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A review Neurofibromatosis Type 1: Quality of Life of Children and Adolescents

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Abstract

Neurofibromatosis 1 (NF1) is a rare disease with worldwide impact. It is also known as von Recklinghausen disease and is an autosomal dominant condition caused by mutations of the NF1 gene, which is located at chromosome 17q11.2. NF1 is believed to be completely penetrant, but substantial variability in the expression of features occurs. Diagnosis of NF1 is based on established clinical criteria. The presentation of many of the clinical features is age-dependent. The average life expectancy of patients with NF1 is probably reduced by 10–15 years, and malignancy is the most common cause of death and there is no treatment found yet for NF1. The prevalence of clinically diagnosed NF1 ranges from 1/2,000 to 1/5,000 in most population-based studies. A wide variety of NF1 mutations has been found in patients with NF1, but no frequently recurring mutation has been identified. Most studies have not found an obvious relation between particular NF1 mutations and the resulting clinical manifestations. The variability of the NF1 phenotype, even in individuals with the same NF1 gene mutation, suggests that other factors are involved in determining the clinical manifestations, but the nature of these factors has not yet been determined. Laboratory testing for NF1 mutations is difficult.

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Contents

1 Introduction

The "Neurofibromatosis" are a set of distinct genetic disorders that have in common the occurrence of tumors of the nerve sheath. Neurofibromatosis type 1 is caused by mutations in NF1, the gene coding for neurofibromin 1, a negative regulator of the Ras signal transduction pathway that has a role in both tumor suppression and regulation of cell growth and proliferation (Santos & Pereira, 2022).
There are three types of neurofibromatosis:
Neurofibromatosis 1(NF1): is an autosomal dominant condition with complete penetrance and variable expressivity. The incidence at birth is 1:2.000–3.000 individuals among the general population (Clementi et al., 1990; Friedman, 1999; Kallionpää et al., 2018; Lammert et al., 2005) accounting for as many as 96% of cases.
Neurofibromatosis 2(NF2): is characterized by the occurrence of bilateral vestibular schwannomas, along with multiple other tumors, including other schwannomas of cranial and peripheral nerves, meningiomas, and ependymomas. The frequency of NF2 is estimated to be 1 in 25.000 and it occurs in 3% of the cases. It is an autosomal dominant trait with a high rate of new mutation and complete penetrance (Korf, 2013).
Schwannomatosis: is the most recent addition to the list of the types of neurofibromatosis. It is characterized by the occurrence of multiple schwannomas without other associated features. It is an autosomal dominant trait with incomplete penetrance, variable expression, and a high rate of new mutation. Its occurrence is rarer and more poorly understood(Korf, 2013).

2 History

The earliest examples of neurofibromatosis (in this case type 1, NF1) can be traced in the Ebers Papyrus (Ancient Egypt, 1.500 B.C.), in a Hellenistic statuette (Smyrna, 323 B.C.), in the coinage of the Parthians kings (247 B.C.) and some 13th-century monks' drawings. These earlier examples are somewhat less well defined as compared to the most recent better-defined reports credited as having NF1 including an Inca child mummy (1480—1650 AD), Ulisse Aldrovandi's homuncio ("Monstrorum Historia", 1592 A.D.) with mosaic NF1 or the illustrations seen in the 18th century "Buffon's Histoire Naturelle" and "Cruveilhier's Anatomie Pathologique du Corps Human". The first English language report on NF1 was made by Akenside in 1768 and the first

systematic review was by Robert William Smith in 1849, while Virchow's pupil, Friedrich Daniel von Recklinghausen, in 1882, was the first to understand the origin of skin tumors and to name them neurofibromas. The touching story of Joseph C. Merrick {the "Elephant man," (who had Proteus syndrome and not NF1)}, in 1884, played an important role in the later misconception of NF1, as did the novel by Victor Hugo on the hunchback Quasimodo. The studies by van der Hoeve (1921), Yakovlev & Guthrie (1931), and Van Bogaert (1935), categorized "von Recklinghausen's" neurofibromatosis among the phakomatoses and the neurocutaneous syndromes. The first known mention of an acoustic neuroma (at autopsy) is attributed to Eduard Sandifort (1777 AD) while John H. Wishart made the earliest autoptic description of neurofibromatosis type 2 (NF2), in 1822, in a 21-year-old man with bilateral acoustic neuromas, who manifested signs since his infancy (Wishart subtype NF2).

Smith likely described the first case of schwannomatosis in 1849. Older, Virchow, von Recklinghausen, and Verocay first classified "neuromas" and Masson and Penfield first used the word "schwannoma" taking it from Theodore Schwann's works. In 1903 Henneberg and Koch described NF2 in detail. Young, Eldridge, and Gardner, in the late '70, established NF2 as a distinct familial entity (Gardner subtype NF2). Schwannomatosis, the late entry of the different forms of neurofibromatosis, was credited in the middle of '90 (Ruggieri et al., 2018).

3 Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) encodes neurofibromin, a ubiquitous protein mainly expressed in neurons, Schwann cells, and glial cells (Clementi et al., 1990; Friedman, 1999; Kallionpää et al., 2018; Lammert et al., 2005; Tonsgard, 2006; Reviron-Rabec et al., 2016; Júnior et al., 2019; Arazi-Kleinmann et al., 2002) and is a genetic condition that exposed to multisystemic disorder since it may involve nervous, skeletal, cardiovascular, and endocrine systems, and may present an unpredictable phenotype, age-dependent appearance of key features, and very few genotype-phenotype correlations found to date and an increased oncogenic risk. NF1 can be sporadic or familial depending on whether the NF1 variant is de novo or inherited from an affected parent. In about 50% of cases, it is caused by de novo mutations in NF1 on chromosome 17q11.2. It is due to heterozygous pathogenetic variants in the homonym gene codifying for the ubiquitous protein neurofibromin which is a negative regulator of the RAS/MAPkinase pathway (Legius et al., 2021).

4 Diagnosis

The criteria for the diagnosis of NF1 were established by the National Institutes of Health (NIH) Consensus Conference in 1988.[9] The diagnosis of NF-1 is based on the presence of two or more of the following seven criteria, determined by the clinical evaluation and family history of the patient: six or more café-au-lait spots, diameter > 5 mm before puberty and > 15 mm after puberty, two or more neurofibromas of any type or one plexiform neurofibroma, axillary freckling, two or more iris hamartomas (Lisch nodules), optic glioma, typical bone lesions (sphenoid dysplasia or tibial pseudarthrosis), and one or more first-degree relatives with NF1. These diagnostic criteria were defined in 1987 by the United States National Institutes of Health and have been proven to be strong and reliable, as they have stood well over time (National Institutes of Health, 1988; Nalepa & Wolnicka, 2012; Ferner et al., 2007; Boyd et al., 2009). However, during early childhood, the diagnosis of NF1 based on the clinical criteria may not be possible. Many NF1-associated features are age-dependent. The first symptoms are generally CALM which may be present at birth or occur in the first year of life and until 4 years old, often in the absence of other disease features (Legius et al., 2021). Another problem is that the 1988 clinical diagnostic criteria for NF1 are not specific if children exhibit only CALM and skin-fold freckling. Until then, neither a definite diagnosis of NF1 nor the differential diagnosis of other RASopathies, including Legius syndrome, or the constitutional mismatch repair deficiency (CMMRD) is possible. Also, because cancer is present at an early stage, it may facilitate the diagnosis of NF1 in children with isolated CALM who do not meet the 1988 clinical diagnostic criteria. Therefore, CA has been included in the revised criteria for the diagnosis of NF1 (Legius et al., 2021). The revised diagnostic criteria for NF1 were published

recently as an international consensus recommendation (Richards et al., 2015). They include the detection of a pathogenic variant in the NF1 gene as a diagnostic criterion which allows for an early diagnosis of NF1 in oligosymptomatic children without a family history of the disease.

The revised diagnostic criteria for NF1 also include choroidal anomalies as a new ophthalmic symptom with high sensitivity and specificity for NF1 which may facilitate the diagnosis of NF1 particularly in young oligosymptomatic children. Mutational and molecular analyses help confirm the clinical diagnosis of NF1, notably in patients with paucisymptomatic forms: segmental forms in pediatric cases (café-au-lait spots are often the only clinical findings in young children) and Legius syndrome. Such analyses are also useful for prenatal diagnosis. However, genetic testing is not routinely recommended to establish the diagnosis in the daily clinical care of patients with typical NF1, and consultation with medical specialists is advised before the test is performed (Ferner et al., 2007; Boyd et al., 2009; Kehrer-Sawatzki et al., 2022). One limitation of genetic testing is the lack of genotype-phenotype correlation. Therefore, although useful for diagnostic confirmation, a positive test result cannot be used to predict the severity or outcome of the disease (Ferner et al., 2007; Boyd et al., 2009).

5 Symptoms

These are the most common symptoms that appear in neurofibromatosis:

Café-au-lait spots (CALM)

The brown spots (café au lait) are symmetrical oval-shaped lesions that are the same color in each patient. The brown spots are multiple and they are located mainly on the trunk and in the inguinal and axillary regions, characteristically leaving some areas free such as the palms, the soles, the scalp and eyebrows. If there are more than 6 CALM or any larger than 1.5 cm are common fibroepithelial skin lesions. Despite the very high frequency of occurrence in NF1, they are not a pathognomonic sign of the disease as they are observed in some other pathological conditions while in a percentage of the order of 10% occur in perfectly healthy individuals. Pathologically, the CALMs are characterized by the presence within its melanocyte's epidermis, giant cell elements called macromelanosomes. Their number is increased in NF1 patients compared to healthy people.

Axillary and inguinal freckles
Axillary and inguinal freckles are generally 1–3 mm in diameter and appear as tiny brown spots, often in groups. In contrast to CALM, these freckles become apparent later in childhood (Legius et al., 2021).

Lisch nodules

Lisch nodules are benign hamartomas of the iris. Isolated Lisch nodules are very rarely seen in individuals from the general population. By contrast, the vast majority of adult NF1 patients have multiple Lisch nodules. Hence, Lisch nodules are a highly specific diagnostic criterion. It has been shown that light irises harbor significantly more Lisch nodules than dark irises which may be explicable in terms of the photo-protective effects of pigmentation. Furthermore, Lisch nodules are primarily located in the inferior hemifield (half) of the iris, irrespective of its color. These findings suggest that UV radiation and DNA damage may play a role in the pathogenesis of Lisch nodules (Legius et al., 2021).

Choroidal anomalies

Choroidal anomalies appear as ovoid, bright patches or nodules consisting of proliferating Schwann cells and melanocytes arranged in concentric rings around axons. Fundus examination utilizing near-infrared reflectance with a scanning laser ophthalmoscope (NIR) and ocular coherence tomography (OCT) have indicated that choroidal anomalies are frequent in patients with NF1. These lesions are asymptomatic and not detectable by conventional ophthalmoscopy or fluorescein angiography. The presence and number of

choroidal anomalies (CA) is age-dependent. Their prevalence is lower in children with NF1 than in adults with the disease (Legius et al., 2021).

Cancer (CA)

CA appears to be as frequent as, or even more frequent than, Lisch nodules in children with NF1. Most importantly, CA can be detected in children as young as 2 years of age. By contrast, in many children with NF1, Lisch nodules appear only later, around the age of 3–5 years.

Plexiform neurofibromas and optic pathway gliomas

Plexiform neurofibromas (PNFs) are congenital lesions characterized by tumor cells that spread along multiple fascicles of the nerve, leading to a diffuse mass of thickened nerve fibers embedded within a proteinaceous matrix. PNFs may be located superficially and/or internally and hence only detectable by MRI scans, particularly in young children. Optic pathway gliomas (OPGs) are low-grade astrocytomas observed in 14–20% of patients with NF1 as determined by neuroimaging. NF1-associated OPGs are most often diagnosed during childhood. Visual acuity, strabismus, exophthalmos and proptosis are the most common symptoms caused by these tumors (Legius et al., 2021).

Long-bone dysplasia

Long-bone dysplasia, seen in 5% of patients with NF1 typically involves the tibia and frequently presents with anterolateral bowing that may progress to fracture. In addition to the tibia, fibula, radius and ulna are also potential sites of dysplasia even though less common (Legius et al., 2021).

Sphenoid wing dysplasia

Unilateral dysplasia of the greater wing of the sphenoid bone is one of the most distinctive craniofacial lesions in NF1. Sphenoid wing dysplasia (SWD) is congenital but becomes clinically apparent later in life, frequently before the age of 2 years. SWD can be asymptomatic and is diagnosed by skull radiographs or CT scans. SWD may become progressive and cause disruption of the orbit and consequent pulsating exophthalmos. Abnormal growth of the skull associated with sphenoid wing lesions in children with NF1 may also lead to progressive facial deformities (Legius et al., 2021).

Genetic testing in NF1

New in the revised version of the diagnostic criteria is the inclusion of the detection of a pathogenic NF1 gene variant as a separate diagnostic criterion. Variants identified in the NF1 gene are classified as pathogenic according to the guidelines developed by the American College of Medical Genetics and Genomics, the Association for Molecular Pathology and the College of American Pathologists (Mirzaa et al., 1993). The NF1 gene is relatively large, encompassing ~ 350 kb and 55 constitutive exons as well as five alternatively spliced exons. NF1 encodes neurofibromin, a multifunctional protein with at least 6 different functional domains involved in the regulation of various signalling pathways (Legius et al., 2021). More than 3600 different pathogenic NF1 variants have now been reported by The Human Gene Mutation Database.

These are located across the gene coding regions as well as within the introns thereby interfering with the splicing process (Legius et al., 2021). Whilst some 31 different pathogenic NF1 variants exhibit a prevalence of ≥ 0.5% among NF1 patients, it has been estimated that approximately 46% of NF1 patients carry extremely rare or private pathogenic NF1 gene variants (Legius et al., 2021). In addition, copy number variants of single and multiple NF1 exons have been identified, as well as deletions spanning the entire NF1 gene which are observed in 5–11% of all NF1 patients (Legius et al., 2021).

Cognitive difficulties

Cognitive problems are the most common neurological complications in individuals with NF1. Severe intellectual disability with an intellectual quotient < 70 (mental retardation) is rare and only slightly more frequent than in the general population (Hirsch et al., 2001; Ferner et al., 2007). Epilepsy occurs in approximately 6–7% of individuals with NF1 (Ferner et al., 2007).

6 Treatment

Treatment for NF1 is symptomatic, like most genetic diseases. Surgical treatment of diffuse or large plexiform neurofibromas is possible but may be associated with damage to involved nerves or adjacent tissues and stimulate the growth of residual tumor. Complete surgical excision, when possible, of malignant peripheral nerve sheath tumors is the treatment of choice. Moreover, chemotherapy may be beneficial in some individuals. Treatment of optic gliomas is generally unnecessary as they are usually asymptomatic and clinically stable. Dystrophic scoliosis often requires surgical management, whereas no dystrophic scoliosis can usually be treated conservatively. Individualized developmental and educational interventions may be beneficial, and methylphenidate treatment often benefits individuals with attention-deficit/hyperactivity disorder (Wang et al., 2022).

Cutaneous neurofibromas are benign and do not require removal unless they are symptomatic. Rapid growth, particularly in a subcutaneous or plexiform neurofibroma, may mandate biopsy or excision, as that may signify malignant degeneration. Surgical excision, laser, and electrocautery have been commonly employed. However, surgical resection is often difficult because neurofibromas lack a well-defined capsule and demonstrate high tumor vascularity. Tumor recurrence is more common in patients younger than 10 years of age and those with incomplete surgical resection. For individuals with a high number of cutaneous neurofibromas, excision may not be feasible. Carbon dioxide laser treatment under general anaesthetic has been proposed for small to medium-sized neurofibromas. One drawback to carbon dioxide ablation is the development of depigmented, atrophic scars. Interestingly, in the setting of MPNSTs, adjuvant radiation is occasionally provided to reduce the risk of local recurrence and as a limb-salvaging strategy. Adjuvant chemotherapy has a role in advanced or metastatic disease, but prognosis remains poor even with treatment. Optic pathway gliomas (OPGs) are the most common type of gliomas in NF1, generally asymptomatic, and are treated with carboplatin (with or without vincristine) chemotherapy, for progressive OPGs. Radiation is typically avoided due to the increased risk of inducing malignancy or moya vasculopathy in the exposed field. Surgical treatment is usually reserved for cosmetic palliation in a blind eye. Children with NF1 & low-grade progressive gliomas (most of which were OPG) had better survival with carboplatin & vincristine than children without NF1 who had similar tumors.

Targeted Genetic Treatment

Sirolimus, an immunosuppressant, has been successfully used to delay PN progression and decrease associated pain. This drug inhibits the mTOR pathway, which is commonly implicated in tumor growth in NF1. Sirolimus is generally well-tolerated. Tipifarnib, blocks RAS signalling by inhibiting farnesylation of RAS, thus downregulating this pro-oncogenic pathway. While it does not prevent PN progression, tipifarnib improves the emotional domain of quality of life compared to placebo, perhaps by acting on hippocampal neurons. Pirfenidone, an inhibitor of fibroblasts, has also been shown to inhibit disease progression with the most common side effect of gastrointestinal discomfort. However, it does not cause tumor regression. The use of pegylated interferons due to their antiproliferative and antiangiogenic properties has been shown to induce tumor regression and decrease pain levels. Imatinib, a tyrosine kinase inhibitor, has also been used for PNs. In contrast to sirolimus, this drug may result in tumor regression, with a median reduction of 26.5% in tumor volume, in addition to halting tumor progression. However, use is limited by side effects, including edema, skin rash, pain, weight gain, aminotransferase elevation, and neutropenia. Direct tyrosinase inhibitors, such as kojic acid, have been suggested to target the hyperpigmentation and CALMs in NF1. Other genetic pathway

inhibitors include MEK inhibitor PD032059 and PKA-cAMP pathway inhibitor HA1004. More established treatments for CALMs include pulsed radiofrequency and topical vitamin D3. In addition, as vitamin D levels tend to be significantly lower in NF1 patients, the use of ultraviolet B irradiation has been proposed to increase vitamin D levels and potentially reduce hyperpigmentation (Doser et al., 2022).

Manifestation/Concern Treatment Considerations/Other Plexiform neurofibromas

Assess size, extent and monitor growth with MRI. Monitor for pain, neurologic deficit and/or tumor growth, which suggests MPNST. Exam by MRI, PET, or PET/CT when MPNST is suspected, but a definitive diagnosis of MPNST requires a biopsy. Selumetinib, a MEK inhibitor, is FDA-approved for the treatment of NF1-related inoperable plexiform neurofibromas. Surgical removal of small superficial plexiform neurofibromas may be possible. Surgical treatment of larger tumors is often unsatisfactory because of involvement with nerves and tendency to grow back. Radiotherapy is contra indicated due to risk of inducing MPNST.

Malignant peripheral nerve sheath tumors (MPNST)

Management per surgical and/or medical oncologists familiar with NF1. Complete surgical excision, when possible, is the only treatment that offers the possibility of a cure. Adjuvant chemotherapy or radiotherapy may be helpful in some cases. Treatments for MPNST involving MEK inhibitors, immunotherapy and/or radiation therapy are currently being evaluated in clinical trials. Brain tumors monitoring by brain MRI and brain stem and cerebellar gliomas in those with NF1 are usually less aggressive than in persons without NF1. Avoid radiation therapy, as MPNST or other gliomas may develop during treatment. Transformation of a pilocytic astrocytoma to a more malignant brain tumor may occur after radiation therapy in persons with NF1.

Breast cancer
Although more aggressive breast cancer is reported in NF1, women with NF1 should be treated in the same manner as others with similar pathology and tumor markers. Avoiding radiotherapy, if possible, is reasonable.

Pain
Depends on the nature, severity and degree to which it interferes with everyday activities. It is empiric and similar to that in those without NF1. Persons with intractable pain that interferes with everyday activities despite conventional treatment should be referred to a pain specialist.

Dystrophic scoliosis
Management per orthopedist and spine specialist with experience in the treatment of NF1. Often requires surgical management, which may be complex and difficult. Nondystrophic Scoliosis is treated similarly to that of idiopathic scoliosis.

Osteopenia /Recurrent fractures
Vitamin D & calcium supplementation to reduce the risk of developing osteoporosis. Bisphosphonate treatment of osteoporosis may be helpful. Hypovitaminosis D is common in persons with NF1 of all ages.

Hypertension
Treatment per nephrologist and/or cardiologist based on the cause of hypertension.

7 Quality of Life

The World Health Organization (WHO) defines QoL as a multidimensional construct, comprising domains such as physical, social, emotional, and role functioning. Health-related Quality of Life (HRQoL) reflects the impact of disease and treatment on QoL. Improving the quality of life (QoL) of our patients is an essential objective for all physicians and health workers. This objective is even more important in patients with rare

disorders as they must frequently deal with ignorance and incomprehension. There is a difference in the quality of life between women and men. Individuals with NF1 were less likely to form a marital or cohabiting relationship contributing to knowledge of the social challenges that individuals with NF1 may face, including loneliness and social dysfunction. The probability of becoming pregnant was similar for women with and without NF1, but women with NF1 had an increased risk of spontaneous abortions and stillbirths. Other studies have observed an increased risk for pregnancy complications in women with NF1, but have not investigated the pregnancy outcomes.

There is also reported a lower educational level in individuals with NF1, which has later been confirmed in a population-based Finnish cohort study. We found that adults with NF1 had an impaired QoL and a high need for professional support for both physical, psychological and work-related problems. Disease severity and partly visibility were associated with psychosocial well-being and the requirement for support. An impaired QoL among adults with NF1 has also been reported in other studies as well as the association between disease severity and QoL or skin-specific QoL. As disease severity and to some degree visibility seem to be associated with QoL, the burden of psychological symptoms and special needs of support, screening for these characteristics might be useful to identify the most vulnerable individuals with NF1(Dhaenens et al., 2023). NF1 displays a wide range of disease manifestations in almost all organ systems.

Cognitive impairment, emotional difficulties and behavioral problems occur frequently, with cognitive impairment being the most common neurological manifestation in pediatric patients. Due to the above-mentioned disease manifestations, NF1 can significantly impact the QoL. Studies have shown that children with NF1 and their parents report a significantly poorer HRQoL compared to population norms (Carotenuto et al., 2023).

8 Sleep

Among the NF1-related neurological morbidities, sleep disorders (e.g., sleep-related breathing disorder, insomnia) are very frequently seen in clinical practice. However, a limited number of studies focusing on NF1-related sleep disorders have been described. To date, only a few data on the sleep habits of NF1 patients have been reported such as a single case report of an old man suffering from sleep apnea syndrome due to the mechanical superior vena cava obstruction, or two questionnaire-based pediatric studies. This is the first study describing the macrostructure of a sample of pre-pubertal children with NF1. Compared to a control group, they showed a shorter sleep duration with an increased number and length of awakenings during the sleep period. Children with NF1 further demonstrated reduced N2%. Overall, disruptions of sleep continuity may inflate the daytime neurocognitive deficits exhibited by children with NF1 (National Institutes of Health, 1988). A better definition of sleep disturbances in the NF1 patient population, in particular during childhood, could address a personalized treatment and so reduce their possible related impact on their neurocognitive deficits (Bulian et al., 2022).

9 Respiratory System

The respiratory system may be affected in NF1 due to upper airway involvement with either upper airway obstruction by the tumor or increased airway collapsibility caused not only by the involvement of cranial nerves or surrounding soft tissues but also because of alveolar hypoventilation due to central or peripheral nervous system involvement. NF1 may also cause a restrictive lung disease due to dysplastic scoliosis. One remarkable observation is the high prevalence of hypertrophy of the lymphoid organs of the upper airway. This high prevalence, which is quite unusual in children aged >6–8 years, may suggest the presence of an associated ongoing inflammatory process of the upper airways which may contribute to the pathogenesis of OSA. The thorax and lungs can be affected in several ways, including by the development of cutaneous and subcutaneous neurofibromas on the chest wall, kyphoscoliosis, ribbon deformity of the ribs, posterior vertebral scalloping, intrathoracic neurogenic neoplasms, meningoceles, bullous lung disease, pulmonary hypertension (PH), and interstitial lung disease (Guerra et al., 2023).

At pathologic analysis, NF1-associated interstitial lung disease is similar to diseases with interstitial fibrosis, ultimately destroying the alveoli (47). At CT, this manifests as linear and ground-glass opacities that are bilateral, symmetric, and basal predominant. Apical-predominant cysts (Fig 15) and centrilobular nodules are also seen. The cysts become clustered in advanced stages, which can be mischaracterized as centrilobular emphysema (47). There are no specific treatments for these manifestations (Vasiljevski et al., 2021).

10 Muscle System

Neurofibromatosis type 1 (NF1) can affect multiple systems in the body. An under-recognized phenotype is one of muscle weakness. While tumors are often the focus of clinical management at all stages of life, children with NF1 can be challenged by reductions in lean tissue mass, global muscle weakness, and problems in fine and gross motor functioning.

They also express higher levels of physical and cognitive fatigue. It showed that double inactivation of Nf1 in murine muscle leads to intramyocellular lipid accumulation, which was also observed in NF1 patient muscle biopsies. Greater than 95% of the body's total carnitine is localized in skeletal muscle, where it is necessary for the transport of long-chain fatty acids through the mitochondrial membrane for beta-oxidation. Normally, the body's requirements for carnitine are met by the consumption of meat, but endogenous synthesis and increased renal absorption efficiency can contribute to whole-body carnitine homeostasis. Impairments in L-carnitine synthesis, transport or metabolism can result in primary or secondary deficiencies, which can in turn lead to elevated levels of intramyocellular lipids in muscle biopsies. Carnitine deficiency often results in muscle weakness and increased physical fatigue. Other skeletal abnormalities that are commonly associated with NF1 are scoliosis, posterior vertebral scalloping, various bone dysplasias, and multiple nonossifying fibromas. Scoliosis is the most common bone abnormality associated with NF1, occurring in 21% of patients. Younger, female NF1 patients are at a higher risk of developing scoliosis. Additional studies have also proven female NF1 patients to be at a higher risk of scoliosis compared to their male counterparts. This could be because neurofibromin, which is non-functional in NF1 patients, acts as an oestrogen receptor corepressor. Oestrogen receptor activation in the paraspinal muscles has been thought to decrease muscle strength and increase muscle flexibility, leading to a lack of muscular support for the spine and an increased susceptibility to scoliosis. Thus, without neurofibromin's repressible activity on the oestrogen receptor, there could be unregulated activation of the oestrogen receptor leading to increased likelihood and progression of scoliosis in female NF1 patients. Idiopathic scoliosis (IS) is the most common type of scoliosis and is typically genetically acquired. Approximately 2% of all pediatric scoliosis is due to a comorbidity of NF1. It often involves the lower cervical and upper thoracic spine. Nondystrophic scoliosis manifests similarly to childhood idiopathic scoliosis. Nondystrophic scoliosis can be managed with bracing to prevent progression. Dystrophic scoliosis involves four to six vertebral bodies associated with vertebral scalloping, neuro foraminal widening, transverse process spindling, and rib pencilling, which can potentially result in respiratory compromise. Surgery with spinal fusion is often required for correction. Vertebral body scalloping occurs as a result of dural ectasia, neurofibromas, or thoracic meningoceles and is possibly related to dural weakness. Posterior vertebral scalloping is typically seen, although anterior and lateral scalloping has been reported. At imaging, posterior vertebral body scalloping exhibits exaggerated posterior vertebral concavity, with greater than 3-mm or 4-mm scalloping depth in the thoracic or lumbar spine, respectively. There are various bone abnormalities related to mesodermal dysplasia and extrinsic pressure from neurofibromas. They manifest as thinning of the pedicles, transverse processes, laminae, neural foraminal enlargement and calvarial defects. Bone remodeling from adjacent neurofibromas can cause rib deformities. Additionally, involvement of the extremities can be seen, especially in the tibia and fibula, with anterolateral tibial bowing, fracture, and pseudarthrosis due to abnormal bone remodeling. Bracing is recommended to prevent fracture, while bone grafting and fixation may be necessary to stabilize fractured bone. Multiple nonossifying fibromas, also known as fibroxanthomas, are associated with NF1. They are asymptomatic and manifest as slightly expansile lesions in the metaphysis of long bones with thin sclerotic borders and a narrow zone of transition. Additionally, short stature involving the axial and appendicular skeleton and decreased bone mineral density are associated with NF1.

In the 20th century, specific skeletal muscle abnormalities had not been identified as a recognized feature of NF1. It was in a small cohort of children and adults with NF1, that were the first to show that the maximal grip force was significantly reduced compared to controls matched for age, gender and physical activity, even after accounting for the reduced arm muscle cross-sectional area in individuals with NF1. This reduced grip force has been observed in patients with other Ras-MAPK pathway disorders, suggesting that it is dysfunction of this pathway that may underlie muscle weakness. Furthermore, in another study, it's been demonstrated using peripheral quantitative computed tomography (pQCT) that children with NF1 had significantly reduced muscle cross-sectional area in the tibia compared to controls, even after controlling for age, gender, height and pubertal staging (Coleman et al., 2022).

11 Heart System

Patients with neurofibromatosis type 1 exhibit an unusually high frequency of arterial abnormalities, including those associated with pediatric renovascular hypertension (RVH). While NF1 is inherited in an autosomal dominant manner, the etiology of vascular lesions in NF1 remains undefined. Nonvascular genotype-phenotype correlations in NF1 have been reported, predominantly in association with large *NF1* gene deletions in children having dysmorphic facial features, developmental delays and increased frequencies of cutaneous, subcutaneous and plexiform neurofibromas. The spectrum of NF1 genetic variation in clinically affected individuals and the severity of NF-1-related arterial diseases have not been previously reported. The histopathologic appearance of the NF-1 ostial renal artery stenoses consistently revealed intimal fibroplasia, disruption of the internal elastic lamina and medial discontinuity. The histologic character of arteries from four probands, including three probands with known truncating NF1 variants, included intimal hyperplasia and focal medial fibrosis as predominant features. No Wagner-Meissner bodies were identified. NF-1 is a common cause of pediatric RVH.

NF1-associated vasculopathy can affect any arterial vessel, resulting in hypertension from renal artery stenosis, cerebrovascular events, or peripheral vascular insufficiency. The underlying pathogenesis is unclear, although arterial mesodermal dysplasia is thought to contribute to arterial lumen narrowing. Renal artery stenosis is the most common vascular abnormality in individuals with NF1. The stenosis can be focal or multifocal and is often unilateral. In the US, it demonstrates increased peak systolic velocity (>180 cm/sec) at the site of stenosis and increased renal-to-aortic ratio (>3.5). At CT and MRI, smooth narrowing at the ostia can be seen along with narrowing of other vessels, including the mesenteric arteries and abdominal aorta. Management includes renal artery reimplantation, bypass, arthroplasty, and stenosis resection with reanastomosis. Similarly, midaortic syndrome manifests with narrowing of the abdominal or distal descending thoracic aorta with stenoses of its branches, including the renal and mesenteric arteries. This can be surgically managed with patch aortoplasty or bypass grafting. Aside from renal artery stenosis, NF1-associated vasculopathy can manifest as cerebrovascular disease with stenosis or occlusion of the internal carotid, middle cerebral, or anterior cerebral artery (Laspa et al., 2020).

12 Cognitive System

Neurofibromin regulates prefrontal and striatal inhibitory networks and is required for working memory performance. Well-known for its cutaneous manifestations, morbidity in NF1 children often results from cognitive, social and behavioral difficulties which impact significantly academic achievement. As school grades are of great importance for entering and accessing academic or career paths, low school performance may limit occupational options. Thus, schoolchildren with NF1 require early support to enhance their school performance and complete school at the same age as their peers. NF1 is commonly associated with Attention Deficit Hyperactivity Disorder (ADHD) in about 40%–50% and Autism Spectrum Disorder in 25% of the pediatric population. Both ADHD and autism spectrum disorder are more prevalent in children with NF1 than in the general population]. ADHD is, however, more often underdiagnosed in girls than in boys, and they consequently receive less support, which could limit their performance and may explain in part our finding of

a larger effect of NF1 on school grades of girls with NF1 than boys with NF1. For a substantial majority, there is a generalized neuropsychological impairment, but certain areas of learning may also be differentially affected. Impairments are seen in all aspects of executive function including attention, cognitive flexibility, and planning but visuo-spatial Working Memory (WM) impairment is considered one of the hallmark features of NF1. Pathogenic variants of the NF1 gene and consequent increase in Ras/MAPKinase signaling result in GABAergic overactivity. This increased GABAergic inhibition disrupts corticostriatal activity and contributes to WM impairments in NF1. It's been found significant hypoactivation of the left dorsolateral prefrontal cortex (DLPFC) and right parietal cortex during working memory tasks in adults with NF1 as compared to controls. The people who are affected by NF1 showed a more diffuse pattern of brain activation possibly suggestive of a less efficient pattern of neural activity. Overall, the handful of studies which have investigated the neural underpinnings of WM impairments in NF1 using functional neuroimaging suggest altered neural activity including hypoactivation of key working memory areas, abnormal activation between parietal regions and deficient deactivation of default mode network during task.

Management and Surveillance

Although many patients with NF1 survive into adulthood, average life expectancy is decreased to 54 years, largely due to malignancy. NF1 surveillance includes annual evaluation for cutaneous, ophthalmic, and neurologic manifestations and blood pressure measurement. Surveillance for asymptomatic patients includes screening mammography starting at the age of 30 years and dual-energy x-ray absorptiometry (DEXA) for osteoporosis. Suggestive symptoms should prompt targeted imaging, such as that for evaluating CNS gliomas, plexiform neurofibromas, and malignant peripheral nerve sheath tumors (PNSTs). Recently, whole-body MRI has emerged as a potential option for NF1 surveillance, owing to its lack of radiation and new more efficient imaging protocols. Although whole-body MRI can allow early detection of many NF1 manifestations, it may be particularly useful in detecting and quantifying PNSTs. This is important, as both an increased number and whole-body volume of PNSTs have been associated with an increased risk of malignant PNST development. Additionally, PNSTs are often asymptomatic and can cross anatomic boundaries, supporting the use of whole-body MRI over localized imaging (Wilson et al., 2021).

13 Evaluation Of Motor Disorders And Deviations Of The Quality Of Life In Children With Nf1

Children with NF1 have been reported to have specific learning disabilities, attention deficit hyperactivity disorder, delays in language, executive functioning, visual perceptual skills, and memory contributing to problems with academic achievement. The cognitive problems and the musculoskeletal impairments in children with NF1 may contribute to difficulty learning and executing motor skills. Also, several studies have shown that children with NF1 suffer from psychological problems such as anxiety, depression, inattention and impulsivity, internalizing and externalizing problems, difficulties in socializing, and everyday adaptive behavior. Learning disabilities, poor attention span, and problematic relationships with peers are amongst the most common complaints on the part of parents of children with NF1. The quality of life (QoL) of young people with NF1 is consistently below the acceptable standard found amongst healthy subjects and is different from that of patients with other clinical conditions. Many studies have attempted to establish the nature of the complications associated with NF1 that impact the health and/or QoL. PBS, JAMAR dynamometer and PEDSQL were the tools that we searched according to the motor ability and quality of life.

14 Pediatric Balance Scale

The PBS was originally developed in the United States as a modified version of the Berg Balance Scale (BBS). It consists of 14 items based on activities of daily living starting from the easiest to the most difficult. Each PBS item is rated on a 5-point scale, with zero indicating inability to perform the activity without assistance, and four indicating the ability to perform the task completely independently. Each item's scores are summed to

obtain the total PBS score (maximum = 56 points). Intended for use in school-aged children (5-15 years) with mild to moderate motor impairments such as cerebral palsy and other pediatric disorders. It can be easily performed and scored in less than 20 minutes using minimal equipment commonly found in schools and clinics. Its purpose is to evaluate the functional balance and motor disorders of school-aged children with mild to moderate motor dysfunctions in the context of daily activities. PBS also can distinguish between normally developing children and those with mild motor impairments, as well as, those with moderate to severe motor impairment. In the research, the form, which was used, was translated into Greek by Laspa et al. (2020). [43]

15 Jamar Dynamometer

The JAMAR dynamometer for the measurements of the upper limbs was chosen and the Pediatric Balance Scale (PBS) for the assessment of Balance. Handgrip Strength (HGS) is used as a means of predicting a person's health throughout life. The HGS is an important indicator that helps identify the level of development and degree of disability. It also helps determine the effectiveness of rehabilitation and assess the integrity of upper extremity function. The JAMAR dynamometer has a dual scale readout which displays isometric grip force from 0-90 kg (0-200 lb). The outer dial registers the result in kg and the inner dial registers the result in lb. It has a peak hold needle which automatically retains the highest reading until the device is reset. The handle easily adjusts to five grip positions from 35-87 mm (1½ - 3¼") in 13 mm (½") increments. Always use the wrist strap to prevent the dynamometer from falling on the floor if accidentally dropped (Mathiowetz et al., 1985; Mathiowetz et al., 1984; Mathiowetz et al., 1986; Mathiowetz et al., 1986).

Pediatric Quality of Life Inventory

The PedsQL (Pediatric Quality of Life Inventory) is a modular instrument for measuring health-related quality of life (HRQOL) in children and adolescents ages 2 to 18. The PedsQL 4.0 Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL Disease-Specific Modules. The PedsQL 4.0 Generic Core Scales consist of 23 items applicable for healthy school and community populations, as well as pediatric populations with acute and chronic health conditions. The 23-item PedsQL 4.0 Generic Core Scales encompass: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items), and were developed through focus groups and cognitive interviews. The items for each of the forms are essentially identical, differing in developmentally appropriate language, or first- or third-person tense. The instructions ask how much of a problem each item has been during the past 1 month. A 5-point response scale is utilized across child self-reports for ages 8 to 18 and parent proxy-report (0 5 never a problem:

1- rarely a problem, 2- sometimes a problem, 3- often a problem, 4 - almost always a problem. To further increase the ease of use for the young child self-report (ages 5–7), the response scale is reworded and simplified to a 3-point scale (0- not at all a problem, 2- sometimes a problem, 3- a lot of a problem), with each response choice anchored to a happy to sad faces scale. Parent proxy report also includes the toddler age range (ages 2– 4), which does not include a self-report form given developmental limitations on self-report for children younger than 5 years of age, and includes only 3 items for the school functioning scale. Items are reverse-scored and linearly transformed to a 0 to 100 scale (0-100, 1-75, 2-50, 3-25, 4 -0), so that higher scores indicate better HRQOL. Scale Scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the Scale Score is not computed. The Physical Health Summary Score (8 items) is the same as the Physical Functioning Subscale. To create the Psychosocial Health Summary Score (15 items), the mean is computed as the sum of the items divided by the number of items answered in the Emotional, Social, and School Functioning Subscales. PedsQL Family Information Form The PedsQL Family Information Form, completed by parents, contains demographic information on the child and parents. It also asks for information on the number of days during the past 30 days that the child needed care or missed school because of health, the number of days the parent missed work because of the child's health, and the impact of the child's health on the parent's daily work routine and ability to concentrate at work.

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