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TYPE 1 NEUROFIBROMATOSIS AND EFFECTS ON THE STOMATOGNATIC SYSTEM

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Abstract: Neurofibromatosis is a systemic hereditary disorder that mainly affects the skin and nervous system. It was identified for the first time by Friedrich Von Recklinghausen, being called the Von Recklinghausen syndrome. Some of the clinical symptoms can be visible since birth, however, most of them start to show up during childhood and adolescence and, in women, phenotype becomes evident during pregnancy, due to the severe hormonal changes that occur.

The goal of this research was to understand the way type I neurofibromatosis can affect the oral cavity and how the dental doctor can help. For that, several papers were selected from the search on the websites Pubmed, Elsevier and UptoDate using the following keywords: *neurofibromatosis*, *oral health*, *neurofibroma*, *oral cancer*, GTP, *type 1 neurofibromatosis*.

Concerning clinical features at the oral cavity, more than one fourth of patients with this disorder can show neurofibromas in the mouth, usually isolated. Phenotype can include increased fungiform papillae, head and neck polyps, nodules in the posterior portion of the back of the tongue, dental mobility caused by lesions in the gingival-dental-alveolar complex, changes in the number of teeth, molar retention, dental calculus, aplasia of the second bottom molars and advanced periodontal disease. Bone changes can be present like subperiosteal erosion, hyperplasia, hypoplasia, dysplasia in the wings of the sphenoid and short size.

Concerning therapeutic strategies, some studies suggest that proteins of the mTOR pathway (mammalian target of rapamycin) can be the target for therapy of this disease in case of malignant transformation.

Keywords: "Neurofibromatosis", "Oral Health", "Neurofibroma", "Oral Cancer", "Type 1 Neurofibromatosis", that were interconnected in several ways.

INTRODUCTION

Neurofibromatosis (NF) is a systemic hereditary disorder mainly affecting the skin and nervous system.

Although its existence has been referred in the 13th century, the first published report on neurofibromatosis dates from 1768 describing an affected individual as a "patient having skin neurofibromas transmitted by his father" [1]. In 1882, neurofibromatosis was described by Friedrich Von Recklinghausen, giving the name to the syndrome [2-4]. Riccardi & Kleiner [5] were also some of the first researchers studying neurofibromatosis patients, having classified the disease according with the intensity/gravity of symptoms in each patient (Table 1).

There are several forms of this pathology: type 1 (NF1) that is the most studied, type 2 neurofibromatosis (NF2) and Schwanomatosis. NF1 represents 85-90% of neurofibromatosis cases, having an incidence of one case in three thousand births.

NF2 affects mainly the central nervous system while NF1 interferes with peripheral nerve sheath [1,6]. Incidence of NF2 is lower than NF1 and is one in thirty-three thousand births [7]. Type 2 neurofibromatosis is caused by mutations associated with the *NF2* gene located on chromosome 22 (22q12.2). This gene codes for a protein known as schwanomin or merlin whose function is to stablish links between glycoproteins of cell membrane and cytoskeleton proteins [8].

Although NF2 patients also show brownish spots, these spots have irregular edges and are lighter than the ones shown by NF1 patients. As in NF1, NF2 patients can also have ophthalmic manifestations like cataracts, retina harmatomas and meningioma of the optical nerve [9].

At last, Schwannomatosis is associated with mutations in the *IN11/SMARCB1* gene, also present in chromosome 22 [9], close to the*NF2* gene. In this way, NF2 patients frequently show associated schwannomas, including bilateral vestibular schwannomas that are essential for diagnosis of the disorder [8,9].

Schwannomas are tumours with origin in Schwann cells both in peripheral as well as central nerves. In almost all sporadic schwannomas there is inactivation of the two alleles of the *NF2* gene whatever the location of the tumours. On the other

hand, NF2 patients are heterozygous for *NF2* gene mutations, and the developed tumours exhibit loss or mutation of the wild allele. In this way, loss of function of the protein coded by the *NF2* gene (merlin/schwanomin protein), boosts the start and development of all schwannomas [8,10].

Some clinical symptoms of type 1 neurofibromatosis can be present since birth, however, most of them develop during childhood and adolescence [1].

MATERIALS AND METHODS

Several searches were performed on websites: Pubmed, B-On, SciELO, Science Direct and UptoDate, as well as on the repository of Medicine Faculty of O'Porto University and Fernando Pessoa University.

From this search, papers in Portuguese, English, French and Spanish were selected, together with some books to complete the search.

ETHIOLOGY

Type 1 neurofibromatosis is a disorder with an autosomal dominant transmission, complete penetrance and variable expression [11].

After positional cloning, the gene involved in the development of this pathology was thought to be present in chromosomes 5 or 17 [11]. It was Barker that, in 1987, observed a considerable connection between markers of chromosome 17 and the *NF1* gene [12]. Nowadays, it is known that this disease is associated with mutations in the long arm of chromosome 17 (17q11.2) [1,10]. The *International NF1 Genetic Analysis Consortium* described and named numerous mutations in the *NF1* gene, including deletions, insertions, splice mutations, aminoacid changes and chromosomic rearrangements [11,13].

The *NF1* gene has 60 exons and extends for 350 kb. The coding region of this gene has 8454 bp being transcribed in the direction centromere-telomere [14-18].

Transcription of the *NF1* gene gives rise to different mRNAs by alternative splicing with sizes ranging from 11 to 13 kb, leading to multiple isoforms expressed in different tissues like neurons, oligodendrocytes and Schwann cells [19]. This alternative splicing occurs in exons 9, 23 and 48 [20]. The stop codon is present in exon 49 followed by a 3'-untranslated region of 3,5 kb [21].

The 13 kb transcript is the most common and codes for a protein of 2818 aminoacids and 220 kDa, known as neurofibromin that is expressed in several tissues like brain, kidneys, thymus and spleen [19,22,23]. This protein has a central domain, codified by exons 21 to 27 of the *NF1* gene, known as GRD (GAP related domain), of 360 aminoacids, homologous to the catalytic domain of the activator protein of GTPase [22,24].

This group of enzymes called GAP act in the regulation of several cellular functions including cell growth, signal transduction and cytoskeleton organization. The GRD domain has an important role in negative regulation of a mitogenic signalling pathway mediated by the p21-ras gene (proto-oncogene homologous to the oncogene of mouse sarcoma) [25]. The Ras protein coded by this gene, attaches guanosine triphosphate (GTP) and is involved in the signal transduction pathway. The role of neurofibromin, as well as the role of the GAP protein, is to interact with Ras linked to GTP, being involved in GTP hydrolysis in guanosine diphosphate (GDP), with consequent inactivation of the Ras protein [20]. As a result, the inactive Ras protein, controls cellular growth and multiplication. In this way, the decrease in neurofibromin levels resulting from mutations in the coding gene, leads to over-activation of the *p21-ras* gene, consequent increase of active Ras protein and subsequent disorganized cell growth and tumour development (development of neurofibromas) [18].

SYSTEMIC TRAITS

As a result of variable expression, this disorder can lead to the development of several degrees of symptoms intensity. For this reason, Riccardi & Kleiner [5] stablished several degrees of neurofibromatosis (Table 1).

Table 1. Classification of intensity of Neurofibromatosis according to Riccardi & Kleiner [5].

Intensity	Clinical traits
Minimal	Brownish spots Few skin neurofibromas without aesthetical or functional involvement
Light	Big number of skin neurofibromas Asymptomatic internal lesions Low aesthetical involvement
Moderate	Big number of skin and visceral neurofibromas Pseudarthrosis Scoliosis Controlled convulsions
Strong	Big health involvement Frequent surgical interventions Symptoms associated with several types of cancer like intracranial and spinal tumour, malignant schwannoma, neurofibersarcoma, uncontrolled convulsions, mental retardation, hydrocephaly, progressive hypertrophies.

According with the *National Institute of Health* (NHI) of USA, for NF1 diagnosis, the patient must show two or more of the following characteristics [11,26]:

i) Six or more brownish spots
ii) Two or more neurofibromas of any type or one plexiform neurofibroma; false eels in the axillar or inguinal region
iii) Optic glioma
iv) One distinct bone lesion, like sphenoid dysplasia or thinning of long bones with or without pseudarthrosis
v) A first degree relative having NF1, according with the stablished criteria.

Pathognomonic characteristics of the disease are easy to diagnose and include brownish spots present in skin of most patients [1,13,27]. According with Crowe criteria [4], to be considered a neurofibromatosis phenotype the patient must show six or more spots with a diameter bigger than 1,5 cm in adults and 0,5 cm in children [1,27].

Another typical characteristic is the presence of neurofibromas. As previously referred, for diagnosis of neurofibromatosis, a patient must have two or more neurofibromas of any type or a plexiform neurofibroma with itching. These manifestations can be circumscribed to just a segment of nervous distribution, while plexiform neurofibromatosis is usually distributed close to nerves, having easy relapse after surgical removal [27,28]. Sometimes, itching intensity is proportional to the size and number of neurofibromas. Heat increases itching, and cold water relieves [27]. Lesions in the peripheral nervous system can affect the functioning of the stomatognatic system, as described above.

Moreover, these patients frequently show Lish nodules in the anterior face of iris, that are pigmented focal malformations like benign tumours called harmatomas [1,27]. These structures can have a colour from yellow to light brown and are formed by melanocytes with neural crest origin [1,29].

The most common SNC tumour associated with NF1 is the optic glioma [13], being astrocytomas (tumours associated with astrocytes) the most frequent [30]. The anterior visual path is most frequently affected. NF1 patients usually present one unilateral glioma [13]. In very severe NF1 cases, affected individuals can show high commitment of vision due to ocular neurofibromas [28,31].

The sphenoid wing dysplasia is congenital and usually unilateral and non-evolutionary. It is normally associated with a plexiform orbital neurofibroma [32]. According with Burrows [33], NF patients can show dysplasia in the wings of the sphenoid bone affecting the orbit wall and the torsal seal, thus manifesting exophthalmia resulting from the herniation of the dura into the orbit [31,33].
NF1 patients can also show dysplasia in long bones, being tibia the most affected, often showing fractures with secondary pseudarthrosis [32].

Concerning non-pathognomic symptoms, the most usual are visceral, neoplastic and bone manifestations, besides the ones already mentioned before [27].

Visceral manifestations can vary according with the location of neurofibromas. When they are close to the stomach or ileum, patients can present digestive complications [27].

Patients with neurofibromatosis showing changes in the endocrine system, can develop scoliosis, short size with an increase in the chance of bone fracture [13]. Neoplastic complications, besides optical neurofibromas and gliomas previously referred, also include other tumours that can associated with NF1, as can be checked in Riccardi & Kleiner's scale (Table 1). More severe complications can occur by the development of *Malignant Peripheral Nerve Sheat Tumour* (MPNST), name given to malign tumours or neural origin [6]. MPNST can appear *de novo* or be a consequence of malign transformation of pre-existing neurofibromas. *De novo* tumours can develop all over the body while the associated with neurofibromas have a more centralized location. As a rule, these MPNST are hypercellular, hyperchromatic and cells with mitotic spindle and sometimes present a fasciculated pattern similar to fishbone [31]. Öztürk & Tutkun [6] reported a case of a 16-year-old male patient who presented a severe dysphagia, mandibular and temporomandibular pain and respiratory difficulty due to a MDNST of the retromolar area.

Concerning bone growth, some authors suggest that this may result from tumour development inside the bone or in bone direction resulting in bone reabsorption or hypoplasia [4]. Other studies suggest that the presence of a tumour adjacent to the bone can stimulate bone growth resulting in a hyperplasia. However, bone complications might appear by dysplasia not related to its proximity with the bone tissue, as the cases of mesodermal dysplasia. Based on presented data, it is believed that neurofibromatosis might have neuro-ectoderm or mesoderm origin [4,34].

Oral cavity manifestations:

Other typical symptoms seen in the oral cavity are increased fungiform papillas, nodules in the posterior portion on the back of the tongue, teeth mobility as a result of lesions in the gingival-dental-alveolar complex, change in teeth number, molar retention, dental calculus, aplasia of the second inferior molars and advanced periodontal disease [35]. Tongue and oral mucosa are the most affected regions. Shapiro et al. [34] detected oral neurofibromas in soft tissues in 6 of 22 analysed patients.

Neurofibromas present in the trigeminal nerve can affect sensorial capacities of the patient, while if they are present in the facial or hypoglossal nerves, might compromise his motor functions [34]. Moreover, a plexiform neurofibroma in the trigeminal nerve is frequently the main cause of hemifacial disfiguration observed in patients [29]. Pain and paraesthesia are characteristic of an affected inferior dental nerve. Since neurofibromas are benign tumours, they show slow growth. During its growth, it moves the nerve laterally giving pain or paraesthesia. However, cases with fast development of the neurofibroma can be a sign of haemorrhagy or sarcomatosa malignant degeneration [27].

The increase of mandibular canal, mandibular and mental foramen are some of the radiographic findings that can point to Von Reckling Hausen disease [29]. The most common craniofacial change is the skull increase, as a result of the higher production of glia cells. Among bad bone formations, it is also possible to see mandibula hypoplasia, decrease or elongation of the coronoid process and zygomatic arch [36].

Due to growth of neurofibromas in parapharynx space, patients may also present hoarseness, dysphagia and tongue atrophy by paresis of the last four pairs of cranial nerves (glossopharyngeal, vagus, accessory and hypoglossal) [36]. Souza et al. [3] observed that 56,7% of NF1 patients (183 of 206) showed changes in voice and oral motor. It is believed that those changes result from neurological disturbances that give rise to insufficiency of velopharyngeal muscle and oropharyngeal musculature. The same study also observed

that 67% of individuals diagnosed with NF1 showed less muscular strength when compared with undiagnosed individuals [3]. These patients can show nasal and week speech with stimulated rhythm and defect in sibilant sounds pronunciation [36].

Although several oral manifestations associated with NF1 are known, very few cases of hyposalivation and xerostomia have been reported in literature. Cunha et al. [37] performed a case-control study with 49 individuals diagnosed with NF1 and a control group of 40 individuals not diagnosed with NF1. They observed that NF1 patients had higher prevalence of hyposalivation when compared with the control group [37].

Transformation of plexiform neurofibromas into malignant tumours compromises prognosis. In these cases, surgical resection complemented with radiotherapy or chemotherapy is the indicated treatment [36].

DIAGNOSIS

Clinical diagnosis of NF1, as previously mentioned, is performed according with the phenotypic characteristics established by the National Institute of Health (NIH) of USA shown in Table 1. When an individual shows only some of the traits, NF1 diagnosis cannot be established or discarded.

Hence, other exams can be done as a diagnosis complement, namely computer tomography, proton spectroscopy to evaluate brain metabolites, image magnetic resonance, neurofibromas biopsy, skin exams of hyperpigmentation using a Wood lamp, IQ test, psychological analysis, ophthalmologic exam and auditive evaluation [38].

In cases of pregnancy where one of the parents is affected by NF1, it is useful the use of genetic tests for mutation screening of *NF1* gene. Among these tests are conformational polymorphism analysis of single strand and of heteroduplex, FISH, electrophoresis in temperature gradient gel or denaturing gel and the protein truncation test [11]. Samples can be obtained from the amniotic fluid or chorionic villi [11].

TREATMENT

Clinically, neurofibromas are a sessile and pedunculated mass of fibrous consistency with slow growth [39]. Histologically, they are composed of bundles of spindle-shaped cells with undulated nucleus and having a variable amount of myxoid material [40].

Prognosis and treatment depend on compromised systems and tissues. Due to potential relapse, surgical removal is mostly performed in cases with high aesthetic and functional commitment or with tendency for malignant tumours transformation [36,41].

During this procedure, major nervous structures should be kept since surgical excisions do not have as goal to induce neoplastic changes. Some factors like neurofibromas infiltrations, blood vessels hypertrophy and abnormal response to muscle relaxants anaesthetics recently reported can prevent surgery [36].

So far, there is still no pharmacological treatment for NF1. However, itis believed that proteins of the mTOR pathway (mammalian target of rapamycin) can act as a therapy for this disease, since they have a crucial role in regulation of tumour cells division and growth of blood vessels [42,43]. The mTOR protein is a serine/threonine kinase that besides its action in cellular growth, plays an important role during protein synthesis. Changes in this signalling pathway are associated with tumorigenesis, angiogenesis, tumour growth and metastization. Inactivation of certain tumour suppressor genes leads to activation of the mTOR pathway, as is the case of p53 gene. The first discovered inhibitor of this pathway was rapamycin, however, analogues of this were developed due to its pharmacokinetics and pharmacodynamics properties [8,42,44,45].

In cases of neurofibromas that are not associated with Von Reclinghausen syndrome, other techniques have been developed. In a study of Angiero et al. [46] ten individuals having neurofibromas in different places of the oral cavity were submitted to a treatment of diode laser with a wave length of 980 nm, 2.0 W, optical fibre of 320 µ, for an exposure period of 45 seconds in average, at a distance of 1 cm from the source. After 15 days, all patients showed cure, and only half of them felt a slight discomfort after surgery. This technique allows an easier excision of soft tissues than surgical intervention. However, the risk of necrosis, ulceration and drilling of tissues is bigger due to the chance of contact between the laser and adjacent mucosa, being required to keep refrigeration of the mucosa [46].

CONCLUSION

Neurofibromatosis type 1 is a hereditary disease associated with a gene present in chromosome 17. This disorder affects multiple organs including the stomatognatic system. Due to the typical phenotype observed in patients, this disease has a big impact on patient's life from the clinical and psychological points of view, since the aesthetic condition might lead to low self-esteem.

Therefore, it is very important that doctors are aware of this condition since different degrees of symptomatology might be present, due to the variable expressivity shown in this disorder.

NF1 treatment depends on which systems and/or tissues are affected. No pharmacological treatment is available and surgical removal of neurofibromas is usually performed in patients with high aesthetic and functional commitment or with tendency for malignant tumours transformation, due to frequent relapse.

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