NEUROFIBROMATOSIS TYPE 1: CLINICAL CHARACTERISTICS, DIAGNOSIS AND MANAGEMENT

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Abstract

Neurofibromatosis type 1 (*NF1*) is caused by *NF1* gene pathogenic variants that are either inherited in an autosomal dominant pattern or occur *de novo*. Both the peripheral and the central nervous system are commonly affected in *NF1*, with neurofibromas, nerve sheath tumors, and optic pathway gliomas being the most prominent features. This nervous system involvement leads to heterogeneous clinical manifestations, including affective, cognitive, and behavioral problems, visual disturbances, sensory and motor deficits, and epilepsy. Other common manifestations of *NF1* concern the skin (café-au-lait macules, axillary freckling and dermal neurofibromas), the eye (Lisch nodules) and the skeleton (scoliosis, other bone abnormalities). Diagnosis rests largely on the clinical picture, following recently revised diagnostic criteria, and often entails the use of MRIs or other imaging techniques. Lately, confirmation of the diagnosis of *NF1* is increasingly pursued through genetic testing. Management of the disease has been symptomatic and occasionally surgical, with removal of tumors that cause functional or other type of disability. Advances in the understanding of the molecular pathophysiology of the disease, including the elucidation of the mechanism of the *NF1* gene-mediated suppression of tumorigenesis, have led to the development of targeted molecular therapies. Despite the advent of these novel diagnostic and therapeutic approaches, the mainstay of management is still based on high suspicion for the disease, even in the absence of family history, to enable early detection and accurate diagnosis. This timely diagnosis of *NF1* should be followed by a multidisciplinary approach targeting the multiple facets of this challenging disease.

Key words: neurofibromatosis type 1, *NF1* gene, neurofibromas, café au lait macules, optic pathway glioma

INTRODUCTION

Neurofibromatosis type 1 (*NF1*) is one of the most common neurogenetic disorders and the most common of the neurofibromatoses, a group of disorders that also includes neurofibromatosis type 2, and schwannomatosis [1, 2]. *NF1* invariably affects the central and the peripheral nervous system, but also other organs, including the skin and the bones, with the clinical manifestations of the disease being highly heterogeneous. It is a multisystemic genetic condition with high risk of benign and malignant tumor development, leading to significant morbidity and mortality.

Historically, there have been accounts of patients possibly affected by *NF1* dating several centuries ago [3]. However, Friedrich Daniel von Recklinghausen was the first to give a comprehensive description of a patient and coined the term "neurofibroma" in 1882; thus the disease came to bear his name [3]. More than a century had to pass before the formulation of the first widely adopted clinical criteria for the disease in 1987 [4] and the identification of the *NF1* gene where *NF1*-causing variants reside in 1990 [5-8]. Three decades later, advances in understanding of the molecular pathophysiology of the disease have led to targeted therapeutic options. These new treatment approaches have rekindled the interest of neurologists and other specialists to *NF1*. The purpose of this review is to offer an update on the developments in the field and better equip the general neurologist and other clinicians for early detection, accurate diagnosis, and effective management of patients with *NF1*.

GENETICS AND PATHOPHYSIOLOGY

The cause of *NF1* are germline loss-of-function pathogenic variants in the *NF1* gene, a large tumor-suppressor gene residing on chromosome 17q11.2, spanning 61 exons and generating several alternatively spliced transcripts [9, 10]. The *NF1* gene encodes a large (> 2,800 amino acids long) cytoplasmic protein called neurofibromin 1. This protein is found in various tissues, with high levels observed in the nervous system. Neurofibromin acts as regulator of RAS, a signaling protein that is primarily found in an inactivated (GDP-bound) form. Its activated (GTP-

bound) form regulates multiple cellular targets and promotes cell proliferation and survival. Neurofibromin inhibits activated RAS by enhancing hydrolysis of the RAS-bound GTP [9] and this translates to decreased cell proliferation and survival. In patients with *NF1*, dysfunctional neurofibromin encoded by an *NF1* gene carrying loss-of-function pathogenic variants fails to properly modulate RAS, which becomes hyperactivated and promotes cellular proliferation and tumorigenesis. RAS effects are mediated by various signaling cascades, such as the MEK-ERK and PI3K/AKT pathways [9]. Downstream, these two pathways activate, among others, the mammalian target of rapamycin (mTOR) and the mitogen-activated protein kinase (MAPK) pathway [11, 12].

Interestingly, approximately one out of two cases of *NF1* is caused by a *de novo* mutation, namely a mutation not present in the parents [11]. The other half of *NF1* cases result from autosomal dominant inheritance of the disease trait. There are two types of *NF1*, termed generalized (or non-segmental) and segmental (or mosaic). The latter is a rare form of *NF1* that involves only part of the body, mostly unilateral, due to a genetic variant emerging during post-fertilization embryogenesis [11]. If the variant emerges at the initial stages of embryonic development, the phenotype resembles generalized neurofibromatosis [10]. Patients with segmental *NF1* display a milder phenotype, account for one-twelfth of total *NF1* patients and have a low probability of passing the pathogenic variant to their off-springs [13].

In at least some patients with single heterozygous germline pathogenic variants in one copy of the *NF1* gene, affected cells from tissue biopsies display an additional loss-of-function variant in the second *NF1* gene copy. This is compatible with the "two-hit" theory, with the "first hit" being the parental germline *NF1* gene pathogenic variant and the "second hit" brought about from an additional mutational event disrupting the other wild-type allele in a specific somatic cell. This additional mutational event could be either a *de novo* loss-of-function variant or even deletion of the entire wild-type allele, with this process termed loss of heterozygosity [9]. Since the site and time of the second hit is highly unpredictable, the "two hit" theory explains the heterogeneity of the clinical picture of *NF1*, even among relatives, and the difficulty to perform genotype-phenotype correlations. Among the few genotype-phenotype correlations described thus far is the severe phenotype, with malignant peripheral nerve sheath tumors and learning disabilities, caused by germline deletion of the entire *NF1* gene [10].

EPIDEMIOLOGY

NF1 is one of the most common neurogenetic disorders with a prevalence approximately 1 in 2,000 to 6,000 people worldwide, with varying estimates among various countries [14]. These differences in prevalence, if not attributed to different methodologies used for prevalence estimation, may relate to founder effects or factors that affect the *de novo* mutation rate in the *NF1* gene [11]. To better interpret the various prevalence rates in different countries, one should take into account that NF1 leads to an 8-25-year reduction of life expectancy compared to the general population, which is mainly due to the increased rate of malignancies in these patients [14-16].

CLINICAL MANIFESTATIONS

Patients with *NF1* display a variety of symptoms and signs, predominantly related to the skin, the nervous system, and the bones, with onset at a young age [17]. Regardless of the rich phenotypic variability of the disease that often makes accurate diagnosis challenging, there are some common clinical features shared by most patients. Based on these features, the 1987 National Institutes of Health (NIH) Consensus Development Conference formulated diagnostic criteria for *NF1* [4]. These criteria dictate that for the diagnosis of *NF1* to be justified, two or more of the following manifestations should be present: 1) six or more cafe-au-lait macules in the skin (greater than 5mm in pre-pubertal individuals or 15mm in post-pubertal individuals), 2) axillary or inguinal freckling, 3) neurofibroma (two or more of any type, or one plexiform neurofibroma), 4) optic glioma, 5) distinctive osseous lesion (such as dysplasia of the sphenoid bone), 6) two or more Lisch nodules (iris hamartomas), 7) a first-degree relative with *NF1*. Even though these criteria show rather high sensitivity and specificity, there are not always optimal, especially in children that have not developed yet several of the *NF1*-associated clinical manifestations [18]. Having this in mind and following the advances on the understanding of the disease pathogenesis and the improvement of diagnostic methods, an update on the 1987 NIH diagnostic criteria has been published in 2021 [19, 20]. This update includes 1) the presence of two or more choroidal abnormalities (defined as bright, patchy nodules imaged by optical coherence tomography or near-infrared reflectance imaging) as an alternative to the Lisch nodules, 2) the extension of the optic glioma criterion to cover all the visual pathway tumors, 3) the addition of tibial dysplasia or pseudarthrosis of a long bone on the distinctive osseous lesions criterion, 4) the modification of the family history criterion to the presence of a parent with *NF1*, 5) the inclusion of a heterozygous *NF1* gene pathogenic variant with an allele fraction of 50% in apparently unaffected tissue, such as white blood cells, as an additional criterion.

NEUROLOGICAL CLINICAL MANIFESTATIONS

Neurodevelopmental abnormalities

For decades limited attention was paid to the neurodevelopmental manifestations of *NF1*; these are increasingly recognized in recent years and are nowadays considered among the most common features of the disease [21]. Even though children with *NF1* rarely score under the 70 IQ limit defining intellectual disability, they often score at the lower end of the population norms. Also, neurodevelopmental abnormalities are common in children with *NF1* and include impairment in general cognition, cognitive processing, learning (such as in reading, writing, and mathematics), executive function and visuospatial abilities [21]. Two common forms of neurodevelopmental disorders, attention-deficit-hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have been recognized in *NF1* patients. Specifically, for ASD, it has been rather recently recognized as a feature of *NF1*, even though clinicians have long been reporting social difficulties of children with *NF1.* Finally, patients with *NF1* are at increased risk for anxiety, depression, and sleep disturbances. How *NF1* gene pathogenic variant- related neuronal dysfunction leads to neuropsychiatric disturbances is a matter of study. Regardless of this, early recognition of neuropsychiatric symptoms in children with *NF1* is imperative for effective management.

Neurological neoplastic disease

Neurofibroma, a benign tumor emerging from the nerves sheath of peripheral nerves, is the hallmark of *NF1* (Figure 1A, 2). In histological sections of neurofibromas, fibroblasts, blood vessels, perineural cells, mast cells and Schwann cells are found [22]. Neurofibromas are categorized in different subtypes, depending on the location they arise and other features: cutaneous, subcutaneous, spinal, paraspinal, plexiform and atypical [23]. Cutaneous neurofibromas, the most common form of neurofibroma, are well defined elastic masses that derive from the nerves of the skin. Subcutaneous neurofibromas arise underneath the epidermal layer, have not well-defined texture, and are often diagnosed with palpation. With advancing age, both cutaneous and subcutaneous neurofibromas increase in size and quantity, with an accelerated rate on adolescence and pregnancy. Neurofibromas forming near the spine (paraspinal) or rarely in the spine (spinal), even though benign, can lead to scoliosis, spinal deformities, and spinal cord and root compression due to their space-occupying character [24]. Plexiform neurofibromas are complex tumors that involve multiples nerves. They commonly occur at birth and grow faster that other forms of neurofibromas. They are frequently found in the head and neck and occasionally in deep body regions, with variable manifestations, from asymptomatic presentation to severe clinical picture involving pain, disfigurement, local compression, and neurological deficits. Finally, atypical neurofibromas are characterized by hypercellularity with atypical nuclei, even though they have only few mitoses and no necrotic areas. Atypical neurofibromas and plexiform neurofibromas have a high rate of evolving into malignant peripheral nerve sheath tumor (MPNST). MPNST is a type of aggressive soft tissue sarcoma, occurring in 8-16% of patientσ with *NF1* and carrying a bad prognosis, since most patients have distal metastases at the time of diagnosis [25]. Risk factors for developing MPNST include, among others, large subcutaneous neurofibroma burden, presence of atypical neurofibroma, younger age and positive family history of MPNST [25].

Optic pathway glioma (OPG) is one of the most common tumorous manifestations of *NF1* [25, 26]. OPG is classified as astrocytoma, but it can also include oligodendrocytes, neurons, and microglia. It can form outside the orbit, everywhere in the optic nerve pathway and occasionally, it affects areas outside the optic nerve pathway, mainly the brainstem. It occurs approximately at 5-25% of patients with *NF1*, most commonly at a young age [26]. Even though OPG is characterized as a benign tumor and remains asymptomatic for years, it can in the long run affect vision and endocrine function and occasionally undergo malignant transformation, with poor outcome. Besides OPG, another, less common, CNS tumor in patients with *NF1* is brainstem glioma, including glioblastoma.

Epilepsy and other central nervous system manifestations

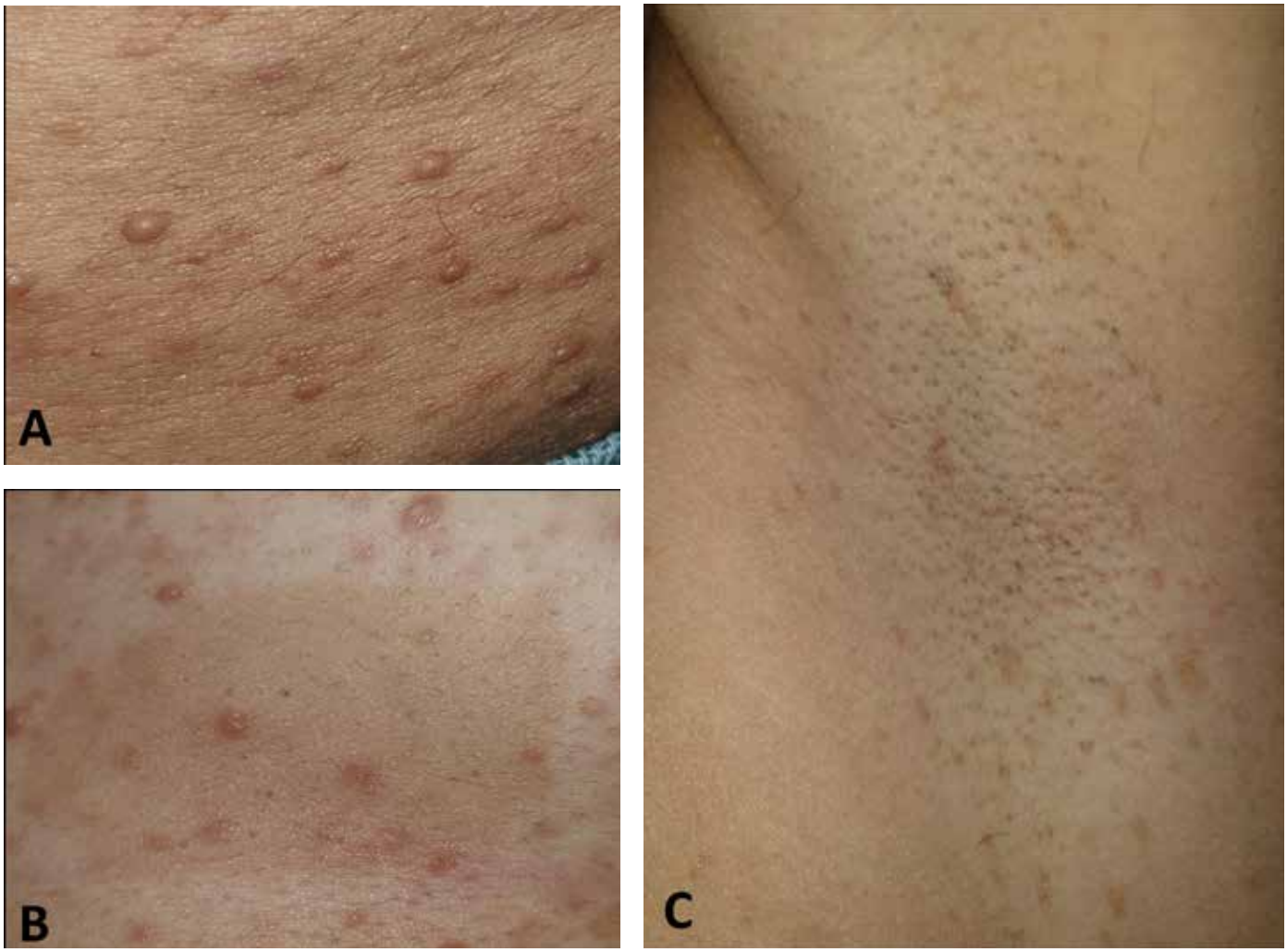
Epilepsy is commonly found in patients with *NF1* (with a prevalence of 4-14%), and includes focal epilepsy (associated with brain tumors, mesial temporal sclerosis, and cortical dysplasia) and primary generalized epilepsy [27-29]. Localization-related epilepsy in patients with *NF1* is often drug-resistant and occasionally may need epilepsy surgery for the seizures to resolve. Additionally, headache, hydrocephalus, cerebrovascular disease, and unidentified bright objects (UBOs) in MRI imaging are few of the many neurological abnormalities that have been occasionally observed in patients with *NF1* [29, 30].

NON-NEUROLOGICAL CLINICAL MANIFESTATIONS

Skin lesions

Apart from the neurofibromas described above, pigmentary abnormalities are another typical feature of *NF1* observed on the skin. The predominant skin indicator of *NF1*, the café-au-lait macules (CALMs), are frequently the first sign that clinicians and the

Figure 1. **Typical skin manifestations of *NF1***. In this figure, the skin hallmarks of NF1, namely Café au lait macule (A), neurofibromas (B) and axillary freckling (C) are shown in a 32-year-old female patient. Informed consent from the patient was obtained for publication of this image



family notes (Figure 1B, 2). These flat hyperpigmented macules with clear boundaries are observed in 95-99% of *NF1* patients and are included in the clinical criteria of *NF1* [22]. CALMs typically appear during infancy in *NF1* patients and are found all over the body except for the feet, hands, eyebrows, and scalp. It should be noted that CALMs are not always associated with *NF1*, especially if they are isolated or have irregular boundaries and non-uniform pigmentation (atypical CALMs) [31].

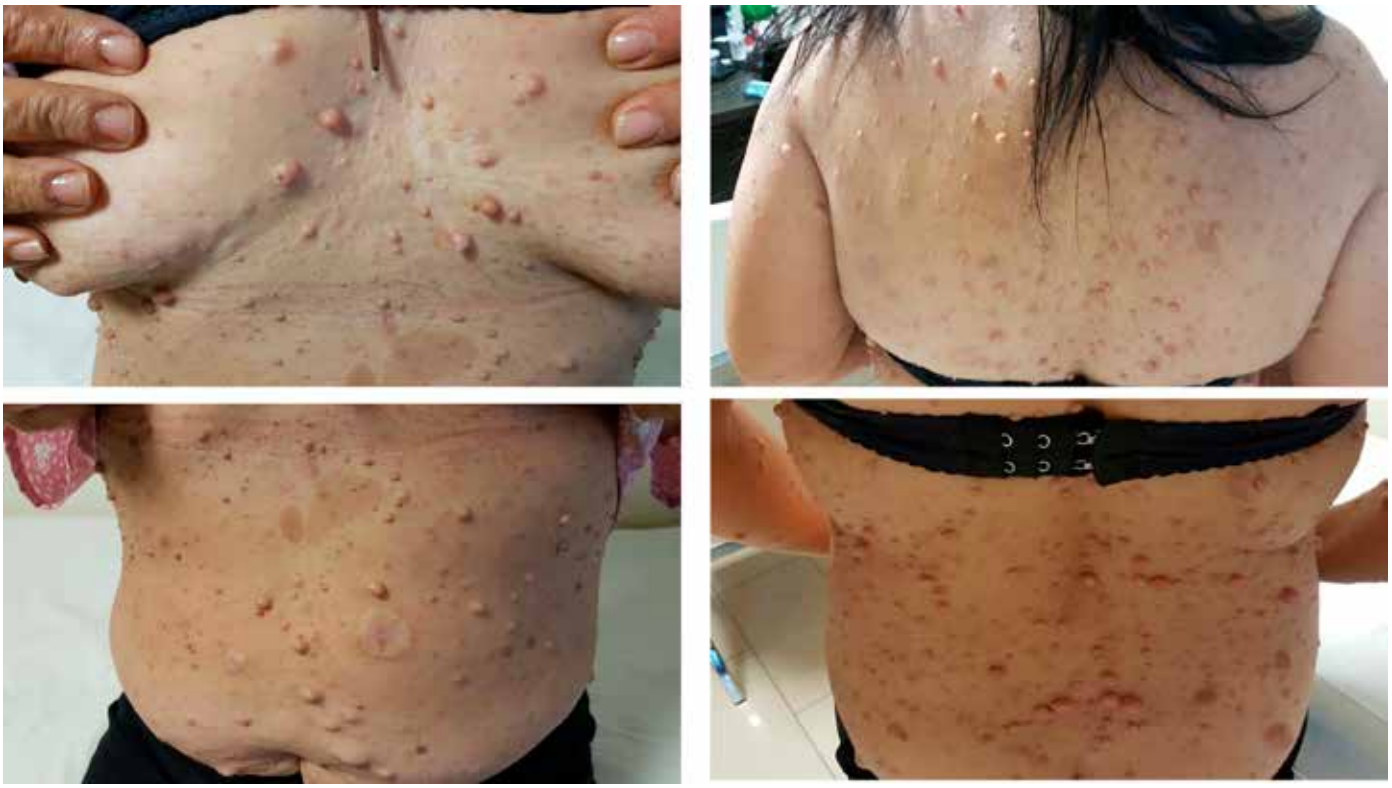
Skinfold freckling, historically called Crown sign from the physician Frank Crowe who described it in 1964, consists of pigmentary skin lesions found in most patients and included in the clinical criteria of *NF1* (Figure 1C) [22]. These skin lesions are small, light brown in color, with onset in a very young age and gradual development until adulthood. Interestingly, they are formed on the axillae or inguinal areas and not on areas exposed to sunlight [22].

In addition to neurofibromas, CALMS and skinfold freckling, patients with *NF1* display several other cutaneous signs, even though at lower frequency [22]. These additional skin manifestations include lipomas (encapsulated bulks of fat cells), nevus anemicus (pale skin area with sharp margins), nevus spilus (skin patches with multiple dark macules), juvenile xanthogranuloma (benign orange papules or nodules), vitiligo (macular skin depigmentation, an immune-mediated condition), Becker nevus (skin hamartoma with hyperpigmented, hypertrichotic lesions), poliosis circumscripta (patch of white hairs) and melanoma [18, 22].

Ocular involvement

Lisch nodules, described in 1937 by Karl Lisch, are among the most common clinical manifestations of *NF1*, along with CALMs and freckling, and are simi-

Figure 2. **Typical skin manifestations of *NF1***. The skin hallmarks of NF1, namely Café au lait macules and multiple neurofibromas are shown in the trunk of a 49-year-old female patient. Informed consent from the patient was obtained for publication of this image.



larly included in the diagnostic criteria for *NF1*. These nodules are in essence a melanocytic hamartoma of the anterior iris surface [32]. Even though prevalence is low in children, they are present in virtually all adult patients over 21 years old. They have a benign course and they usually do not cause vision or other impairment. The main clinical significance of Lisch nodules is their diagnostic value for *NF1* [26, 32]. Other less frequent ocular conditions associated with *NF1* include glaucoma, choroidal abnormalities, and, rarely, retinal involvement [26].

Bone abnormalities

Bone abnormalities in patients with *NF1* are commonly present since early childhood [33]. Osteopenia resulting from dysfunction of osteoclasts and osteoblasts, and bone dysplasia are among the main bone manifestations of *NF1* [24]. The resulting bone deformities severely affect the quality of life of these patients and commonly involve the spine, resulting in scoliosis in 10-26% individuals with *NF1*. Scoliosis in patients with *NF1* can be categorized further to dystrophic and non-dystrophic. Non-dystrophic scoliosis shares common feature with idiopathic scoliosis. In contrast, dystrophic scoliosis is characterized by short-segment and sharply angulated curves and is less frequent in *NF1* patients [24]. In addition to the spine, bone dystrophy can also affect the long bones. These skeletal abnormalities predispose to pseudarthrosis, sphenoid wing (defective orbital plate and frontal bone), congenital thoracic deformities, and congenital tibial dysplasia (bowing of the lower leg). Skeletal involvement in *NF1* often leads to neuropathic pain and neurological symptoms ranging from mild paresthesia to severe motor deficits. The low levels of vitamin D frequently found in patients with *NF1* are thought to contribute to the bone mineralization disorder and the high frequency of fractures.

Cardiovascular manifestations

Several cardiovascular abnormalities have been reported to be associated with *NF1* [34]. Hypertension is the most common one, usually characterized as essential but occasionally occurring in the context of pheochromocytoma or renal artery stenosis. Other cardiovascular problems found in patients with *NF1* are vasculopathies, such as stenotic or occlusive arteries, aneurysms, arteriovenous fistulas and moyamoya syndrome [1, 35].

Non-neurological neoplastic disease

The presence of mutated tumor-suppressor *NF1* gene, causing impairment of the function of neurofibromin, predisposes to tumorigenesis not only in the nervous system but also in other tissues. For instance, individuals with *NF1* have increased likelihood to develop leukemia compared to the general population. Types of leukemia found in these patients include juvenile myelomonocytic leukemia or chronic myelomonocytic leukemia [36, 37]. Pheochromocytoma, another neuroendocrine tumor associated with *NF1* [38], mostly presents with episodic hypertension accompanied by sweating and flushing. Occasionally, distant metastases are found at the time of the diagnosis. Breast carcinoma is more common in *NF1* patients under 50 years old compared to the general population [39], with increased frequency of triple-negative and human epidermal growth factor receptor 2 (HER2)-positive subtypes. Part of the *NF1* phenotype is the development of small, benign, tumors from the glomus bodies, called glomus tumors. Sarcomas are also found in patients with *NF1*, including rhabdomyosarcomas and gastrointestinal stromal tumors, with the latter causing abdominal pain, bleeding, and intestinal obstruction. Finally, other non-nervous tissue tumors possibly associated with *NF1* are gastrointestinal well-differentiated neuroendocrine carcinomas and malignant melanomas [23, 35].

DIAGNOSIS OF *NF1*

The diagnosis of *NF1* is largely based on clinical evaluation and use of published clinical criteria. One of the most important parts of the clinical examination of patients possibly affected with *NF1* is the evaluation of the skin, for identification of CALMs, skinfold freckling and neurofibromas. Of note, CALMs in children should be 6 or more to be considered as an *NF1* sign. In addition to the clinical examination, neurofibromas are also evaluated with magnetic resolution imaging (MRI), especially in the presence of new or deteriorating neurological symptoms, to assess possible involvement of nerves or other structures and to exclude malignant transformation [40, 41]. In the case of a plexiform neurofibroma possibly evolving to MPNST, functional MRI and positron emission tomography (PET) scans can assist in the recognition of malignant transformation [40].

Specific neurological manifestations of *NF1* may need more targeted investigation. In cases of epilepsy, electroencephalograms, and a brain MRI, preferably with contrast material administration, should be performed. Brain MRI could reveal areas of high signal in T2 sequences, called neurofibromatosis bright objects (NBOs) [42]. These NBOs are characteristic findings of *NF1* and tend to reduce with advancing age [43]. Brain MRIs are also useful to detect OPGs, tumors in the cerebral hemispheres and mesial temporal sclerosis. In addition to MRI scans, emerging evidence shows the potential of PET CT in the evaluation, monitoring and therapeutic management of *NF1* patients with tumors, especially MPNSTs. Even though imaging can identify the lesions associated with *NF1*, in several cases it cannot determine the underlying pathology. In cases of accessible lesions, MRI-guided or CT-guided biopsy is used to obtain specific histological diagnosis, the gold standard in differentiating benign from malignant tumors.

Given the increasingly recognized occurrence of *NF1*-associated neurodevelopmental abnormalities and the potential benefit of available interventions if initiated early, any sign of delay in child development regarding language and other cognitive functions or social interaction, should be detected as early as possible [21]. Parents of these patients and primary care clinicians should be aware of those manifestations and refer the child to an expert for evaluation.

Investigation of the eye manifestations of *NF1* is most often performed by an ophthalmologist, evaluating visual acuity, color vision and visual fields, along with a slit-lamp examination for anatomic assessment of the eye and identification of Lisch nodules in the iris [26]. In cases of an abnormal initial screening examination, the possibility of optic pathway glioma and other central nervous systems gliomas and tumors should be further investigated, most often with MRI of the orbits and brain. Even though most clinicians suggest performing MRI scans only when there are abnormal ocular signs or symptoms, there are some advocates of including brain and orbit MRIs in the annual monitoring of *NF1* patients.

Skeletal abnormalities, especially in children, should be assessed annually. This assessment should include evaluation for spine deformities and blood screening for vitamin D deficiency [24]. If there are indications of skeletal abnormalities, imaging of the spine and other bones with X-rays or other modalities, DEXA screening for osteoporosis and pulmonary function testing, should be performed.

In case of hypertension and other cardiovascular disorders, patients with *NF1* should receive the standard of care, but often CT angiography of renal arteries and additional tests may be needed to better characterize the cardiovascular phenotype [1, 34]. In case of drug resistant hypertension, clinicians should consider the possibility of pheochromocytoma.

Women, especially between 30 to 50 years old, should undergo regular mammogram examination and if needed breast MRI, due to the high breast cancer rate in individuals with *NF1* [25].

Genetic testing, despite not considered essential for diagnosis in the past, has gained popularity in

recent years, especially given the decreasing cost of the next generation sequencing methods. Genetic testing is especially useful to diagnose the disease in individuals that don't fulfill all the clinical criteria for *NF1* or in young children with negative family history that have not yet expressed the full *NF1* phenotype. Early diagnosis achieved through genetic testing can help guide proper management, provide better understanding of the natural history of the disease, enable genotype/phenotype correlations and provide the basis for genetic counseling [44].

MANAGEMENT OF *NF1*

Even though there is no definite cure for NF1, accumulating knowledge in recent years, based on *in vitro* and *in vivo* research in animal models, as well as results of clinical studies, has provided tools to better manage the disease and improve the quality of life of *NF1* patients.

Pigmental manifestation (CALMs, freckling) and cutaneous neurofibromas that cause severe esthetic problems, can be removed if deemed necessary by the patient and the attending physician. Subcutaneous, spinal and paraspinal neurofibromas often cause neuropathic pain and motor and sensory impairment that require medical attention and treatment by surgical resection or removal by other means such as laser or electrocautery [45]. Likewise, for plexiform neurofibromas that cause symptoms or display potential to develop to MPNSTs, surgical resection is needed. However, for neurofibromas that are close to nerves or vital organs and body structures, surgical removal can be challenging. Beyond surgical management, several medical treatment approaches including sirolimus, an inhibitor of the mTOR pathway, tipifarnib, a RAS signaling inhibitor, imatinib, a tyrosine kinase inhibitor, and interferons have been tried with mixed results [46]. However, additional hope has emerged with the promising results of selumetinib [47, 48], an inhibitor of the mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). Selumetinib has recently earned FDA and EMA approval for use in patients with inoperable plexiform neurofibromas [49, 50]. Fortunately, most individuals carrying a plexiform neurofibroma don't require surgical or medical treatment, with annual monitoring being the standard of care. In case of a neurofibroma evolving to MPNST or if a MPNST is found independently from neurofibromas, aggressive management should be pursued. This includes resection of the affected area with wide surgical margins and, if needed, radiotherapy. Chemotherapy is a last resort option in cases of MPNSTs that are locally advanced or have given metastasis.

OPG, even if in most patients with *NF1* is a benign, low-grade pilocytic astrocytoma, in some cases visual problems or signs of malignant transformation can emerge. For these patients, treatment is needed in an emergency basis. Due to the complex anatomical location of OPG that hinders surgical removal, first line therapy is chemotherapy. Adjunctive radiotherapy is usually avoided due to the potential risk of local complications, secondary malignancies, and risk of neurocognitive disturbances. As in the case of plexiform neurofibromas, recent studies have shown potential benefits from the use selumetinib for OPGs [51]. For the other rare brain tumors in NF1 patients besides OPGs, surgical removal with adjunctive chemotherapy and radiotherapy can be performed, depending on the specific tumor type and location. In women with breast cancer or patients with leukemia and lymphoma, standard clinical care should be applied.

For the *NF1* associated bone abnormalities, management is dictated by the specific skeletal disorder and ideally should be offered by a specialized orthopedic surgeon [33]. Spinal and other bone abnormalities caused by bone dysplasia in children should be treated with bracing from a young age, with surgical stabilization of the spine and other bones reserved only for extreme disabling bone abnormalities. Supplementation with vitamin D could be given in cases of osteoporosis associated with vitamin D deficiency. For the less prominent manifestations of NF1, such as hypertension and other cardiovascular disorders, if they are not associated with a tumor, standard medical treatment should be provided. However, if the cause of hypertension is a pheochromocytoma, surgery is the first line option.

As in other neurogenetic disorders, there has been intensive research in the development of genetic treatments for *NF1*, that promise to change the natural history of the disease [46]. Among the techniques currently being investigated are genome editing, replacement of the mutated *NF1* gene with a full length normal *NF1* gene, and engineering of transcription activator-like effector protein to increase transcription of the wild-type *NF1* allele.

CONCLUSION

NF1 is a complex neurocutaneous hereditary disorder affecting multiple tissues and displaying large clinical heterogeneity. Despite the benign nature of most of its manifestations, *NF1* can be associated with significant morbidity and mortality. The cause of *NF1* are loss-of-function pathogenic variants in the *NF1* gene, which encodes a dysfunctional neurofibromin protein that fails to inactivate the RAS and other pathways. This failure causes unregulated cellular proliferation with multiple pathophysiological consequences, including benign and malignant tumors. Abnormalities on the skin, the eyes and the

nervous system are the cardinal clinical manifestations of the disease; however, the spine and other bones, the cardiovascular system and several other tissues are often affected. Diagnosis remains essentially clinical, following recently revised diagnostic criteria. In addition, novel diagnostic modalities, such as MRI, PET, MRI or CT-guided biopsies and improved genetic testing methods are increasingly used for faster and more accurate diagnosis. This timely diagnosis enables earlier and thus more effective initiation of specific lesion-targeted management. Furthermore, better understanding of the pathophysiology of *NF1* has led to the development of ground-breaking genetic and other molecular therapeutic approaches that hopefully will improve the quality of life of patients with *NF1.*

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