ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 11 | November - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

NEUROFIBROMATOSIS TYPE 1: A GENETIC DISORDER

Dental Science

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ABSTRACT

Neurofibromatoses are genetic disorders of the nervous system. Mainly, these disorders affect the growth and development of nerve cell tissue. The disorders are known as neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (Nf2). NF1 is the more common type of neurofibromatosis. Schwannomatosis has recently been identified as a third and more rare type of neurofibromatosis, but little is known about it. NF1 is characterized by multiple café au lait spots and neurofibromas on or under the skin. Enlargement and deformation of bones and curvature of the spine may also occur. The main aim of presenting the case report of neurofibromatosis type 1 in 48 years old male patient with dermal and oral manifestations is because of its rare occurrence and also due to variability in its severity as some people have only mild symptoms, whilst others can be severely restricted.

KEYWORDS

Neurofibromatosis, Neurofibromas, Caif au lait spots, Genetics.

INTRODUCTION

Neurofibromatosis represents a heterogeneous group of hereditary syndromes that includes neurofibromatosis type 1 (NF1, 96%), neurofibromatosis type 2 (NF2, 3%), and schwannomatosis (SWN), all of which confer susceptibility to the development of tumors in the central and peripheral nervous systems. Neurofibromatosis type 1 is an autosomal dominant tumor predisposition syndrome characterized by pigmentation e.g., café-au-lait spots, freckling in the inguinal and axillary regions, Lisch nodules in the eye and growth of multiple neurofibromas of the peripheral nerves in the skin, brain, and other parts of the body, as well as other tumors e.g., gliomas, malignant peripheral nerve sheath tumors, juvenile chronic myelomonocytic leukemia, rhabdomyosarcoma, pheochromocytoma, and breast cancer.[1] Here we report a unusual case of Neurofibromatosis 1 in 48 years old male with well demarcated dermal and oral findings.

Case study

A 48 year old male patient reported to the Dept of Oral Medicine & Radiology with a chief complaint of bleeding gums. Oral examination revealed poor oral hygiene with moderate generalised gingivitis, carious upper left central incisor, missing lower left first molar and generalised staining. Patient was well built and appeared to be well nourished with intermediate socioeconomic status and normal intelligence. No relevant medical history was mentioned. Physical examination revealed unique features. Large light brown macules corresponding to cafe au lait spots were noticed unilaterally on left lower and middle half of abdomen and also covering the chest bone. (Fig 1) Several freckling and nodular like areas were seen on legs and foot, (Fig 2) arms (Fig 3) facial and neck region (Fig 4) Orally, unilateral enlargement of tongue was seen on the left anterior half of the tongue with small nodular lesions.(Fig 5) Patient gave the history that he was born with this type of dermal and oral manifestations. He also gave family history of similar condition. Based on the history and clinical examination a diagnosis of NF type 1 was made.

DISCUSSION

Dr Friedrich Von Recklinghausen first described the condition in the 19th century. He described the main features of neurofibromatosis shown by 90% of sufferers. NF1 accounts for about 96% of all neurofibromatosis cases, with 30% being family-related, and 70% attributing to sporadic mutations that often occur in paternally derived chromosomes. The mean age of NF1 patients is 38.5 years, and the mean age of NF1 diagnosis is 14.5 years. In the case presented patient gave history of its congenital manifestations with family history. At the molecular level, NF1 is attributable to loss of function heterozygous mutations in the NF1 gene on chromosome 17q11.2 that encodes neurofibromin (NF1) with tumor suppressor function.[2]

Cell growth within the mammalian body is typically controlled by two main types of genes, proto-oncogenes and tumor suppressor genes. NF1, NF2 and SWN are examples of tumor suppressor syndromes caused by germline mutations in a tumor suppression gene. As tumors associated with NF1, NF2, and SWN predominantly affect the central nervous system (CNS) and peripheral nervous system (PNS), significant neurologic morbidity is observed. NF1 occurs due to mutations in the tumor suppressor gene NF1. Targeting peripheral nerves and their supporting structures (including neurilemmal cells), NF1 causes multiple café-au-lait spots (or flat, dark patches) on the skin, freckles in the underarms and groin, Lisch nodules in the colored part of the eye (the iris), and neurofibromas on or just under the skin, often near the spinal cord or along nerves elsewhere in the body. Neurofibromas are benign tumors with mixed cell types including Schwann cells, perineural cells, and fibroblasts, along with mast cells, axonal processes, and a collagenous extracellular matrix. However, these tumors have the potential to transform into malignant peripheral nerve sheath tumors, which contribute to early death in affected patients. As a variant of neurofibroma, plexiform neurofibroma arises from muscle nerve fascicles, and may infiltrate into the surrounding structures. [3] The NF1 gene located on chromosome 17q11.2. Composed of ~350 kb and 57 exons, the NF1 gene produces at least three alternatively spliced transcripts, with the 2818 aa, 327 kDa cell membrane protein, neurofibromin, somatic cell division, adenylyl-cyclase activity and intracellular cyclic-AMP generation. Some affected individuals who acquire de novo NF1 mutation may have somatic mosaicism associated with segmental or unusually mild disease manifestations. Mosaicism may result in segmental, generalized, or gonadal NF1 gene. A person harboring a NF1 pathogenic variant has a 50% chance of passing it to offspring with each pregnancy. However, a person with mosaicism for an NF1 pathogenic variant may have 50% chances of transmitting the disease to offspring.[4]

Nf1 has an estimated incidence of 1 in 2500–3500 births worldwide, without sexual or racial predilection, which makes NF1 the most common autosomal dominant disorder of the nervous system and one of the most common single-gene inherited conditions. NF1 accounts for about 96% of all neurofibromatosis cases, with 30% being family-related, and 70% attributing to sporadic mutations that often occur in paternally derived chromosomes. The mean age of NF1 patients is 38.5 years, and the mean age of NF1 diagnosis is 14.5 years. NF1 is usually associated with the following: Skin lesions: Multiple café-au-lait spots (ovoid tan-brown macules of 0.5–5 cm in size appearing anywhere on the body, with six or more found in 99% of cases by 1 year of age), freckles (axillary and inguinal freckling, with axillary freckling or Crow's sign being pathognomonic for NF-1, 40% of infant cases and 90% by 7 years of age), Lisch nodules (or pigmented iris hamartomas; small, often multiple dome-shaped melanocytic nodules around the iris; 93% of adult cases). Tumors: Neurofibromas (soft iliac-pink tumors of few mm to several cm in diameter, mostly sessile and domeshaped or pedunculated, on the trunk and limbs, or the areola of

female breasts; 60% of cases), papillomatous neurofibromas (on the hard palate, tongue, etc., 5%–10%), gliomas (indolent pilocytic astrocytomas, 15% by the age of 7 years), malignant peripheral nerve sheath tumor (10%), Wilms tumor, rhabdomyosarcoma, leukemia (especially juvenile chronic myelogenous leukemia), myelodysplastic syndromes, retinoblastoma, and malignant melanoma. Other symptoms: Learning disabilities (50%), kyphoscoliosis (2%), pseudarthrosis of tibia or radius (1%), sphenoid wing dysplasia (a characteristic abnormality in NF1), seizure, and vasculopathy. Patients with NF1 have a shortened life expectancy of average of 54 years (due largely to malignancy).[5,6] Cafe au lait spots, freckling and multiple nodules were seen in the case presented.

Despite the advances of molecular biology, the diagnoses of NF I is still based on clinical criteria. The National Institutes of Health Consensus Development Conference has suggested clinical criteria diagnostic of NF I and NF II. Diagnosis of Neurofibromatosis Type I (NF I):

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
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions (Crowe´s sign)
4. Optic glioma
5. Two or more Lisch nodules (iris harmartomas)
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
7. A first-degree relative (parent, sibling, or offspring) with NF I by the above criteria.

The criteria are met in an individual if two or more of the features listed are present as seen in our case.[7]

Histopathologically, NF1-related neurofibroma is a wellcircumscribed, rarely encapsulated spindle cell mass in a mucinous background, along with mast cells, Schwann cells, perineural cells, and blood vessels. Cutaneous neurofibroma is pedunculated, nodular, or plaque-like, whereas internal or deep neurofibroma occurs in the periorbital, retroperitoneal, GI tract, and mediastinal locations. Plexiform neurofibroma shows a variety of cell types (e.g., neuronal axons, Schwann cells, fibroblasts, mast cells, macrophages, perineural cells, and extracellular matrix). Diffuse neurofibroma involves the dermis and subcutaneous fat, fitting the characteristic “bag of worms” description. Plexiform neurofibroma shows an increased risk of transformation into malignant peripheral nerve sheath tumor (MPNST), an aggressive spindle-cell sarcoma that accounts for 5% of all soft tissue sarcomas. About 50% of MPNST occurs in the setting of NF1, with affected patients having an 8%–13% risk of developing this malignant tumor in their lifetime. Cafe-au-lait spots show hyperpigmentation of the basal epidermis with macromelanosomes (giant melanosis). [8]

Neurofibromas in oral cavity most commonly involve the tongue as seen in our case. Other affected sites include lips, palate, buccal mucosa, gingiva, floor of the mouth or the pharynx. Neurofibromas of the tongue are nearly always nodular which was also present in our case. Mild hemimacroglossia was also noted. Oral radiographic findings unique to NF include lengthening, narrowing and rarefaction of coronoid and articular process, deepening of sigmoid notch, an enlarged mandibular canal, mandibular foramen and mental foramen. Other findings are Shortening of the ramus, notching of the inferior border of the mandible and even asymmetrically formed maxillary sinus .Osseous alterations can be the result of soft tissue tumor growing against or within bone, resulting in hypoplasia or resorption. A change in size of a pre-existing mass, compression, or infiltration of the adjacent structures indicates malignant degeneration.[9]

Treatment is mainly symptomatic. Surgical removal of swellings is recommened that give rise to irritation or pressure problems. Regular follow-up is ideal. Deafness, or visual problems such as squint or blurred vision, must be investigated early. Genetic counselling should be given as the child approaches maturity. Blood pressure should be monitored regularly, as there is a higher incidence of a specific tumour of the adrenal gland (phaeochromocytoma) and also narrowing of the renal artery in neurofibromatosis sufferers. Emotional problems associated with neurofibromatosis must not be overlooked. Adolescents are especially concerned regarding skin blemishes, and as the appearance of dermal neurofibromata begins at this time of life, this can be traumatic. Parents will also need support, as their 'guilt' regarding the genetic inheritance of the disease can be very real. NF1 patients with MPNST have a poor 5-year survival rate due to frequent lung and bone metastases as well as local recurrence.[10]

CONCLUSION

Neurofibromatosis is a rare hamartomatous genetic disorder that causes typically benign tumors of the nerves and growths in other parts of the body. NF1 has many dermal manifestations. Occasionally, oral manifestations and oral tissue specimens may provide the opportunity to diagnose NF. The oral manifestations of NF are well-documented but may not be at the forefront of the clinician's mind in the differential diagnosis of intra-oral swelling. A thorough examination and trained eye will provide the opportunity to diagnose NF.

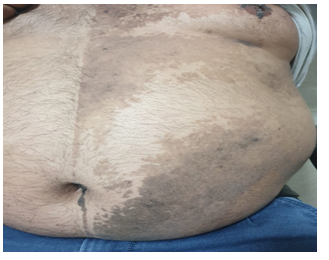

Fig 1: Light brown tan cafe au lait spots in abdomen

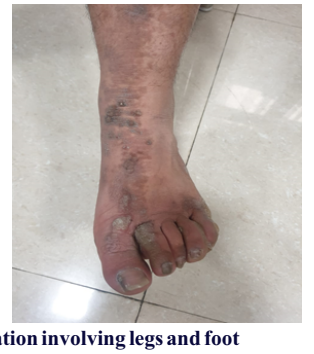

Fig 2: Pigmentation involving legs and foot

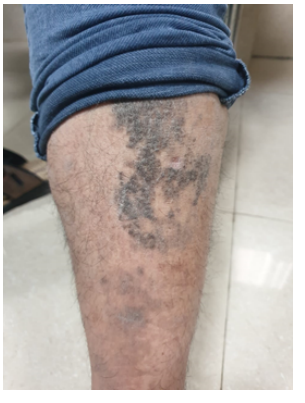

Fig 3: Pigmentations and nodular on arms

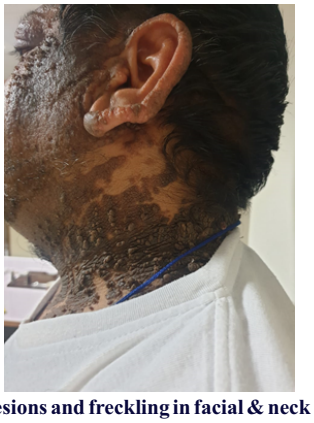

Fig 4: Nodular lesions and freckling in facial & neck region

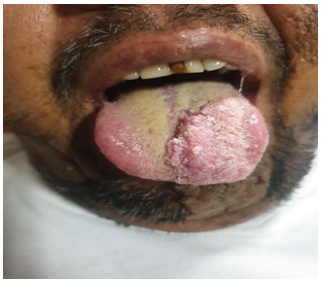

Fig 5 : Hemimacroglossia with small nodules

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