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Review Article

Neurofibromatosis - A Practical Guide to Diagnosis and Management

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Abstract

Neurofibromatosis is an autosomal dominant genetic disorder that affects the nervous system and skin. There are two main types: neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2). NF1 is more common and presents with neurofibromas, café-au-lait spots, freckles, and optic gliomas. NF2 is characterized by bilateral vestibular schwannomas, leading to hearing loss, and meningiomas. Segmental NF1 is a form in which the features are confined to a specific area of the body. Both types of neurofibromatosis are caused by specific genetic variations. Treatment involves clinical monitoring and medical intervention when necessary.

Review articles and textbooks are essential tools for educators and students; thus, it is important to have comprehensive and up-to-date information on this subject. Currently, there are no a lot of articles or books that focus exclusively on this topic, in many counties. This highlights the need for the development of a review article that comprehensively addresses neurofibromatosis. Additionally, since it affects the nervous system and requires proper diagnosis and management, qualified information is necessary. Adequate knowledge is crucial to ensure that patients have access to proper treatment by a neurologist.

Keywords: *Neurofibromatosis; Genetics; Clinical Presentation*

Introduction

Neurofibromatosis is an autosomal dominant genetic disorder characterized by neurocutaneous manifestations, including tumors in the nervous system and skin. There are two main types: Neurofibromatosis Type 1 and Type 2. Neurofibromatosis Type 1, also known as von Recklinghausen disease, is a genetic condition with an autosomal dominant inheritance pattern and represents the most prevalent form of this pathology. NF1 presents with neurofibromas, café-au-lait spots, axillary freckling, and optic gliomas [1,2]. It can also be termed segmental NF1 when it exhibits characteristics limited to a specific body area, constituting somatic mosaicism for a pathogenic variant in the neurofibromin gene [1].

Neurofibromatosis Type 2 (NF2) is characterized by bilateral vestibular schwannomas leading to hearing loss, and meningiomas. NF2 is caused by variations in tumor suppressor genes such as moesin-ezrin-radixin-like protein (MERLIN), which produces merlin, a tumor suppressor. The treatment for both types of neurofibromatosis involves clinical monitoring and medical intervention when necessary [2].

Objectives of the Study

General objectives

- Develop a comprehensive text on neurofibromatosis, covering all its aspects and updates.
- Emphasize risk factors, diagnostic methods, appropriate management, and treatment.

Specific objectives

Create a text on Neurofibromatosis aimed at physicians and healthcare professionals, providing information on the disease's epidemiology, clinical presentation, diagnostics, differential diagnoses, and treatment. Additionally, bring forth updates on the disease and conduct a review leading to publications in national and international journals.

Proposed Methodology

This study is a narrative literature review, a non-systematic approach aiming to synthesize information found in the existing literature [3]. This study seeks to play a crucial role for both educators and students by providing comprehensive and updated information on neurofibromatosis, addressing the scarcity of narrative reviews on the subject. In January 2024, a broad and comprehensive search was conducted across four electronic databases (MEDLINE, Scielo, Web of Science, and LILACS). The selection of these databases is directly related to the objective of broadening the research scope and mitigating potential biases, providing an extensive approach that allows access to a wide range of academic and scientific sources. This reduces the likelihood of omitting relevant information and helps ensure a more complete and unbiased analysis of the topic.

Relevant descriptors and synonyms related to neurofibromatosis were used during the search: "Neurofibromatosis type 1", "Neurofibromatosis type 2", "Schwannomatosis", with data spanning the last 35 years (1989-2024). Articles analyzed in this study were selected based on inclusion criteria. Original articles and review papers written in Portuguese, English, or Spanish with relevant content for the objectives of this narrative review were considered. Articles published before 1994 and non-original or non-review articles were excluded. Data obtained were exported to EndNote Web™ (Thomson Reuters™, Toronto, Canada), where duplicate removal was performed automatically. This step was essential to ensure the integrity and accuracy of the data, avoiding redundancies and ensuring that only one copy of each study was considered in the subsequent analysis, thus guaranteeing the quality and relevance of the studies selected for analysis.

After removing duplicates, articles underwent title and abstract review. During this stage, it was observed that despite using initially derived descriptors, many studies did not directly relate to the topic under review. Although related themes were covered, some were too specific or superficial, not contributing relevant information to the article's preparation. This highlighted the importance of a rigorous screening process to ensure the selection of the most pertinent and useful studies for the review objectives. Studies that did not meet eligibility criteria were recorded separately, while eligible studies were analyzed, and their data extracted by a reviewer organized into a spreadsheet.

Epidemiology

Neurofibromatosis type 1 (NF1), formerly known as von Recklinghausen disease, is a rare genetic disease with autosomal dominant transmission and an estimated incidence of 1:2500-3000 live births. In approximately 50% of individuals, the disease results from a spontaneous mutation, while in the other 50%, it is hereditary [4]. A systematic review showed that among 20 fully evaluated studies, 12 were included, revealing a combined prevalence of NF1 of 1 in 3,164 (95% CI: 1 in 2,132-1 in 4,712), higher in studies screening for NF1 compared to identification through medical records. Conversely, the combined NF1 birth incidence was 1 in 2,662, with only 2 studies on NF2 prevalence, hence data were not combined. The combined NF2 birth incidence was 1.08 per 50,000 births. NF1 prevalence in

screening studies exceeds those in medical record studies, suggesting under-recognition of the disease. More studies are needed on NF2 prevalence [5]. NF1 prevalence is approximately 1/3,000. No ethnic groups are known where NF1 does not occur or is unusually common. Prevalence is slightly higher in young children than adults, a difference likely due, in part, to early mortality in some NF1 patients. NF1 is fully penetrant in adults, but many disease features increase in frequency or severity with age. The reproductive fitness of NF1 patients is reduced by about half. About half of all cases result from new mutations. The estimated high rate of new mutations in NF1 is not yet understood [6].

Genetics and pathophysiology

Neurofibromatosis type 1 (NF1)

NF1 is an autosomal dominant disorder with complete penetrance, meaning individuals with one allele manifest the expected phenotype for the disease; in this dominant case, only one altered allele is necessary (heterozygous) for phenotype presentation. The genetic alteration is in the gene located at chromosome 17q11.2, known as NF1, responsible for encoding the protein neurofibromin, a cytoplasmic protein that modulates cellular growth and differentiation. Types of mutations leading to the NF1 phenotype include complete deletions of the gene, insertions, stop mutations, and splice mutations, along with amino acid substitutions and rearrangements [7].

NF1 manifests in distinct mosaic forms, classified as segmental, gonadal, or generalized. Mosaicism is a genetic condition where an individual has two different cell lineages originating from a post-zygotic mutation, meaning from the same zygote. The segmental pattern may present with pigmented changes in body regions, tumor growth, or both conditions. The rarer gonadal type occurs when only the egg or sperm is affected, so if a child of unaffected parents develops the disease, this disorder may be suspected. The generalized type clinically presents as non-mosaic cases [8].

When the NF1 gene is functionally altered, its protein product, neurofibromin, is compromised. Expressed predominantly in neurons, glial cells, Schwann cells, and during melanocyte development, neurofibromin suppresses tumors by regulating Ras activity, a GTP-binding protein, thereby controlling cellular proliferation and differentiation signals. Neurofibromin interacts with GTP-bound Ras, aiding in GTP hydrolysis to GDP, subsequently inactivating Ras. Mutations in NF1 lead to defective neurofibromin, losing the ability to adequately inactivate Ras, resulting in elevated GTP-bound Ras, altering signals controlling cell growth and multiplication, inducing unregulated cell growth and tumor formation [6,10].

Neurofibromatosis type 2 (NF2)

Like NF1, NF2 is autosomal dominant, but genetic alteration occurs on chromosome 22q12.2 in the NF2 gene, producing merlin, also known as neurofibromin 2 or schwannomin, linking the cytoskeleton to the plasma membrane. Neurofibromin 2 has tumor-suppressing activity, coordinating signaling responses to tumor growth factors through various pathways, including actin cytoskeleton interaction. Expressed in nervous tissue cells and neuroepithelial tissues of vertebrate eyes, NF2 can be inherited autosomally dominantly, with half of cases from sporadic mutations, also associated with mosaicism [10,11].

Symptoms typically begin at age 20, with 90% of patients exhibiting the hallmark: bilateral vestibular schwannomas. Other presentations include meningiomas, spinal schwannomas, ependymomas, and dermal schwannomas, differentiating from NF1's neurofibromas [12]. Diverse mutations on the chromosome can contribute to NF2 genesis, such as nonsense, splice site, and missense mutations, with nonsense and frameshift mutations being common, linked to aggressive phenotypes [10].

Schwannomas or other NF2 tumors require inactivation of both NF2 gene alleles, as tumors develop only in cells without normal NF2 alleles. This involves normal NF2 gene loss and complete or partial chromosome 22 inactivation, though point pathogenic variants

or promoter methylation may occur. Normal copy loss can occur via mitotic recombination, duplicating the mutated copy without chromosomal material loss [13].

Chromosome 22 dysfunction is implicated in meningioma pathogenesis, with a common genesis pathway for NF2 tumors through neurofibromin presence on chromosome 22q12.2. Meningioma patients may have deletions, nonsense mutations, splicing site mutations, and translocations in NF2/Merlin, sometimes losing chromosome 22 in tumor tissue. Merlin or chromosome 22 loss mechanism remains unclear, known to activate oncogenic pathways like Ras and Notch downstream targets [14].

NF2 hallmark vestibular schwannomas (VS) originate from Schwann cells on the vestibulocochlear nerve (VIII), causing hearing loss, tinnitus, balance issues, and facial paresthesia or paresis. They may lead to life-threatening brainstem compression, causing hydrocephalus. Their development stems from both NF2 alleles' inactivation, with inherited mutated NF2 allele and suppressor gene loss due to heterozygosity loss in Schwann cells allowing VS genesis [15-17].

Patients inheriting a mutant NF2 gene allele have a 95% chance of developing VS, but 50% of NF2 patients lack familial history, indicating new germline mutations, and 33% show mosaicism from post-fertilization mutation, resulting in two separate cell lineages [18].

NF2 gene alterations were found in most VS, but Merlin activity alteration occurs when mutations aren't detected, suggesting post-translational events affecting Merlin activity. Tumor-suppressing mechanisms of Merlin remain elusive, but studies show Merlin limits Ras oncogene-induced cell growth and transformation, losing cell growth control with NF2 gene inactivation in Schwann cells. Merlin affects several mitotic signaling pathways such as phosphoinositide-3 kinase (PI3K) and mitogen-activated protein kinase (MAPK), known for oncogenesis involvement, critical for cell growth and proliferation [11,19].

Schwannomatosis

Schwannomatosis is a genetic syndrome resulting in multiple non-cutaneous schwannomas on peripheral nerves, spinal roots, and cranial nerves, less commonly meningiomas. Schwannomas affect the spine (74%) and peripheral nerves (89%), and less often cranial nerves (8%) [20]. There is a strong correlation between schwannomatosis and NF, yet they are distinct diseases with differences. Intradermal schwannomas, ependymomas, cataracts, and retinal abnormalities occur in NF2 patients but not in Schwannomatosis, nor were NF2's hallmark bilateral vestibular schwannomas reported in Schwannomatosis patients [21].

The SCH genetic component is not fully explained, but germline mutations were found in 2 genes in schwannomatosis patients: SMARCB1 and LZTR1. These tumor suppressor genes are located on chromosome 22, proximal to NF2. SMARCB1 germline mutation accounts for 48% of familial SCH and 10% of sporadic SCH cases. LZTR1 germline mutations explain 38% of familial SCH and 30% of sporadic cases. Tumors frequently show chromosome 22 loss [22].

SMARCB1, previously known as INI1, acts as a tumor suppressor regulating gene expression for cell cycle, growth, and differentiation. Schwannomas with SMARCB1 mutations often have additional genetic changes, including chromosome 22 copy loss and inactivated NF2 variants, or the moesin-ezrin-radixin-like tumor suppressor (MERLIN) (NF2) [23,24]. These cases suggest a four-hit, three-step tumor genesis model: first mutation is the germline-altered SMARCB1 copy in the tumor, second and third mutations involve deletion of chromosome 22 regions with unaltered SMARCB1 and NF2, and fourth mutation alters the remaining normal NF2 gene [13,23].

LZTR1 gene alteration induced SCH in many patients without SMARCB1 pathogenic variants. A study found LZTR1 pathogenic alterations in 6 of 16 familial SCH patients, 11 of 49 sporadic SCH patients, and 2 of 39 unilateral vestibular schwannoma patients. Like SMARCB1-associated cases, the genetic alterations pattern suggests a four-hit, three-step tumor genesis model: the first mutation

involves LZTR1 germline gene alterations present in the tumor; second and third mutations result from chromosome 22 segment deletions containing natural (normal) SMARCB1 and NF2 gene copies; the fourth mutation alters the remaining natural NF2 gene. LZTR1, located on chromosome 22q11.21, is centromeric to both SMARCB1 (22q11.23) and NF2 (22q12.2). It is described as a tumor suppressor gene that also assists in activating glioblastomas [24].

Clinical presentation and diagnosis

Clinical manifestations

NF1

Neurofibromatosis Type 1 (NF1) is characterized by benign tumor development in various body tissues. The typical clinical picture includes several manifestations appearing in a specific sequence. The first common manifestations are café-au-lait macules, flat, hyperpigmented skin patches, typically appearing during the first year of life, increasing in number during childhood. Six or more café-au-lait macules strongly indicate NF1 [25].

Another clinical feature is axillary and/or inguinal freckling, known as "Crowe sign." Smaller than café-au-lait macules, they typically appear in clusters in skin folds [26]. Lisch nodules, elevated, tan-colored iris hamartomas, are specific to NF1 and aid in diagnosing the disease in children and assessing parental involvement. Detected in less than 10% of children but over 90% of adults [27].

Neurofibromas are benign peripheral nerve sheath tumors, a major NF1 clinical manifestation. They can appear on the skin, along peripheral nerves under the skin, or deeper in the body. The two main types are cutaneous neurofibromas, discrete, soft skin tumors, and plexiform neurofibromas, tumors extending along nerves that may cause deformities and complications [26]. Additionally, NF1 patients have a higher risk of optic pathway gliomas (OPGs), central nervous system tumors affecting optic nerves, mainly in children under six with the disease [28].

NF1-related complications include bone dysplasias, hypertension, malignant tumor transformation, and other benign or malignant tumors throughout life. NF1 patients face an increased risk of developing gastrointestinal stromal tumors (GISTs), soft tissue tumors of the gastrointestinal tract. Clinical severity varies among individuals, necessitating regular medical follow-ups and appropriate treatment for management [29].

NF2

Neurofibromatosis Type 2 (NF2) is an autosomal dominant genetic syndrome affecting the nervous system, eyes, and skin, characterized by a predisposition to develop schwannomas and other nervous system disorders, with ophthalmic and cutaneous manifestations. Symptoms typically begin between ages 20 and 25, with celebrated clinical presentations. In NF2 children, initial symptoms are often atypical but more severe, including visual issues, hearing loss, weakness, pain, mononeuropathy, skin tumors, and seizures. In adults, hearing loss and tinnitus are most common [30].

NF2's main clinical features include bilateral vestibular schwannomas, affecting auditory nerves, causing hearing loss and imbalance. Other observed disorders include schwannomas of other cranial nerves, intracranial meningiomas, spinal tumors (intramedullary and extramedullary), and peripheral neuropathies. Vestibular schwannomas are usually bilateral, potentially leading to progressive deafness. The exact auditory mechanism isn't well understood, but intralabyrinthine protein accumulation might be involved. Untreated, vestibular schwannomas can compress the brainstem, causing hydrocephalus [31].

About half of NF2 patients develop meningiomas, predominantly intracranial; spinal meningiomas may also be present. NF2-related meningiomas tend to be more atypical or anaplastic than sporadic disorders. Spinal tumors, like schwannomas and meningiomas,

are common in NF2 patients, causing pain, muscle weakness, and paresthesias. Neuropathies, including mononeuropathies and polyneuropathies, can occur. NF2 ophthalmic manifestations include cataracts, optic nerve meningiomas, retinal hamartomas, and epiretinal membranes. Cataracts affect many patients, impacting vision since childhood [32].

Skin manifestations, like tumors, occur in about 70% of NF2 patients, varying in form, such as plaque-like lesions, subcutaneous nodules, and intracutaneous tumors. In summary, NF2 is a genetic syndrome predisposing to nervous system disorders, affecting eyes and skin, with clinical manifestations including bilateral vestibular schwannomas, meningiomas, spinal disorders, neuropathies, and ophthalmic issues [33].

Main differences between NF1 and NF2

Lisch nodules (raised and pigmented iris hamartomas) are characteristic of NF1, not significant in NF2.

Schwannomas in NF2 rarely, if ever, undergo malignant transformation into neurofibrosarcoma (malignant peripheral nerve sheath tumor [MPNST].

"Dumbbell" spinal root tumors seen in NF2 and NF1 are schwannomas in NF2 and neurofibromas in NF1.

NF2 lacks the cognitive impairment often seen in NF1.

Diagnosis

NF1

Neurofibromatosis type 1 (NF1) diagnosis is based on specific clinical features. Genetic testing is usually unnecessary but can confirm diagnosis in children not meeting clinical criteria or showing only café-au-lait spots and axillary freckles. Suspected NF1 children should undergo multidisciplinary evaluation by pediatric neurologists, geneticists, and ophthalmologists, examining diagnostic criteria, identifying treatable complications, providing anticipatory guidance, and referring to specialists if needed. Guidelines exist for managing NF1 children and adults [34,35].

Initial screening confirms diagnosis by identifying NF1 clinical features. Medical history is essential for associated disease symptoms like pain, vision issues, weakness, neurological deficits, headaches, and seizures. Developmental history and school performance should be reviewed. Physical exams focus on cutaneous, skeletal, and neurological systems. Ophthalmic evaluations identify Lisch nodules and early optic glioma signs [34-36].

NIH Consensus Conference diagnostic criteria are based on NF1's specific clinical features. In individuals without disease family history, diagnosis is confirmed if at least two criteria are met: six or more café-au-lait macules over 5 mm in pre-pubertal and 15 mm in post-pubertal individuals, two or more neurofibromas of any type, axillary or inguinal freckling, optic glioma, two or more Lisch nodules or choroidal abnormalities, a distinct bony lesion (like sphenoid dysplasia), long-bone pseudoarthrosis, and a pathogenic NF1 variant with 50% variant allele expression in normal tissue [2].

Diagnostic criteria have high specificity and sensitivity, except in very young children. Most individuals meet NIH criteria by age eight. In a study of NF1 individuals under 21, about 46% without family history didn't meet NIH criteria by one year old. Young children with a single clinical manifestation and no family NF1 history should be monitored for other manifestations before a definitive diagnosis, usually by age four. Genetic testing can be considered for molecular diagnosis [2,34,35,37].

Genetic testing confirms diagnosis in doubtful cases and assists in family member screening. It's necessary for prenatal or preimplantation diagnosis. However, a positive NF1 mutation test doesn't predict disease severity or complications, though specific features can be identified. Thousands of distinct pathogenic NF1 variants exist in confirmed individuals. Few genotype-phenotype correlations are known for gene research. However, some variants are linked to milder or more severe phenotypes and other conditions. About 1% to 5% of NF1 individuals have large deletions encompassing the entire NF1 gene, associated with additional features like intellectual disabilities, developmental delays, and increased malignant tumor risk [2,34,35,37].

Genetic testing is increasingly used in NF1 diagnosis, especially in patients meeting only two or one clinical criteria. A positive genetic test can reduce diagnostic observation periods and initiate appropriate screening estimates. If NF1 mutation testing is negative, other genetic tests for related syndromes may be considered. A detailed family history is essential to detect possible NF1 symptoms in parents when diagnosing a child. Family member genetic screening can be performed as discussed earlier. Additionally, prenatal testing, like amniocentesis or chorionic villus sampling, can be conducted if a family mutation is known. Preimplantation genetic testing is also an option to identify embryos without a known family mutation [2,34,35,37].

NF2

NF2 diagnosis is based on clinical and molecular genetic characteristics. Genetic testing is recommended for all suspected schwannomatosis predisposition syndromes patients but isn't necessary for NF2 diagnosis in patients meeting clinical criteria. It is particularly useful in younger patients not meeting diagnostic criteria without genetic data. Genetic testing is also crucial for first-degree relatives of individuals with NF2, potentially diagnosed based on identified NF2 pathogenic variants, even without clinical characteristics [18,38].

NF2 clinical diagnosis is based on any of these criteria: bilateral vestibular schwannomas; a pathogenic NF2 variant in at least two anatomically different NF2-related disorders (schwannoma, meningioma, and/or ependymoma); if allele variant translation in blood is clearly < 50%, the diagnosis is mosaic. Initial NF2 suspicion evaluation includes a detailed clinical and family history, skin examinations, ophthalmological care, and brain and full-spine contrast MRI. A complete skin and eye exam is recommended. High-resolution contrast MRI assesses spinal involvement and excludes NF2 spinal cord impact [2,22].

Genetic testing is recommended for suspected schwannomatosis predisposition syndrome patients but isn't necessary for NF2 diagnosis in patients meeting clinical criteria. Genetic testing is particularly valuable for younger patients not meeting diagnostic criteria without genetic data. It's also crucial for first-degree relatives of NF2 individuals, potentially diagnosed based on a pathogenic NF2 variant, even without clinical characteristics. NF2 differential diagnosis includes sporadic vestibular schwannomas, other schwannomatoses, multiple spinal tumors (schwannomas, meningiomas), gall schwannomas, solitary meningiomas, and other specific tumors. These syndromes are caused by variants in other genes besides NF2, such as SMARCB1 and LZTR1. LZTR1-related schwannomatosis has the greatest diagnostic overlap with NF2, as individuals may have unilateral vestibular schwannomas and other disorders [39,40].

Treatment

NF1

No general treatment exists for Neurofibromatosis type 1 (NF1), but discussions on mitogen-activated protein kinase (MAPKK or MEK) inhibitors address plexiform neurofibromas (PNs) management. Clinical trials are underway for associated disease problem treatments. Treatment of NF1-associated tumors depends on tumor type and complications. Minimizing radiation use is crucial for central nervous system disorders in NF1 patients due to secondary neoplasm and vascular complication risks. No evidence suggests specific NF1 examination associates with differential radiation or chemotherapy sensitivity [41].

Cutaneous and subcutaneous neurofibromas aren't usually removed unless causing pain, bleeding, function interference, or disfigurement. Removal options include surgery, laser, or electrodesiccation. Some patients may experience itching often unresponsive to antiallergic treatments but may improve with medications treating neuropathic pain. Plexiform neurofibromas (PNs) involve multiple nerve segments, potentially causing pain, motor dysfunction, and visual loss [42,43].

PN respiratory and pain management is challenging, especially with progressive growth leading to spinal cord compression lesions. Selumetinib, a selective oral MEK protein kinase inhibitor, is FDA-approved for treating symptomatic and/or progressive, inoperable NF1-associated PNs in children aged three or older. Other clinical trials with targeted therapies are underway for PNs. Low-grade glioma treatment approaches vary but may include observation with close monitoring, chemotherapy, or targeted therapy. High-grade gliomas usually undergo biopsy or surgical resection followed by radiotherapy and sometimes chemotherapy [43,44].

Malignant peripheral nerve sheath tumor (MPNSTs) treatment involves surgical resection and adjuvant radiotherapy. Chemotherapy usage is also under investigation. Importantly, specific NF1 case treatment should be discussed with a specialist, considering patient characteristics and disease progression [45].

NF2

Neurofibromatosis Type 2 (NF2) treatment is multidisciplinary, primarily aiming to preserve function and improve patient quality of life. There is no definitive NF2 cure, but various approaches manage symptoms and complications. Vestibular schwannoma treatment focuses on preserving function and quality of life. Not all tumors require treatment, indicated when brainstem complications, hearing impairment, and/or facial nerve dysfunction are at risk [46].

Surgery typically manages vestibular schwannomas, especially in NF2 patients. However, NF2 surgery can be more complex due to tumor multifocality and facial nerve damage risk. Radiotherapy may be considered, though its role in NF2 vestibular schwannoma management is less clear. Bevacizumab, a monoclonal antibody, is used as first-line medical therapy for NF2-associated vestibular schwannomas. Studies show bevacizumab might induce tumor reduction and auditory improvement in some NF2 patients. Side effects include amenorrhea, proteinuria, and hypertension [33].

Besides bevacizumab, other targeted therapies are under investigation for NF2-related disorder treatment, including everolimus, lapatinib, erlotinib, brigatinib, and histone deacetylase inhibitors. NF2 meningioma management involves possible surgery, with radiotherapy considered for surgically inaccessible or partial resection disorders. Targeted therapies like lapatinib and bevacizumab are also studied for NF2-associated meningioma treatment [47].

Intramedullary spinal tumors, like ependymomas, generally prefer surgical resection over radiotherapy. Bevacizumab might have activity in spinal cord cystic components. NF2 at-risk family member screening is crucial for early diagnosis. Genetic testing can be conducted when a specific pathogenic variant is identified in the index case. Tumor follow-up and surveillance are necessary for NF2 individuals [47].

It is important to note that treatment options may vary depending on the specific case, and specialized medical follow-up is essential to determine the most appropriate approach for each situation. Importantly, NF2 treatment is highly individualized, considering each patient's specific characteristics and needs. A multidisciplinary approach involving neurology, otorhinolaryngology, neurosurgery, radiotherapy, genetics, and other health professionals is crucial for providing optimal NF2 patient care [46].

Comorbidities and differential diagnoses

Besides cutaneous manifestations, neurofibromatosis patients commonly develop skin tumors, often appearing during puberty anywhere on the skin [48]. Neurological events like neurofibroma development, a primary clinical condition of the disease, are also noted. Less frequently, epileptic manifestations, learning difficulties, and headache with migraine characteristics are reported.

Retina, iris, optic nerve, soft tissues, and orbital bones can be affected, with optic glioma being the most commonly reported ophthalmologic event. This condition affects both eyes, potentially involving the chiasm and optic tract. Another described feature is Lisch nodules, melanocytic and fibroblastic iris proliferations. These lesions are considered exclusive to neurofibromatosis, present in 90% of affected adult patients [48].

Common orthopedic problems include hypotonia and motor coordination deficits, possibly accompanied by dysplasia, erosion, and bone demineralization, caused by adjacent plexiform neurofibromas or tumor-associated vascular proliferation [48]. NF patients may present with vascular complications, including arterial stenosis, aneurysm, and arteriovenous fistulas, affecting the abdominal aorta and its branches. Recent reports include multifocal stenosis in intracranial arteries causing fatal ischemia. Over 6% of NF patients develop hypertension at any age. In most cases, hypertension is essential, but pheochromocytoma and renal artery stenosis should be considered in NF patients. Vascular dysplasias, including renal and carotid artery stenosis, may occur [49].

Numerous conditions qualify as neurofibromatosis (NF) differential diagnoses, divided into groups. These groups unite pathologies with signs common to NF. In patients with only café-au-lait spots, consider NF alongside Fanconi anemia, blood syndrome, piebaldism, and others. Conversely, patients with NF presenting with nodules are differentially diagnosed with lipomatosis, multiple endocrine neoplasia type 2B, congenital generalized fibromatosis, and others [50].

General Conclusion

This narrative review comprehensively explores the neurofibromatosis publication landscape. The primary research aim was to enhance understanding of key aspects discussed thus far, highlighting the necessity of intensifying studies on the disease to improve patient quality of life. Despite scientific advancements, particularly in molecular biology and neuroimaging, offering better clinical approaches that reduce complication morbidity and enhance patient quality of life, the pathology's natural history largely remains hidden.

Predictors of disease progression and local risks for subsequent malignant neoplasm development remain unknown, requiring further study. Current treatment primarily relies on symptomatic approaches, occasionally only palliative. However, significant expectations are placed on advances in genetics and new molecular pathogenesis insights to discover more effective approaches that may slow and prevent disease-associated complications. Thus, increasing neurofibromatosis awareness is crucial to propel new research development and expand public knowledge on the topic, potentially resulting in significant diagnostic, treatment, and care advancements for affected patients.

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