Von Recklinghausens Disease: A Series of Four Cases with Variable Expression

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Abstract Though neurofibromatosis type I (NFI) is a fairly common condition, it has a variable expressivity and penetrance. Here we present a series of cases with striking differences in the presentation especially in the oral cavity. NFI, also known as von Recklinghausen's neurofibromatosis, is an autosomal dominantly inherited neurogenetic disorder affecting 1:3000 newborn (Bongiorno et al., *Oral Dis* 12:125–129, 2006). About 50 % of NFI patients have no family history of the disease. There is no prevalence for gender or race in NFI. Expressivity in NFI is tremendously variable, but subtle phenotypic patterns may exist within subgroups of affected patients. Furthermore, 50 % of cases are sporadic and arise from germ cell mutation (Bongiorno et al., *Oral Dis* 12:125–129, 2006). The precise constellation of findings in any one individual is extremely variable, both within a family and between different families (Batsakis, *Tumors of the head and neck: clinical and pathological considerations*, 2nd edn. Williams and Wilkins, Baltimore, pp 313–333, 1979). Only 4–7 % of patients affected by neurofibromatosis exhibit oral manifestations (Güneri et al., *Turk J Pediatr* 48(2):155–158, 2006).

Keywords Neurofibromatosis I · Von Recklinghausens disease · Auxillary freckling · Cafe au lait spots

Introduction

Von Recklinghausen's disease, also known as neurofibromatosis type I (NFI), was first described by pathologist Friederich Daniel Von Recklinghausen in 1882. It is an autosomal dominant neurogenetic disorder affecting 1:3000 individuals world wide and 1 of every 200 with mental retardation [8]. The hallmark of the disease is the neurofibroma which is a benign peripheral nerve sheath tumor and one of the criteria for the diagnosis of the disease. Other criteria include café-au-lait macules, bone malformations and central nervous system tumors. About 50 % of NFI patients have no family history of the disease. NFI is a highly variable disorder with signs and symptoms that may begin at birth and evolve over a lifetime. Only about 4–7 % of patients present with oral manifestations.

Here we present a series of four cases with different clinical presentations, without a positive family history which describe the variable expression of the disease.

Case History

Case 1

A 52 year old male patient reported with a solitary soft tissue growth (Fig. 1) on the right posterolateral aspect of tongue since 4–5 months. There were no signs of malignancy except for the dysphagia owing to the grotesque size of the mass. The surface of the lesion was covered by fibrous pseudomembrane and was firm in consistency and

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Fig. 1 Intra oral soft tissue growth arising from the left posterolateral aspect of tongue

non tender. He presented with multiple cutaneous nodules and café au lait spots. Family history was non contributory. Growth of the tongue was provisionally diagnosed as benign tumor of tongue. Differential diagnosis of neurofibroma, neurilemmoma, rhabdomyoma, fibroma, leiomyoma was also considered. Conventional and advanced imaging was carried out. An excisional biopsy was done to confirm the diagnosis.

Orthopantomography (OPG) (Fig. 2) showed a well defined radiolucency in the left ramus with apical displacement of left lower wisdom tooth and also enlarged left mental foramen. Computed tomography (CT) showed presence of hypodense mass originating from the posterolateral surface of tongue on the left side.

The lesion was surgically excised (Fig. 3) and histopathologically proved as neurofibroma.

Taking into consideration all these findings final diagnosis of NFI was given.

Case 2

An 85 year old male patient presented with diffuse enlargement of the left lateral side of tongue and a solitary nodule about 1 cm in the region of the missing right mandibular canine (Fig. 4). He also presented with multiple cutaneous nodules, café au lait spot and axillary freckling (Fig. 5).

OPG (Fig. 4) showed bilateral enlargement of mental foramen and mandibular canal.

The nodule was excised and histologically proved to be neurofibroma.

Case 3

A 40 year old female patient presented with multiple firm nodules intraorally on the gingiva, hard palate and on the dorsal surface of the tongue (Fig. 6). She also presented with multiple cutaneous nodules and café au lait spots.

Case 4

A male patient aged 63 years reported with multiple cutaneous nodules all over the body (Fig. 7). This patient did not present with oral findings as in other cases. He presented with scoliosis and a limping gait. The chest radiograph postero-anterior (PA) view (Fig. 7) shows the curvature of the spine. In both cases 3 and 4 biopsy was not performed due to lack of willingness of the patients.

Genetic examination was not carried out as the cases satisfied the criteria by National Institutes of Health Consensus Development Conference in 1988 [9] to be diagnosed as von Recklinghausen's disease (NFI).

Discussion

NFI which is also known as Von Recklinghausen's disease is an autosomal dominant neurogenetic condition with high penetrance and variable expressivity. Incidence reported is 1: 3000 births in general population [4]. NFI is a highly variable disorder with signs and symptoms that begin at birth and evolve over a life time [28]. The disease has one of the highest rates of spontaneous mutations within the genetic diseases [8].

Fig. 2 OPG showing multiple radiolucencies in the jaws and CT showing the soft tissue mass arising from the tongue and also multiple hypodense areas in the jaws of case 1

Fig. 3 Surgically excised specimen and pictomicrograph

Fig. 4 Case 2 diffuse enlargement of tongue, nodule on the alveolar ridge and OPG showing enlargement of mental foramen and mandibular canal

Fig. 5 Axillary freckling

There are different type of neurofibromatosis [30] including

1. Neurofibromatosis type I (Von Recklinghausens disease),
2. Neurofibromatosis type II (acoustic type),
3. Neurofibromatosis type III (Ricardi type),
4. Neurofibromatosis type IV (intestinal type),
5. Neurofibromatosis type V (segmental neurofibromatosis), and
6. Familial spinal neurofibromatosis.

There are definite diagnostic criteria for NFI which satisfy any two of the following criteria given by National Institutes of Health Consensus Development Conference in 1988 [9]:

1. Six or more than 6 cafe'-au-lait macules, >5 mm diameter in prepubertal and >15 mm diameter in postpubertal patients.
2. Two or more neurofibromas of any type, or one plexiform neurofibroma
3. Axillary or groin freckling
4. Optic glioma

Fig. 6 Case 3 multiple intraoral neurofibromas and OPG showing enlarged mental foramen and mandibular canal

Fig. 7 Case 4 presenting with multiple cutaneous nodules and scoliosis

5. Two or more Lisch nodules
6. A distinctive bony lesion, dysplasia of the sphenoid bone, dysplasia or thinning of long bone cortex
7. First-degree relative with NFI

NFI was first reported in 1849, by Robert Smith who revealed the clinical and necropsy findings in two cases of neurofibromatosis, but did not recognize the neural elements [2].

Von Recklinghausen's disease was named after the man who first described the disease in 1882 caused by mutation in pericentromeric proximal gene locus on chromosome 17 q 11.2 (tumor suppressor gene NFI). This gene encodes a protein known as neurofibrin which plays a role in cell signaling. NFI is a tumor suppressor gene, however, mutation of NFI may be responsible for tumorigenesis in the NFI patients but the actual mechanism is still a mystery [27]. There is no considerable sex predilection [30].

NFI becomes evident in the first few years of life when café-au-lait spots develop. These are hyperpigmented macules that may vary in colour from light brown to dark brown, borders may be smooth or irregular. These can occur anywhere on the body, mainly on unexposed surfaces of the body, rarely on the face [8]. Characteristic is the axillary freckling known as Crowe's sign. The hallmark of the disease is the cutaneous neurofibromas which make their appearance during childhood or adolescence after the café-au-lait spots. The skin over the tumor is frequently discoloured, brownish or bluish or reddish through enlarged capillaries [26]. Neurofibromas are focal growth arising from cells of nerve sheath and consist of a mixture of Schwann cells, fibroblasts, perineural cells and mast cells [20, 28].

These tumors are slow growing; number and size increase with age [8]; acceleration is seen during puberty or pregnancy. If there is a sudden increase in size of the tumor, malignancy can be suspected. Along with peripheral nerve sheath tumors, central nervous system tumors, like optic gliomas [22, 28] and pigmented hamartomas of iris (Lisch nodules) can also occur in NFI affected patients.

In adults diagnosis is made easily by physical examination; but in children café-au-lait macules can remain the only manifestation for a long period of time and in the absence of family history diagnosis often remains in abeyance [24].

Although these neurofibromas do not progress to malignant neoplasms, cross-sectional studies have shown that 1–2 % of patients with NFI develop malignant peripheral nerve sheath tumor [11]. A subset of neurofibromas, termed plexiform neurofibromas, carry a 5 % lifetime risk of malignant transformation [16, 23, 29]. These plexiform neurofibromas extend along the length of the nerve involving several fascicles and including nerve

branches [21]. These are infiltrating tumors that can sometimes lead to the abnormal growth of bone when in contact [25].

Skeletal abnormalities is seen in 40 % cases [8, 27], kyphoscoliosis being the most commonest one [4, 8]. Atrophy and hypertrophy of individual bones [18] is also seen. Erosive defects secondary to impingement of tumors and primary defects such as scalloping of vertebrae, congenital bowing of long bones with pseudoarthrosis [8], unilateral orbital malformation with cystic osteolytic lesions [19].

Oral cavity involvement appears in 66–72 % of the cases of NFI [8]. The most common site in the oral cavity is the tongue [4, 8, 14]. Localized oral neurofibromas usually appear as asymptomatic nodules covered by normally coloured mucosa [7]. Gingival neurofibromas may cause dental malposition or impaction. These neurofibromas when adjacent to cranial nerves, can impair motor function of facial or hypoglossal nerves or the sensitivity of trigeminal nerve [3, 8].

Radiological findings of oral neurofibromas include widening of mandibular canal and mental foramen [7, 8]. A similar finding is presented in the first and second cases reported in this article. CT scans of neurofibroma generally show low attenuation and sometimes soft tissue density. Low density signifies presence of variable amount of Schwann cells rich in lipids where as high density suggests collagen rich areas [17]. In MRI scans there is low signal in T1 and high signal in T2 weighted images. Also Bull's sign i.e. high peripheral signal with a low central signal in T2 weighted images is a distinctive feature of neurofibroma [17].

Neurological complications have been observed in 55 % of patients [6]. These may include, principally, neurophysiological disorders with cognitive defects and learning difficulties. Other major complications are secondary to visceral neurofibroma compression of urinary, digestive, vascular and pulmonary systems [13]. Risk of sarcomatous changes was reported in 5 % of cases in NFI but is relatively uncommon in head and neck region [5, 10].

Syndromes associated multiple mucosal neuroma syndrome (multiple endocrine neoplasia syndrome type Iib).

1. Klippel–Trenaunary syndrome.
2. Jaffe–Campanacci syndrome.
3. McCune Albright's syndrome.

About 50 % of the patients did not have positive family history [8]. Variable presentation on the tongue, presence of intraosseous neurofibromas with periapical and pericoronal radiolucencies mimicking odontogenic etiology were the other features satisfying the diagnostic criteria—neurofibromas may seldom be primarily intraosseous; in that case they usually appear as a unilocular, well-defined radiolucency [1, 3, 7]. Case 1 reported here presents with such a finding.

Occasionally, oral manifestations and oral tissue specimens may provide the opportunity to diagnose NFI. The oral manifestations of NFI are well-documented but may not be at the forefront of the clinician's mind in the differential diagnosis of intra-oral swelling. One concern that should not be overlooked is the risk of isolation or loneliness in people with NFI.

There is no specific medical management available. Treatment should be directed towards genetic counselling, education about NFI and prevention or management of complications.

The ultimate cure for an inherited disease maybe gene therapy, but it is not so easy to treat NFI with gene therapy for several reasons. NFI being autosomal dominant, successful therapy requires correction of mutant NFI gene which is difficult as NFI often involves multiple tissues with a high variation. It would be very difficult to deliver normal NFI copies to all target tissues [27].

It is anticipated that the next several years will witness the development and testing of targeted therapies based on our improved understanding of the clinical behavior and the molecular biological features of neurofibromin in neurons, astrocytes, and Schwann cells. Patients should be reviewed for long time to have a check on malignant transformation as well as complications. ¹⁸Fluorodeoxyglucose positron emission tomography has shown some promise in distinguishing benign and malignant lesions [12], however this requires further study.

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