ABSTRACT

Neurofibromatosis (NF) is a genetically transmitted autosomal dominant disorder with variable penetrance and about 50% of cases representing new mutations. It is progressive in nature and one of its unique features is the diversity of clinical expression from one patient to another and even within a family. The disease is often characterized by complex and multicellular neurofibroma. It may also lead to different complications throughout the life of an affected individual. We report a case of NF involving alveolus of maxilla and mandible causing expansion of the buccal and lingual cortical plates in a 10-year-old girl.

Keywords: Neurofibromatosis, Mandible, Hypoplastic, Cafe au lait spots.

How to cite this article: Kini R, Naik V, Baliga A, Shetty AP, Girish YR. Neurofibromatosis Type 1 with Unusual Oral Manifestations. J Indian Aca Oral Med Radiol 2012;24(3): 226-229.

INTRODUCTION

Neurofibroma is the most common type of peripheral nerve neoplasm, arising from Schwann cells, perineural fibroblasts or both. The term neurofibroma was coined by von Recklinghausen in 1881. It is a benign tumor that may occur in isolation or as part of neurofibromatosis (NF).

NF is a well-documented multisystem, genetic disorder which has been classified into seven different types by Riccardi.2

The most common type of these are neurofibromatosis 1 and neurofibromatosis 2 (NF1 and NF2). NF1 is an autosomal dominant hereditary disorder due to an alteration in the long arm of chromosome 17. NF1 also known as von Recklinghausen’s disease of skin which accounts for 85 to 97% of the cases of NF.3

Along the course of the disease the embryonic and mesodermal derivatives are mostly affected due to the defect in embryonic neural crest cells.

Neurofibroma, cafe au lait spots and Lisch nodules in the iris forms the cardinal features of NF1.

The second most common type of NF is NF2 which is also an autosomal dominant disorder characterized by bilateral acoustic neuromas, schwannomas and other central nervous system (CNS) tumors like meningiomas. Cafe au lait spots and cutaneous neurofibromas are seen less frequently in NF2. Although NF2 can affect children, it is less common than NF1 among pediatric cases.3

The present case belongs to NF1 form, the clinical features and radiographic changes will be discussed with special emphasis on etiopathogenesis.

CASE REPORT

A 10-year-old girl reported to our department with deformity of left side of the face since birth. The deformity was noted at birth which was very mild to begin with, and the disfigurement increased with the age. No other member in the family had similar defect. Past medical and dental histories were noncontributory. On extraoral examination, head was dolichocephalic and face was leptoprosopic (Fig. 1). Facial asymmetry was noticed in the middle third with increased growth on the left side of the face. Temporomandibular joint showed deviation of the mandible to the right side on opening the mouth. Cafe au lait spots were present in the chin and in neck area (Fig. 2). Two brownish colored macules were present in the chin region, one was 2 × 2 cm in size and other was 1 × 1 cm in size. In the midline of the neck three to four macules were present less than 1 cm in size. On palpation the lower border of the mandible on the left side was thinned out and irregular with a prominent antegonial notch. Multiple right and left submandibular lymph nodes were palpable which were nontender, firm, mobile and less than 1 cm in size. Left ear was lower in position when compared to the right ear and had a small swelling nearly 1 cm in size with brownish pigmentation.

Intraorally, the maxillary and mandibular left alveolar ridges were diffusely enlarged (Fig. 3). In the maxilla the

Fig. 1: Frontal view of the patient showing facial deformity with inferiorly placed left ear
enlargement was pronounced in 25 and 26 region causing expansion of both buccal and palatal cortices. In the mandible it extended from 74 to 36 regions and more on the buccal aspect. On palpation, enlarged alveolar ridges in both maxilla and mandible were bony hard in consistency with a smooth surface. Buccal mucosa on the left side showed folded appearance. Left side of the tongue was enlarged and had scalloped margins. Clefting of the soft palate was noticed with bifid uvula. There was gingival overgrowth in the lingual aspect of mandibular anterior teeth. The color of the gingiva in this region was pale pink. Neither there was bleeding on probing nor tenderness on palpating the area.

Based on these findings a provisional diagnosis of NF was made. Hemifacial hypertrophy and fibro-osseous lesions were considered in the differential diagnosis. The patient was advised hematological and radiological investigations. Hematological values were within normal limits. OPG revealed hypoplastic condylar process and ramus and a well-defined antegonial notch on the left side (Fig. 4). Further, a CT was made which also revealed hypoplastic left ramus and head of the condyle (Figs 5A and B). No additional information was obtained on a CT. As these reports were not conclusive an incisional bone biopsy was performed from the left mandibular alveolar region and the specimen was sent for histopathological examination. Microscopically, it revealed proliferating bundles of fibrous tissue, within which many nerve tissue components were seen. The nerve tissue component also showed proliferation among themselves (Figs 6 and 7). Based on the clinical, radiological and histopathological findings a definitive diagnosis of NF1 was established.

**DISCUSSION**

NF is a slowly progressive genetic disorder affecting skin and nervous system. Apart from the seven types described by Riccardi, Gortin et al identified two other forms of NF namely NF8 and NF9.4

NF1 is an autosomal dominant disorder caused by an alteration in long arm of chromosome 17. The prevalence rate is approximately one in 3,000 births.5

Genetic linkage analysis done in 1987 identified NF1 locus close to the centromere on the long arm of chromosome 17. In 1990, the NF1 gene was identified by positional cloning and it was located at 17q 11.2. NF1 gene is complex, expressed in almost all tissues and most highly in the brain, spinal cord and peripheral nervous system. The protein product of NF1 gene is neurofibromin, which is a large peptide (220 KD) with 2,818 amino acids. It is most abundant in the nervous system. In adults, it is also found in neurons, oligodendrocytes and Schwann cells. It is also expressed in a variety of other cell types in adults, such as keratinocytes, adrenal medulla and white blood cells. Neurofibromin is ubiquitously expressed during embryonic development and the adult pattern of tissue expression is established after the first week of postnatal life. It acts as a tumor suppressor, accelerating the conversion of the oncogene Ras to its inactive form. Therefore, its absence could lead to higher Ras activity in Schwann cells, resulting
44.8% of 303 cases of benign nerve sheath tumors to be located in head and neck region and only 9% of them occurred intraorally. Other oral manifestations include macroglossia, enlarged fungiform papillae, bony deformities, wide inferior alveolar canal and enlarged mandibular foramen. However, the dental status in NF1 patients has not been fully investigated. Our case presented oral manifestations, such as enlarged tongue, enlargement of alveolar ridges in maxilla and mandible, cleft in soft palate, bifid uvula and gingival overgrowth. Sailor et al in 1988 reported changes such as deformity or hypoplasia of the ascending ramus with perforation defects and inferiorly displaced external ear, same kind of presentation was also seen in our case. Muller and Slootweg stated that the skeletal lesions may be pathognomonic. Jaffe stated that skeletal abnormalities seen in NF patients represent direct destruction from NF tissue proliferation and aberrations of skeletal development and growth either localized or systemic indicating that NF is a disorder deeply rooted in germ plasm. Diagnosis of NF is done based on clinical criteria. According to National Institute of Health (NIH)
Consensus Development Conference, the diagnostic criteria of pediatric NF1 include presence of two or more of the following criteria:

- Six or more cafe au lait spots greater than 5 mm in prepubertal patients and greater than 15 mm in postpubertal patients
- Two or more neurofibromas of any kind or 1 plexiform neurofibroma
- Crowe sign (freckles in the inguinal or axillary area), optic pathway tumors
- Two or more Lisch nodules
- A distinctive bone lesion designated as dysplasia of wing of sphenoid bone or thin cortex in long bones with or without pseudoarthrosis and
- Direct relatives (parents, siblings, offspring) with established diagnosis of NF1.5

Investigations, such as radiographs, CT scans, MRI, biopsy and immunohistochemical detection of S-100 protein which is specific for cells of neural crest origin are invariably helpful in diagnosis of NF1.

Although most individuals in childhood are mildly affected, prompt diagnosis of NF1 is of utmost importance since 3 to 30% of NF1 cases develop complications, such as neurofibrosarcoma, pheochromocytoma, leukemia, rhabdomyosarcoma, Wilm’s tumor, CNS tumors, optic gliomas3 and GI tumors.11 As the disease has variable clinical presentation that can occur along with age and show wide range of severity, periodic lifelong evaluation of the patient is important to check for new disease manifestations and to prevent severe disease complications. Treatment requires multidisciplinary approach.

CONCLUSION

A good understanding of the molecular bases of NF1 will not only help to understand the disease properly but will also aid in therapeutic applications and prevent unforeseen complications.

REFERENCES


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