Case Report

Pediatric zygomaxillary neurofibromatosis type 1: case report

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Neurofibromatosis type 1 (NF-1) is a genetic disorder predominantly affecting tissues derived from neural ectoderm producing a multifocal neurocutaneous disease. It is usually inherited as an autosomal dominant trait with variable penetrance and phenotypic expression, affecting one in 2500–3300 live births.[1] A closely related condition, neurofibromatosis type-2 (NF-2) occurs much less frequently (approximately one in 50,000 births) and is manifested primarily as multiple neurilemomas and acoustic neuromas.[2]

The clinical diagnosis of NF-1 requires two or more of the following manifestations:

1. At least six cafe au lait clinical macules with diameters of at least 5 mm occurring in prepubertal individuals and diameters greater than 15 mm in postpuberal individuals
2. Two neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions
4. Optic gliomas
5. At least two Lisch nodules (pigmented hamartomas of the iris)
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-1.[1,3]

The oral cavity is involved in as many as 92% of cases reported. The tongue is affected most frequently, often demonstrating unilateral macroglossia with or without enlargement of the fungiform papillae (53%). The mandibular canal may be enlarged (29%) or branched (24%), or there may be widening of the mandibular foramen (34%).[4,5]

The lips, palate, buccal mucosa, gingiva, and oral floor also can be affected, with the maxillary and mandibular alveoli involved less often. Plexiform neurofibromatosis also can occur, producing large neuromas of the lingual, glossopharyngeal, or even the vagus nerves.[6,7] Invasion of the trigeminal nerve can produce variable degrees of paresthesia or neuralgia. The formation of acoustic neuromas also can produce a variety of symptoms reflecting vestibulocochlear nerve involvement resulting in deafness or vertigo.

The clinical course can be exacerbated by or precipitated during pregnancy. This is thought to occur because of undefined nerve growth factors present in amniotic fluid in high concentrations. Some individuals may experience accelerated growth of the lesions during adolescence, because B-estradiol appears to stimulate the production of nerve growth factor.[8] However, a clinical diagnosis of NF-1 is possible in the vast majority of cases (>90%) at infancy or early childhood.

Case report

A 10.5-year-old Asian female was referred to the College of Dentistry Hospital pediatric dental clinic by her dentist for consultation concerning the delayed eruption of her maxillary left first permanent molar. The patient was a pleasant, intelligent, cooperative, and mentally alert child. Her medical history was significant for NF-1, affecting the spine, legs, and cranium. There were multiple cafe au lait spots on the trunk and extremities, in some cases larger than 1x2 cm (Fig 1). A
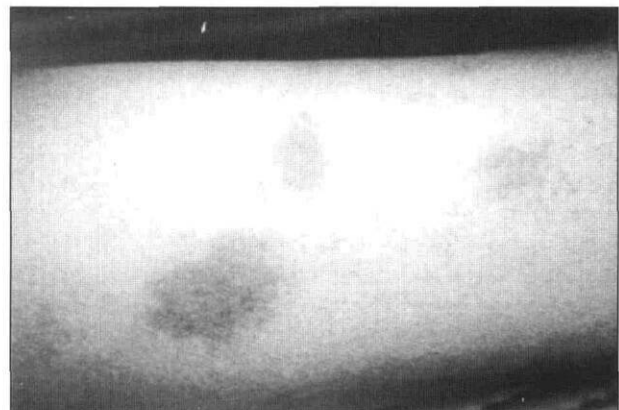

Fig 1. Cafe au lait macules on upper extremity.

left temporofacial plexiform neurofibroma with secondary complete atrophy of the left globe was readily apparent (Fig 2). The subcutaneous tissues of the left forehead and preauricular area were thickened with an underlying soft tissue mass. The patient's left eye demonstrated a shrunken and scarred globe with thickening of the subcutaneous tissues of the lid with ptosis. The upper extremities appeared normal; however the lower extremities displayed pseudoarthrosis with profound asymmetry, marked tibial bowing, and deformities of the distal tibia and ankle, and the patient was *status post* multiple corrective surgeries (Fig 3). There was a marked leg length discrepancy of approximately 5 cm, with the left leg longer than the right, which produced an obvious asymmetry of the pelvic bone and mild thoracic scoliosis.

Fig 2. Left temporofacial plexiform neurofibroma.

Fig 3. Marked asymmetry and pseudoarthrosis of lower extremities.

A radiographic examination revealed congenital absence of the left greater wing of the sphenoid medially and centrally. Bony hypertrophy of the zygomatic arch and posterior wall of the left maxillary sinus apparently was related to the underlying disease. Deformity of the left maxillary sinus and orbit, middle cranial fossa, sphenoid sinus, sella, and displacement of the left cavernous sinus and orbital structures also were noted. Magnetic resonance imaging, including a coronal scan through the orbits, revealed a large plexiform neurofibroma extending into the left orbit and producing marked atrophy of the left globe (Fig 4). Over the past year there had been unilateral enlargement of the left maxilla and a delay in the eruption of the dentition on the affected side.

An intraoral examination revealed a partially erupted maxillary left second premolar, and a large space between the maxillary left first and second premolars. No teeth were erupted distal to this point (Fig 5). There also was a broad, nontender unilateral enlargement of the left maxilla. The mucosa was smooth surfaced and intact, but exhibited several areas of pinpoint hyperpigmentation. Subsequent biopsy and histopathologic examination of specimens taken from the posterior left maxillary alveolar ridge mucosa confirmed the diagnosis of neurofibroma (Fig 6).

The patient's oral hygiene was excellent and no evidence of caries was detected. On a pantomograph, it was noted that the maxillary left first and second molars were present, and there was evidence that the maxillary posterior alveolar arch exhibited tumor involvement due to the substantial degree of tooth drifting and distofacial ridge expansion. While there were no clinically apparent signs of left mandibular tumor involvement, we suspected that the mandible was at least partially affected because: 1) the radiographs indicated that development of the third molar was in question, 2) the lower left second molar appeared inferiorly displaced and unerupted, and 3) the bony architecture was atypical in the retromolar pad region with evidence of a widened mandibular foramen (Fig 7).
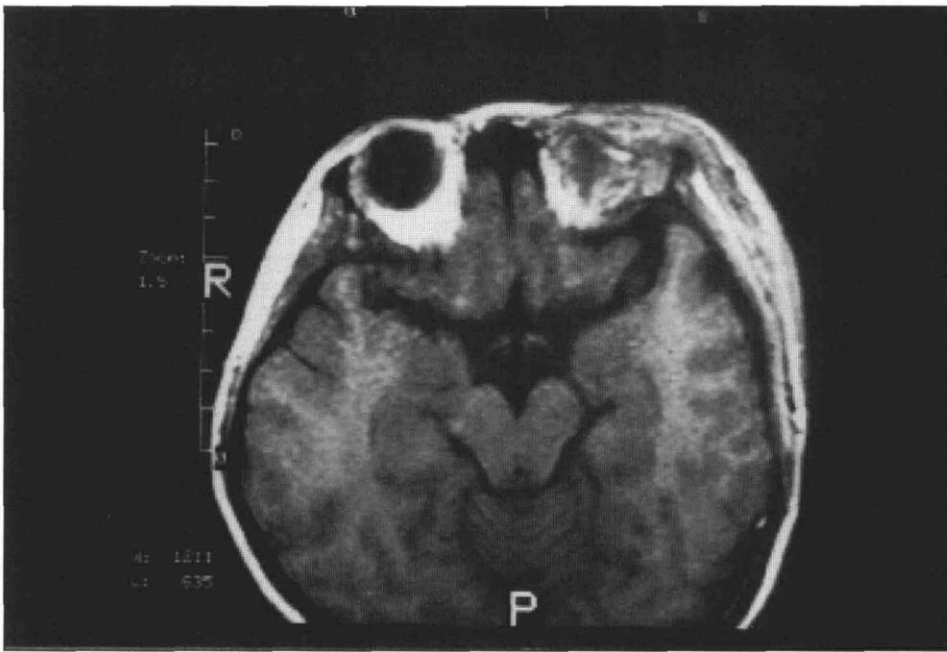
A pedigree assessment was not possible because the patient had been adopted as an abandoned child.

Discussion

Neurofibromatosis type 1 can affect any of the body systems. That its occurrence cannot clearly be predicted, even within families, makes the disorder particularly distressing. The most frequent complications of type 1 neurofibroma is the plexiform neurofibroma, which is rarely seen as an isolated lesion and presents a difficult management problem.[3] Histologically, the plexiform neurofibroma can be considered a hallmark of NF-1 and sometimes underlies a somewhat darker form of cafe au lait macules such as those seen in this case. Such lesions present as dif-

Fig 4. MRI (T-1 weighted) demonstrating involvement of the left orbit.

such enlargements are directly due to tumor or to vascular changes resulting from blood flow interference. Ideally, CT scanning provides the best opportunity to assess change in maxillofacial and cranial foramen architecture. Glossal involvement, while frequently reported in patients with significant oral involvement, was not evident in this case.

Other forms of neurofibromas, such as neurilemomas also may occur.[11] Certain other conditions that mimic NF-1, such as Watson's syndrome (characterized by cafe au lait spots, Lisch nodules, pulmonary valvular stenosis, and mental retardation), have been linked to the same chromosomal markers that have been established as the locus assignment for NF-1.[12]

fuse ill-defined swellings, often with overlying skin hypertrophy or pigmentation.

Osseous lesions can be the result of soft tissue tumor growth or of osteoclastic resorptive processes secondary to tumor impingement against bone. Alternatively, it has been suggested that osteoblastic activity may be stimulated by adjacent neurofibromas leading to asymmetric bony growth. In addition, other conditions, which can produce maxillofacial asymmetry with variable calcification patterns, may occur concurrently with neurofibromatosis (i.e., fibrous dysplasia, ameloblastomas, myxomas). Finally, some evidence for foci of mesodermal dysplasia exists in areas distant to neural tumors. It can be concluded that the clinical manifestations of NF-1 may involve tissues of both ectodermal (neural crest) and mesothelial origin.[9]

The routine use of pantomographic imaging has enhanced identification of neurofibromatosis affecting the jaws, with frequencies reported as high as 93%.[4, 10] The patient in this case demonstrated asymmetry in the inferior alveolar canals as well as a suggestion of widening of the mandibular foramen (blunderbuss foramen), which appears in one of every three cases.[4] It is important to determine whether
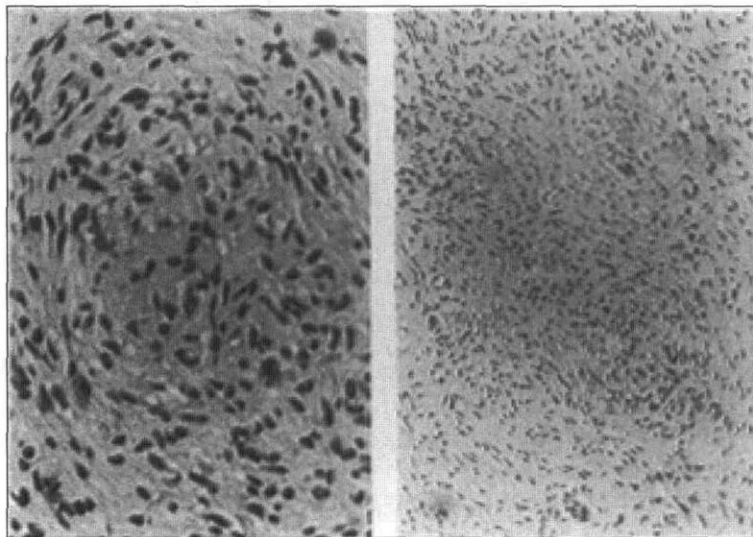

Fig 5. Intraoral view of left maxillary alveolar arch.

Recent genetic advances have lead to the isolation of a large gene (200-300kb), which is thought to be responsible for von Recklinghausen neurofibromatosis (NF-1). Its location on the pericentromeric region of the long arm of chromosome 17 within band q11.2 is highly conserved across species.[13] This is in contrast to NF-2, which is thought to result from a mutation in chromosome 22.[14] The NF-1 gene has been found to code for a large, ubiquitously expressed protein (neurofibromin) that has both structural and functional similarity to a family of proteins possessing guanosine triphosphate-activating properties (neurofibromin has been shown to be associated with cytoplasmic microtubules).[15] Another postulated function of neurofibromin is the regulation of the proto-oncogene *ras* and its mediation of cellular growth, development, and differentiation.[16] This is thought to occur through the promotion of signal transduction by stimulating the conversion of the *ras* protein from a GTP-bound active form to a GDP-bound inactive form.[17] Aberration of normal *ras* function may play an im-

Fig 6. Benign spindle cells with Schwannian characteristics typical for neurofibroma (H&E).

The five-year survival rate in such cases has been reported to be less than 15%.[19, 20]

Gene mutations identified in NF-1 thus far have been characterized as small, with only 45 specific germ-line mutations reported in more than 500 unrelated patients. Of these, 25 mutations involve focal changes, of which 17 resulted in the formation of an inappropriate stop codon. A single focus or "hot spot" for mutations in NF-1 type-1 has not been identified.[21] Therefore, damage to the NF-1 gene resulting in conformational changes in neurofibromin may be an important initial step in the genesis of this complex multistep disorder.[13, 22] There is hope for the development of specific gene therapies for use in utero with fetuses genetically predisposed to NF-1. Alternatively, the application of pharmacotherapies directed at the downregulation of proto-oncogenes (*ras*) may be

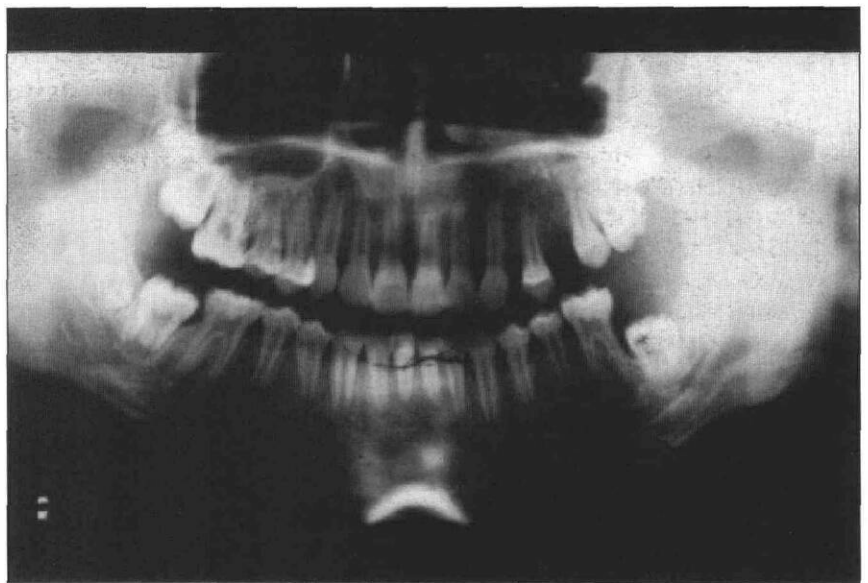portant role in the generation of the NF-1 phenotype.

Current research strongly suggests that the NF-1 gene may act as a tumor suppresser gene through its gene construct, neurofibromin. Such antioncogenes, or tumor suppresser genes, as negative regulators of cell division, stand in contrast to oncogenes (such as those involved in leukemias and lymphomas). In neurofibromatosis and for most human cancers, the more frequently mutated genes are the antioncogenes.[18] Persons heterozygous for germ-line mutations in antioncogenes are strongly predisposed to one or more kinds of cancer, and most dominantly inherited cancer is attributable to such heterozygosity. Similarly, it has been reported that patients with NF-1 demonstrate a higher incidence of unrelated second malignant tumors than does the general population. The most frequent of these is the central nervous system glioma. Neurogenic sarcomas of the peripheral nervous system also occur infrequently. Specifically, alterations at the p53 locus on the short arm of chromosome 17 appear to be critical for the conversion of neurofibroma to neurosarcoma.[12] Malignant transformation of neurofibromas or *de novo* appearance of malignant neurofibrosarcoma are still considered a very real threat in long-term NF-1, and are estimated to occur overall in 3–30% of all patients.[11] Sarcomatous degeneration in patients with the head and neck NF-1 is relatively infrequent and occurs in 9–18% of all cases.

possible for decreasing cellular growth rates in NF-1 after birth.

Fig 7. Pantomographic evidence of maxillofacial involvement delayed dental eruption pattern.

Currently, there is no specific treatment for NF-1, and most complications are managed in exactly the same way as when they occur as isolated lesions. Therefore, NF-1 sufferers should have an annual clinical assessment to monitor for complications. Screening investigations, such as cranial computed tomography, generally are not justified unless there are clinical indications. Since many complications can develop in childhood, it is important to monitor children with NF-1 closely. Examinations should be focused on monitoring for variations in blood pressure measurement

and to evaluate the spine and nervous system in particular for signs of an optic glioma. As educational problems secondary to mental retardation may be present, a preschool psychological assessment also is recommended to assess the need for early intervention for learning disabilities.

The clinical management of NF-1 is complex and must be individualized, taking into account the location and severity of the lesions. Surgical procedures that maintain or produce positive cosmetic or functional results are justified even though some residual tumor may be left. While solitary tumors often are amenable to resection, such procedures are of limited value when lesions demonstrate significant infiltration of normal or essential tissues. Lesional margins typically are poorly defined, and thus complete surgical removal is often impossible. Therefore, unless these lesions are causing severe cosmetic problems or localized bony overgrowth, conservative management is advisable. Given the extent of the intraosseous lesions in this patient, removal by radical excision was not pursued, as such approaches must be weighed against the postsurgical quality of life and probability of recurrence or tumor stimulation. However, cosmetic removal of the left eye followed by prosthesis replacement was performed. When the dentition and occlusion are compromised, one can consider the fabrication of a removable appliance that can be corrected periodically to conform to gradual remodeling of the maxillofacial bones. Fixed appliances are contraindicated in cases that demonstrate rapid growth and developing asymmetry.

The prognosis for achieving an acceptable occlusion in the reported case continues to be largely dependent on the patient's maxillary tumor growth pattern. In this case, the progessive nature of maxillofacial tumor growth necessitated construction of a series of interim appliances over the patient's lifetime. At the time of this patient's initial presentation, a reasonable occlusal relationship was achieved through the surgical exposure and utilization of the maxillary left first molar, which was normally developed. The recovery of the submerged mandibular left second molar was deemed not possible by orthodontic extrusion because of the limited alveolar bone level. Alternatively, prosthetic occlusal augmentation of this tooth could be considered at a later date. Long-term clinical follow-up including clinical intraoral photographs and radiographs are required to allow growth comparisons and identification of atypical behavior of the maxillary lesion suggestive of malignant change.

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