Neurofibromatosis type 1: a clinicopathological study of the orofacial manifestations in 6 pediatric patients

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Abstract

Neurofibromatosis type 1 (NF1) is a relatively frequent mucocutaneous syndrome, which is transmitted as an autosomal dominant trait or which may represent neomutation. It is characterized by a variety of clinical manifestations, including multiple neurofibromas that are associated with a high risk of sarcomatous transformation. The aim of this report was to elucidate the orofacial manifestations observed in 6 pediatric patients (between 4 and 15 years of age) diagnosed with NF1. Physical, clinical, radiological, histological, and immunohistochemical studies were performed. Orofacial lesions were observed in all studied patients, located either in the soft tissues (4 cases) or centrally in the jaws (2 cases). All cases showed facial asymmetry, one of them exhibiting marked facial hemihypertrophy. All cases with soft tissue involvement were plexiform neurofibromas, while the intraosseous cases were diagnosed as solitary neurofibromas. Knowledge of the variability of presentation of orofacial soft tissue and bone manifestations of NF1 in children is necessary for prompt diagnosis. (*Pediatr Dent*. 2002;24:575-580)

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Neurofibromatosis type 1 (NF1, or von Recklinghausen's disease) is a genetic disorder transmitted as an autosomal dominant trait with variable expressivities and complete penetrance; however, approximately 50% of all NF1 cases appear to represent new mutations.[1-6] It affects 1 out of 3,000 to 4,000 live births.[6] The syndrome has been associated with mutations on the long arm of chromosome 17 (17q11.2) and with aberrations in neurofibromin, the protein product of the NF1 gene.[5] Neurofibromin is believed to act 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 in uncontrolled growth through a cascade of events not yet elucidated.[6] Also, high levels of Kit expression in the neurofibrosarcoma-derived Schawn cells correlate with a decrease in neurofibromin expression.[7] Recent advances in our understanding of the molecular basis of NF1 offer promise for both diagnostic and therapeutical applications in the near future. [6]

NF1 accounts for about 85%-97% of the cases of neurofibromatosis.[4] At least another 7, more rare, forms of neurofibromatosis have been described.[8,9] The most common of these is neurofibromatosis type 2 (NF2), characterized by alterations located on chromosome 22.[1,8] NF2's predominant features include bilateral acoustic neuromas, schwannomas, intracranial meningiomas and lens opacities, however, café au lait spots and neurofibromas are uncommon.[1,9] Although NF2 can affect children, it is less common than NF1 among pediatric cases.[1]

According to NIH,[10] the diagnostic criteria of pediatric NF1 include the presence of 2 or more of the following signs: (1) 6 or more "café au lait" spots greater than 5 mm in prepubertal patients and greater than 15 mm in postpubertal patients, (2) 2 or more neurofibromas of any kind or 1 plexiform neurofibroma, (3) Crowe sign (freckles in the inguinal or axillary area), (4) optic pathway tumors, (5) 2 or more Lisch nodules (iris hamartomas), (6) a distinctive bone lesion designated as dysplasia of the wing of the sphenoid bone or thin cortex in long bones with or without pseudoarthrosis, and (7) direct relatives (parents, siblings, or offsprings) with established diagnosis of NF1. Additional features of NF1 in children include macrocephaly, short stature, or scoliosis. Between 30%-60% of the patients may also exhibit brain lesions that can be found in the thalamus and

Table 1. Orofacial Manifestations of 6 Pediatric Cases of NF1

Case	Age*	Sex	Location	Genetic background	Clinical features	Radiological findings	Histological diagnosis	Treatment
1	14	M	Right buccal mucosa and face	Neomutation	Mass on right side of the face, multiple skin nodules, café au lait spots, axillary freckles, hemifacial hyperplasia, scoliosis, and Lisch nodules	Condylar and coronoid hypoplasia, thinning of body and ramus of mandible, and mandibular canal enlargement	Plexiform neurofibroma	Surgical removal and cosmetic surgery, orthodontic treatment, and orthognathic surgery
2	4	F	Upper lip and mucobuccal fold	Neomutation	Macrocheilia, elevated nostril, facial asymmetry, café au lait spots, axillary freckles, and scoliosis	None	Plexiform neurofibroma	Surgical excision
3	6	M	Right maxilla (molar area)	Neomutation	Maxillary expansion, ptosis of the right eye, facial asymmetry, café au lait spots, and axillary freckles	Unilocular radiolucency extending to the floor of the orbit	Neurofibroma	Surgical excision
4	6	M	Mandible	Neomutation	Mandibular expansion, facial asymmetry, axillary freckles, and scoliosis	Multilocular radiolucency, mandibular canal enlargement, and condylar and coronoid hypoplasia	Neurofibroma	Surgical excision
5	8	F	Buccal mucosa and face	Autosomal dominant	Facial asymmetry and axillary freckles	None	Plexiform neurofibroma	Surgical excision
6	15	M	Buccal mucosa and face	Autosomal dominant	Facial asymmetry, axillary freckles, and scoliosis	None	Plexiform neurofibroma	Surgical excision

*Age at presentation. This was the same with the age of initial diagnosis for all cases except case 1, which was first diagnosed at age 5.

are related with low IQ, memory and attention disturbances, deficits in the fine motor area, and reduced oral skills.[9,11]

The frequency of oral manifestations among patients with NF1 varies among different studies. Earlier reports supported a 4%-7% incidence of oral manifestations. However, in the more recent series of Shapiro et al[2] and D'Ambrosio et al,[3] 72% and 92% of their cases, respectively, presented clinical or radiographic oral findings. Both soft and hard tissues of the orofacial region can be affected.[2,3] Neurofibroma, a benign nerve sheath neoplasm that is the predominant feature of NF1, is frequently found in the head and neck and can appear as a solitary or generalized, peripheral or central lesion. The most common location of peripheral neurofibromas within the oral cavity is the tongue, often causing macroglossia. Lips, mucobuccal fold, gingiva, floor of the mouth, and palate are other common sites.[2] Enlargement of the fungiform papillae is another commonly reported oral soft tissue finding in patients with NF1.[2] Intraosseous neural lesions of the jaws are very rare, appearing as central unilocular or multilocular radiolucent lesions.[12,13] Clinically, they present as slow growing masses that produce deformities of the anatomical structures and may displace the adjacent teeth. Other NF1 radiological characteristics include enlargement and/or ramification of the mandibular canal, thinning and concavity of the ramus, enlarged and lower mandibular foramen, increased coronoid notch, increased bone density, decreased mandibular angle, notching of the inferior border of the mandible, and hypoplastic

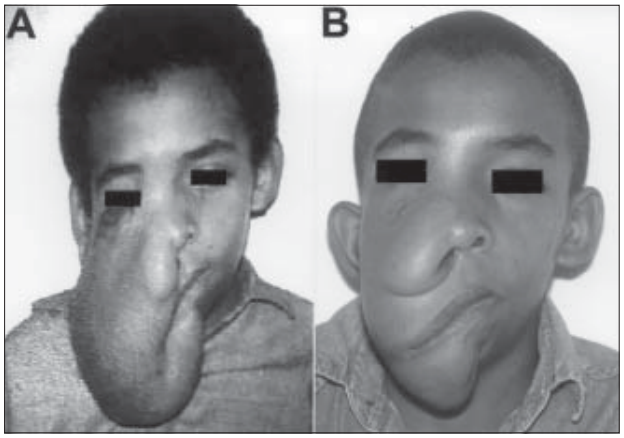

Fig 1a. Facial appearance of the case 1 patient at diagnosis; pronounced facial hemihypertrophy is evident on the right side

Fig 1b. Facial appearance of the same case 1 patient after removal of the lesion and completion of the first phase of cosmetic surgery. Further surgical procedures will follow according to cosmetic surgery protocols.

coronoid processes and condyles.[2,13,14] Pressure on cranial nerves by adjacent neurofibromas may also occur and produce different levels of paresthesia or neuralgia.[2,3] Finally, the most fearsome complication of NF1 is the increased risk of malignant tumors; the most common NF1-associated malignancy is the neurofibrosarcoma that has also been reported to occur in the oral cavity.[4,9,15]

The aim of this study was to report the clinical, radiographic, and histological orofacial characteristics observed in 6 pediatric patients diagnosed with NF1 according to NIH criteria.[10]

Methods

Six pediatric patients, ranging in age from 4 to 15 years, were referred to the Pedodontics Graduate Clinic, Faculty of Dentistry, Central University of Venezuela, for diagnosis and treatment. All patients were diagnosed with NF1, according to NIH pediatric criteria.[10] Physical, clinical, imaging, histopathological, and immunohistochemical studies were performed for each patient. Imaging studies included periapical and panoramic radiographs, computed tomography (CT), and magnetic resonance imaging (MRI) scans. Histopathological examination was performed in each case. Immunohistochemical studies for S-100 protein (DAKO, Carpinteria, Calif) were also done.

Results

The age at presentation, sex, anatomic location, genetic background, clinical, radiological, and histopathological features, and treatment for all 6 patients are summarized in Table 1.

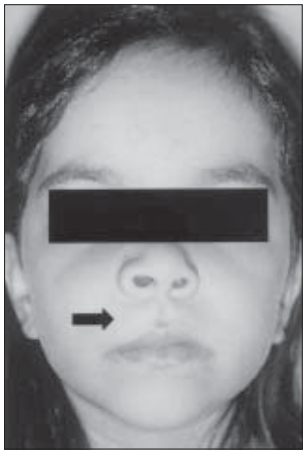

Fig 3. Facial appearance of the case 2 patient. The arrow points to the lesion, which affects the upper lip extending into the mucobuccal fold, causing macrocheilia and elevation of the nostril.

Only 2 cases (cases 5 and 6) had a positive family history—the other 4 cases probably representing a neomutation. In the sporadic cases, the primary presenting features that led to a suspicion of NF1 were café au lait spots (cases 1, 2, and 3), facial asymmetry (cases 2, 3, and 4) and axillary freckles (cases 2, 3, and 4). The mean age of the 6 patients was 8.8 years (range 4-15). Four of them were male. Orofacial lesions were found in all 6 patients. All 6 cases showed facial asymmetry. Four of them presented with soft tissue involvement, while 2 had intraosseous lesions. Involvement of the buccal mucosa and

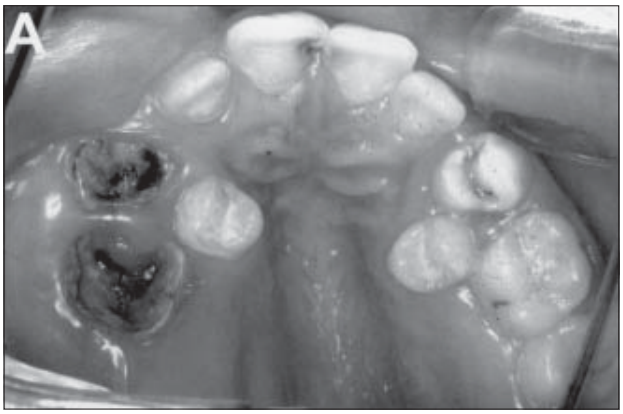

Fig 2a. Marked bone alterations and displacement of maxillary teeth (case 1)

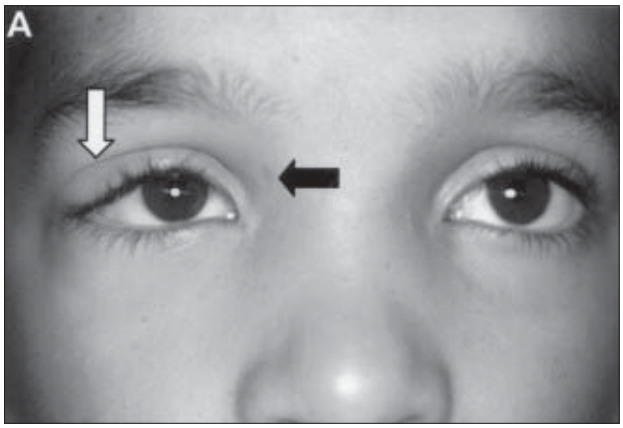

Fig 4a. Café au lait spot (black arrow) and palpebral ptosis of the right eye (white arrow; case 3)

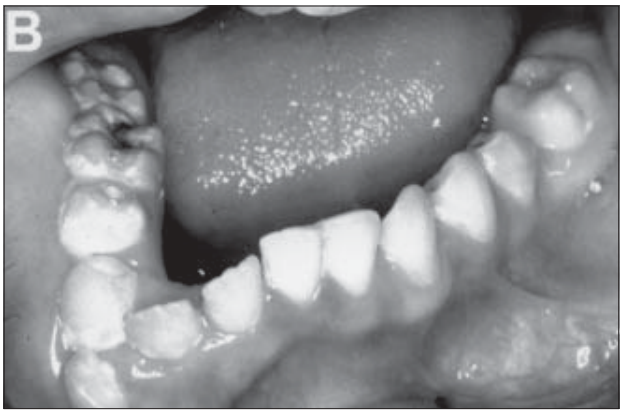

Fig 2b. Mandibular deformity and malocclusion (case 1)

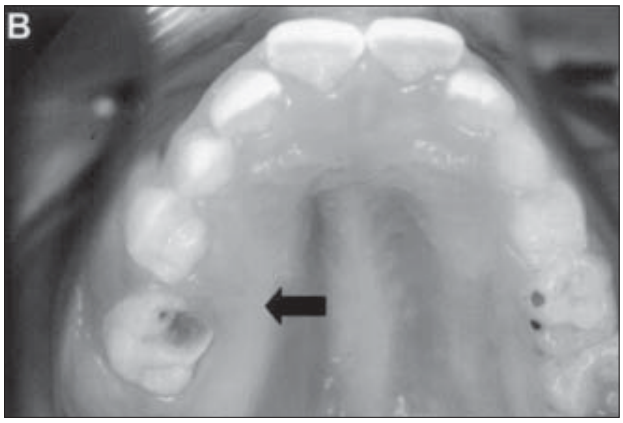

Fig 4b. Marked expansion of the right maxillary cortical plates (arrow; case 3)

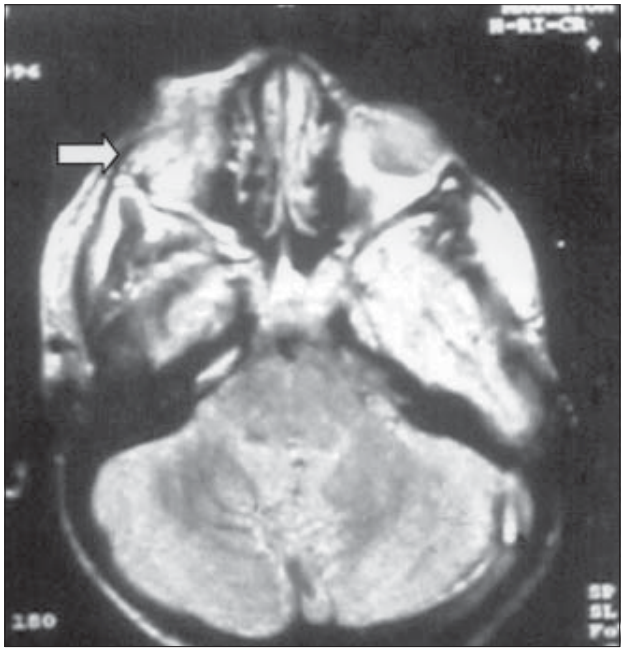

Fig 5. Magnetic resonance imaging showing extension of the tumor into the orbital floor (arrow; case 3)

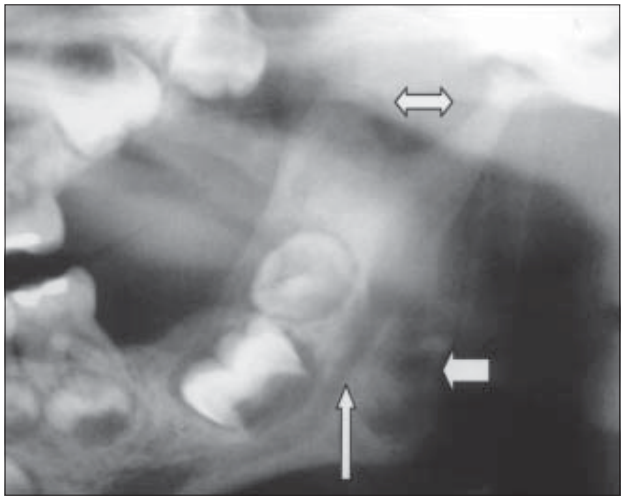

Fig 6. Cropped panoramic radiograph of case 4 showing multilocular radiolucency in the angle of the mandible (thick arrow), mandibular canal enlargment (long arrow), and condylar and coronoid hypoplasia (double arrow)

face was seen in 3 cases; in one of them (case 1), the tumor grew to massive proportions, causing pronounced facial hemihypertrophy (Fig 1), and compression of the maxilla and mandible. The latter resulted in marked bone alterations and malocclusion (Fig 2) and manifested radiographically as condylar and coronoid hypoplasia and thinning of the mandibular body and ramus. In one case (case 2), the upper lip was affected, resulting in macrocheilia and elevation of the nostril (Fig 3).

The other 2 cases presented as intraosseous lesions, one in the posterior maxilla (case 3), causing expansion of the maxillary cortical plates with extension to the orbital floor (Figs 4 and 5), and one in the posterior mandible (case 4), presenting as multilocular radiolucency (Fig 6). Case 4 also exhibited enlargement of the mandibular canal and condylar and coronoid hypoplasia, similar to case 1 (Fig 6). Various other signs of neurofibromatosis, such as skin neurofibromas, "café au lait" spots, axillary freckles, Lisch nodules, and scoliosis, were observed in different combinations in all cases (Table 1).

Upon histopathological examination, the 4 cases affecting the soft tissues were diagnosed as plexiform neurofibromas, while the 2 intraosseous cases demonstrated features of solitary neurofibroma (Fig 7). Immunohistochemical detection of S-100 was performed to confirm the neural origin of the lesions; positive intracytoplasmic staining was evident.

All 6 cases were treated surgically. In one of them (case 1), a single surgical procedure was not sufficient to achieve a cosmetically acceptable result (Fig 1). Accordingly, the treatment plan included multiple surgical interventions as well as orthodontic treatment followed by orthognathic surgery for correction of the severe dental arch deformity. Genetic counseling was provided to the families of all 6 patients.

Discussion

In this paper, 6 new pediatric cases of neurofibromatosis are presented, which are characterized by prominent orofacial manifestations.

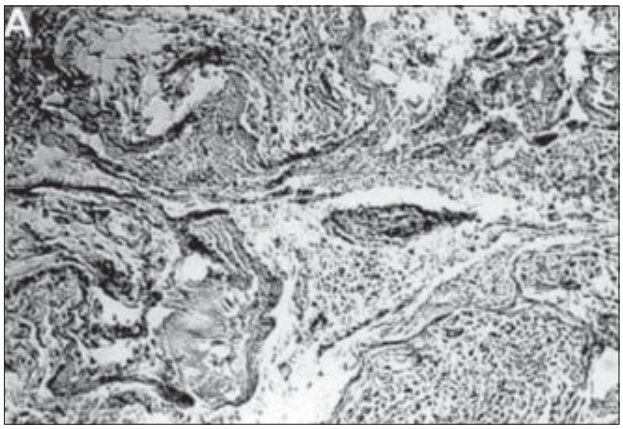

Fig 7a. Histopathological appearance of a plexiform neurofibroma (case 2; H&E, original magnification X10)

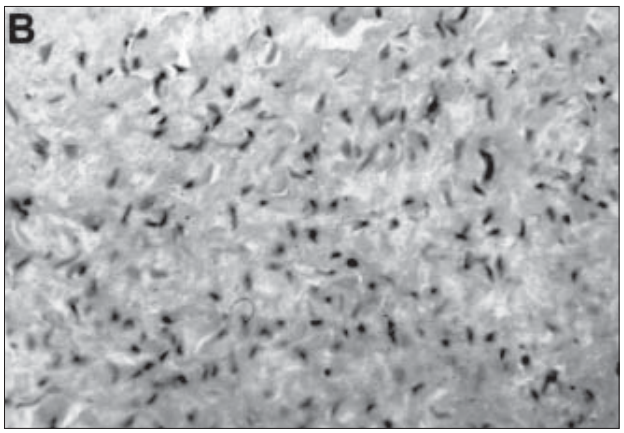

Fig 7b. Histopathological features of a solitary neurofibroma showing bundles of collagen and fusiform cells with wavy nuclei (case 3; H&E, original magnification X40)

Neurofibroma, a benign nerve sheath neoplasm, is the predominant feature of NF1. Oral soft tissue neurofibromas are relatively common lesions in the context of NF1[3] and were seen in 4 patients in this series, affecting the buccal mucosa (3 cases) and the lip (1 case), respectively. Moreover, all 6 patients presented with facial asymmetry, a well-documented sign of NF1, which may result from soft or hard tissue involvement.[16]

Interestingly, hemifacial hyperplasia was observed in one of the patients. This is a rare condition characterized by unilateral enlargement of the face due to various causes including NF1.[3,17]

Intraosseous benign nerve sheath neoplasms are very unusual.[12,13,18-20] Central neurofibromas in the jaws have a predilection for the mandible, mainly related to the mandibular canal,[21,22] while maxillary cases are extremely infrequent.[23,24] In contrast to peripheral neurofibromas, which are associated with NF1 in 20%-60% of the cases, central lesions are rarely related to the syndrome.[14] Interestingly, 2 of the presented cases featured central involvement. One case involved the angle of the mandible, while the other case presented with swelling on the right maxilla, which has caused marked expansion of the cortical plates, delayed eruption, and displacement of teeth. In the latter case, clinical presumptive differential diagnosis included Garre's periostitis and infantile cortical hyperostosis.

Radiographically, central neurofibromas range from well circumscribed to poorly defined unilocular or multilocular radiolucencies; therefore, differential diagnosis must include odontogenic cysts, odontogenic tumors, and other benign and malignant neoplasms. In this study, one of the cases presented as a unilocular radiolucency in the maxilla, while the mandibular case revealed a multilocular radiolucency. Other jaw radiographic findings of NF1 described in the literature and observed in this series included mandibular canal enlargement (2 cases) and hypoplasia of the condylar and coronoid processes (2 cases). It has been suggested that the radiographic changes in NF1 may be due not only to central or adjacent soft tissue neurofibromas but also to "dysplastic" processes, indicative of mesodermal involvement.[14]

Histopathologically, neurofibromas are characterized by an irregular proliferation of Schwann cells, inside or outside the perineurium.[4] Large numbers of cells uniform in size with oval, spindle-shaped or wavy nuclei can be seen. Various amounts of mature collagen fibers forming loosely arranged strands are also evident. Sometimes, a myxomatous component is prominent, necessitating discrimination from other myxomatous soft tissue neoplasms, such as nerve sheath myxomas. Plexiform neurofibroma, a histopathological variant of neurofibroma, is a hallmark of NF1.[4] In 4 of the presented cases, the histopathological diagnosis of plexiform neurofibroma was made; the rest of the cases, corresponding to the 2 central lesions, were diagnosed as solitary neurofibromas. Staining for S-100 protein, specific for cells of neural crest origin, is an important technique to confirm the diagnosis of neural, pigmented or histiocytic lesions. In this study, S-100 protein was positive in all cases, especially in the cells radiating from nerve trunks, confirming the histopathological diagnosis of neurofibroma.

The 6 presented cases in this study exemplify the salient clinical, radiological and histopathological features of orofacial manifestations of NF1 in children. Surgical excision of the lesions that interfere with function and cosmesis usually provides satisfactory results.[17] In cases of oral involvement characterized by dental and alveolar malalignment, orthodontic treatment and/or orthognathic surgery are in order, depending on the severity of the resulting malocclusion. Prompt diagnosis of NF1 in the pediatric population is of utmost importance, since an estimated 3%-30% of NF1 cases develop complications such as neurofibrosarcoma, pheochromocytoma, leukemia, rhabdomyosarcoma, Wilms tumor, CNS tumors, and optic gliomas.[1,9,13] Nontumor effects, such as skeletal dysplasia and learning disability, are also frequent.[6] Accordingly, close follow up by a clinician who is familiar with NF1 and its complications is recommended.[25]

This evaluation should be lifelong, and repeated annually or more frequently if symptoms dictate; it must include thorough clinical examination, as well as other diagnostic tests (such as computed tomography and magnetic resonance imaging) depending on the age of the patient and the presence of specific signs and symptoms of the disease.[25] Rapid growth or pain associated with a pre-existing or newly formed neurofibroma should prompt immediate evaluation, including biopsy and histopathological examination, to rule out the possibility of malignant transformation. Finally, genetic counseling of individuals affected with NF1 and their families is mandatory, given the inherited nature of the disorder in a significant portion of the cases.[1,25]

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Abstract of the Scientific Literature

Odontogenic Bacteremia and Orthodontic Treatment Procedures

Despite the existence of recommendations on antibiotic prophylaxis against bacterial endocarditis for a patient at risk, orthodontic procedures that definitively cause bacteremia remain unclear. This study assesses the prevalence and intensity of bacteremia following orthodontic procedures, as well as alginate impressions, separator placement, band-fitting, and appliance adjustment. After ethical approval and consent, 142 children—adolescents and young adults—were evaluated for dental plaque, gingival inflammation, and baseline and postprocedure blood cultures. Prevalence, intensity (colony-forming unit/ml), and identity of bacteria were analyzed using chi-square and Wilcoxon ranked tests. The results presented no significant difference in prevalence at baseline and following the procedure, and significant differences in aerobes and anaerobes following separator placement ($P<.03$). Though there was no statistically significant difference in the prevalence of bacteremia for any of the procedures, the intensity after separator placement was significant. Further work with a larger sample group may elucidate the need for antibiotic prophylaxis for various orthodontic procedures.

Comments: Antibiotic prophylaxis is recommended by the AHA for band placement for patients at risk for bacterial endocarditis. This study underscores the inconclusive nature of the available data. **AW**

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Lucas VS, Omar J, Vieira A, Roberts GJ. The relationship between odontogenic bacteremia and orthodontic procedures. *Eur J Orthod*. 2002;24:293-301.

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