Neurofibromatosis type 1: A Narrative Review on Epidemiology, Clinical Manifestations and Management

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Abstract-One in 2,500 persons worldwide have neurofibromatosis type 1 (NF1), a prevalent neurogenetic condition. There is a 50% chance of passing it on to their offspring because it is an autosomal dominant disorder. Café-au-lait macules, neurofibromas or plexiform neurofibroma, skinfold freckling, an optic pathway tumour, two or more iris hamartomas, a distinctive bone lesion, or a first-degree relative with NF1 are required for the diagnosis of NF1. Café-au-lait spots, freckled skin folds, generalised hyperpigmentation, blue-red and pseudoatrophic macules, plexiform neurofibroma, juvenile xanthogranuloma, glomus tumour, melanoma, nevus anemicus, and pruritus are examples of cutaneous manifestations of NF1. Learning difficulties and attention deficit hyperactivity disorder (ADHD) are among the NF1 non-cutaneous manifestations, as are orthopaedic, neurologic/psychiatric, ophthalmologic, and other conditions. Treatment options for NF1 include genetic counselling, referrals to other experts, and therapies like speech, occupational, or physical therapy. To create new treatments for NF1, ongoing research is being done.

Keywords: **Neurofibromatosis type-1, neurogenetic disorder, rare disease, Cutaneous manifestations**

INTRODUCTION

The neurogenetic disorder neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, affects 1 in 2,500 persons globally. Art and literature from the third century BCE contain descriptions of NF1 that are compatible with the condition. (1). In 1882, Friedrich Daniel von Recklinghausen published his landmark paper (in German), "On the multiple fibromas of the skin and their relationship to the multiple neuromas," which marked the beginning of the recognition of neurofibromatosis as a distinct disorder. Riccardi classified heterogeneous neurofibromatosis disorders into eight categories in 1982, although several of these categories have not been universally accepted (2). NF1 and NF2 have remained as originally classified. A consensus development conference was held by the US National Institutes of Health (NIH) in 1987 to provide uniform diagnostic standards for NF1 patients. (3)

EPIDEMIOLOGY

The average global prevalence of neurofibromatosis type 1 is one case per 3,000 individuals. However, prevalence estimates vary by country and range from one case per 960 individuals in Israel to one case per 7,812 individuals in Russia (1). Only 50% of people have a family member with NF1, despite the fact that it is an autosomal dominant condition (familial cases). As a result, 50% of patients will have NF1 for the first time in their family due to a sporadic NF1 gene mutation. Malignancy is the primary cause of death before the age of 30, with life expectancy falling by 8–15 years in comparison to the general population.(3). The creation of a global online registry for NF1 patients will probably lead to the discovery of new information on the epidemiology of this widespread disorder.(4). However, epidemiological research on neurofibromatosis type 1 faces many challenges, including the lack of population-based registries that record patients in most countries (1).

CLINICAL PRESENTATION

The NIH Consensus Development Panel initially set the diagnostic standards for NF1 in 1987 and revised them in 1997. Combination of these two clinical characteristics are necessary for the diagnosis of NF1: Six or more café-au-lait macules with diameters larger than 5 mm in a prepubescent patient and greater than 15 mm in a postpubescent patient, more than or equal to 2 neurofibromas or 1 plexiform neurofibroma, skinfold freckling (axillary or inguinal), an optic

pathway tumour, multiple iris hamartomas, a distinctive bony lesion, and a first-degree relative with neurofibromatosis type 1 are other (5).

CUTANEOUS MANIFESTATIONS OF NF1

Pigmentary:

Café-au-lait spots are generally the heralding feature of NF1. Café-au-lait spots are hyperpigmented flat spots that are oval or rounded with fairly smooth borders. They must be at least 0.5 cm in diameter in prepubertal individuals and 1.5 cm in post pubertal patients. Many people have them at birth, and throughout the first five to seven years of life, they get bigger and more numerous. Most, but not all, patients with NF1 have café-au-lait spots (5).

Skin fold freckling (Crowe sign) is the most specific of the cardinal criteria for NF1 (Fig 5). It is considered nearly pathognomonic. It is second only to CALMs in age-related frequency and generally occurs between 3 and 5 years of age in either the axillae or groin; most adults have the freckling (90%) (2). Skinfold freckling occurs in 50% of children with NF1 by ten years of age (3)

Generalized hyperpigmentation also noted (although not extensively studied) is a generalized hyperpigmentation in NF1 patients compared to their unaffected parents or siblings. Interestingly, the active body regions of patients with segmental NF1 often have a background of hyperpigmentation that is sharply demarcated from the uninvolved skin (2).

NONCUTANEOUS MANIFESTATIONS

Children with NF1 are more likely to experience learning difficulties, cognitive delays, and attention deficiencies in addition to clinical issues connected to tumours. The average IQ of children with NF1 is 85 in comparison to the general population.(3).

Orthopaedic

A coordinated interaction between bone-forming cells and bone-resorbing cells (osteoclasts) is necessary for the development and maintenance of healthy bone (osteoblasts). As previously shown in samples from people with tibial dysplasia and neurofibromatosis type1, the bone abnormalities seen in people with NF1 are caused by the loss of both copies of NF1 in osteoclasts and osteoblasts. Numerous Nf1-conditional knockout mice strains that are utilised to simulate tibial bending, dystrophic scoliosis or kyphosis, or poor tibial union have been shown to have enhanced osteoclast and decreased osteoblast activity.(1). The most common orthopaedic problems are hypotonia and poor coordination. Skeletal dysplasia, bony erosion, demineralization, no ossifying fibromas, and scoliosis are all features of NF1 (5).

Scoliosis: The most typical forms of scoliosis in NF1 are upper or lower thoracic. Rarely, scoliosis can become dystrophic and cause severe disfigurement.(3)

Cortical thinning and bending are symptoms of long bone dysplasia, which can result in a pathologic fracture. Pseudarthrosis develops from fractures that cycle repeatedly and heal only partially ("false joint")(3)

NEUROLOGIC/PSYCHIATRIC

Peripheral and Spinal Cord Involvement

Neurofibromatosis type 1 (NF1) affects the peripheral and central nervous systems. Cutaneous neurofibromas involve peripheral nerves, while plexiform neurofibromas involve larger nerves, Plexi, spinal roots, sympathetic nerves, and small peripheral nerve fibres. These tumours can cause pain and erosion of neural foramina or cord compression. High cervical cord lesions can cause ataxia, brisk deep tendon reflexes, bilateral ankle clonus, and paraesthesia of the hands and feet (5).

Dural ectasias can cause back pain, particularly when the affected nerve roots are in the spine's lumbar (lower back) region. Dural ectasias can occur without any nerve root tumours, but they can also be a sign of underlying conditions such as Marfan syndrome or Ehlers-Danlos syndrome. Rarely, Dural ectasias can lead to the development of an anterior meningocele, which is when the membranes encasing the brain and spinal cord protrude through a hole in the skull or spinal column. (5).

Learning disabilities and attention deficit hyperactivity disorder

Neurological signs of NF1 include attention deficit hyperactivity disorder and learning impairments. It is estimated that up to 60% of people with NF1 may have some form of learning disability or attention deficit disorder (ADD). While there is no specific learning disability that is characteristic of NF1, visual-spatial

difficulties are common, and attention deficit disorder with or without hyperactivity is also frequently seen in people with this condition. While the intelligence of people with NF1 is generally normal, mental retardation may occur in fewer cases (less than 3%). It is important to recognize and address learning disabilities and attention deficits in people with NF1, as they can lead to school problems and difficulty achieving academic potential (5).

OPHTHALMOLOGIC

Lisch nodules and optic gliomas are two medical conditions that can occur in people with neurofibromatosis type 1 (NF1). Lisch nodules are small, dome-shaped, hyperpigmented (darkened) patches on the eye's iris. They are a common finding in people with NF1 and are included as a diagnostic criterion for this condition. They do not usually cause any vision impairment and can be detected through a slit lamp examination by an experienced ophthalmologist. If the diagnosis of NF1 is uncertain, it may be necessary to refer the patient or family member for a complete eye examination. (2).

A tumour on the optic nerve, which carries imaging data from eye to brain, is referred to as an optic glioma.. It is present in 15-20% of people with NF1 and can cause symptoms such as eye proptosis (protrusion of the eye), decreased visual acuity, or precocious puberty (early onset of puberty). Optic gliomas tend to present before age 6, and most children with this condition are diagnosed by age 3. There is controversy over the diagnosis and management of optic gliomas. However, it is generally recommended that children under 8 with NF1 undergo annual evaluation by a skilled ophthalmologist or neuro-ophthalmologist. This evaluation should be continued every two years until they are 18. There is no strong evidence that routine screening with neuroimaging (such as MRI) benefits asymptomatic individuals, but imaging may be appropriate if a reliable eye examination cannot be performed. (2).

MANAGEMENT

Since NF1 is inherited in an autosomal dominant manner, which means that if a person has it, they have a 50% chance of passing it on to their kids, they should obtain genetic counselling. Additionally, it is critical that those who have NF1 are informed of the potential complications that may result from the disorder, such as learning difficulties, visual issues, and tumours that may result in physical deformities or other issues. Genetic counselling can help individuals with NF1, and their families understand the risks and potential outcomes of the condition and can also provide support and guidance for managing it (5).

Dermatologists play a key role in diagnosing and managing NF1, as they are often the first healthcare providers to identify the characteristic skin changes associated with the disorder. They may also make referrals to other specialists, such as geneticists or neurologists, for further evaluation and management of the condition. The primary treatment for neurofibromas is surgical removal, which may be done for cosmetic or functional reasons, as the tumours can cause discomfort or functional impairment. Sometimes, the dermatologist may refer the patient to a plastic surgeon or another specialist to remove the neurofibromas. There are also ongoing research efforts to develop new treatments for neurofibromas, including agents specifically directed at the plexiform neurofibroma (a type of neurofibroma that grows along the nerve). These studies may lead to the developing of new treatments that can help manage the symptoms of NF1 and improve the quality of life for people with the condition (2). Lovastatin is a medication that belongs to a class of drugs known as HMG-CoA reductase inhibitors or statins. Statins are primarily used to lower cholesterol levels in the blood and reduce the risk of heart disease. They work by inhibiting the enzyme HMG-CoA reductase, which is involved in the production of cholesterol in the liver. Research in mice has suggested that lovastatin may have some potential benefits for treating NF1 (6).

If a child has developmental delays, it is important to seek appropriate therapies to help them reach their full potential, which may include interventions such as speech therapy, occupational therapy, or physical therapy. These therapies can help children with developmental delays improve their skills and abilities and help them cope better with any challenges they may face. It is a good idea to get a neuropsychological examination if there is suspicion that a kid has a learning or intellectual problem. A neuropsychologist is a specialist who can assess a child's cognitive and behavioral functioning and provide recommendations for treatment and support. If a child has attention deficit hyperactivity disorder (ADHD), stimulant

medications may be considered part of their treatment plan (7).

CONCLUSION

NF1 is a kind of neurofibromatosis sometimes referred to as von Recklinghausen disease. Even though NF1 is an autosomal dominant disease, only 50% of people have a family relative who has the disorder (familial cases). It is expected that fresh information on the epidemiology of this widespread disorder will become available with the creation of a global online registry for NF1 patients. However, there are several obstacles in the way of doing epidemiological studies on neurofibromatosis type 1—among them is the fact that most nations lack population-based registries for patient tracking. Neurological signs of NF1 might include attention deficit hyperactivity disorder and learning impairments. Additionally, it is critical that those who have NF1 are informed of the possible issues that may develop as a result of the disorder, such as learning impairments, visual issues, and tumours that may result in physical abnormalities.

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