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## It is Not a Curse! It is Neurofibromatosis 1 (NF1): A Case Report from Rural Kenya

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### ABSTRACT

Neurofibromatosis 1 (NF1) is an autosomal dominant genetic disorder caused by mutations in the NF1 gene, with near complete penetrance and variable clinical presentation. Patients classically have café-au-lait macules, neurofibromas, skin freckles, and Lisch nodules, among other multisystemic features. Long-term management in a multidisciplinary team focuses on surveillance and treating complications. NF1 is a rare disease in Kenya, often leading to myths and misconceptions about its nature, especially among rural communities. We present a classical case from rural Kenya whose diagnosis was delayed by a belief that it was the result of a curse. We aim to highlight the importance of making this diagnosis and its linkage to a long-term care plan within a primary health care setting.

### INTRODUCTION

Neurofibromatosis type 1 (NF1) is a multisystem autosomal dominant genetic disorder that is commonly associated with skin, neurological, and skeletal manifestations (i.e., café au lait spots, neurofibromas, scoliosis, and long bone dysplasia, etc.). The pooled birth incidence is approximately 1:2600 individuals, while the pooled prevalence is about 1:3000 persons (Lee *et al.*, 2023). The manifestations of NF1 are caused by a mutation in or a deletion of the NF1 gene located on chromosome 17q11.2 (Gutmann *et al.*, 2017). The gene product, neurofibromin, serves as a tumor suppressor gene, and its decreased production or absence leads to the various clinical manifestations of NF1. The penetrance (i.e., the likelihood of an individual carrying the gene variant manifesting clinical disease) of the disease is almost 100%. The clinical features of NF1 are protean, and typical findings include café-au-lait macules (hyperpigmented macules appearing in childhood and increasing in early adulthood, freckling (especially axillary and inguinal regions, called Crowe sign), Lisch nodules (tan-colored hamartomas of the iris virtually pathognomonic of NF1), and tumors that may be benign or malignant (i.e., neurofibromas, gliomas, especially optic gliomas, and soft tissue sarcomas, e.g., rhabdomyosarcomas and glomus tumors). Neurofibromas are the most commonly seen benign peripheral nerve sheath tumors that are composed of a mixture of Schwann cells, fibroblasts, perineurial cells, and mast cells (Ortonne *et al.*, 2018). They include discrete cutaneous neurofibromas (the most common type, usually soft, fleshy, sessile, or pedunculated) (Plotkin *et al.*, 2012), plexiform neurofibromas (located superficially or deeply in the skin and associated with overgrowth of skin and soft tissues with ensuing disfigurement of patients) (Prada *et*

*al.*, 2012), and nodular fibromas. Patients may also have bone abnormalities, e.g., scoliosis, long bone dysplasia, pseudarthroses, and stunted growth. Neurological manifestations include neurocognitive deficits, learning disabilities, and seizures. Cardiovascular features include an increased incidence of congenital heart disease and hypertension. NF1 may be associated with other endocrinological diseases, including pheochromocytoma and multiple endocrine neoplasia type 2B (MEN 2B). When clinically indicated, MRI of the brain in NF1 shows focal areas of increased signal intensities (appearing as bright spots) and increased brain volume (DiMario & Ramsby, 1998; Van Es *et al.*, 1996). The diagnostic criteria for NF1 developed by the United States National Institutes of Health (NIH) Consensus Conference and updated in 2021 are shown in Table 1 (Legius *et al.*, 2021). Consensus guidelines for the management of NF1 patients among various clinical societies generally recommend care by a multidisciplinary team of dedicated specialists throughout the patient's lifetime. Emphasis is given to long-term surveillance for and treatment of complications, as well as genetic counseling for patients and their families (Ferner *et al.*, 2007; Stewart *et al.*, 2018). Patients with NF1 have an increased lifetime risk for both benign and malignant tumors (Masocco *et al.*, 2011). Affected children and adults may experience psychological problems with poor self-image and anxiety (Sanagoo *et al.*, 2019). The life expectancy is 8 years less than in the general population (Wilding *et al.*, 2012). A new emerging technology, e.g., clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (CRISPR/Cas9) gene editing system, may soon be used for specific therapeutic targets in NF1 (Moutal *et al.*, 2017).

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**Table 1:** Revised diagnostic criteria for neurofibromatosis type 1 (NF1) (Legius *et al.*, 2021)

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if 2 or more of the following are present
▪ 6 or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post pubertal individuals*
▪ Freckling in the axillary or inguinal region*
▪ 2 or more neurofibromas of any type or 1 plexiform neurofibroma
▪ Optic pathway glioma
▪ 2 or more iris Lisch nodules identified by slit lamp examination or 2 or more choroidal abnormalities (CAs) – defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging
▪ A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone
▪ A heterozygous pathogenic neurofibromin 1 (NF1) variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells
B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if 1 or more of the criteria in A are present

\*If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1, but exceptionally the person might have another diagnosis such as Legius syndrome. At least 1 of the 2 pigmentary findings (café-au-lait macules or freckling) should be bilateral.

Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.

**CASE SUMMARY**

**Clinical History and Physical Examination**

A 21-year-old single man, a college student from Elburgon, Nakuru County, Kenya, presented to us with a history of increasing numbers of generalized soft nodular, non-tender, and non-pruritic skin swellings and hyperpigmented macular lesions over the last 7 years. The swellings and macular-patchy lesions had been present at birth but had been dramatically increasing in size, number, and distribution since joining high school at age 14. They were now more evenly distributed over the torso, arms, legs, and neck. He was the firstborn among 5 siblings, the rest of whom were in good health. There was no known family history of a similar illness. He was accompanied by his mother, who reported that he was born with a deformity of his upper back, which was slightly bent forward and to the right. He had an otherwise normal childhood with normal developmental milestones, no convulsions, no visual problems, and above-average school performance, leading to his current college enrollment where he was pursuing a diploma in electrical engineering. He was happily dating a girl at the same college. Their main reason for consulting us was to get a medical diagnosis rather than live with a suspicion of a possible ‘cultural curse.’ Apparently, the family thought that he had been “cursed” and had sought numerous “spiritual solutions!”

On clinical examination, he was in good general health, and not in any obvious distress. He had normal vital signs, with a blood pressure of 105/63 mmHg and a pulse rate of 85 bpm. His skin had generalized nodular swellings, especially over the arms, torso, thighs, and neck. These were of various sizes, ranging from 2 to 6cm, soft, non-tender, not attached to the skin, and movable easily in all planes. They were associated with generalized hyperpigmented macules, especially in the torso and axillary regions. He

had bilateral axillary and inguinal freckles, which appeared much darker due to his dark skin color. He had an obvious thoracic scoliosis, while the rest of the musculoskeletal exam was unremarkable. His neurological exam was unremarkable, with grossly normal visual acuity and visual fields by direct confrontation. He was recommended for a full ophthalmological slit lamp evaluation. He had normal heart sounds with no murmurs. The rest of his physical exam was normal.

**Diagnosis**

In view of the nodular swellings being consistent with neurofibromas (Figure 1), the macular hyperpigmented skin lesions being café-au-lait spots (Figure 2), the



**Figure 1:** Cutaneous neurofibromas seen here as numerous nodular lesions (blue arrows) distributed on the torso anteriorly and posteriorly as well as on both upper and lower arms. More neurofibromas were present on the head, neck, and both lower limbs.

*Key: The patient had more than 60 cutaneous neurofibromas of variable sizes, which were soft, fleshy, and non-tender, with some being sessile and others pedunculated. These were distributed all over the skin, especially in the torso (both anteriorly and posteriorly).*



**Figure 2:** Café-au-lait macules seen here as multiple hyperpigmented macules of various sizes distributed over the anterior and posterior torso (red arrows). They were also seen in the neck, arms, hands, legs and feet

*Key: The patient had more than 30 café-au-lait macules diffusely distributed on the skin, particularly on the torso. These are flat, uniformly hyperpigmented macules varying in color from light brown to dark brown with smooth and irregular borders. They resemble coffee with milk, hence the name*



**Figure 3:** Freckles seen in the left and right axillae appearing as dark-brownish discoloration of the skin (blue arrows).

*Key: Freckles are discolorations of the skin due to overproduction of melanin and may range in color from red to dark brown. Due to his dark skin, the patient had dark brown freckles in both the axillary and inguinal areas, with other freckles seen on the torso as well.*



**Figure 4:** Thoracic scoliosis seen in a posterolateral and posterior view images as bending of the upper thorax to the right side

*Key: Scoliosis is the sideways curvature of the spine. The patient has had thoracic scoliosis on the right side since his childhood. This was not causing him any clinical symptoms*

presence of bilateral axillary and inguinal freckles (Figure 3), and scoliosis (Figure 4), a clinical diagnosis of neurofibromatosis type 1 (NF1) (previously called Von Recklinghausen's disease) was made. This was in keeping with the diagnostic criteria for NF1. Presently, he had no clinical indication for any extensive laboratory and imaging studies. A baseline complete blood count, random blood sugar, and creatinine were all normal.

### Management and Follow-Up

We educated them extensively on the genetic nature of the disease, its clinical manifestations, and proposed evaluation and monitoring over the years. This specifically includes an annual clinical evaluation seeking the nature and extent of the physical manifestations of the disease, annual blood pressure monitoring to rule out hypertension, a formal slit lamp examination for Lisch nodules, and surveillance against other associated neuro-endocrinological diseases, e.g., multiple endocrine neoplasia (MEN) syndromes. If he desired a better cosmetic appearance in the future, or if the neurofibromas ever became problematic (painful, disfiguring, interfering with normal function, etc.), he would be offered surgical intervention. Additionally, we informed him about the autosomal dominant mode of inheritance of the disease with a near-100% penetrance. This means each of his future children will have a 50% chance of inheriting the NF1 gene with clinical manifestations of NF1, albeit with variable severity of the disease. We referred him for a formal slit lamp ophthalmological evaluation and dermatological review. We'll follow him up annually in the medical clinic with a multidisciplinary team on a long-term basis, with appropriate surveillance and management of complications as necessary.

### DISCUSSION

Our patient met the diagnostic criteria for NF1 as per the 2021 NIH Consensus Conference diagnostic criteria (Legius *et al.*, 2021). Neither of his parents have NF1. He had >30 café-au-lait macules, bilateral axillary and inguinal freckles (which appeared darker in his dark African skin), >60 cutaneous neurofibromas, and scoliosis. The differential diagnoses included Legius syndrome, which is caused by a mutation in the SPRED1 gene and may have multiple café-au-lait macules, axillary freckling, and macrocephaly but lacks neurofibromas and central nervous system tumors (Legius *et al.*, 2021). Neurofibromatosis type 2 (NF2) is caused by a mutation of the NF2 gene located on chromosome 22 and is predominantly associated with benign schwannomas, bilateral acoustic neuromas, a lack of cognitive impairment, and no Lisch nodules (Plotkin *et al.*, 2022). For our patient, the café-au-lait macules and cutaneous neurofibromas began in childhood and increased in number and distribution in puberty, with no associated visual or neurocognitive disability to date. The thoracic scoliosis was asymptomatic. Presently, none of the neurofibromas were giving him pain or cosmetic-related concerns. The delayed medical diagnosis was due to a poor understanding of the disease in the community,

and its subsequent cultural characterization as a possible "curse." It is not uncommon for rare diseases (including neglected tropical diseases) to be seen as a curse in tropical Africa in general and Kenya in particular. This is largely fueled by illiteracy and entrenched cultural norms and practices, among other factors (Ochola *et al.*, 2021). Luckily for him, this matter has now been resolved with the correct medical diagnosis and a full discussion on the nature of NF1 and its impact on him and his current and future family prospects. Due to practical logistical reasons, his long-term management will be primarily overseen by the hospital physician, who will rationalize any testing needed based on the clinical presentation and oversee consultations with a multidisciplinary team including dermatologists, neurologists, orthopedic surgeons, psychological counselors, etc., as may be necessary. This is consistent with the UK and US consensus management guidelines (Ferner *et al.*, 2007; Stewart *et al.*, 2018). Genetic testing is used in exceptional cases, especially in prenatal or preimplantation diagnosis (Vernimmen *et al.*, 2023). These tests are prohibitively expensive, yet a positive NF1 mutation test does not predict the severity or complications of the disorder (Tamura, 2021). Presently, he is asymptomatic, and none of his parents or siblings have any features of the disease. Most likely, he had a sporadic mutation of the NF1 gene. We have recommended that a dermatologist and ophthalmologist review him for an initial evaluation and the planning of long-term follow-up.

### CONCLUSION

Primary care physicians should easily diagnose NF1 based on the diagnostic criteria and do a thorough clinical evaluation to exclude complications and associated medical conditions. The diagnosis should be fully discussed with the patient and their family to expel any myths and misconceptions about the disease and explore the implications of the autosomal dominant nature of inheritance with a near-complete penetrance. The patient should subsequently be enrolled in long-term care within a multidisciplinary team led by the primary care physician, with an emphasis on regular clinical evaluation and surveillance against any complications.

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