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Management and Treatment of Neurofibromatosis Type I

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Overview

Neurofibromatosis type 1 (NF1) is an autosomal dominant tumour suppressor syndrome associated with benign and malignant tumours, predominantly affecting the skin and nervous system.[1] NF1, the most prevalent neurocutaneous syndrome, and the focus of this review, has a frequency of ~ 1/1,900-1/3,500 people worldwide.[2] Disease manifestations can present at birth and emerge with age, negatively impacting multiple clinical domains and imparting a profound impact on a patient's quality of life and life expectancy.[2] Given its progressive nature and marked clinical variability, NF1 warrants a multidisciplinary approach to management and treatment.

Genetics and Pathogenesis

NF1 is the result of germline mutations in the tumour suppressor gene NF1 located at chromosome 17q11.2.[1] Inherited in an autosomal dominant fashion ~ 50% of neurofibromatosis (NF) cases can arise via de novo NF1 gene mutations.[3] Complete penetrance is seen in NF1, although expression is extremely variable, even within members of the same family.[3]

With thousands of identified pathogenic mutations in the NF1 gene, these pathogenic mutations ultimately disrupt the optimal protein production of neurofibromin, a critical regulator of the proto-oncogene, Ras. Ras is involved in multiple signalling pathways, including: stem cell factor (SCF)/c-kit signalling, mammalian (mechanistic) target of rapamycin (mTOR), and mitogen-activated protein kinase (MAPK) pathways. Thus, loss of neurofibromin expression leads to an up-regulation of the aforementioned pathways, facilitating cellular proliferation, differentiation and ultimately tumour development.[4]

Oculocutaneous Manifestations and Management of NF1

Hallmark cutaneous findings in NF1 include café-au-lait macules (CALMs), axillary freckling and cutaneous neurofibromas (cNFs). These cardinal

Timeline of NF1 Clinical Features
Birth - 2 years
CALMs, plexiform neurofibromas, pseudoarthrosis, sphenoid wing dysplasia, optic pathway gliomas
2 years - 6 years
Axillary freckling, Lisch nodules, optic pathway gliomas, CNS tumours, learning disabilities, plexiform neurofibromas
6 years - 10 years
Learning disabilities, attention deficit disorders, scoliosis, plexiform neurofibromas, increased risk of other cancer types (e.g., rhabdomyosarcomas), headaches
Adolescence
Subcutaneous and cutaneous neurofibromas, malignant transformation of preexisting plexiform neurofibromas, isolated MPNST, hypertension
Adulthood
Cutaneous and subcutaneous neurofibromas, MPNST, hypertension

Table 1. Development of clinical features in NF1. Café-au-lait macules (CALMs), central nervous system (CNS), malignant peripheral nerve sheath tumours (MPNSTs); *courtesy of Andrew Ferrier, MD, PhD, FRCPC, FAAD.*

NF1 Clinical Criteria
6 or more CALMs =/> 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in postpubertal patients
Two or more neurofibromas of any type or 1 plexiform neurofibroma
Freckling in the axillary or inguinal regions (Crowe sign)
Optic glioma (OPG)
Two or more iris hamartomas (Lisch nodules) or at least two choroidal anomalies
Osseous lesion (e.g., sphenoid wing dysplasia or long-bone dysplasia [with associated cortical thickening and medullary canal narrowing], with or without pseudoarthrosis)
A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

Table 2. NIH diagnostic criteria for NF1. A: In an individual who does not have a parent with NF1, the diagnosis is established if at least two of the following criteria are met. B: In a child who does have a parent with NF1, the diagnosis is established if at least one of these criteria is met; *courtesy of Andrew Ferrier, MD, PhD, FRCPC, FAAD.*

features, among others, have a central role in NF1 diagnosis and tend to follow a chronologic order of appearance **(Table 1)**. The United States National Institutes of Health (NIH) recently published and updated diagnostic criteria that rely on certain specific clinical features associated with NF1 **(Table 2)**.[5]

CALMs typically manifest as flat, uniformly hyperpigmented macules or patches with regular, well-defined borders, emerging within the first year after birth and often increasing in number during early childhood.[5] The presence of six or more CALMs by one year of age is observed in 99% of NF1 cases,[7] therefore, they are integral to the diagnostic criteria **(Table 2)**. As infants and young children predominantly present with CALMs alone, the diagnosis of NF1 necessitates the emergence of a second feature. Consequently, it is not uncommon for children with multiple CALMs and no family history of NF1 to undergo several years of follow-up before a definitive diagnosis is made or ruled out. While NF1 accounts for the majority of cases associated with multiple CALMs, such pigmented lesions can also occur in various other conditions.[6] Given that approximately 15% of the general population exhibits one to three CALMs,[6] the presence of three or more CALMs should prompt specialist referral.

Freckling in the axillary or inguinal regions (Crowe sign) occurs in 90% of patients by age 7 **(Table 1)**.[8] Freckling presents as clusters of hyper-pigmented macules and is part of the diagnostic criteria **(Table 2)**. While the axillary and inguinal areas are most often involved, freckling can also present in other intertriginous sites (e.g., neckline or inframammary areas) or can appear diffusely.[9]

Presenting as soft, fleshy, pedunculated, or sessile tumours, cNFs constitute the most prevalent tumour type in NF1.[10] These benign growths affect both the epidermis and dermis, typically emerging just before or during adolescence and demonstrating a tendency to augment in size and quantity with advancing age.[10] While cNFs do not harbor malignant potential, they can provoke irritation, pruritus or cosmetic concerns, thereby warranting surgical intervention if necessary **(Table 3)**.

Plexiform neurofibromas (PNFs) represent a distinct subtype of neurofibroma originating in the subcutaneous tissues, with growth observed throughout childhood, adolescence and adulthood.[11] These tumours, histologically benign in nature, often arise congenitally from one or multiple nerve fascicles. PNFs may manifest as tender, firm nodules with a palpable “bag of worms” consistency or remain non-palpable, featuring deep subcutaneous components potentially leading to soft tissue distortion, bony overgrowth or nerve deficits. Disfigurement and pain

can manifest in various anatomical locations, including the head and neck; orbit; extremities; thorax; paraspinal nerve roots; abdomen; and pelvis, significantly impacting quality of life and increasing mortality risk.[11]

Approximately 50% of NF1 patients have clinically apparent PNFs.[12] Evaluation of such lesions is best achieved with MRI, coupled with annual physical examination to detect symptomatic tumours **(Table 3)**. Multidisciplinary surgical interventions can be employed to debulk symptomatic or progressive PNFs. As well, oral selective mitogen-activated protein kinase (MEK) inhibitors such as selumetinib have

Feature	Diagnostic evaluation	Management
CALMs, axillary freckling	• Cutaneous exam • Refer to genetics, NF specialist, or dermatologists for more > six CALMs	• None required • Camouflage treatment if cosmetically distressing
Cutaneous neurofibromas	• Cutaneous exam • Referral to genetics or dermatology	• Symptomatic or disfiguringlesions: surgery, laser removal, or electrodessication
Plexiform Neurofibromas	•Annual physical + neurologic examination • MRI (w/ contrast) of symptomatic body part	• MRI surveillance if progression or malignancy risk • Surgical consultation for symptomatic lesions • +/- MEK inhibitors (selumetinib • Pain & symptom management
MPNST	• Regional MRI of symptomatic body part • Refer to surgeon for biopsy/resection/ histologic confirmation & oncologist	• Surgical resection and adjunctive radiation or chemotherapy therapy • Educate MPNST signs and symptoms (e.g., pain, unexpected growth of a tumour, or change in texture from soft to firm)
OPGs	• Ophthalmologic exam < 10 years old • Brain/orbit MRI if abnormal eye exam or signs or symptoms of OPG • Annual height and weight measurement to screen for precocious puberty (+/- endocrinology referral	• Annual ophthalmologic screening through adulthood or for 10–25 y after initial diagnosis of OPG
Behavioural/ learning difficulties	• Referral to psychologist or psychiatrist for neurocognitive testing	• Academic support such as individualized educational plans, along with physical, occupational, and speech therapy.
Bone abnormalities	• Orthopedic evaluation • Plain radiographs	• Orthopedic referral for bracing +/- surgery
Osteopenia/ osteoporosis	• DEXA scan • Vitamin D level	• Calcium and Vitamin D supplementation • Regular DEXA scan
Hypertension	• Annual blood pressure assessment • Doppler ultrasonography • Refer to cardiology if murmur	• Routine BP assessment commencing in childhood • Persistent hypertension rule out secondary causes (e.g., renovascular disease or pheochromocytoma)
Breast cancer	• Mammogram +/- MRI • Physical exam	• Annual mammogram at age 30

Table 3. Diagnostic evaluation and management for common clinical features of NF1. Adapted from Miller, DT, et al., 2019 and Stewart, DR, et al., 2018; *courtesy of Andrew Ferrier, MD, PhD, FRCPC, FAAD.*

been approved for symptomatic or inoperable NFs in pediatric patients three years of age and older.

The transformation of PNFs into malignant peripheral nerve sheath tumours (MPNSTs) occurs in ~3-15% of patients, representing the leading cause of death in NF1 patients.[12] Rapid growth, pain, change in lesion texture from soft to firm, or a family history of MPNSTs are some clues of malignant degeneration.[12] Both MRI and PET scans are highly sensitive imaging modalities for malignant transformation **(Table 3)**. For management, a multimodality approach is used including complete tumour resection with negative margins and adjuvant radiotherapy.[13] Chemotherapy is used only for palliation in unresectable and metastatic tumours.[14]

Additional cutaneous manifestations of NF1 include juvenile xanthogranulomas (JXGs) and nevus anemicus. JXGs manifest as small, waxy, yellowish nodules on the skin in some children with NF1, typically resolving spontaneously. Despite speculation about a link between JXGs and leukemia in NF1 children, clinical studies suggest they are not a significant risk factor.[10] Nevus anemicus, a flat skin macule paler than surrounding skin, occurs in approximately half of individuals with NF1.

In approximately 70% of NF1 patients the iris may show tan-coloured hamartomas known as Lisch nodules.[7] Lisch nodules can appear between ages 5 and 10 years and are useful in establishing a diagnosis of NF1 in a child **(Table 1)**. While visible with the naked eye these lesions are best visualized with an ophthalmoscope or slit lamp.[10] These lesions are not malignant, nor do they impact vision. All patients with suspected NF1 should be referred to an ophthalmologist for slit-lamp examination for potential Lisch nodules **(Table 3)**.

Optic pathway gliomas (OPGs) occur in approximately 15% of children younger than six years of age with NF1.[15] As the most common central nervous system-associated tumour seen in children with NF1, the majority of OPGs are asymptomatic and intervention is rare.[16] OPG symptoms can include headache, nausea, vomiting, visual defects, and precocious puberty.[16] While no formal guidelines exist annual eye examinations under the age of 10 is warranted, and every two years up to 18 years **(Table 3)**.

Extracutaneous Manifestations and Management of NF1

The extracutaneous manifestations of NF1 encompass a wide array of cognitive and behavioural challenges, and skeletal, neurologic and cardiovascular abnormalities, along with the development of benign and malignant tumours. Approximately half of individuals with NF1 encounter various forms of learning difficulties, with attention-deficit/hyperactivity disorder observed in 50% of this demographic.[17] It is imperative to conduct routine screening for developmental delays and behavioural issues. Early initiation of psychoeducational, neuropsychological and academic testing should be pursued upon the earliest signs of academic or social concerns **(Table 3)**.

Skeletal abnormalities in NF1 exhibit variability and usually manifest during childhood **(Table 1)**. The diagnostic criteria encompass distinct features such as sphenoid wing dysplasia, dystrophic scoliosis, and long-bone dysplasia **(Table 2)**. Noteworthy focal skeletal manifestations include macrocephaly; hypertelorism; short stature; pectus deformity; and osteopenia. It is imperative to conduct annual surveillance, involving collaboration with relevant specialists (i.e., orthopedist, endocrinologist) for comprehensive monitoring and management.

Cardiovascular system abnormalities are well documented in NF1. Pulmonic stenosis, mitral valve anomalies, septal defects, and tetralogy of Fallot are some of the more often documented heart defects.[18] As these defects increase the risk of fatal cardiovascular events it is critical that physicians screen and make the appropriate referrals or workup.

Primary (essential) hypertension is commonly found in adults, and less commonly in children, with NF1.[10,12] While primary hypertension is most common, secondary hypertension (e.g., moyamoya disease, renal artery stenosis, and pheochromocytoma) is known to occur. Annual blood pressure assessments should be initiated in all NF1 patients and, if clinically suspected, workup for any secondary causes of hypertension including MRI and magnetic resonance angiogram of the abdomen **(Table 3)**.

Tumours associated with NF1 encompass a diverse spectrum including, but not limited to, gastrointestinal stromal tumours; early-onset breast cancer; leukemia; neuroendocrine tumours, and rhabdomyosarcoma.[19] Females with NF1, particularly those under 50 years of age, face an increased risk of breast cancer and exhibit significantly poorer five-year survival rates and excess mortality.[20] According to the National Comprehensive Cancer Network guidelines, women clinically diagnosed with NF1 should undergo annual mammograms starting at age 30 and consider contrast-enhanced breast MRI between ages 30 and 50.[20]

Genetic Counselling and Conception

Patients and their families should receive comprehensive genetic counselling, covering aspects

such as the disorder's inheritance pattern (including potential recurrence risk in other offspring), prognosis and psychosocial adjustment. Addressing the progressive nature of the disease and its variable clinical presentation is essential. Those with NF1 who desire children should undergo preconception genetic counselling to understand inheritance risks and the condition's manifestation variability. While many NF1 patients opt for natural conception, prospective parents should be educated about the array of reproductive options available to them.

Conclusion

NF1 manifests with a wide range of clinical features impacting various organ systems. Recognizing characteristic cutaneous signs and specific tumour types should prompt clinicians to refer patients to specialists well-versed in NF1 and its related conditions. Given the considerable variability in NF1 manifestations both within and among patients, it is crucial to tailor management strategies to each individual's needs at various stages of life.

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Financial Disclosures

None declared.

References

1. Wallace MR, Marchuk DA, Andersen LB, et al. Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. *Science*. 1990;249:181-6.
2. Uusitalo E, Leppavirta J, Koffert A, et al. Incidence and mortality of neurofibromatosis: a total population study in Finland. *J Invest Dermatol*. 2015;135:904-6.
3. Easton DF, Ponder MA, Huson SM, et al. An analysis of variation in expression of neurofibromatosis (NF) type 1 (NF1): evidence for modifying genes. *Am J Hum Genet*. 1993 Aug;53(2):305-13.
4. Gutmann DH, Ferner RE, Listernick RH, et al. Neurofibromatosis type 1. *Nat Rev Dis Primers*. 2017 Feb 23;3:17004.
5. Legius E, Messiaen L, Wolkenstein P, et al; International Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC); Huson SM, Evans DG, Plotkin SR. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. *Genet Med*. 2021 Aug;23(8):1506-13.
6. Nunley KS, Gao F, Albers AC, et al. Predictive value of cafe au lait macules at initial consultation in the diagnosis of neurofibromatosis type 1. *Arch Dermatol*. 2009;145(8):883-7.
7. DeBella K, Szudek J, Friedman JM. Use of the national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. *Pediatrics*. 2000 Mar;105(3 Pt 1):608-14.
8. Korf BR. Diagnostic outcome in children with multiple café au lait spots. *Pediatrics*. 1992 Dec;90(6):924-7.
9. Huson SM, Harper PS, Compston DA. Von Recklinghausen neurofibromatosis. A clinical and population study in south-east Wales. *Brain*. 1988;111(Pt 6):1355-81.
10. Miller DT, Freedenberg D, Schorry E, et al; Council on Genetics; American College of Medical Genetics and Genomics. Health Supervision for Children With Neurofibromatosis Type 1. *Pediatrics*. 2019 May;143(5):e20190660.
11. Nguyen R, Dombi E, Widemann BC, et al. Growth dynamics of plexiform neurofibromas: a retrospective cohort study of 201 patients with neurofibromatosis 1. *Orphanet J Rare Dis*. 2012 Oct 4;7:75.
12. Stewart DR, Korf BR, Nathanson KL, et al. Care of adults with neurofibromatosis type 1: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2018 Jul;20(7):671-82.
13. Ferner RE, Gutmann DH. International consensus statement on malignant peripheral nerve sheath tumors in neurofibromatosis. *Cancer Res*. 2002 Mar 1;62(5):1573-7.
14. Pannu AK, Sharma N. Neurofibromatosis type 1 and disseminated malignant peripheral nerve sheath tumor. QJM. 2017 Sep 1;110(9):583-4.
15. Lewis RA, Gerson LP, Axelson KA, et al. von Recklinghausen neurofibromatosis. II. Incidence of optic gliomata. *Ophthalmology*. 1984 Aug;91(8):929-35.
16. Fisher MJ, Loguidice M, Gutmann DH, et al. Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. *Neuro Oncol*. 2012 Jun;14(6):790-7.
17. Lorenzo J, Barton B, Arnold SS, et al. Developmental trajectories of young children with neurofibromatosis type 1: a longitudinal study from 21 to 40 months of age. *J Pediatr*. 2015 Apr;166(4):1006-12.e1.
18. Pinna V, Daniele P, Calcagni G, et al. Prevalence, type, and molecular spectrum of NF1 mutations in patients with neurofibromatosis Type 1 and congenital heart disease. *Genes (Basel)*. 2019 Sep 4;10(9):675.
19. Walker L, Thompson D, Easton D, et al. A prospective study of neurofibromatosis type 1 cancer incidence in the UK. *Br J Cancer*. 2006 Jul 17;95(2):233-8.
20. Evans DGR, Kallionpää RA, Clementi M, et al. Breast cancer in neurofibromatosis 1: survival and risk of contralateral breast cancer in a five country cohort study. *Genet Med*. 2020 Feb;22(2):398-406. Erratum in: *Genet Med*. 2019 Oct 8; PMID: 31495828; PMCID: PMC7000349.