Neurofibromatosis Type I Associated with Malaria: A Case Report and Review of Literature

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Neurofibromatosis (von Recklinghausen disease) is a genetic disorder which is now not been considered to be most common due to a gradual increase in its number of cases worldwide. Its prevalence found is around 1 in 4000-5000 individuals with the incidence been found equally in all regions and reported in almost all ethnic groups. Two-three million cases are reported all over world so far with this disorder. It is an autosomal dominant trait with varied age range of the cases reported from 6 years to late adulthood. Disease occurs by a genetic mutation in the neurofibromatosis Type 1 (NF1) gene (tumor suppressor gene) which is located on chromosome no. 17 at 17q11.2, responsible for coding of neurofibromin, a cytoplasmic protein. The effect of this mutation is elicited in almost all systems of the body with mild to severe complications. About half of the cases reported are present with new mutations in the NF1 genes. A patient afflicted with NF1 has around 50-60% of chances of transmitting the disease to each of his/her offspring. Presenting here a case of the female patient diagnosed malaria associated with NF1.

Keywords: Neurofibromatosis, Neurofibromin, Von Recklinghausen disease

INTRODUCTION

It is an autosomal dominant disorder affecting multiple systems of the body with worldwide distribution and equal male and female predilection. Genetic mutation in NF1/NF2 gene present on chromosome no. 17 and 22, respectively, elicit clinical features of neurofibromatosis (NF). About 50% of cases show new mutations with vague signs and symptoms.¹,²

CASE REPORT

A 48-year-old female patient reported to the Government Medical Hospital with the chief complaint of fever with loose motion and vomiting from past 10-12 days. High-grade fever was associated with chills and sweat along with abdominal pain, headache, body ache, vomiting, and frequent diarrhea. Upon eliciting the past medical history, patient revealed that after her first delivery, when she was 25 years old, she noticed an appearance of multiple hyperpigmented skin macules along with nodular neurofibroma on her hands. At the age of 40 a lot of cutaneous tumors appeared and started growing bigger all over the body surface. In family history, she gave a history of nodular fibroma on hand of her first child, which gradually involved complete body surface. On general examination, the patient was moderately built and nourished with mild fever of 101 Fahrenheit and pulse of 79 beats/min.

Extraoral examination revealed the presence of multiple nodules on the face. The nodules were present all over the body, especially prominent on the face, trunk, back and upper and lower extremities (Figures 1 and 2). These were round to oval in shape of size varying from millimeters to centimeters, with a smooth surface and skin over the nodules was normal. On palpation, these were sessile or pedunculated, soft to firm and nontender. Dark brown macules were also appreciated in the vicinity of these nodules which were smooth edged and of varying diameters (Figure 3). Nodules present on hand and leg as well (Figure 4). Inguinal and axillary freckling was also present. A provisional diagnosis of pyrexia of unknown origin and an additional finding of neurofibromatosis Type 1 (NF1) was given based on the clinical appearance. On intraoral examination a localized fibrous enlargement of gingival with respect to the right side of the mandible which was erythematous and nodular in appearance and was non tender on palpation. Patient had poor oral hygiene.
with generalized gingival recession, bleeding on probing and halitosis. There were no much radiographic changes other than generalized bone loss and sparse trabecular pattern (Figure 5).

Investigations includes blood sample for detection for malarial parasite, complete blood count and urine complete followed by microscopic examination which revealed plasmodium vivax as the causative agent, malaria was given as the final diagnosis with additional of NF1. For treatment of malaria, antimalarial drug, chloroquine 25 mg base/kg bw divided over 3 days, combined with primaquine 0.25 mg base/kg bw, taken with food once daily for 14 days were prescribed with proper diet a rest followed by recall checkup after 14 days.

**DISCUSSION**

NF is a multisystem genetic disorder that predominantly affects cell growth of nerve tissues. It is an autosomal dominant trait with varied age range of the cases reported from 6 years to late adulthood. Disease occurs by a genetic mutation in the NF1 gene (tumor suppressor gene) which is located on chromosome no.17 at 17q11.2, responsible for coding of neurofibromin, a cytoplasmic protein. The effect of this mutation is elicited in almost all systems of the body with mild to severe complications. Most of the complications are associated with dermatological, neural and skeletal changes followed by cardiac and ophtalmic involvement. It is a significant cause of morbidity in adults and children.
In 1882, Friedrich von Recklinghausen reported 2 cases with NF as - “these skin and nerve tumors represent mingling of both neural elements and connective tissue. The term NF was coined by von Recklinghausen, and hence also termed as von Recklinghausen disorder.\(^4\,5\)

**Types**

On the basis of genetic mutations, NF are been classified into three types, although there are many other genetic variants that are reported with multiple neomutations.

a. NF1: Also called as von Recklinghausen disease, is transmitted on chromosome 17 and is caused by mutation (or rarely, deletion) of the NF1 gene. This type causes multiple areas of hyperpigmentation (i.e. birthmarks) that appear shortly after birth. In late childhood, a few to thousands of tumors appear on the skin (called cutaneous lesions) and under the skin (called subcutaneous lesions). Tumors have carcinogenic potential.

b. NF2: This NF results from a mutation (or rarely, deletion) of the NF2 gene and is transmitted on chromosome 22. In this type, multiple neurofibromas are formed along with numerous small tumors that are usually present within the skull (intracranial tumors) and spinal canal (intraspinal tumors). Tumors on the eighth cranial nerve (vestibulocochlear nerve), which are sometimes referred to as acoustic neuromas, are most common. This type causes hearing loss and loss of sense of balance (equilibrium), during early adulthood. Tumors may or may not have potential to become malignant.

c. Schwannomas: It is a rare form of NF with multiple benign tumors (schwannomas) formed in peripheral nerve fiber cells (called Schwann cells). Schwannomatosis does not cause neurological disabilities or malignant tumors. The hallmark of this condition is chronic pain, which can occur in any part of the body, depending on which peripheral nerves are affected.\(^6\)

**Clinical Features**

Clinical signs and symptoms vary from individual to individual. Early signs and symptoms include multiple cutaneous lesions which are more than 4-5 cm in its greatest dimension, best demarcated on fair skinned individual, having smooth or irregular borders and often present on any part of body termed as café au lait spots. They are 6 or more in patients with NF, more commonly present in infancy.\(^7\) Later on numerous small to large soft benign tumors develop all over the body. They are skin colored and non-tender on palpation. They can be cutaneous, subcutaneous and deep-seated in connective tissues. They can become painful and do have malignant transformation potential in around 4-5% of cases. Other associated features are- scoliosis, bony deformities mostly in long bones, hearing loss, difficulty in understanding, blurred vision, presence of Lisch nodules, axillary and inguinal freckling (Crowe’s sign), optic nerve glioma, high blood pressure, short stature. Patient may give a history of his/her offspring or sibling associated with these features either same or even more complicated.\(^1\,8\)

**Oral and Radiographic Features**

Oral manifestations are been reported only in few cases from 5% to 6% of cases. They include presence oral neurofibromas, enlargement of filiform and fungiform papilla. Radiographic findings include enlargement of inferior alveolar canal space and mandibular foramina, sparse trabecular pattern in mandible and maxilla and occasionally intrabony lesions.

Diagnostic criteria: If 2 or more such clinical features are present then the individual is diagnosed as been suffering from NF1.\(^9\,10\)

**Complications**

Being a multi system variant, various complications are associated with NF including central nervous system tumors, optic glioma, NF, gastrointestinal stromal tumors, attention deficit hyperactivity disorders, pseudarthrosis, pheochromocytoma, renal artery stenosis, malignant peripheral nerve sheath tumors.\(^8\,11\)

**Treatment Modalities**

There is no specific therapy for this condition with the treatment being directed toward the prevention or management of complications. It is a disorder with no or minimal cure. Individuals diagnosed with NF1, routine examinations should focus on the potential complications.\(^12\) Proper whole body examinations permit early detection of problems, decreasing morbidity, and improving quality-of-life, followed by eye examinations are important in early detection of optic nerve lesions. Dermatological examinations play an important role in the detection of cutaneous lesions. Periodic monitoring of blood pressure and bone density with proper follow-up.\(^13\)

**CONCLUSION**

Neurofibromas are slow growing which gradually progress from early childhood to late adolescence. Patients diagnosed with this entity have no exact treatment so far but should be carefully monitored with periodic checkup. In case of more severe complications, surgical excision of the nodular swellings is painful; hence, it should be followed by supportive palliative care is prescribed. As this is a progressive disease, lifelong evaluation of the patients for newly forming or pre-existing lesions is important. Dentists may be the first clinicians to observe the occurrence of neurofibroma in the oral cavity as well as observe any
associated radiographic manifestations. Therefore, oral diagnosticians and general medical practitioners should work combined to reach a correct diagnosis.

REFERENCES