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Diagnostic and therapeutic process of neurofibromatosis type 1 and type 2

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Abstract

Neurofibromatosis is one of the most common genetic diseases. It is inherited in an autosomal dominant manner. It is divided into two genetically distinct subtypes, characterized by multiple skin lesions and tumors of the peripheral and central nervous system. Neurofibromatosis type 1, or Recklinghausen's disease, is the most common phakomatosis. The disease is genetically determined by a mutation of the neurofibromin-1 gene on chromosome 17. Neurofibromatosis type 2 accounts for 3% of all cases. The disease is genetically determined - caused by a mutation of the neurofibromin-2 gene on chromosome 22. The diagnostic and therapeutic process of neurofibromatosis is a major challenge for clinicians. Given the complexity of the problem, we have reviewed the literature on the diagnostic and therapeutic possibilities of the disease.

Keywords: neurofibromatosis; diagnosis of neurofibromatosis; treatment of neurofibromatosis

1. Introduction

A group of patients with a combination of skin lesions and tumors of the peripheral and central nervous system was first described in 1882 by German pathologist Friedrich Daniel von Recklinghausen [1, 2].

The skin and nervous system develop from the same embryonic leaf, the ectoderm. Abnormalities in the embryonic development of these structures result in phakomatoses (skin- nerve diseases). The most important phakomatoses include neurofibromatosis type 1 and type 2, which were only distinguished in the 20th century [1, 2].

Neurofibromatosis type 1, also known as Recklinghausen's disease, affects approximately 1 in 3,500 people and manifests with a number of characteristic abnormalities of the skin and peripheral nervous system. The disease is genetically determined by a mutation of the neurofibromin-1 (NF1) gene on chromosome 17. The NF1 gene encodes the neurofibromin protein. Neurofibromin acts as a tumor suppressor by negatively regulating mitogenic Ras signaling through GTPase-activating protein (GAP), which is essential for neurofibromatosis type 1-associated tumorigenesis [1, 2, 3, 4, 5, 6, 7].

Neurofibromatosis type 2 occurs in less than 1 in 25 000 people. Often, the first clinical signs of NF2 are revealed in late teens with sudden hearing loss due to the development of vestibular neurofibromas. The disease is genetic - caused by a mutation of the neurofibromin-2 (NF2) gene, which is located on chromosome 22. The NF2 gene is

thought to affect cell growth and remodeling by inhibiting the transmission of extracellular mitogenic.

signals [1, 2, 3, 8, 9, 10].

2. Material and method

The aim of this article is to present the diagnostic and therapeutic process of neurofibromatosis type 1 and type 2. Publications outlining the diagnostic and therapeutic approaches for neurofibromatosis were reviewed using the PubMed platform. The search included the keywords 'neurofibromatosis', 'diagnosis of neurofibromatosis', 'treatment of neurofibromatosis'.

3. Symptoms

3.1. Neurofibromatosis Type 1.

Neurofibromatosis Type 1 (NF1) is a genetic disorder predominantly associated with mutations in the NF1 gene located on chromosome 17q11.2, which encodes the neurofibromin protein. Approximately 50% of mutations in individuals with neurofibromatosis occur de novo. The neurofibromin protein is responsible for the negative regulation of the Ras proto-oncogene in the body. NF1 encompasses skin changes, tumor formation, nervous system alterations, bone changes, and vascular system changes [11, 12, 13].

One of the classic symptoms of NF1, which typically raises suspicion of the disease, is skin changes. In a clinical study by Miraglia et al., approximately 96.5% of patients had skin changes in the form of café-au-lait spots, 90% had axillary and inguinal freckling, and 78% had neurofibromas. Patients in this cohort study also exhibited other skin changes such as lipoma, psoriasis, spilus nevus, juvenile xanthogranuloma, vitiligo, Becker's nevus, and melanoma [11, 14].

Café-au-lait spots are one of the typical pathological changes in NF1. They are usually first noticed in children within the first two years of life. The presence of 6 or more spots larger than 5 mm before puberty or larger than 15 mm in size is one of the diagnostic criteria for the disease. Café-au-lait spots typically have a uniform distribution of pigment and smooth edges. There is a possibility that café-au-lait spots may darken due to sun exposure or the patient's age. It is worth mentioning other diseases in which café-au-lait spots also occur, such as Legius Syndrome, where mutations in the SPRED1 gene lead to macrocephaly, ADHD, lipomas, and intertriginous freckling. Others include McCune-Albright syndrome, Silver-Russell syndrome, and Noonan syndrome [11, 12, 13, 14, 15].

Axillary and inguinal freckling, also known as Crowe Sign, typically appear in individuals with NF1 around the age of five, usually after café-au-lait spots begin to appear.

Freckles appear in areas not exposed to sunlight [11, 12, 14].

Neurofibromas are benign nodules of the peripheral nerve sheath. They originate from Schwann cells, perineural cells, and fibroblasts. In the diagnostic guidelines for NF1, a patient must have at least two neurofibromas or one plexiform neurofibroma. They can be classified into four types: cutaneous, subcutaneous, nodular, or diffuse plexiform [11, 12, 14].

Cutaneous and subcutaneous neurofibromas usually appear in adolescence and typically occur in every adult with NF1. They usually first appear on the trunk and then on the limbs. The number of neurofibromas varies depending on the patient. Neurofibromas can significantly impair a patient's quality of life, causing pain or significant changes in the patient's appearance. It is important to consider consulting a plastic surgeon to remove these.

lesions. These changes are benign [11, 12, 13, 14].

Plexiform neurofibromas usually occur around the neck, head, orbits, limbs, chest, abdomen, and pelvis. They arise from one or multiple nerve branches. They typically occur in about 30-50% of individuals with neurofibromatosis type 1. Hyperpigmentation, palpable masses, or a hairy patch may appear on the skin overlying plexiform neurofibromas. MRI of the body is performed to detect them in patients. They may cause compression of adjacent organs or pain, often without any symptoms. Surgical excision of the tumor is the treatment method. Plexiform neurofibromas can transform into Malignant Peripheral Nerve Sheath Tumors (MPNST). A cohort study by Evans et al. showed that the occurrence of MPNST during the patient's lifetime is between 9-13%. MRI and PET-CT are used in the diagnosis of the disease [11, 12, 13, 14, 16, 17].

Bone changes in NF1 include osteopenia, scoliosis, congenital tibial dysplasia, and pseudarthrosis, the latter two common in patients with NF1. Osteopenia may result from low levels of vitamin D in patients, which is associated with the high risk of bone fractures in individuals with NF1. Approximately 10-20% of children with NF1 have scoliosis. Congenital tibial dysplasia leads to frequent fractures of the tibia bone, which can lead to the development of pseudarthrosis [11, 12, 13, 17].

Lisch nodules are benign hamartomatous changes appearing on the iris, usually around 5-10 years of age. The diagnostic criterion for NF1 is at least 2 Lisch nodules

in a patient. Lisch nodules do not affect vision in patients; nevertheless, patients should be under the care

of an ophthalmologist [11, 12, 13, 18].

Optic gliomas are benign glial neoplasms and occur in about 15-20% of patients with NF1. These changes typically appear in childhood. Most optic gliomas are asymptomatic, sometimes causing visual disturbances, and may lead to precocious puberty. About 80% of gliomas involve the optic pathway, and about 20% involve the brainstem, causing cranial neuropathies, gait instability, and headaches. Children with NF1 should have an annual

ophthalmological examination to exclude optic gliomas [11, 12, 13, 18].

Vascular changes often occur in patients with NF1, including pulmonary artery stenosis and vasculopathies such as cerebral and renal artery stenosis, arteriovenous malformations, and aortic coarctation. Moreover, many adolescent patients with NF1 suffer from hypertension. Cerebrovascular abnormalities occur in 3-6% of patients and can be asymptomatic, or their narrowing can worsen, leading to an increased risk of stroke [11, 12, 13].

Developmental deficits manifest as ADHD, autism spectrum disorders, and behavioral abnormalities. Children with NF1 have learning difficulties and speech problems such as speech dyspraxia, misarticulation, and disfluency [11, 12, 13, 20].

Tumors are more common in individuals with neurofibromatosis type 1. These include the aforementioned optic/brainstem gliomas, glioblastomas, gastrointestinal stromal tumors, breast cancers, leukemia and lymphoma, pheochromocytoma, carcinoids, and rhabdomyosarcomas [11, 12, 13, 21].

3.2 Neurofibromatosis Type 2

Neurofibromatosis Type 2 (NF2) is a dominant inherited disorder caused by a mutation in the NF2 tumor suppressor gene located on chromosome 22q12. This mutation leads to the development of tumors in the nervous system, peripheral neuropathy, ophthalmological lesions, and cutaneous diseases in affected individuals. The disease typically manifests around 20 to 30, with hearing impairment associated with vestibular schwannomas being the primary initial symptom [11, 12, 13, 14].

Vestibular schwannomas occur in approximately 90-95% of NF2 patients. The presence of bilateral vestibular schwannoma is one of the diagnostic criteria confirming NF2. In the case of unilateral vestibular schwannoma, the patient must have two other NF2-

associated changes, such as meningioma, glioma, or cataracts. About 99% of vestibular schwannomas in NF2 are benign. Symptoms associated with vestibular schwannoma include tinnitus and progressive hearing loss. There is no correlation between tumor size and the degree of hearing loss. MRI of the brain confirms the presence of vestibular schwannomas.

[11, 12, 13, 14, 15].

Intracranial meningiomas are observed in 45-58% of NF2 patients. It is important to conduct genetic testing in children with meningiomas, as about 20% have NF2. Approximately 20% of meningiomas in NF2 patients involve the spinal cord. Symptoms associated with intracranial meningiomas depend on the location and size of the tumor.

MRI

confirms the presence of meningiomas [11, 12, 13, 14, 15].

Spinal tumors occur in 63-90% of NF2 patients. These include spinal cord ependymomas and intramedullary astrocytomas. Spinal cord ependymomas account for about 75% of spinal cord tumors. Symptoms of tumors depend on their location and size and may include back pain, weakness, and sensory disturbances. MRI is used to visualize spinal cord.

ependymomas [11, 12, 13, 14, 15].

Peripheral neuropathy develops in the majority of NF2 patients during their lifetime. It is usually not associated with the presence of a compressive tumor. Diagnosis of peripheral neuropathy involves MRI of the head and spinal cord, as well as nerve conduction studies. The development of peripheral neuropathy in patients is likely associated with the loss of both myelinated and non-myelinated nerve fibers or abnormalities in Schwann cell proliferation.

[11, 12, 13, 14, 15].

Ophthalmological lesions, including cataracts (60-81%), epiretinal membranes (12- 40%), and retinal hamartomas (6-22%), affect the vision of NF2 patients, who should undergo

annual ophthalmologic examinations [11, 12, 13, 14].

Cutaneous lesions include skin tumors (59-68%), skin plaques (41-48%), and subcutaneous tumors (43-48%). Skin tumors include schwannomas, similar to NF1, and neurofibromas. Skin plaques are characterized by slightly raised, less than 2 cm lesions

with hyperpigmentation and hypertrichosis. Café-au-lait spots also appear on the skin of 33-48% of NF2 patients [11, 12, 13, 14].

4. Diagnostics criteria

The original diagnostics criteria for NF1 and NF2 were established at the National Institutes of Health (NIH) consensus meeting in 1987. Since that time, we have increased our knowledge about genetic disorders and genes that cause NF1 and NF2 [22].

Diagnosis of NF1 is difficult due to the different time of onset of symptoms. For example: CALM may appear either from birth or after the first year of life, Lisch nodules arise during childhood while neurofibromas occur during early adulthood [22]. Due to difficulties in diagnosing NF1, Legius syndrome and other conditions with CALM; diagnostic criteria of NF1 have been revised in 2021 [22, 23]. To diagnose NF1, we use the achievements in genetics, dermatology, ophthalmology and neuroimaging [23].

Usually the diagnosis can be made on the basis of medical interview and physical examination but through the addition genetic testing in diagnostics criteria it is particularly important in children with isolated multiple CALM without family occurrence [22].

Revised diagnostics criteria for neurofibromatosis type 1 [23].

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:

-
1. Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals^a
 2. Freckling in the axillary or inguinal region^a
 3. Two or more neurofibromas of any type or one plexiform neurofibroma
-

-
4. Optic pathway glioma

 5. Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging

 6. A distinctive osseous lesion such as sphenoid dysplasia,^b anterolateral bowing of the tibia, or pseudarthrosis of a long bone

 7. A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells
-

B: A child of a parent who meets the diagnostic criteria specified in A merit a diagnosis of NF1 if one or more of the criteria in A are present

^aIf only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.

^bSphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.

The Manchester criteria (1992) were usually used for making a diagnosis of NF2 [25]. However, in recent update (2022) the diagnostics criteria for NF2 are based on both, physical examination and genetic tests. It allowed for the effective identification and diagnosis of NF2 at an earlier stage especially in patients without bilateral vestibular schwannoma but with suspected schwannomatosis predisposition syndromes [24, 25]. As in the case of NF1, we use different diagnostics methods to confirm the diagnosis. The most important are physical examination, medical interview, ear and eye examination or MRI.

For patients with familial NF2 there is a method with a detection rate of up to 90% called next-generation sequencing (NGS), which detects inactivating mutations in the NF2 gene located on chromosome 22. [24].

Revised diagnostic criteria for neurofibromatosis type 2 [25].

1. Bilateral vestibular schwannomas, or

 2. FDR family history of NF2 and unilateral VS, or
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3. FDR family history of NF2 or unilateral VS and two of meningioma, cataract, glioma, neurofibroma, schwannoma, cerebral calcification (if UVS+, ≥ 2 schwannomas only need negative LZTR1 test^a), or

 4. Multiple meningiomas (2 or more) and two of unilateral VS, cataract, glioma, neurofibroma, schwannoma, cerebral calcification, or

 5. Constitutional pathogenic NF2 gene variant in blood or identical in two tumors^b
-

NF2: neurofibromatosis type 2, FDR: first-degree relative, VS: vestibular schwannoma, UVS: unilateral vestibular schwannoma, LZTR1: leucine zipper-like transcription regulator 1

^aIncludes two of any tumor type, such as schwannoma

^bRequires molecular analysis

5. Treatment

5.1. Treatment of Neurofibromatosis Type 1

NF1 is mainly treated symptomatically or surgically. There is no possibility of treating it causally [26].

New drugs used in the treatment of NF1 include:

Sulmetinib

In May 2020, the FDA approved sulmetinib for the treatment of children with NF1 who are above the age of two and have inoperable plexiform neurofibromas. Its mechanism of action involves inhibiting the RAS pathway. In phase I clinical trials, approximately 31% of participants experienced a reduction in the size of plexiform neurofibromas. In phase II clinical trials, 84% of participants showed no progression in tumor size since the beginning of treatment. Additionally, participants reported an improvement in quality of life by 48% and a decrease in the impact of pain on daily functioning by 38%. Side effects of the drug include nausea, diarrhea, and elevated.

creatinine kinase levels [26, 27].

Imatinib

This drug is a tyrosine kinase inhibitor. It may lead to a reduction in the size of plexiform neurofibromas by approximately 26.5%. However, it has several side effects, such as neutropenia, elevated aminotransferase levels, edema, and weight gain [28].

Trametinib

Trametinib is a MEK inhibitor. In clinical trials, it is used to treat inoperable low-grade gliomas and plexiform neurofibromas. Interestingly, the drug has better results in

younger patients. It shows efficacy in halting disease progression at around 44.2% for low-grade gliomas and 42.9% for plexiform neurofibromas. Side effects of trametinib include paronychia, diarrhea, skin toxicities, and elevated creatinine kinase levels [26,29].

For the treatment of skin lesions, dermatological care is employed. If pigmentation issues affect quality of life, camouflage techniques can be utilized. Surgical excision is an option for neurofibromas that lower quality of life, cause pain, and impair functioning. Plexiform neurofibromas can be treated surgically or with the aforementioned medications if they are.

inoperable [11, 12, 26, 27, 28, 29].

Early detection of bone abnormalities is crucial. Therefore, children with NF1 should undergo annual orthopedic examinations. Congenital tibial dysplasia requires the care of a skilled pediatric orthopedist experienced in such cases. Scoliosis can be treated with exercises, braces, or, in severe cases, surgery [11, 12].

Patients with NF1 should undergo cardiovascular examinations by experienced pediatric cardiologists if abnormalities are detected during physical examinations. They should also undergo echocardiography and imaging of renal arteries [11, 12].

In cases of neurocognitive deficits, neuropsychological assessments are important, followed by early implementation of appropriate therapy, which may include pharmacological treatment [11, 12].

For symptomatic gliomas, surgical treatment, chemotherapy with carboplatin and vincristine should be considered. NF1 patients should be under the care of an ophthalmologist. In case of seizures in children, brain imaging should be performed [11, 12].

Additionally, NF1 patients should undergo regular imaging examinations to monitor for the presence of new tumors [11, 12].

5.2. Treatment of Neurofibromatosis Type 2

Treatment of NF2 typically involves symptomatic management or surgery. There is no curative treatment available [26].

There is a possibility to halt the development of vestibular schwannoma by using bevacizumab, a monoclonal antibody against VEGF-A. This can lead to tumor size reduction and improvement in hearing in more than half of the patients. Side effects of the medication include menstrual cessation, proteinuria, and hypertension [26, 30].

Patients with NF2 should undergo regular ophthalmologic, neurological, dermatological, and audiological evaluations annually. Cranial and spinal MRI scans should be conducted every 2-3 years starting from the age of 10 [31].

Vestibular schwannomas can result in sensorineural hearing loss, and both radio-surgical and surgical treatments can further contribute to hearing loss. To improve the quality of life for patients, auditory brainstem implants, cochlear implants, and hearing aids are utilized. Additionally, auditory rehabilitation is important [31, 32].

6. Conclusions

The diagnostic and therapeutic process of neurofibromatosis type 1 and type 2 is a major challenge for clinicians. Given the complexity of the problem, the authors of this article wish to emphasize the importance of effective diagnosis of phakomatosis. In conclusion, clear and lucid diagnostic criteria based on scientific research can facilitate physicians in making a diagnosis and introducing therapeutic processes with a particular focus on anticancer prevention.

Author's contribution

Conceptualization, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; methodology, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; software, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; check, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; formal analysis, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; investigation, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; data curation, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; writing – rough preparation, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; writing – review and editing, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; supervision, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; project administration, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska; receiving funding, Michał Leśniewski, Iwona Welian-Polus, Izabela Oleksak, Karolina Maliszewska.

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