



Neurofibromatosis: A Family Case Report and Literature Review.

Orthopaedics

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ABSTRACT

The term neurofibromatosis (NF) is used for a group of genetic disorders that primarily affect the cell growth of neural tissues. It is broadly divided into two categories: (a) von Recklinghausen's neurofibromatosis or NF-1, (b) bilateral acoustic neuroma or NF-2. Neurofibromatosis type 1 (NF1) is the most common type of NF, and accounts for about 90% of all cases. It is one of the most frequent human genetic diseases, with a prevalence of one case in 3,000 births. The expressivity of NF1 is extremely variable, with manifestations ranging from mild lesions to several complications and functional impairment. We describe three cases of neurofibromatosis type 1 in a family. The aim of this article is to report the NF1 in a family with different manifestations and to review the literature.

KEYWORDS:

Genetic diseases, Neurofibromatosis type 1, von Recklinghausen's disease, café-au-lait spots, Lisch nodules.

Introduction:

The term neurofibromatosis (NF) is referred to a group of genetic disorders that primarily affect the cell growth of neural tissues. There are two forms of NF: Type 1 (NF1) and type 2 (NF2) [1-3]. These two forms have few common features and are caused by mutations on different genes [4,5].

Neurofibromatosis type 1, also known as von Recklinghausen's disease, is a neurodermal dysplasia. This disease was first described by Friederich Daniel Von Recklinghausen, the pathologist, in 1882 [4,6]. The pathological alterations behind it begin in the embryonic period, prior to differentiation of the neural crest [4,7]. NF1 is the most common type of NF and is estimated to occur in 90% of all cases. It is one of the most frequent human genetic diseases, with a prevalence of one in 3,000 births [1,8]. There is no sex or racial predilection.

Nf1 is an autosomal dominant disease caused by a spectrum of mutations that affect the NF1 gene located at the 17q11.2 chromosome. It has one of the highest rates of spontaneous mutation among genetic diseases in humans. Around 50% of the NF1 patients have a positive family history of the disease. The rest of the patients represent spontaneous mutations. The expressivity of the disease is extremely variable, with manifestations ranging from mild lesions to several complications and functional impairment. The penetrance, otherwise, is 100% [2,8].

Café-au-lait spots, axillary and inguinal freckling, optic gliomas, Lisch nodules (pigmented hamartomas of the iris), spinal and peripheral nerve neurofibromas, neurological or cognitive impairment, scoliosis, abnormalities in the oral and maxillofacial region, malignant tumors of the nerve sheath, pheochromocytoma, vasculopathy, and specific bone lesions are common clinical features of NF1 [2,5]. Oral manifestations can be found in almost 72% of NF1 patients [9]. We report on a family with NF1, who have different manifestations of the disease.

Case report:

A 15 year old male boy brought to Orthopedic OPD with complaints of abnormal swelling in leg. During clinical examination, we found clinical manifestations of neurofibromatosis. On taking detailed history we found similar complaints in other family members also. We examined all of them and described them in the following text:

Case 1 - A 15 year old male child presented to orthopaedic opd. The disease started with swelling right lower limb since 11 years with gradual lengthening of limb. Patient had difficulty in walking for 9 years for which he consulted many doctors.

On clinical examination patient had nodules over right thigh with multiple hyperpigmented macules over chest and back about 5mm to 1 cm in size which were gradually increasing in size. Lisch nodules, scoliosis, anterior bowing of right tibia, right ASIS at higher level was present. Axillary freckling or plexiform neurofibroma was absent.



(Case 1st clinical photograph)



(Case 1st clinical photograph)



(Radiograph of Pelvis with both Hip joints AP View)



(Radiograph of Right Leg)

(Radiograph of Right Thigh)

Case 2- A 34 year male patient who was father of above patient presented with multiple nodular swelling all over his body including face and neck. Swellings initially started on left thigh and gradually involved whole body and gradually increased in size. Swellings were painless.

On examination multiple non tender nodules all over body with hyperpigmented macules on chest and on both thighs. Lisch nodules were present on ophthalmic examination. Axillary freckling or plexiform neurofibroma was absent.

(Case 2nd Clinical Photograph)(Case 2nd Clinical Photograph)

Case 3- A 38 year old male who was uncle of 1st patient presented with multiple nodules all over the body. Initially Nodule appeared on chest around 25 years back and gradually involved whole body.

On examination multiple non tender nodule all over the body including face and neck. No Lisch nodules were present on ophthalmic examination. No skeletal deformity. Axillary freckling was present.

Discussion:

NF-1 is caused by an alteration of the *NF-1* gene. This gene is a tumor suppressor located on the long arm of chromosome 17 (17q11.2).[3,7] Loss of this gene's function due to a mutation leads to an increase in cell proliferation and development of tumors.[3]

The *NF1* gene encodes neurofibromin, a cytoplasmic protein that is predominantly expressed in neurons, Schwann cells, oligodendrocytes, and leukocytes [10].

This disease is a slowly evolving neurodermic dysplasia. Troubles begin at the embryonic stage before differentiation of the neural crests. After birth, the disease evolves in bursts, especially during growth, puberty, and pregnancy. This is a dominant autosomal hereditary disease with total penetrance and variable expression; about 50% of cases, however, are sporadic. Von Recklinghausen's neurofibromatosis has the highest rate of spontaneous mutation in all human genetic diseases. Its incidence is 1 to 2 in 2000 to 3000 of the population as a whole, but reaches to 1 in 200 of mentally retarded individuals [4,11].

Pigmented lesions are a common manifestation in NF-1 called Café-au-lait spots [3-5,7]. Café-au-lait spots are hyperpigmented maculae that may vary in color from light to dark brown. Their borders may be smooth or irregular. They may appear anywhere on the skin, but they are less common on the face. Inguinal and axillary freckles (Crowe's sign) are frequently present. In some patients with NF1, freckling may occur diffusely over the trunk, extremities, upper eyelids, and base of the neck.[3]

Neurofibromas are benign complex tumors. They arise from peripheral nerve sheaths and constitute one of the main manifestations of NF1. A solitary neurofibroma may occur in an individual who does not have NF1, but multiple neurofibromas tend to develop in a person with NF1. Clinical observations suggest that there are at least two major types of neurofibroma which may differ widely in their natural history: 'Discrete' or 'localized' and 'plexiform' neurofibroma. [3,5]

A localized neurofibroma arises from a single site along a peripheral nerve and presents as a focal mass with well-defined margins. It can occur superficially or may involve deeper peripheral nerves. A localized neurofibroma is the most common type of neurofibroma occurring in NF1 patients. They are rarely, if ever, present at birth and usually appear in late childhood or early adolescence.[3] The number of localized neurofibromas tends to increase with age, which varies widely from person to person. Neurofibromas are found mostly on the skin. Nevertheless, many organs may be involved, including the stomach, intestines, kidney, bladder, larynx, and heart. In the head and neck region, the most commonly affected sites are the scalp, cheek, neck, and oral cavity.[1]

Plexiform neurofibroma spreads along the peripheral nerve and may affect some nervous rami. The cranial nerves most involved are the fifth, ninth, and tenth.[3,5] About 21% of the patients with NF-1 have plexiform neurofibromas.[7] The morbidity of plexiform neurofibromas in NF-1 is high, as they tend to grow up to a great size, producing disfigurement. Moreover, the risk of malignization is between 2-5%.[3] Plexiform neurofibroma on the face can also cause facial asymmetry.[12]

Skeletal involvement is present in almost 40% of the patients with NF-1. Scoliosis is the most common skeletal pathology.[4,6,7]

Various neurological pathologies can also be found, such as, hamartomas of the iris, neurinomas of the acoustic nerve, tumors of the central nervous system (gliomas, glioblastomas), macrocephalies, and mental retardation (in 40% of cases).[4,5]

Optic pathway tumors (OPT) are a frequent finding. OPT is usually localized in the prechiasmatal, chiasmatal, and postchiasmatal regions. Massive involvement of the optic system can damage the optic nerves and result in blindness.[13]

Oral manifestations were found in 72% of the patients with NF1.[12] According to a survey performed by D'Ambrosio *et al.*, 66% of his NF1 patients had at least one intraoral manifestation of the disease and

58% presented with manifestations in the maxilla and the mandible, which were detected on panoramic radiographs.[9] Neurofibromas may appear in any tissue, soft or hard, in the oral cavity. The most commonly affected site is the tongue.[3,4,7,14]

Histologically, neurofibromas are composed of a mixture of Schwann cells, perineurial cells, and endoneurial fibroblasts, which are not capsulated.[16] Schwann cells account for about 36 to 80% of the lesional cells. These constitute the predominant cellular type and they usually have widened nuclei with an undulated shape and sharp corners. In an electron microscope image, Schwann cells can be seen embracing the axons.

Neurofibromatous lesions usually evolve slowly, without pain, but during growth, puberty, or pregnancy, their evolution may be accelerated.[4]

Multiorgan occurrence of NF1 requires a multidisciplinary approach. As there is no medical treatment for NF1, the management must be toward prevention and control of the complications. The rate of malignant transformation of NF1 is low (3 – 5%). Surgical treatment is not always satisfactory, as the complete removal of large and also multiple lesions is very difficult. Surgical intervention is indicated when the patient's function is impaired. Risk, possible complication, and expected benefit gained by such procedures should be considered.[17]

The NF1 patients may receive genetic consulting.[18] These patients should be advised that the disorder is autosomal dominant and that the inheritability is 50% in both sexes. As NF1 is one of the most common genetic diseases, and oral manifestations can be found in almost 72% of the cases, dentists should be aware of the characteristics of this disease. It is important to conduct a long-term follow-up, because of local complications and the risk of malignant transformation. In cases with a rapid increase in size of the neurofibroma and presence of pain, the probability of malignant transformation must be considered.[19] Incisional biopsy should be performed for histopathological evaluation.

Conclusion:

Nf1 is a multisystem disorder requiring management by multiple disciplines, often coordinated through a primary care physician or a geneticist. As neurofibromatosis is an autosomal dominant inherited disease, genetic consulting is necessary before marriage and before becoming pregnant, as well.

Conflict of interests: None.

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