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Orapuh Journal

REVIEW ARTICLE

Neurofibromatosis: A brief review for the dental health care professional

Adamu, V. E. [2, 3], Adebo, D. O. [1], & Eneojo, N. I. F. [2]

[1] Dental Therapy Department, Federal College of Dental Technology & Therapy, Enugu, Nigeria
[2] Allied Health & Biological Sciences Department, Legacy University, Banjul, The Gambia
[3] School of Global Health & Bioethics, Euclid University (Pôle Universitaire Euclide)

ARTICLE INFO

Received: 18 September 2020
Accepted: 24 October 2020
Published: 16 April 2021

Keywords:
Neurofibromatosis, oral manifestations, dental health care professional, NF1, NF2, schwannomatosis

Peer-Review: Externally peer-reviewed

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Correspondence to:
Lead-Author: Dorcas Ojone Adebo
@gmail.com

To cite:
Adamu, V. E., Adebo, D. O., & Eneojo, N. I. F. (2021). Neurofibromatosis: A brief review for the dental health care professional. *Orapuh Journal*, *2*(1), e806.

ISSN: 2644-3740

ABSTRACT

Neurofibromatosis is a genetic neurological disorder that affects cell growth in nerve tissue. It produces tumors, which may become malignant, and may cause severe pain and debilitation, learning disabilities, behavioural dysfunction, and hearing and vision loss. Sporadic cases of this disorder have been reported in some parts of the oral and maxillofacial complex. It is important for dental health care professionals to be aware of the characteristics of this disorder so they may evolve strategies to promote oral health and improve the quality of life for sufferers. This review paper provides summarized information on the concept, classification, epidemiology, aetiology, oral manifestations, other signs and symptoms, diagnosis, and management of neurofibromatosis that may be necessary for the practice of the dental operator.

INTRODUCTION

The term neurofibromatosis (NF) is used for a group of genetic neurological disorders that affects cell growth in nerve tissue (Hanemann, 2008; Beltrani, 2013). It produces tumors of the skin, internal organs, and nerves that may become cancerous (malignant). It can also affect bones, causing severe pain and debilitation, and may result in learning disabilities, behavioral dysfunction, and hearing and vision loss. There are three major clinically and genetically distinct forms of neurofibromatosis: neurofibromatosis type 1 and 2 (NF1 and NF2) and schwannomatosis (Hanemann, 2008). According to Beltrani et al. (2013), neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease, 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 1 case in 3,000 births. The expressivity of NF1 is extremely variable, with manifestations ranging from mild lesions to several complications and functional impairment. Oral manifestations can be found in almost 72% of NF1 patients.

NF manifests in the oral cavity. Evans (2009) posited that sporadic cases of NF have been reported in the submandibular gland, tongue, and on the periosteum at the mental foramen. Beltrani et al. (2013) reviewed the case of a patient with NF1 who presented with gingival neurofibroma in the attached gingivae of the lingual aspect of the lower central incisors. The lesion was nodular, with a sessile base, non-ulcerated, painless, with normal colour, and measured 1 cm in diameter. An excisional biopsy of the oral lesion was performed. Histopathological and immunohistochemical analysis confirmed the clinical hypothesis of neurofibroma.

There is no cure for neurofibromatosis (Hanemann, 2008).

Because NF is one of the most common genetic neurological disorders and oral manifestations are very common, dental operators should be aware of the characteristics of this disease (Beltrani, 2013).

CLASSIFICATIONS OF NEUROFIBROMATOSIS

According to Sau et al. (2009), NF has been classified into three distinct types:

Neurofibromatosis 1 (NF1): also known as von Recklinghausen NF or Peripheral NF is the most common type of NF. Occurring in 1:3,000 births, it is characterized by multiple spots (macules) and neurofibromas on or under the skin. The condition is called segmental NF1 when clinical features are limited to only one area of the body. Enlargement and deformation of bones and curvature of the spine (scoliosis) may also occur. Occasionally, tumors may develop in the brain, or on cranial nerves, or the spinal cord. About 50% of people with NF1 also have learning disabilities.

Neurofibromatosis 2 (NF2): also known as Bilateral Acoustic NF (BAN), is much rarer, occurring in 1:25,000 births. NF2 is characterized by multiple tumors on the cranial and spinal nerves, and by other lesions of the brain and spinal cord. Tumors affecting both of the auditory nerves are the hallmark. Hearing loss beginning in the teens or early twenties is generally the first symptom.

Schwannomatosis: a rare form of NF that has only recently been recognized and appears to affect around 1 in 40,000 individuals. It is less well understood than NF1 and NF2, and features may vary greatly between patients. Unlike NF1 and NF2, the inheritance patterns of schwannomatosis are not understood due largely to the lack of cases to study. However, it is estimated that 85% of cases are, in fact, sporadic (no previous family history) and 15% are inherited

EPIDEMIOLOGY OF NEUROFIBROMATOSIS

According to Haris et al. (2008), the prevalence of NF is about 1/3,000. There are no known ethnic groups in which NF does not occur or is unusually common. The prevalence is somewhat higher in young children than in adults, a difference that probably results at least in part from the early death of some NF patients. NF is fully penetrant in adults, but many diseases feature an increase in frequency or severity with age. Haris et al further stated that the reproductive fitness of NF patients is reduced by about one-half. About half of all cases result from new mutations. The estimated rate of new NF mutations is unusually high, but the basis for this high mutation rate is not known.

The typical age of onset of symptoms is in the late teens to early 20s, but the age range covers the entire life span, including congenital forms in infancy through the elderly. Some evidence indicates that the age of onset of clinical symptoms is lower in maternally transmitted NF. While NF is quite variable in severity from person to person, family studies have shown some intrafamilial consistency in the age of onset. Somatic mosaicism for the NF mutation in sporadic cases may also complicate the clinical picture, resulting in under-diagnosis or late diagnosis (Haris et al., 2008).

AETIOLOGY OF NEUROFIBROMATOSIS

NF is the most common genetic neurological disorder that is caused by a single gene (Sahin et al., 2011).

According to Marocchio et al. (2007), NF occurs throughout the world and affects men and women of all races and ethnic groups.

NF is caused by gene mutations. The mutated genes cause uncontrolled cell growth. Mayo Clinic (2021) posited that the following as the causes of the NF types (also supported by the work of Goutagy & Parfait (2013):

"NF1: The NF1 gene is located on chromosome 17. This gene produces a protein called neurofibromin that helps regulate cell growth. The mutated gene causes a loss of neurofibromin, which allows cells to grow uncontrolled

"NF2: The NF2 gene is located on chromosome 22, and produces a protein called merlin (also called schwannomin), which suppresses tumours. The mutated gene causes a loss of merlin, leading to uncontrolled cell growth

"Schwannomatosis: 2 genes are known to cause schwannomatosis. Mutations of the genes SMARCB1 and LZTR1, which suppress tumours, are associated with this type of neurofibromatosis."

ORAL MANIFESTATIONS OF NEUROFIBROMATOSIS

Oral manifestations of this disorder are showing an incidence ranging from 4% - 7%. The most frequently involved sites are the tongue, buccal mucosa floor of the mouth, and vestibule. The palate and maxillary and mandibular bones are rare localization of the disease. Impacted, displaced, or missing teeth, paresthesia, pain, and bleeding are infrequent manifestations of NF that may occur in association with neurofibromas in the oral cavity. Oral manifestations usually present as sub-mucosal, non-tender, asymptomatic, raised lesions, multiple neurofibromas on the tongue, solitary neurofibroma on the hard palate, and isolated palatal lesions. The manifestations that are specific to the oral cavity include enlarged fungiform papillae on the dorsum of the tongue and diffused enlargement of the gingivae, and involvement of the alveolar bone (Johann et al., 2008).

OTHER SIGNS AND SYMPTOMS OF NEUROFIBRPOMATOSIS

NF causes tissue along the nerves to grow uncontrollably. This growth can put pressure on affected nerves. It can cause pain, severe nerve damage, and loss of function in the area served by the nerve. Problems with feeling or movement can occur, depending on which nerves are affected.

The condition can be very different from person to person, even among people in the same family who have the NF1 gene (Johann et al., 2008).

"Coffee-with-milk" (café-au-lait) spots are the hallmark symptom of NF (New York Times [NYT] (n.d.). Many healthy people have 1 or 2 small café-au-lait spots. However, adults who have six or more spots that are bigger than 1.5 cm in diameter (0.5 cm in children) are likely to have neurofibromatosis. In most people with the condition, these spots may be the only symptom (Safavi-Abbasi et al., 2010).

Other symptoms may include:

- Blindness
- Convulsions
- Freckles in the underarm or groin
- Large, soft tumors called plexiform neurofibromas, which may have a dark color and may spread under the surface of the skin
- Pain (from affected nerves)
- Small, rubbery tumors of the skin called nodular neurofibromas

(Selch et al., 2004)

DIAGNOSIS OF NEUROFIBROMATOSIS

According to Hivelin et al. (2010), a doctor who treats NF, such as a neurologist, geneticist, dermatologist, or developmental pediatrician will diagnose this condition. The diagnosis will usually be made based on the unique symptoms and signs of NF.

Signs include:

- Colored, raised spots (Lisch nodules) on the colored part (iris) of the eye
- Fracture of the long bones of the leg in early childhood
- Freckling in the armpits, groin, or underneath the breast in women
- Large tumors under the skin (plexiform neurofibromas), which can affect the appearance and put pressure on nearby nerves or organs
- Many soft tumors on the skin or deeper in the body
- Mild cognitive impairment,
- attention deficit hyperactivity disorder (ADHD),
- learning disorders

Tests may include:

- Eye exam by an ophthalmologist familiar with NF
- Genetic tests to find a change (mutation) in the neurofibromin gene

- MRI of the tissue is another test for complications (Aboukais et al., 2013).

MANAGEMENT OF NEUROFIBROMATOSIS

Treatment of neurofibromatosis

According to Pasmant et al. (2010), there is no specific treatment for NF. Tumors that cause pain or loss of function may be removed. Tumors that have grown quickly should be removed promptly as they may become cancerous (malignant). Experimental treatments for severe tumors are under investigation. Some children with learning disorders may need special schooling.

Prevention of neurofibromatosis

Genetic counseling is recommended for anyone with a family history of NF, and annual eye exams are strongly recommended (Femer, 2007).

CONCLUSION

The intra- and extra-oral burden of neurofibromatosis can be enormous. A good understanding of the disorder is essential to step down its negative impact, plan oral interventions, or improve quality of life, for sufferers.

Acknowledgment: We are grateful to the authorities that were cited in this article.

Ethics Approval: No ethical clearance was needed for this work.

Conflict of Interest: The authors declare no conflict of interest.

OrCID iDs: Nil identified.

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