


# VON RECKLINGHAUSEN disease/type I neurofibromatosis and its association with orofacial changes: Literature review and case report

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## Abstract:

Neurofibromatosis is an autosomal dominant genetic disorder and an inherited condition. This pathology represents 90% of the cases found in the general population. Oral manifestations of neurofibromatosis type I can occur in 70 to 92% of cases, especially when a detailed clinical examination is performed associated with complementary imaging tests. Because of this, it is not uncommon for the dental surgeon to be the first health professional to perform the diagnosis of the disease. The importance of having an early diagnosis correlates with the possible complications of the disease. The carrier may have offspring that manifest the disease in its severe form because of the large capacity for variation, which can be avoided with prior genetic counseling. In this study we report a case of a woman diagnosed and treated for central giant cell lesion 44 years ago, with dental, spine and mandible alterations, also with a family history of neurofibromatosis.

**Keywords:** Neurofibromatosis 1; Maxilla; Mandible; Oral Manifestations.

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## INTRODUCTION

Neurofibromatosis is an autosomal dominant genetic disorder and an inherited condition, first described by Friedrich Daniel Von Recklinghausen who named neurofibromatosis type I as von Recklinghausen's disease. This pathology represents 90% of the cases found in the general population, as a proportion of 1 to every 3,500 live births. Type II neurofibromatosis is more uncommon, presents the ratio of 1 case per 50,000 births and is associated with chromosome 22. It is characterized by disorders of the central nervous system. Other types of the disease are also found due to their high mutational capacity<sup>1</sup>.

Multiple associations of neurofibromatosis type I with central giant cell lesion (CGCL) are related in the literature. These associations may represent a genetic relationship, or susceptibility due to abnormal bone quality. The biological behavior varied from slow to aggressive and may present pain, root resorption, paraesthesia and recurrence after curettage<sup>1,2</sup>.

It is important to emphasize that although the patient with neurofibromatosis type I presents distinct characteristics, two thirds of the patients present a mild manifestation of the disease, presenting a sub clinical sign, which can often make diagnosis difficult<sup>1,3</sup>.

There is still no treatment for Von Recklinghausen/NF1 disease, the conduct will depend on each case and the manifestations developed by the patient, often the functional esthetic treatment is associated. Genetic counseling should be approached in all cases so that there is no risk of manifestation of the disease in severe form in the following generations<sup>1,4</sup>.

## CASE REPORT

A 13 years-old female patient, was referred for evaluation due to a bone alteration in the anterior region of the mandible. Under general anesthesia, removal of the lesion was performed through segmental mandibulectomy from angle to mandibular angle, with submandibular access, and placement of acrylic endoprosthesis in the region. The anatomopathological result of the excisional biopsy was of CGCL.

In 26 years of follow-up, another osteolytic lesion was identified in the left border infraorbital region.

The patient underwent a new surgical with removal of the lesion and graft placement. The anatomopathological diagnosis of the second excisional biopsy was of CGCL.

After a year of the second surgery, a fracture of the mandibular acrylic endoprosthesis was diagnosed. The removal of the acrylic endoprosthesis and the placement of a titanium reconstruction plaque were conducted.

After two years of reconstruction with titanium plate, the patient was submitted to the fourth surgical procedure. It was proceeded the removal of the titanium plate and the microsurgical flap of the fibula was placed for reconstruction of the mandible, however, the patient presented with venous thrombosis of the flap and the same was lost during the postoperative period.

Currently, she reports difficulty in chewing, and in times of cold says to feel pain in the jaw and limitation of opening of mouth. In her medical history, she underwent the removal of a tumour in the right suprarenal gland with a diagnosis of pheochromocytoma 7 years ago. She also reports that her mother had neurofibromas and Café-au-Lait spots.

At clinical examination, neurofibromas present on the face, coast, abdomen, lower limbs and upper limbs approximately 0.5cm<sup>2</sup> (Figure 1), Café-au-Lait spots greater than 5mm in the abdominal region, with the most evident spot on the lower abdomen right, scar on abdomen on the right side due to the removal of tumor in suprarenal gland (Figure 2) and Lich nodules, represented by hamartomas in the iris of the right and left eyeball (Figure 3), cervical spine scoliosis, facial asymmetry due to segmental mandibulectomy surgery performed on the mandible.

In the intra-oral examination, presents discreet alveolar ridge hyperplasia, maxillary atresia. In the lower arch, edentulism is observed due to the bone discontinuity, due to the segmental mandibulectomy performed to remove the lesion (Figure 4).

Panoramic radiographic examination for the mandible shows the absence of the anterior region of the mandible, the presence of bone thinning of the left and right mandibular remnants, thickening of the bilateral mandibular canal and absence of the dental element 22, with no previous history of exodontia (Figure 5).





**Figure 1.** Multiple neurofibromas in the face, neck and back, facial asymmetry with loss of mandibular projection due to partial mandibulectomy.



**Figure 2.** Café-au-Lait Spots > 5 mm in the abdomen. Scar on right side due to removal of tumor in adrenal gland.



**Figure 3.** Lisch nodules, represented by hamartomas in iris in the left eyeball.



**Figure 4.** In the intraoral examination, lack of mandibular projection due to segmental mandibulectomy is observed.





**Figure 5.** Panoramic radiograph of the mandible showing the absence of the body and angle of the mandible due to segmental mandibulectomy.

## DISCUSSION

In order for the diagnosis of Von Recklinghausen/Neurofibromatosis type I (NF1) disease to be confirmed, the patient must present the criteria defined in 1988 by the National Institutes of Health (NIH)<sup>5</sup>, requiring the carrier to present at least two or more of the characteristics following:

- Six or more Café-au-Lait spots with more than 5 mm in prepubertal patients, or more than 15 mm in postpubertal patients;
- Two or more neurofibromas of any type, with at least one plexiform neurofibroma;
- Ephelides (freckles) in the axillary and inguinal regions;
- Optic glioma (a brain tumour that causes an alteration in the optic nerves);
- Two or more Lisch nodules (pigmentation of iris hamartomas);
- Characteristic bone lesion (dysplasia of the sphenoid wing or thinning of the cortical bone of the long bones, with or without pseudoarthrosis);
- A first-degree relative with any of the changes that meet the NIH criteria, although it is already defined in the literature that in 50% of the cases the patients have no family history, which is believed to be new mutations.
- These characteristics of Von Recklinghausen/NF1 disease are described in the following.

### Neurofibromas

Neurofibromas are benign tumours of softened texture and represent the primary clinical feature of the disease.

They are observed in about 5% to 25% of cases, causing aesthetic and psychological problems, and there is also the possibility of malignant transformation. Its removal can be done surgically, but due to the high vascularization, there may be recurrences. They may also extend along the path of a nerve, being called plexiform neurofibromas or occur intraosseously<sup>1</sup>. In the case reported it was possible to verify the presence of numerous neurofibromas in the head and neck region and distributed throughout the body.

In the mouth, the sites most commonly affected by neurofibromas are the tongue and buccal mucosa, 20-60% of which are associated with neurofibromatosis. In some cases, plexiform neurofibromas can travel through the trigeminal nerve pathway, in which cases there may be hemifacial deformation and enlargement of the mandibular canal<sup>6,7</sup>.

Correlation between temporomandibular disorder and neurofibromas present in the joint structures are also described<sup>8</sup>.

### Osseous and radiographic alterations

The bone changes most frequently found in von Recklinghausen/NF1 disease include pseudoarthrosis, cortical thinning of long bones, cystic bone lesions, pedicle tapering, sphenoid wing dysplasia, osteolytic lesions in the skull, facial and mandibular deformity<sup>1</sup>. In the case reported, the patient had tapering of the remaining cortical of the mandible and facial and mandibular deformity.

Oral radiological findings include the thickening of the mandibular canal, mandibular and mental foramen. Bilateral thickening of the mandibular canal is an important radiographic evidence of Von Recklinghausen/NF1 disease, as well as the enlargement of the mandibular foramen. Also seen are hypoplasia of the condylar and coronoid process, elongation of the condylar neck, irregularities in the mandibular cortical, wear and lateral curvature of the cortical of the mandibular ramus<sup>3</sup>. Many of these findings were found in the radiographic examinations of the aforementioned case.

Neurofibromas may also occur intraosseous, resulting in a well-circumscribed unilocular area, which may cause bone asymmetries. Other cases are found in the literature with reports of excessive growth of alveolar ridge<sup>6</sup>.

In on study, the authors observed a prevalence of periapical cementum dysplasia associated with vital teeth in women. In the report, no significant periapical changes were found<sup>9</sup>.

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Magnetic resonance imaging is the most used imaging test to complement the diagnosis<sup>10</sup>.

### **Central giant cell lesion**

The CGCL is a benign bone neoplasm that affects the jaws. It presents as radiolucent, uni or multilocular lesions, being preferred by the anterior region of the mandible crossing the midline. It occurs most commonly in young adults, in the third decade of life, with females being the most affected<sup>3</sup>.

The lesion may present either as slow and asymptomatic growth or with aggressive behaviour, being able to cause facial asymmetry, dental displacement, bone resorption and pain<sup>11</sup>.

The aetiology of CGCL may be related to local or systemic factors. Among the systemic causes, we can mention the association with syndromes such as neurofibromatosis I, Noonan syndrome, as well as hormonal disorders, such as hyperparathyroidism and pregnancy<sup>12</sup>. Cases of multiple CGCL in the maxilla and mandible are related to diseases or syndromes, such as Von Recklinghausen/NF1 disease<sup>3,13</sup>. In the case reported, the patient presented a history of surgical removal of two distinct CGCL with aggressive behavior.

There appears to be an association of Von Recklinghausen/NF1 disease with an increased incidence of CGCL in the jaw, which may represent a genetic change, resulting from the chromosomal deletion of two or more genes in the same region of the chromosome. However, it is not yet known whether there is a genetic relationship or susceptibility due to abnormal bone quality or vascular abnormalities<sup>2,7</sup>.

CGCL are commonly treated with surgical removal and curettage. More aggressive lesions are treated with resection<sup>3</sup>. In the present case, the first lesion was treated through a segmental mandibulectomy from angle to mandibular angle, while the second lesion the lesion was curetted, with no evidence of recurrence.

Due to the biological behaviour of CGCL, especially in association with diseases or syndromes, this should be the most emphasized orofacial alteration in cases of Von Recklinghausen/NF1 disease. In the aforementioned case, the patient presented an aggressive lesion, causing pain and functional impairment, and in which the indicated treatment was a mutilating surgical procedure that brought many aesthetic and functional sequels.

### **Occlusal changes**

It is not uncommon for patients with von Recklinghausen/NF1 disease to have malocclusion<sup>14</sup>. Friedrich et al.<sup>15</sup>, analyzing dental position changes, maxillary deformities and malocclusions in patients with the disease, verified that these signs are strongly associated with the presence of plexiform neurofibroma originating from the trigeminal nerve.

There are several studies in the literature on maxillofacial malformations associated with adjacent tumours and of genetic origin associated with the disease, being these congenital malformations. The alterations found are maxillary hyperplasia, maxillary atresia, and dental migrations among others<sup>15</sup>. In the case described, the presence of maxillary atresia can be observed, with joint and mandibular alterations caused by surgical mandibular removal.

### **Dental alterations**

The presences of impacted teeth, tooth dislocation or missing teeth are oral findings found in patients with Von Recklinghausen/NF1 disease. The cause of agenesis may be due to the growth of plexiform neurofibroma or of genetic origin due to the primary skeletal impairment, affecting the development of the dental germ. There may also be a lack of dental germs, migration or dental intrusion<sup>14,15</sup>. In the clinical case presented the patient does not present the dental element 22, having no previous history of dental extraction.

### **Gingival hyperplasia**

Gingival changes are rare but can be found. In these situations, hyperplastic gingiva is diffuse and unilateral, characteristic of vascular and neurological alterations<sup>9,16</sup>. These findings are seen in this report in the bilateral maxilla.

### **Other changes**

Von Recklinghausen/NF1 disease is a generally asymptomatic condition, but the patient may present pain or paresthesia when there is an association of neurofibromas with the inferior alveolar nerve. Other signs may also be seen in the oral cavity, such as increased fungiform papillae<sup>6,10</sup>.

The patient of the described case reports painful symptomatology in the facial region, associated with cold periods, chewing and mouth opening. It was not clear if the painful symptomatology is related to the disease or due to the multiple surgeries. The other findings were not found.

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## CONCLUSIONS

Von Recklinghausen/NF1 disease presents several clinical diagnostic criteria associated with orofacial manifestations.

Among the orofacial manifestations that should have greater relevance is the Central Lesion of Giant Cells, due to its growth and treatment characteristics that, if not performed early, can lead to large mutilations and functional problems.

It is important to emphasize that the general clinical picture is often not evident, and there are relevant orofacial alterations that can help in the diagnosis of the disease. The dental surgeon may be the first health professional to recognize this condition.

The importance of having an early and accurate diagnosis of Von Recklinghausen / NF1 disease correlates with its autosomal dominant trait and its possible complications. A carrier of the disease that has no obvious signs and consequently is unaware of it may have offspring that manifest the disease in its severe form due to the large capacity for variation. This can be avoided with prior genetic counseling.

In the present case the patient presented the majority of the orofacial alterations found in the literature and in this way it was possible to conclude the diagnosis of Von Recklinghausen / NF1 disease. With this it is possible to institute the follow-up of this patient, thus preventing major commitments in the future.

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