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REVIEW

Neurofibromatosis Type 1: Optimizing Management with a Multidisciplinary Approach

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Abstract: Neurofibromatosis Type I (NF1) is a complex genetic condition that affects multiple organ systems and presents a unique set of challenges for clinicians in its management. NF1 is a tumor predisposition syndrome that primarily affect the peripheral and central nervous systems via the impact of haploinsufficiency upon neural crest lineage cells including Schwann cells, melanocytes, fibroblasts, etc. NF1 can further lead to pathology of the skin, bones, visual system, and cardiovascular system, all of which can drastically reduce a patient's quality of life (QOL). This review provides a comprehensive examination of the many specialties required for the care of patients with Neurofibromatosis Type 1 (NF1). We delve into the pathogenesis and clinical presentation of NF1, highlighting its diverse manifestations and the challenges they pose in management. The review underscores the importance of a multidisciplinary approach to NF1, emphasizing how such an approach can significantly improve patient outcomes and overall QOL. Central to this approach is the role of the NF expert, who guides a multidisciplinary team (MDT) comprising healthcare professionals from many areas of expertise. The MDT collaboratively addresses the multifaceted needs of NF1 patients, ensuring comprehensive and personalized care. This review highlights the need for further investigation to optimize the workflow for NF1 patients in an MDT setting, and to improve implementation and efficacy.

Keywords: multisystemic, multidisciplinary team, quality of life, neurofibromatosis, NF expert, NF1, tumor predisposition syndrome

Introduction

Neurofibromatosis Type I (NF1) is a tumor predisposition syndrome characterized by a genetic mutation in the NF1 gene that affects the growth and regulation of the nervous system. Haploinsufficiency (50% decrease of functional protein) of the NF1 gene product neurofibromin is due to loss of function of one allele. The result is an increase in the proliferation rate, autocrine and paracrine signaling, and inflammatory cell signaling of Schwann cell precursors in the neural crest population.[1] NF1 has the propensity to manifest in multiple organ systems, providing a just rationale for multidisciplinary management. The loss of one NF1 allele in all tissues of the body results in multi-system abnormalities that can immensely complicate a patient's treatment plan and greatly impact outcome measures.[2] This review will delve into the pathogenesis and clinical presentation of NF1, in addition to closely examining how a multidisciplinary approach can benefit outcomes and quality of life (QOL).

Pathogenesis and Presentation

NF1 is the most common of the peripheral nerve tumor genetic syndromes, which also includes schwannomatosis and NF2-related schwannomatosis. Its incidence is approximately 1 in 3000 live births. The condition stems from a heterozygous mutation in the NF1 gene on Chromosome 17q11.2 that occurs during gametogenesis. The NF1 gene encodes the protein known as neurofibromin, a known tumor suppressor which inhibits the GDPase-activating domain (GAP) of the intracellular signaling protein Ras (rat sarcoma). Ras resides within a family of GTPases that is involved in promoting cellular proliferation. Loss of the wild type NF1 allele during propagation of cells in the Schwann lineage directly causes the growth of peripheral nerve sheath tumors and is the only mutation typically identified.[3] With regard to

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clinical presentation, the most apparent features of NF1 include cutaneous neurofibromas (CN) purportedly arising from small nerves of the skin, and plexiform neurofibromas (PN) that derive from Schwann cells supporting large peripheral nerves and can invest in multiple bundles of nerves (nerve plexi).

The diagnostic criteria of NF1 (Table 1), were updated in 2021. NF1 patients are susceptible to both benign and malignant nerve sheath tumors,[4] as well as neurocognitive and developmental deficits, mood disorder, osseous lesions including dystrophic scoliosis and pseudoarthrosis, neuroendocrine tumors, breast cancer, and others.[2]

Genetics of NF1

NF1 is an autosomal dominant tumor predisposition syndrome caused by germline mutation of one NF1 allele and resulting haploinsufficient GAP activity and dysregulated Ras.[5] As neurofibromin is active in nearly every tissue lineage, holo-corporal loss of 50% of functional neurofibromin impacts every organ system in the body with a penetrance of 100%, meaning that every patient with a pathogenic mutation will show signs of the disease.[6] Tumors arise after loss of the remaining NF1 allele, most commonly in Schwann cell progenitors which beget nerve sheath tumors.[7] Additional signs and of symptoms of NF1 such as learning disabilities, autism, and respiratory and GI abnormalities are attributable not to loss of heterozygosity, but rather to the developmental impact of 50% decrease in functional neurofibromin protein.[8] Genotype and phenotype are not closely allied in NF1, partly because origination of a plexiform neurofibroma during embryogenesis is most likely a random event affecting early neural crest derivatives that later form a tumor harboring pluripotent potential. Multiple or large plexiform neurofibromas may proliferate in childhood and invest in all 3 developing tissue layers during development, resulting in physically apparent and physiologically impactful tumors in some but not all individuals with the same germline mutation.[9] As a major determinant of quality of life and a major contributor to disease morbidity, plexiform neurofibromas can greatly alter the severity of disease phenotype.[10] In the authors' experience, the burden of disease of NF1 is often grossly similar between different first degree family members harboring the same mutation; for example, if skin lesions are extensive in a parent with NF1, they are more likely to be apparent in the child with NF1. In contrast, a heavy burden of internal plexiform and paraspinal tumors are most likely to impact children of NF1 patients with the same phenotype.

The Multi-Systemic Nature of Neurofibromatosis Type 1

NF1 is a complex genetic disorder with a wide range of manifestations. The most common features include café-au-lait macules that are present in ~95% of patients,[11] and cutaneous or subcutaneous neurofibromas – noncancerous tumors with self-limited growth that arise in the skin beginning in late childhood.[12] Freckles under the arms or in the groin (Crowe's Sign) and benign hamartomas of the iris known as Lisch nodules, are observable during childhood.[13] Learning disabilities and attention-deficit/hyperactivity disorder (ADHD) occur frequently in affected individuals.[12]

Table 1 Revised Diagnostic Criteria for NF1, as of 2021

Diagnostic Criteria of NF1	
Two or More of the Following:	**Criteria:**
1	At least six café-au-lait macules (> 5 mm diameter in prepubertal individuals and >15 mm in postpubertal individuals)
2	Freckling in axillary or inguinal regions
3	Optic pathway glioma
4	At least two Lisch nodules (iris hamartomas)
5	At least two neurofibromas of any type, or one plexiform neurofibroma
6	A distinctive osseous lesion (sphenoid dysplasia or tibial pseudoarthrosis)
7	A first-degree relative with NF1

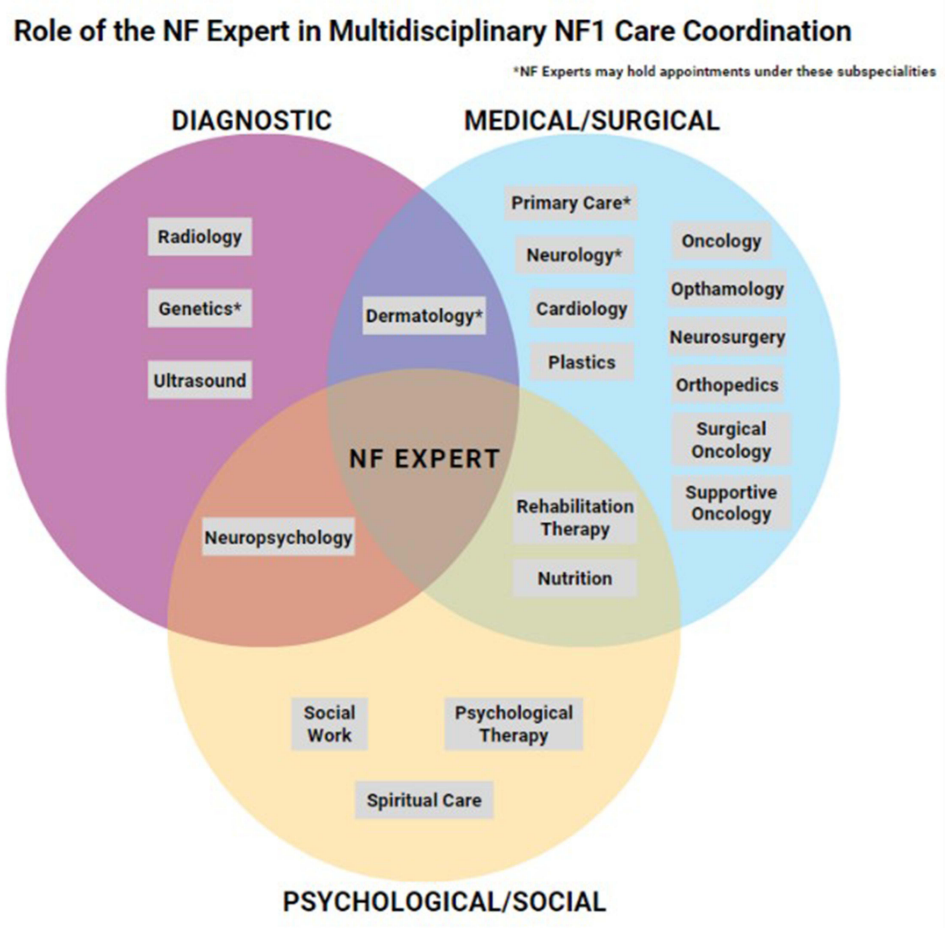

Figure 1 Venn diagram that illustrates the NF expert's role in a Multidisciplinary NF1 Care Team.

Optic pathway gliomas, tumors that grow along the optic nerve or optic pathways in the brain and which can impair vision, occur in 15–20% of NF1 patients. Increased risk of glaucoma is also associated with NF1. Distinctive boney lesions, usually in the long bones or a bone of the skull[12,13] affect ~50% of patients. Skeletal issues may include osseous lesions and malformations, pseudoarthrosis affecting the tibia, sphenoid wing dysplasia, scoliosis, kyphosis, short stature, and osteoporosis. Gastrointestinal manifestations such as irritable bowel syndrome, constipation, dyspepsia, occur in 15–30% of NF1 patients,[14,15] and women with NF1 have a 4–8x higher risk of breast cancer in the under 50 population. The risk of endocrine disorders is not documented in the NF1 population, but it can involve short stature and failure to thrive, growth hormone deficiency or excess can be attributed to intracranial tumors affecting the pituitary, as can central precocious puberty, whereas delayed menarche, tumors, while not common, can occur in NF1 as well. Cardiovascular conditions affect ~15% of NF1 patients and may include aneurysm, coarctation of the aorta, valvular insufficiency, hypertension that can be related to renal artery stenosis versus idiopathic, moyamoya syndrome, and stroke.[13]

The following section describes the different clinical manifestations mentioned above in depth.

Tumors of the Nervous System

Plexiform Neurofibromas (PN)

PN occur in up to 60% of NF1 patients, although this is likely an underestimate as patients harbor internal PN that are only discovered upon active surveillance imaging that many patients do not receive.[16] PN are believed to be present, sometimes microscopically, at birth due to their origin in early neural crest lineage cells, but can continue to grow during adolescence and early adulthood. PN grow concentrically from within the epineurium of large nerves, often growing to

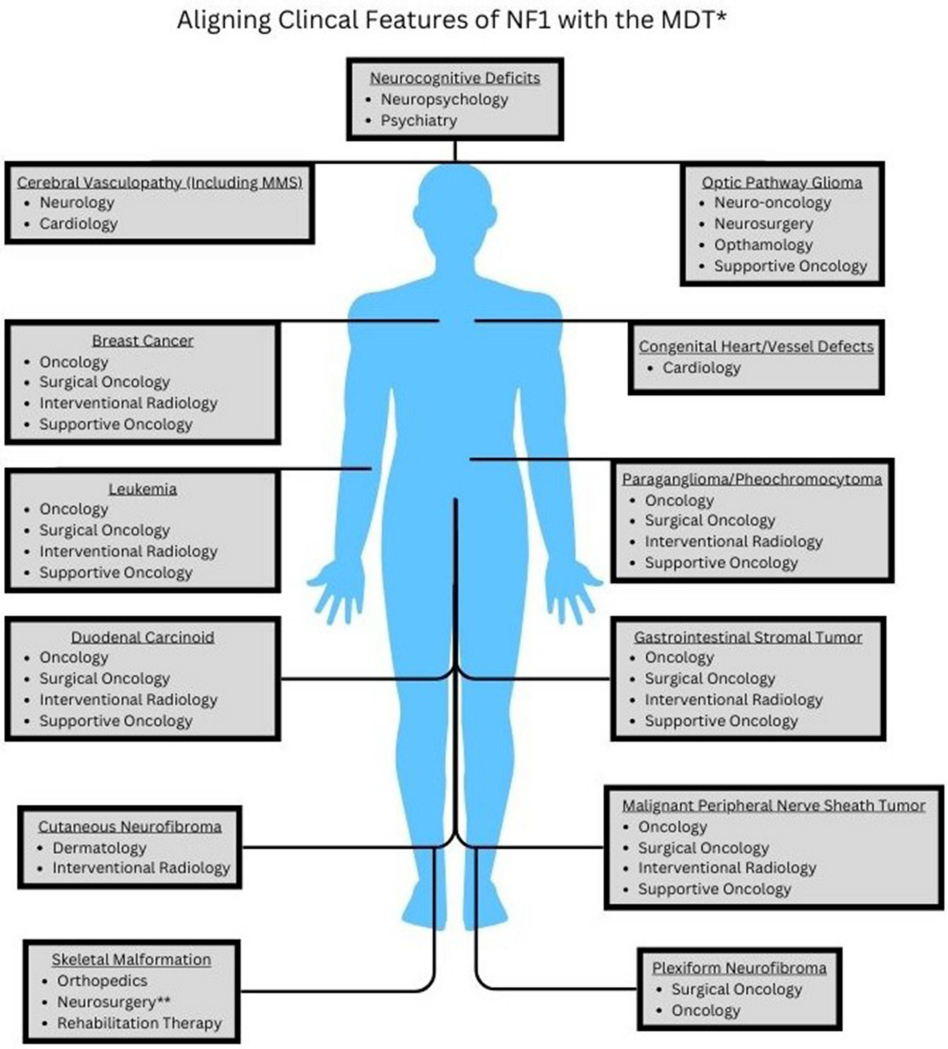

Figure 2 Schematic outlining the necessary specialties to be included when dealing with specific clinical manifestations of NF1. *For optimal management, it is advisable to consult with a NF expert for all these conditions, prior to referral to specialties included above. **Neurosurgery should be considered imperative when addressing skeletal malformations involving the spine.

encapsulate part or all of the associated plexus. As a result of the tumors growing within and spreading the nerve fascicles, macroscopic debulking or resection is highly likely to disrupt nerve function. Dermally involved diffuse PN exhibit a soft, velvety pillow-like texture, frequently with a melanotic and rugated/elephantine appearance. These neurofibromas have unlimited growth potential and can grow to massive size, resulting in disfigurement, neuropathy, substantial pain, and or interference with basic bodily functions or ambulation. A sudden escalation in pain signals a potential malignant transformation into a treatment-resistant form of sarcoma known as a malignant peripheral nerve sheath tumor (MPNST). Sudden pain, weakness, or numbness warrants immediate attention as there is approximately a ~15% lifetime chance of PN malignant transformation, necessitating continuous and vigilant surveillance.[16–18]

Treatment for PN is currently limited. Surgical intervention, either total or subtotal resection, is the most effective option; however, given the size or location of the PN, it may be technically impossible or confer unacceptable post-operative debility.[2,17] In 2020, the mitogen-activated protein kinase (Mek) inhibitor selumetinib became the first FDA approved drug to treat pediatric NF1-associated inoperable PN.[19] Further research conducted on both children and adults has shown that selumetinib can decrease the overall burden of spinal plexiform neurofibromas.[20,21] Additionally, it often, but not always, alleviates symptoms of disfigurement and associated pain, occasionally even without reducing the tumor size.[17] Of note, selumetinib must be taken on an empty stomach and results in a disfiguring acneiform rash and diarrhea

in the majority of patients. Time to onset of action is 4–6 months. For these reasons, Mek inhibitors should be discussed in conjunction with the possibility of surgery to determine the best individualized treatment plan according to the QOL goals of the patient.

PN sarcomatous transformation may occur through the accumulation of additional mutations resulting in a direct pathway to MPNST, or in a stepwise fashion via an intermediate grade tumor first defined in 2016 as an atypical neurofibromatosis neoplasm of uncertain biologic potential (ANNUBP). The distinction between MPNST and ANNUBP is significant, as ANNUBP bears a lower risk of post-resection recurrence and metastasis.[17]

Malignant Peripheral Nerve Sheath Tumors (MPNST)

MPNST tumors in NF1 always originate in pre-existing PN and primarily affect 20–40-year-old patients[22] although they can occur at any time of life. The risk of MPNST is greater in those with a positive family history in a first degree relative, after prior radiation exposure, or de novo after treatment of a previously diagnosed MPNST.[17] The current prognosis of MPNST is poor, with only approximately a 50% 5-year survival rate, and a median overall survival (mOS) of around 48 months from initial diagnosis.[17,23] mOS is further reduced for inoperable tumors and tumors with metastases at diagnosed (to 11 and 12 months, respectively).[17]

Given that MPNSTs are both radio- and chemo-insensitive, gross total resection with margins is required for any chance at a cure. Even when this is accomplished; however, local and distant recurrence is common via seeding of the operative bed and hematologic dissemination. Radiation is frequently offered following resection, but efficacy evidence is limited, and its use must also be weighed against a risk of secondary malignancy, especially in patients with a strong likelihood of long-time survival.[17]

Cutaneous Neurofibromas (CN)

CN are one of the cardinal clinical manifestations of NF1. These skin tumors are believed to originate from small cutaneous nerves and/or hair bulge cells, and form discrete, rubbery, pedunculated, or sessile nodules in the dermis that are frequently eumelanotic or erythematous.[17] Subcutaneous neurofibromas (SCN) exhibit indistinct borders and often appear violaceous. These tumors do not manifest until late childhood or early adolescence when they begin to surface most commonly on the trunk, arms, and face. They have limited growth potential and typically remain smaller than 2 cm in diameter. However, they can cause discomfort, itching, and visible disfigurement, and some may grow to much larger size. The potential for malignant transformation in CN and SCN is almost nonexistent. The only effective methods to eliminate these tumors involve physical removal or destruction through surgical resection (ensuring complete removal of the dermal moiety), CO2 laser ablation, electrodessication, or more contemporary methods such as erbium-doped yttrium aluminum garnet laser and neodymium-doped yttrium aluminum garnet laser photocoagulation.[24–26]

Gliomas

NF1 incurs a susceptibility to optic pathway gliomas (OPG) and brain stem gliomas, most frequently pilocytic astrocytomas.[27–29] Approximately two-thirds of these tumors belong to the OPG category. OPG are World Health Organization (WHO) grade I astrocytic tumors[27] that almost always remain fully benign, but which can lead to blindness or other symptoms associated with tumor location. NF1-associated OPG are observed in 15–20% of patients, often manifesting within the initial 5 years of life, and frequently requiring no intervention due to spontaneous regression with age.[17,30–32] Children diagnosed with these tumors have a 5-year overall survival rate ranging between 75–80%. For up to two-thirds of individuals with NF1-associated OPG, there is minimal tumor progression followed by spontaneous regression, leading to the preservation or restoration of vision. The remaining patients may suffer from vision impairment and/or endocrine disturbances due to compression of the pituitary stalk by tumors in the optic chiasm.[17,30] It is advisable to conduct annual ophthalmologic examinations from the time of NF1 diagnosis until the age of 8–10, and subsequently, bi-annually until 18 years old to monitor for the presence of OPG. Adults with no history of OPG have little to no risk of later tumor development.

For treatment, surgery can lead to permanent neurological damage[30] and is only recommended in patients with progressive vision loss. Chemotherapy, usually carboplatin with vincristine, is commonly recommended.[33] Radiation is avoided, if possible, as it leads to a 3-fold increased risk of secondary malignancy.[2] Conservative watch-and-wait

approaches to treatment can risk tumor spread across the optic chiasm resulting in bilateral vision loss. If necessary, early exenteration prior to chiasmal involvement would be preferable for a definitive cure and for ensuring vision retention in the contralateral eye. This could further decrease a patient's quality of life. NF1 patients, too, have a 50-fold increased risk of developing a high-grade glioma, typically in adulthood.[34] Studies have indicated the beneficial use of MEK inhibitors in the treatment of OPG. One shows significant radiographic improvement of OPG in a patient with known NF1 following a year-long MEK monotherapy treatment. Another, after demonstrating that MEK/ERK signaling pathways are largely responsible for neurofibromin regulation of mTOR activity, finds that sustained MEK inhibition can suppress OPG proliferation in addition to lessen retinal ganglion cell death in vivo.[35,36]

Non-Nervous System NF1-Related Tumors

Leukemia

Patients with NF1 face a 3–7x increased risk of chronic myeloid leukemia, juvenile myelomonocytic leukemia, acute lymphocytic leukemia, and non-Hodgkin lymphoma. The prognosis and treatment options for these hematologic tumors are the same as in the general population.[2]

Breast Cancer

A 5-fold increase in the risk of developing breast cancer has been recorded in patients with NF1 younger than 50 years-old.[37,38] The mOS for women with NF1 and breast cancer is 5 years—significantly lower than the mOS for breast cancer patients in the normal population of 20 years. 64% of patients with both breast cancer and NF1 die prior to 50 years of age.[37] Early mammography in NF1 patients is therefore universally recommended, however, while some sources indicate a starting age of 40, others ideally begin screening at 30 with the inclusion of supplemental breast screening MRI from the ages of 30–50.[39] While it was initially thought that treatment for NF1 patients with breast cancer should not differ from treatment of the general population,[2] a recent study shows that NF1 confers a poorer prognosis in hormone receptor +/human epidermal growth factor receptor 2- breast cancer (the most aggressive phenotype). Loss of NF1 indicates a shorter time to recurrence in these patients, usually as a result of endocrine therapy resistance. This resistance usually occurs through both Estrogen Receptor (ER) dependent and independent mechanisms, frequently with MAPK pathway-driven expression of cyclin D1 and S-phase entry.[40]

Gastrointestinal Stromal Tumors (GIST)

GIST are the most common gastrointestinal tumors in NF1 patients with a prevalence of 5–25% in the NF1 population,[41,42] and in addition, 1.5% of all diagnosed GISTs are associated with NF1.[43] NF1-associated GISTs are typically multiple, small, and located in the small intestine.[44] They have low mitotic activity and a relatively benign growth pattern.[43] Their presence should not be underestimated, as they can cause significant symptoms such as abdominal pain, bleeding, intestinal perforation, and intestinal obstruction. Treatment options include surgical resection for localized disease, or neoadjuvant tyrosine kinase inhibitors prior to resection for advanced disease.[45–47] One difference between sporadic and NF1-associated GIST is that in NF1 patients, GIST do not respond well to imatinib. This indicates that an NF1 mutation is the driving force of tumorigenesis rather than KIT mutations in sporadic GIST.[45]

Pheochromocytomas and/or Paragangliomas

Pheochromocytomas and Paragangliomas (PCC/PGL) are rare neuroendocrine tumors that develop from chromaffin cells of the adrenal medulla (PCC) and the chromaffin cells of the autonomic nervous system ganglia (PGL).[48] Previous studies have suggested that 0.1–5.7% of NF1 cases are complicated by PCC, compared to a prevalence of 0.002–0.008% in the general population.[2,49] Approximately 30% of PCC/PGL are associated with germline genetic mutations, including NF1.[50] Key symptoms of this tumor include unprovoked flushing, sweating, headaches, and heart palpitations,[2] and signs include rapid spikes in blood pressure sometimes causing malignant hypertension. Identification of PCC/PGL in NF1 patients can be accomplished through abdominal MRI ± contrast and measurements of serum and 24 hour urine catecholamines.[51] Surgical resection is the primary treatment for localized lesions and can be approached using minimally invasive procedures rather than traditional open field surgery.[52] Metastatic and recurrent PCC/PGL can be treated with targeted therapies. Tyrosine kinase inhibitors, such as sunitinib, axitinib, and cabozantinib have been used,

and therapies in development are focused around the hypoxia-associated signal pathway, which is associated with the cluster 1 genes of PCC/PGL.[53–56]

Duodenal Carcinoids

Duodenal carcinoids in NF1 patients occur with an incidence of ~1%. Duodenal carcinoids are distinctive glandular somatostatin-rich carcinoids that occur in the periampullary region of the duodenum.[57] Therefore, afflicted patients may present with jaundice and non-specific abdominal pain.[58,59] Diagnosis of carcinoid tumors can be made through imaging studies and measurement of urinary and serum 5-hydroxyindoleacetic acid and chromogranin A.[60] Treatment options include surgery for localized lesions, which may require gross total resection of the duodenum depending on the size of the tumor, or use of somatostatin analogs (eg octreotide), which can slow the production of hormones, gastric acid, and other secretions.[61,62]

Rhabdomyosarcomas

Rhabdomyosarcoma (RMS) is a type of cancer that forms in soft tissue, specifically skeletal muscle tissue or sometimes hollow organs such as the bladder or uterus. Children with NF1 present with a 20-fold increased risk of developing these tumors. Often, they present as palpable masses. Surgical resection, chemotherapy, and/or radiation therapy can be used as possible treatment options for rhabdomyosarcoma.[2,63] The exact incidence of RMS in patients diagnosed with NF1 is not well understood due to its rarity, however one study shows that up to 25% of NF1 patients develop intra-abdominal tumors, which include RMS amongst other tumor types.[64] Following treatment, lifelong monitoring by an oncologist is recommended for surveillance of possible secondary neoplasm induced by chemotherapy or radiation.

Abnormalities in Pigmentation

Café-Au-Lait Macules

These are usually the earliest clinical manifestations of NF1, typically developing within the first two years of life. Café-au-lait macules have no malignant potential but can impact QOL depending on their extent and which body regions are affected. In these cases, topical bleaching ointment could be provided for cosmetic reasons.[2,65]

Axillary and Inguinal Freckling

This type of freckling is usually detected by the age of 5–8 years and is a major diagnostic finding in NF1 patients.[65]

Lisch Nodules

Lisch nodules are tiny hamartomas on the iris of the eye. After puberty, they are present in nearly all patients with NF1. Identification requires slit-lamp examination by an ophthalmologist to detect 3-dimensional protrusion that can distinguish Lisch nodules from benign pigmentation of the iris.[66] These lesions do not cause visual impairments or any other medical issues.[67]

Skeletal Deformities

NF1 can affect the bones and cause a wide range of osseous and skeletal manifestations contributing to physical deformity, pain, and dysfunction. These include macrocephaly, short stature, sphenoid wing dysplasia, scoliosis (which may be dystrophic), congenital pseudoarthrosis of the long bones, increased fracture risk, osteoporosis, osseous lesions and malformations, and tibial dysplasia.[68,69] Lifestyle modifications such as an increase in exercise or supplementation with vitamin D might provide some alleviation from skeletal deformities associated with NF1; however, when bony anomalies affect social and motor development, referral to a pediatric orthopedic surgeon is favorable to avoid additional decline in quality of life.[2] Treatment for congenital long bone pseudoarthrosis associated with NF1 is mainly surgical involving bone grafting following resection of the diseased tissue. Amputation is indicated following the inefficacy of two or more primary surgical interventions, the manifestation of gross deformities affecting the leg and ankle, significant limb length disparity, recurrent fractures, and the attainment of a nonfunctional limb subsequent to unsuccessful reconstructive procedures.[70]

Cardiovascular and Neurovascular Complications

NF1-related cardiovascular complications affect up to 27% of NF1 patients. Conditions include congenital heart defects, hypertension, endothelial vasculopathy, arteriosclerosis, and aneurysms.[2,71,72] Common congenital heart and vessel defects seen in NF1 patients include pulmonary stenosis, aortic coarctation, mitral valve prolapse, and atrial septal defect. The incidence of congenital heart defects in NF1 patients as 10 times higher than the general population, thus strongly warranting early diagnosis by a cardiologist to avoid future hemodynamic consequences.[73,74] Moyamoya syndrome (MMS), the most prevalent type of NF1-associated cerebral vasculopathy is developed in 2–6% of children with NF1 and can be a driving force leading to ischemic and hemorrhagic stroke. Recent studies have shed light on the impact of cerebral vasculopathy on the outcome and quality of life of patients with NF1. In particular, it has been found that in patients with MMS, the occurrence risk of Moyamoya does not appear to be modified by susceptibility gene RNF213. Instead, the loss of neurofibromin 1, the protein encoded by the NF1 gene, is likely responsible for the excessive proliferation of vascular smooth muscle cells, eventually causing arterial stenosis (i).[75] Furthermore, it has been suggested that Selumetinib, a drug used for treating severe NF1-related tumors, may interfere with cerebral neovascularization in patients with MMS requiring surgical revascularization.[76] In terms of surgical management, there has been indication that patients with a positive overall prognosis and initial cerebrovascular disease could benefit from prophylactic surgical revascularization to prevent cognitive impairment due to the progression of vasculopathy.[77] Lastly, it has been found that the spatial coefficient of variation of arterial spin labeling cerebral blood flow (ASL-CoV) may contribute to predict surgical outcomes in pediatric MMS patients undergoing encephalo-duro-arterio-myo-synangiosis (EDAMS).[78] These findings underscore the importance of understanding the unique challenges and considerations in managing NF1-associated cerebral vasculopathy. However, as our understanding of NF1 and moyamoya disease continues to evolve, future studies are needed to further refine these strategies and improve patient outcomes.

Frequent neuroimaging is recommended for management of MMS, and surgical revascularization can be an option in children experiencing ischemic stroke symptoms.[75] A study further cites cardiovascular disease as a frequent cause of premature death in individuals with NF1.[79] Therefore, regular check-ups and monitoring with a cardiologist are essential for managing these complications as they arise throughout an NF1 patient's life.

Neurocognitive Deficits

Neurocognitive deficits are extremely common in patients with NF1 (up to 80%). Manifestations include cognitive and behavioral deficits such as autism, attention deficit and/or hyperactivity disorders (ADHD), depression, learning disabilities (particularly spatio-motor) which can impact academic performance and subsequent career opportunities. Specialists in pediatric neuropsychology, neurology, and psychiatry are crucial in managing mental health symptoms associated with NF1.[80,81]

The General Role of Multidisciplinary Care

Multidisciplinary care is a collaborative approach wherein professionals from different disciplines work together to deliver comprehensive patient care. This approach is particularly relevant in managing complex conditions like NF1, which affect multiple organ systems and therefore require input from various medical specialties. The core function of a multidisciplinary team (MDT) is to bring together a group of healthcare professionals from different fields to determine patients' treatment plans. Most comprehensive NF clinics are currently led by NF experts working within and along MDTs that include specialists from surgical, medical, and psychological/psychiatric fields.[82]

Components of a NF1 Multidisciplinary Care Team

The MDT often includes physicians and advanced practice providers from many disciplines, as well as supportive medical professionals such as therapists/social workers, case managers, child-life experts, nutritionists, physical and occupational therapists, and speech therapists. The overall team is led by an NF specialist who can coordinate the diverse aspects of care and ensure that the patients' needs are met in a holistic manner (Figure 1).[83] This section will break down the various components making up the MDT by subspecialty and specific role in the care team.

Geneticists play a crucial role in diagnosing NF1 by providing genetic counseling and advising on disease severity based on point mutations vs microdeletions,[84,85] as well as drawing up family trees and providing recommendations for testing of family members.

Radiologists (pediatric and adult; nuclear medicine, body/musculoskeletal, and neurologic) are collaborative partners in detecting whole body tumor burden, identifying volumetric changes that may herald malignant conversion of a plexiform neurofibroma, identifying MPNST metastases, and diagnosing other more rare tumors. Regular surveillance imaging is indicated for patients with known PN or MPNST, at a frequency determined by disease severity.[86,87]

Primary Care Physicians including Pediatricians are the most frequent diagnosticians and in areas that are underserved by comprehensive NF clinics, and they may be solely responsible for administering the recommended workup as patients age. Pediatricians convey important facts to parents about developmental expectations, tumor signs and symptoms to be vigilant for, and NF society resources and/or summer camps.[88] They may be the first to identify symptoms of optic pathway glioma, including a white reflex, or sphenoid wing dysplasia or facial PN. Primary care doctors and advanced practice providers refer patients to speech, occupational, and physical therapists who can mediate neurocognitive delays and social workers or psychologists to help patients deal with psychological distress stemming from primary disease manifestations or social anxiety linked to stigmata of disease.

Ophthalmologists might assist in diagnosing NF1 by identifying iridial (Lisch nodules) and retinal hamartomas using a slit lamp exam that requires specialized equipment and which is not routinely performed alongside basic eye examinations. Children with NF1 < 10 years of age should have an annual screening with an ophthalmologist to monitor for signs of OPG.[89,90]

Neurologists monitor neurological symptoms including pain, weakness, and numbness which can be treated symptomatically but which may also signal tumor growth. They also manage complications such as seizures, headaches, and neuropathy,[91] and perform peripheral nerve ultrasound, electroencephalography, and electromyography/needle studies. Similar to primary care, neurologists frequently find themselves managing NF1 patient longitudinal care.

Oncologists including neuro-oncologists, when not NF1 experts, are usually involved in patient care after diagnosis of MPNST, PCC/PGL, GIST, breast cancer, etc. These are typically the physicians to order pharmacotherapy with targeted Mek inhibition, other TKI inhibition, or chemotherapy, as indicated.[92]

Cardiologists may be involved in managing cardiovascular complications associated with NF1, particularly congenital malformations which may require intervention.[93] The ages at which cardiovascular complications arise in NF1 patients vary, but for those that present with cerebral or arterial vasculopathy or congenital heart defects, early diagnosis and lifetime follow up may be required.[73,75]

Dermatologists who are familiar with NF1 are highly sought after, as resection technique is important in preventing new and recurrent CN growth. Dermatologists perform surgical resection, laser ablation, electrodessication, or biopsy of cutaneous manifestations of NF1 including CALM, CN and SCN, either under general or local anesthesia.[17] They also manage glomus tumors.

Neurosurgeons resect brain, spinal cord, nerve root, plexiform, or peripheral nerve tumors associated with NF1.[94]

Orthopedic Surgeons determine when to surgically intervene on skeletal abnormalities such as scoliosis, pseudoarthrosis, limb length discrepancy, or radial or tibial dysplasia that occur with higher incidence in NF1.[95]

Plastic Surgeons, Ear Nose and Throat Doctors, and General Surgeons may also resect cutaneous and subcutaneous tumors. When performed under general anesthesia, many more tumors can be resected, but post-operative pain can be extensive. Many patients with NF1 are afflicted with large and visible plexiform neurofibromas that need to be reduced/debulked on multiple occasions for medical and cosmetic reasons.[26]

Neuropsychologists assess cognitive function and help patients develop coping strategies to deal with cognitive challenges associated with NF1 such as autism, ADHD, and learning disabilities.[96]

Psychiatrists/Psychologists/Therapists should meet with all adolescents and teens with NF1, and many adults living with the emotional burden of a chronic tumor predisposition syndrome.[96]

Social workers assist with coordinating care, navigating insurance issues, and connecting patients with NF1 community resources.[97] Given economic challenges facing individuals who have a high incidence of apparent physical deformities, low IQ, or neurocognitive abnormalities, social workers can be a lifeline linking patients with their NF doctor.

Physical, Occupational, and Speech Therapists can improve strength, dexterity, and the ability to perform the activities of daily life (ADLs) during recovery from major surgery, amputation for pseudoarthrosis, or deconditioning related to chronic pain or physical impediments.[98,99] Speech therapy is recommended more for NF1 patients than the general population to address speech and language difficulties that may arise due to cranial nerve dysfunction.[100]

The management of NF1 requires a multidisciplinary approach involving various medical specialties (Figure 2). There is a clear benefit of this team being led by an NF specialist in that this ensures diverse aspects of the patient's care are coordinated effectively. They possess the expertise necessary to understand the complexities of every facet of NF care and are responsible for sharing their nuanced knowledge to their subspecialist referrals, which could vary on case by case basis.[83] A designated NF clinic, therefore, serves the patient as a "home-base" and a portal for access to multidisciplinary care, making coordination far more seamless for both patient and provider (Figure 1).

NF1-Adjacent Syndromes

NF1 is diagnosed clinically and shares many features with overlapping conditions such as Noonan Syndrome and Legius Syndrome,[101] which are also autosomal hereditary disorders characterized by hyperpigmented café au lait macules and Crowe's Sign (freckling of the axilla and inguina).[102]

Noonan Syndrome (NS) is a heterogenous autosomal dominant genetic disorder characterized by café au lait macules, intellectual delay (particularly language deficits) and physical features such as short stature, distinctive facial features (low-set posteriorly rotated ears, blue-green irises, widely spaced down-slanted palpebral fissures/epicanthal folds and ptosis, broad/webbed neck, widely spaced nipples, undescended testes/cryptorchidism, lymphedema of the lungs/intestines/legs, congenital cardiovascular abnormalities (large vessel/cardiac valvular stenosis, hypertrophic cardiomyopathy, septal defects, Tetralogy of Fallot), and increased risk of leukemia and glioma. Features of NF1 and NS may overlap, although if a pathologic mutation is identified, it is likely to clarify the diagnosis. The etiology of NS is a heterozygous pathogenic variant in genes of the RAS/mitogen-activated protein kinase (MAPK) pathway[103] including BRAF, RAS, MAP2K1, PTPN11, RAF1, RASA2/ RRAS2, RIT1, SOS1/2 or LZTR1.

Legius Syndrome (LS) is a distinct benign disorder caused by a SPRED1 mutation resulting in multiple café-au-lait macules and skinfold freckling but no additional features of NF1. LS confers no additional risk of tumor growth. The detection of multiple café-au-lait macules with or without freckling and no other manifestations of NF1, these two conditions can only be definitively differentiated based on genetics.[102] Misdiagnosis of NF1 in the actual presence of a related syndrome can result in improperly recommended surveillance imaging and/or labs that can be financially and emotionally detrimental to the patient.

NF1 microdeletion syndrome is a subtype of NF1 found in ~4% of all NF1 patients caused by a large deletion of the NF1 gene and its flanking regions that is associated with a more severe NF1. Patients with NF1 deletions exhibit more severe clinical manifestations including facial dysmorphic features, overgrowth, severe global developmental delay, severe autism, and considerably reduced cognition.[104] Genes co-deleted with NF1 are likely to be modifiers responsible for this severe disease phenotype.[105]

Discussion

The management NF1 presents a unique set of challenges due to the complex nature of the disease, which affects multiple organ systems and manifests in a wide range of symptoms. The use of a multidisciplinary approach to NF1 care, led by an NF expert, has emerged as an effective strategy to address these challenges.

The MDT brings together healthcare professionals from many specialties, each contributing their unique expertise to provide comprehensive care for NF1 patients. This collaborative approach ensures that all aspects of the patient's health are considered and addressed, from physical symptoms to psychological impacts. It allows for the development of personalized treatment plans that consider the individual patient's needs and circumstances (Figure 2).

While the multidisciplinary approach to NF1 care has been recognized and given significant validation in previous publications,[106,107] it is crucial to highlight the often overlooked role of the NF expert. The role of the NF expert in guiding and informing the MDT is indispensable for the seamless orchestration of this multidisciplinary care. As a specialist in NF1, the NF expert has a deep understanding of the disease and stays up to date with the latest research

and advancements in treatment strategies. This expertise guides the team's decision-making process and ensures that patients receive the most current and effective care. If sufficient cases are seen, a multidisciplinary NF tumor board can be started, with input from surgery, radiology, NF, oncology, pathology, and others.

The multidisciplinary approach benefits not only patients but also educates and builds trust amongst physicians thereby fostering a collaborative environment that facilitates knowledge sharing and outcomes learning amongst healthcare professionals. The implementation of this approach is not without its challenges. Financially, hospital income will be divided between different services, which may make it difficult to justify the cost of running an NF center underneath a single specialty department. It requires a willingness to collaborate on a challenging patient population using effective communication and coordination among team members. Acquiring support from healthcare institutions is challenging, but the benefits of the multidisciplinary approach in managing NF1 are clear, and with a detailed business plan, many institutions can be shown the economic as well as the academic benefits.

Conclusion

In conclusion, it is imperative to underscore that the management of NF1 is most effectively undertaken through the utilization of an MDT, ideally spearheaded by an expert in NF. Future research should focus on optimizing this model by determining which key roles can be adopted by other specialties when resources are lacking, exploring ways to enhance communication and coordination within the MDT, and evaluating its effectiveness in different settings. The potential benefits of this approach in managing other tumor predisposition syndromes could also be explored. In summary, the multidisciplinary approach to NF1 care, directed by an NF expert, represents a significant advancement in the management of this complex and lifelong condition. It provides the best chance to enhance the quality of life for NF1 patients and pave the way for further improvements in patient care. NF1 clinics are financially justifiable for academic hospitals due to the many varied imaging, laboratory and specialist consultations recommended for excellent care of these patients. However, for institutions in which different Departments are held independently financially distinct, justification for allocating such resources should focus on the overall benefit to the institution as a whole, including financial, prestige, and patient care benefits.

Disclosure

The authors report no conflicts of interest in this work.

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