Oral Manifestations of Neurofibromatosis Type 1 in Children with Facial Plexiform Neurofibroma: Report of Three Cases

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Neurofibromatosis type 1 (NF1) is a common autosomal genetic disorder with a prevalence of 1 in 3,000 births. NF1 is a complex syndrome characterized by many abnormalities and may affect all organ systems. Oral manifestations of NF1 occur frequently, but reports including NF1 children with facial plexiform neurofibromas and oral alterations are scant. Facial plexiform neurofibroma may cause asymmetry, disfigurement and usually arises from the trigeminal nerve. The aim of this paper is to to report three pediatric NF1 cases with facial plexiform neurofibroma presenting with oral manifestations, which were evaluated clinically and radiographically, and also to briefly review the literature. Patients presented with changes in the oral soft tissues, jaws, and teeth ipsilateral to the tumor.

Key words: Neurofibromatosis 1, plexiform neurofibroma, oral manifestations, child

INTRODUCTION

Neurofibromatosis type 1 (NF1) is one of the most common genetic disorders, with a prevalence of 1 in 3,000 births.[1] It is an autosomal-dominant condition with full penetrance and variable expressivity; 50% of cases have a positive family history.[2,3]

NF1 is a complex syndrome characterized by multiple changes that can affect all organ systems.[4] Oral soft tissue involvement and radiographic changes occur in 72–92% of all NF1 patients.[5,6] Unilateral jaw malformations have been reported in 60.4% of adults and children with NF1, and 82.8% of these patients had facial plexiform neurofibroma on the same side.[7] Visnapuu *et al* [8] observed oral radiologic abnormalities in 28% of 102 NF1 patients. Most significant findings were present in six patients with plexiform neurofibroma in the craniofacial region, three of which were children.

In terms of prevalence, although oral manifestations of NF1 occur frequently, there are scant reports in NF1 children, especially those with facial plexiform neurofibroma, who may present with pronounced oral alterations.[8,9] Here we present three NF1 pediatric cases with facial plexiform neurofibroma presenting with oral manifestations. All patients fulfilled the diagnostic criteria for NF1.[10]

Case Reports

Patient 1

A 6-year-old Caucasian male with sporadic NF1 was diagnosed at 6 months of age with a congenital facial plexiform neurofibroma. The diagnosis of plexiform neurofibroma was confirmed by biopsy. The patient had Lisch nodules diagnosed by an ophthalmologist, several cutaneous café-au-lait macules, and freckle-like pigmentations in the axillary and inguinal regions (Crowe's sign). No cutaneous or subcutaneous neurofibromas were observed.

Extraoral examination revealed a tumor on the right hemiface with a "bag-of-worms" consistency, involving the upper and lower eyelid, the temporal and occipital region, and the cheek, upper lip, and chin (Fig. 1A). Hemimacroglossia was present (Fig. 1B) and the magnetic resonance imaging was suggestive of a plexiform neurofibroma in tongue. There was a firm gingival diffuse overgrowth on the lingual side of the lower anterior teeth that was clinically diagnosed as a neurofibroma (no biopsy was performed) (Fig. 1C). Malocclusion, with a cross-bite of the right molars and canines, and an anterior open-bite, were also observed. A panoramic radiograph showed right-sided mandibular changes including a narrowed mandibular ramus, elongation and narrowing of the condylar and coronoid processes, deepening of the mandibular notch, enlargement of the mandibular foramen, flattening of the mandibular angle

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with a spicule-like osseous extension, and delayed eruption of the lower first molars (Fig. 1D).

Patient 2

A 9-year-old black female presented with NF1 and a congenital facial plexiform neurofibroma. The patient had café-au-lait macules, Crowe's sign, and Lisch nodules diagnosed by an ophthalmologist. Cutaneous or subcutaneous neurofibromas were not present. The patient's mother also had NF1.

Extraoral examination revealed a plexiform neurofibroma on the right hemiface with a "bag-of-worms" consistency that extended from the lower part of the cheek to the submandibular region (Fig. 2A). She had been previously submitted to an extraoral biopsy, which confirmed the diagnosis of plexiform neurofibroma. There were no intraoral alterations. A panoramic radiograph revealed irregularity and rarefaction of the mandibular angle, elongation and narrowing of the condylar and coronoid processes, deepening of the mandibular notch, enlargement of the mental and mandibular foramina, enlargement of the mandibular canal, and delayed eruption of the upper canine and the lower first and upper second molar on the right side. The left lower first molar had been extracted (Fig. 2B).

Patient 3

An 11-year-old black male presented with sporadic NF1 that was diagnosed at 2 years of age. The patient had café-au-lait macules and Crowe's sign. No cutaneous or subcutaneous neurofibromas were present. He had a plexiform neurofibroma on the left hemiface affecting the upper and lower eyelids, the temporal region, and the upper lip, cheek, and chin (Fig. 3A), which was observed at one year of age. The diagnosis of plexiform neurofibroma was previously confirmed by biopsy.

There was buccolingual alveolar enlargement of the upper and lower jaw on the left side. A flaccid soft tissue overgrowth on the left posterior region of the mandibular alveolar bone was also observed. A panoramic radiograph revealed multilocular radiolucency with well-defined borders on the left mandibular body extending to the ramus causing impaction of the first and second molars. There was flattening of the mandibular angle, angulation of the condylar process, enlargement and dislocation of the mandibular foramen, delayed eruption of the left second upper molar, and aplasia of the left and right upper third molars and the right lower central incisor (Fig. 3B).

A prior incisional biopsy of the upper and lower jaw (including the soft tissue overgrowth on the posterior region of the mandible) had been performed and the histopathological findings confirmed the clinical diagnosis of localized neurofibroma (Fig. 4A and B). No plexiform aspect was observed.

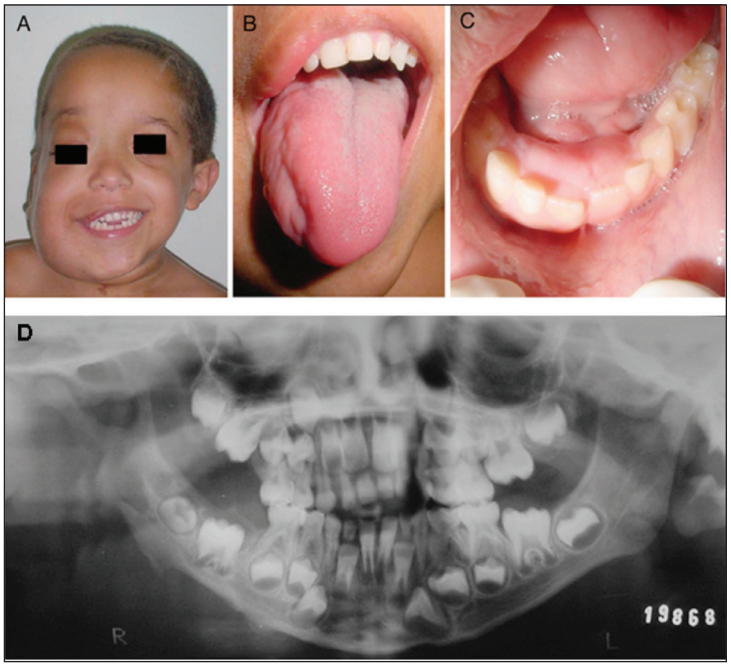


Figure 1. Patient 1: **1A**. Facial plexiform neurofibroma; **1B**. Right hemimacroglossia caused by a plexiform neurofibroma ipsilaterally to the facial tumor; **1C**. Inferior alveolar ridge showing a gingival overgrowth on the lingual side of the lower anterior teeth. **1D**. Panoramic radiograph showing elongation and narrowing of the condylar and coronoid processes, with deepening of the mandibular notch, enlargement of the mandibular foramen, flattened mandibular angle with spicule-like osseous extension, and delayed eruption of the right lower first molar.

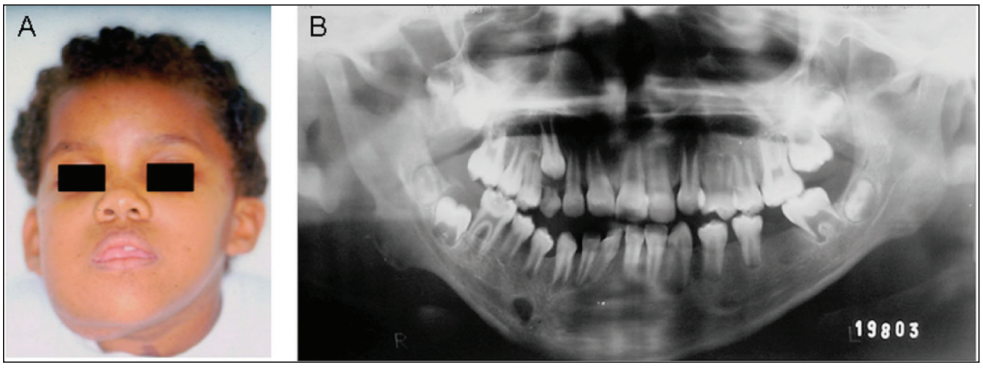


Figure 2. Patient 2: **A.** Facial plexiform neurofibroma. **B.** Panoramic radiograph. Right side: irregularity and rarefaction of the mandibular angle, elongation and narrowing of the condylar and coronoid processes, with deepening of the mandibular notch, enlargement of the mental foramen, mandibular foramen and mandibular canal, and delayed eruption of the upper canine and lower first and upper second molars, compared to the other side. The left lower first molar had been extracted.

DISCUSSION

Localized cutaneous and subcutaneous neurofibromas are important manifestations of NF1. They begin to develop in late childhood to early puberty, and increase in size and number during pregnancy suggesting a hormonal influence.[11–13] This hormonal influence explains why the cases in this report did not present with localized cutaneous or subcutaneous neurofibromas.

Plexiform neurofibromas are generally associated with NF1, occurring in 30% of cases.[14] They may be present at birth, but may become apparent during the first or second year of life.[15,16] They may involve multiple nerve fascicles from large branches of a major nerve, and are a major source of morbidity due to a tendency to reach large sizes and cause disfigurement.[15] Facial plexiform neurofibromas may cause facial asymmetry, generally arise from the trigeminal nerve,[16,17] and may involve any combination of its three branches as observed in this report.

Plexiform neurofibroma rarely affects the oral region and associated structures (tongue, cheek, jaw, and salivary glands).[15,18–21] As observed in the first case, tongue involvement with plexiform neurofibroma may cause hemimacroglossia.

Alterations of the jaws and teeth adjacent to neurofibromas have been reported. Nevertheless, many previous reports did not describe this in detail and did not specify the type of neurofibroma associated with these changes (localized or plexiform).[5,6] Two recent publications found a close association between facial plexiform neurofibromas, unilateral jaw changes, and teeth malpositioning.[7,8]

Although the unilateral jaws and dental changes observed in this paper have previously been reported,[7,8] to our knowledge, the radiological finding of angulated condylar process have not yet been described. Other unilateral changes close to the plexiform neurofibroma have been reported: excavated alveolar ridge, hyperplastic or hypoplastic maxillary tuberosity, narrowed or duplicated mandibular canal, increased radiolucency of the mandible (compared to the contralateral side), supernumerary teeth, root malformation and resorption, and more distal positioning of the molars.[7,8]

The relationship between maxillofacial malformations and plexiform neurofibromas remains unclear, but the malformations may be caused by the tumor.[7,8] It has been suggested that the flattened mandibular angle is caused by tumor invasion of the skeletal muscles, pressure caused by the growing tumor, tumor cells stimulating osteoclasts, embryological effects of the trigeminal nerve acting on mandibular development, or a combination of these factors.[7]

Enlarged of the mandibular canal and mandibular and mental foramen are presumed to be caused by widening of the inferior alveolar nerve, and some authors have described it as a plexiform neurofibroma of this nerve[7]. However, histological evidence supporting this hypothesis is lacking.[8] Uni- or bilateral widening of the mandibular canal can be observed in patients without facial plexiform neurofibroma.[7,8] Postmortem histological studies would help to elucidate this issue. It has been postulated that deepening of the mandibular notch, rarefaction of coronoid and condylar processes, and mandibular foramen enlargement may also be associated with the increasing size of a plexiform neurofibroma of the inferior alveolar nerve proximal to the mandibular foramen.[7]

Displacement of the teeth have been associated with extension of facial plexiform neurofibroma.[22] Intraosseous neurofibromas of the jaws may cause tooth impaction, as observed in the third case. However, as previously reported and observed in this report, the physical development of a tooth inside a neurofibroma is not affected as far as the dimensions of the tooth crowns.[22]

Figure 3. Patient 3: **A.** Facial plexiform neurofibroma. **B.** Panoramic radiograph. On the left side: Multilocular radiolucency (arrows), with well-defined borders, in the left mandibular body, extending to the ramus, as well as teeth impaction, flattened mandibular angle, angulated condylar process, enlarged mandibular foramen, delayed eruption of the left second upper molar, compared to the other side, and aplasia of the left and right upper third molars and right lower incisor.

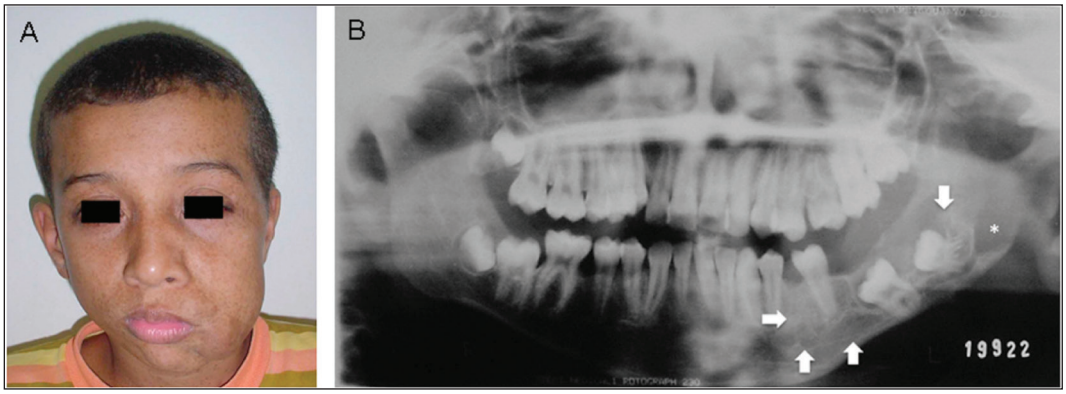
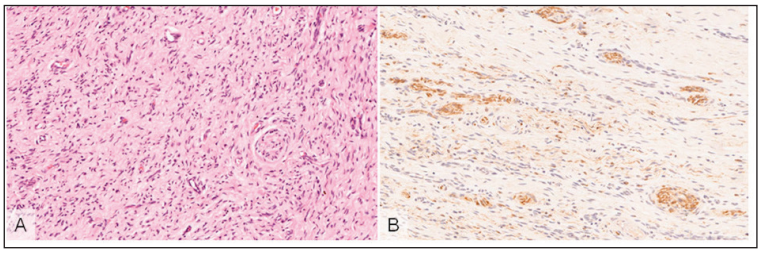


Figure 4. Patient 3: **A.** Histopathological features of the maxillary intraosseous neurofibroma showing a neoplasm composed spindle cells having elongated, wavy and normochromatic nuclei, immersed in a stroma of delicate collagen bundles (H&E, original magnification, 200x). **B.** Patient 3: Immunohistochemical analysis for S-100 protein showing positivity in nerve bundles and spindle-shaped tumor cells (original magnification, 200x).



Other oral manifestations may occur in NF1 patients with or without facial plexiform neurofibroma. Although localized neurofibromas are common on the skin, they occur in the oral cavity in 26% of cases with the tongue most commonly affected.[6] In a recent study on 50 NF1 pediatric cases,[23] localized intraoral neurofibromas were not found. Enlargement of the fungiform papillae has been reported in half of NF1 patients,[6] but was not observed in this case report or in a previous pediatric study.[23] Radiographic changes were present in 26% of NF1 children, but this did not include patients with facial plexiform neurofibroma.[23]

CONCLUSION

Dentists and physicians should be aware of the oral manifestations of pediatric NF1 patients and perform a careful exam to investigate these alterations. Long-term follow-up monitoring for oral manifestations is needed. Also, follow-up monitoring of plexiform neurofibromas are important due to the potential for malignant transformation, occurring in up to 5% of patients.[25] Pain and rapid growth may indicate malignancy, and further diagnostic investigation, such as positron emission tomography and biopsy, should be pursued.

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