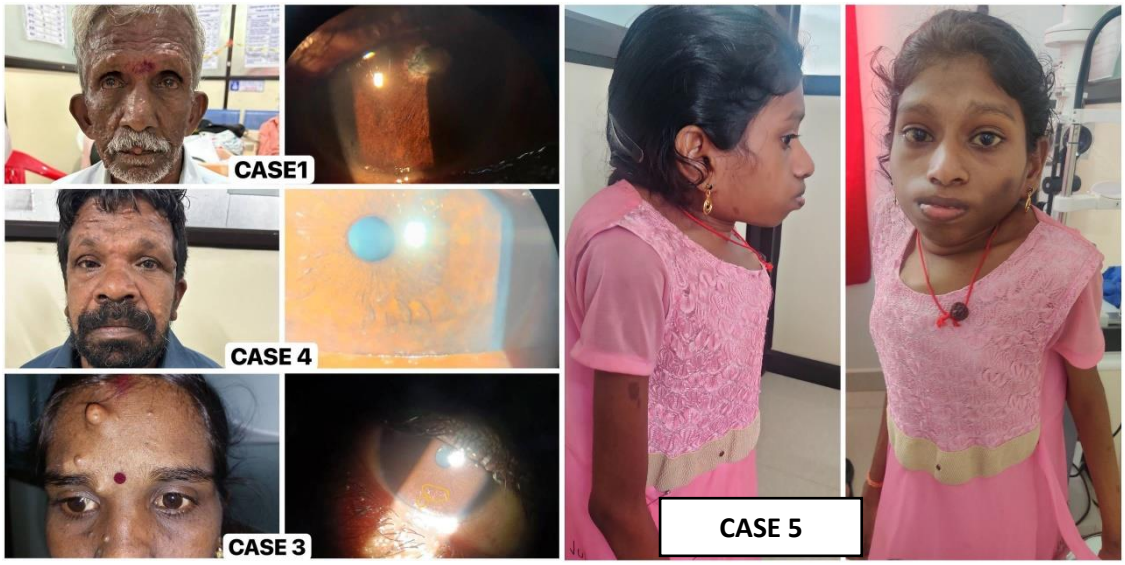
Lisch nodules and neurocognitive function in children with NF1. The findings suggested that children with a higher number of Lisch nodules might have a higher risk of neurocognitive impairments, emphasizing the need for comprehensive care that includes neurological and educational support. In our case with probable syndromic features of Noonan's syndrome certain grade of neurocognitive impairment was found which substantiates the need for routine examination.

In a study by L. R. Korf, et al. concluded that CALMs (café-au-lait macules) are a critical marker for the early diagnosis of NF1 in pediatric patients. Pediatricians should be vigilant in identifying multiple CALMs and consider further evaluation and genetic testing for NF1. Early diagnosis allows for timely intervention and monitoring, potentially improving outcomes and quality of life for affected individuals.

In a longitudinal study by S. Chen, et al. tracked changes in the number and size of CALMs in NF1 patients over a decade. The findings indicated that while CALMs often increase in number during childhood, their size and number tend to stabilize in adulthood. The study also noted that monitoring CALMs can provide insights into disease progression.

Conclusion:

This discussion reflects the critical need for awareness and understanding of NF-1 among healthcare providers to ensure timely and effective diagnosis and management. Education on the variable expressions of NF-1 can enhance patient care and potentially improve outcomes through early intervention and appropriate management strategies. This series also advocates for the continuation of research to explore the full scope of phenotypic manifestations and the development of targeted therapies for NF-1.



Informed consent :

Informed consent was obtained from all individual participants included in the study.

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