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Literature Review

Hereditary Gingival Fibromatosis: A Short Review of the Literature

Rebeca Serrano Zamora[1], Carmen Mallagray[1], Carlos M Cobo Vázquez[2,3]* and Juan López Quiles[4]

[1]Oral Surgery and Implantology Master Student, Department of Clinical Specialities, Faculty of Dentistry, Complutense University of Madrid, Madrid, Spain

[2]Associate Dentist, Department of Stomatology and Dentistry, Gregorio Marañón University General Hospital, Spain

[3]Associate Professor, Department of Clinical Specialities, Faculty of Dentistry, Complutense University of Madrid, Spain

[4]Titular Professor, Department of Clinical Specialities, Faculty of Dentistry, Complutense University of Madrid, Spain

***Corresponding Author:** Carlos M Cobo Vázquez, Associate Dentist, Department of Stomatology and Dentistry, Gregorio Marañón University General Hospital, Spain.

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Abstract

Introduction: Hereditary gingival fibromatosis (HGF) is an uncommon, inherited disorder with slow and progressive fibrous hyperplasia of the gingiva. The excess gingival tissues can cause dental, masticatory and phonetic problems, which cause functional and esthetic problems.

Objective: To describe the main epidemiology, clinical signs, symptoms, histopathological and therapeutic aspects of HGF.

Materials and Methods: A comprehensive search of the literature was conducted in the PubMed/MEDLINE (National Library of Medicine) and Web of Science electronic databases. The search strategy was done using the following terms: "hereditary gingival fibromatosis", "palatal fibromatosis", "gingival fibromatosis".

Results: Discuss the main clinical characteristics, diagnosis and treatment of HGF found in the literature.

Conclusion: HGF is an uncommon condition that causes enlargement of the gingival tissues affecting the maxilla or mandible. Its diagnosis is based on clinical observation, family history and histological analysis. Although the prediction of recurrence after surgical treatment is difficult to estimate, it is necessary to prevent patient discomfort.

Keywords: *Hereditary Gingival Fibromatosis; Palatal Fibromatosis; Gingival Fibromatosis*

Introduction

Hereditary gingival fibromatosis (HGF), also known as hereditary gingival hyperplasia, hypertrophic gingiva and elephantiasis gingivae, is an uncommon and hereditary condition characterized by a slow and progressive benign overgrowth of the gingival tissues non-dental plaque-induced. It was first described by Goddard and Gross in 1856. HGF presents a prevalence of 1:175.000 with men and women being equally affected [1-5].

The mode of inheritance is controversial. Although it is generally considered to be an autosomal dominant disease condition, there are some studies which demonstrate that it may also follow an autosomal recessive pattern. When gingival fibromatosis has a genetic origin, it can occur in isolation or be part of a syndrome [1,2,5].

The gingival overgrowth could affect maxillary and mandibular tissues. The hyperplasia is firm, painless and does not usually affect the alveolar bone, but can lead to the appearance of pseudo-pockets. The most common clinical complications are difficulties in speech, chewing and occlusion, as well as changes in facial features [5].

The underlying mechanisms causing excessive gingival tissue accumulation in HGF is controversial, but it is known that there is an increased proliferation of subepithelial fibroblasts and a higher synthesis of collagen combined with a reduction of matrix metalloproteinases (MMPs) involved in collagen degradation [2].

Aim of the Study

The aim of the present review is to summarize the main epidemiology, clinical, histopathological and therapeutic aspects of hereditary gingival fibromatosis.

Materials and Methods

Inclusion criteria:

- Studies published in English.
- Publication deadline 5 years prior to the current year 2022.
- Literature and systematic reviews, observational studies and case reports were contemplated.

Exclusion criteria:

- Studies prior to 2018.
- Studies with no full-text were rejected.
- *In vitro* studies, letters to the editor, comments, and errata.
- Studies limited to drug-induced gingival fibromatosis.

A comprehensive search of the literature was conducted in the PubMed/MEDLINE (National Library of Medicine) and Web of Science electronic databases. The search strategy was done using the following terms: “hereditary gingival fibromatosis”, “palatal fibromatosis”, “gingival fibromatosis”.

An additional manual search with no time restriction has been done applying boolean operator “AND” in the following forms: “hereditary gingival fibromatosis” AND “treatment”, “hereditary gingival fibromatosis” AND “differential diagnosis”. Moreover, the following terms were searched manually: “enamel renal syndrome”, “Zimmermann-Laband syndrome”, “Costello syndrome”, “Rutherfurd syndrome”, “Murray-Puretic-Drescher syndrome”, “Prune belly syndrome”, “Ramon syndrome”.

Results

Using the keywords mentioned above, 502 articles (PubMed n = 218; Web of Science n = 284) were obtained from electronic databases. Following the previously established inclusion and exclusion criteria and eliminating duplicates, 447 articles were discarded.

Discussion

Inheritance

A wide spectrum of clinical and genetic heterogeneity is described in literature. HGF may appear as an autosomal dominant disease or more rarely, as an autosomal recessive tract. The recessive pattern is often associated with systemic diseases or syndromes [4].

Its etiology is complex and involves genetic factors and biochemical mechanisms. Currently two genes, SOS-1 gene (Son of Sevenless 1) and REST gene (RE1-silencing transcription factor), as well as four loci (2p22.1, 2p23.3–p22.3, 5q13–q22, and 11p15), have been identified as associated with HGF [1,4,67].

Clinical manifestations

Clinically, HGF appears as a gingival hyperplasia that could be generalized, affecting symmetrically the whole gingiva of the mandible and maxilla, or localized to a specific region of the mouth, including the labial gingiva, maxillary tuberosities and the area around the lower molars [4]. It presents a higher prevalence on the maxillary arch. Limited cases of bilaterally symmetrical palatal fibrous enlargements have been described in the literature. They are sessile masses, located in the hard palate, converging in the midline [1,8,9].

Gingival overgrowth has a pale pink, compact, painless and non-hemorrhagic appearance with a fibrous, nodular or lobular consistency. Although gingival enlargement does not directly affect the alveolar bone, gingival edema favors biofilm accumulation due to difficulties in oral hygiene, inducing pseudo-pockets and calculus deposits, causing gingivitis, periodontal disease and bone resorption. Another clinical manifestation that patients could present is halitosis [2,5].

Excess gingival tissue can cause teeth fully or partially covered crown, diastema, tooth displacement and impaction. In addition, delayed eruption of primary and permanent teeth has been seen in pediatric patients [2,5].

Gingival fibromatosis may finally cause problems in chewing, swallowing and phonation, creating patient discomfort, in addition to a negative impact on their quality of life due to poor aesthetics [2,5].

Extraoral manifestations such as tension in the facial muscles and lip incompetence with open bites can cause difficulties in breathing, snoring and a higher risk for obstructive sleep apnea episodes [1,5].

HGF has been associated with several clinical manifestations such as hypertrichosis, epilepsy, mental retardation, hearing deficiencies, supernumerary teeth and growth hormone deficiency, etc [5].

Its development occurs during the eruption of the permanent dentition. Few cases report an early detection in primary dentition and it is rare at birth [1].

Histologic features and pathogenesis

From a histologic point of view, HGF is characterized by a dense epithelium with elongated rete ridges extending into the underlying connective tissue [10].

Abundant collagenous fibers with little vascularization and fibroblasts are commonly found in the connective tissue. Studies demonstrated that fibroblasts from HGF produce 30% to 50% more collagen than normal gingival fibroblasts. Moreover, collagen accumulation is caused by an altered collagen phagocytosis. Small osseous calcifications have also been reported [1,11].

While the molecular mechanisms that induce this pathological process are not fully known, numerous hypotheses have been suggested. On one hand, the expression of Transforming Growth Factor-beta (TGF-β) is upregulated triggering an excess of extracellular matrix (ECM) by increasing its synthesis in the connective tissue and inhibiting ECM degradation by down-regulating the expression of MMPs [12]. On the other hand, epithelial to mesenchymal transition (EMT) has been suggested as another pathway that promotes gingival fibrosis in which the basal lamina is disrupted and epithelial cells penetrate through connective tissue and transform to fibroblast-like cells [4].

However, histologic findings are nonspecific and an adequate history and clinical examination are necessary for definitive diagnosis.

Associated syndromes

There are numerous syndromes associated with HGF. In table 1 is described the syndromes associated with HGF and their main clinical features. Some of them are discussed below:

Syndrome	Features
GF with hypertrichosis	GF, hypertrichosis, mental retardation, muscular hypotonia
Congenital generalized hypertrichosis	Hypertrichosis Affected females have asymmetric, patchy hirsutism
Gingival fibromatosis with distinctive facies	GF, macrocephaly, bushy eyebrows, synophrys, hypertelorism, down-slanted palpebral fissures, flat nasal bridge, hypoplastic nares, cupid-bow mouth, high arched palate
Jones syndrome–GF with progressive deafness	GF, progressive sensor, neural hearing loss
Zimmermann–Laband syndrome	GF–hypertrophy, absence/dysplasia of the terminal phalanxes or nails of the hands or feet and thick lips, bulbous soft nose, thick floppy ears, mental retardation, hepatosplenomegaly, hypertrichosis, hyperextensibility of the joints, ocular symptoms
Ramon syndrome	GF, cherubism, seizures, mental deficiency, hypertrichosis, stunted growth, juvenile rheumatoid arthritis
Congenital generalized fibromatosis	Multiple fibroblastic tumors involving skin, striated muscles, bones, and viscera
Juvenile hyaline fibromatosis (Murray Puretic–Drescher)	GF, multiple subcutaneous tumors, sclerodermiform atrophy, osteolytic and osteoclastic skeletal lesions, recurrent suppurative infections, painful flexural joint contractures, osteolysis of terminal phalanges, stunted growth/early death
Systemic infantile hyalinosis	Gingival hypertrophy, thickened skin/focal skin nodularity, joint contractures/osteoporosis, diarrhea/failure to thrive, recurrent infections/death (infancy)
Rutherford syndrome–gingival hypertrophy with corneal dystrophy	Gingival hypertrophy, corneal opacity, mental retardation, failure of tooth eruption, aggressive behavior
Cross syndrome	Hypopigmenation/silver grey hair color, microphthalmia with cloudy corneas, mental retardation/spasticity, athetoid movements/ growth retardation
Prune belly	Absence of abdominal muscles, abnormalities of urinary tract, cryptorchidism, facial dimorphism
Gangliosidosis	Gingival hypertrophy, macroglossia, coarse face/micrognathia, loose skin/inguinal hernia, delayed growth/hepatosplenomegaly, neonatal hypotonia, delayed motor development

Borrone dermato-cardio-skeletal syndrome	Gingival hypertrophy/coarse face, late eruption of teeth/loss of teeth, thick skin/acne conglobata, osteolysis/large joint flexion contractures, short stature/brachydactyly/congestive heart failure, inguinal hernia
Mannosidosis	Gingival hypertrophy/macroglossia, coarse features/prognathism, thick eyebrows/low anterior hairline, deafness/lens opacities, hepatosplenomegaly, recurrent respiratory tract infections, muscular hypotonia/mental retardation
Costello syndrome	Characteristic faces, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, congenital heart disease, atrial arrhythmia, cardiomyopathia, autistic behaviors, short stature increased risk of malignancy (rhabdomyosarcoma
I-cell disease (mucolipidosis)	Coarse facial features, normal head circumference relative to body size, puffy eyelids with slight exophthalmia, excessive prominence of the epicanthic folds, depressed nasal bridge, full cheeks exhibiting multiple fine telangiectasia, incompetent lips, gingival and alveolar enlargement with buried teeth, thick tongue
Donohue syndrome–leprechaunism	Hirsutism, acanthosis nigricans, large mouth, thick lips, gingival hypertrophy, paucity of lymphatic tissue, hepatic cholestasis, and fibrosis, large hands, feet, retarded bone age, reduced muscle mass, distended abdomen
Ectro-amelia	Split hand/foot malformation
Cantu syndrome	Congenital hypertrichosis, osteochondrodysplasia, cardiomegaly, mental retardation, macrocephaly, enlarged sella turcica, prominent mouth, narrow shoulders-thorax, broad ribs, platyspondyly and coxa valga
Amelogenesis imperfecta	Deficiency in enamel formation, defects in the mineral and protein contents, unerupted teeth, pulpal calcifications, root and Crown resorptions, hypercementosis, taurodontism, GF
Schinzel–Giedion syndrome8	Multiple skull anomalies, congenital heart defect, hydronephrosis, club feet
Sweet-like syndrome	Fever, neutrophilia, cutaneous lesions/plaques, nodules, GF

Table 1: *Syndromes associated with gingival fibromatosis.*

- Enamel renal syndrome: Is a rare autosomal recessive disorder. The diagnosis is based on orodental alterations and renal findings that represent the degree of impairment of the kidneys [13]. However, as renal changes occur late, the presence of the characteristic oral phenotype, even in the absence of other manifestations, is sufficient to clinically diagnose this syndrome [14].

- Zimmermann-Laband syndrome: is part of a rare and heterogeneous group of disorders with autosomal dominant and recessive inheritance. It is characterized by abnormalities of the facial area and the extremities (hands and feet) [15].

- Costello syndrome: it involves a wide range of cardiac, musculoskeletal, dermatological and developmental abnormalities. Craniofacial features include macrocephaly and ears are commonly low-set [16-18].

- Rutherfurd syndrome: is transmitted as an autosomal dominant trait, characterized by three major features: gingival fibromatosis, delayed tooth eruption and corneal dystrophy [19].

- Murray-Puretic-Drescher syndrome: is inherited as an autosomal recessive disease. Associated features of the condition include multiple soft tissue swellings involving the nose, orbital ridges, ears, bony prominences of the ulna and tibia and the parietal and occipital prominence and had gum hypertrophy [20,21].

- Prune belly syndrome: absent or hypoplastic abdominal muscles cause the clinical appearance and the full syndrome includes cryptorchidism and obstructive nephropathy [22].

- Ramon syndrome: is the association of cherubism with gingival fibromatosis, epilepsy, mental retardation, stunted growth, and hypertrichosis [23].

Diagnosis and differential diagnosis

The diagnosis is based on the patient's medical and family history, the clinical presentation, the pattern of recurrence, and the characteristic microscopic features of the histology samples. There are currently no specific immunohistochemical markers available for the disease.

Among benign tumors of the gingiva, giant cell fibroma, irritation fibroma, neurofibroma, angiofibroma, inflammatory myofibroblastoma and epulis fissuratum should be considered. Malignant neoplasms to be regarded are oral squamous cell carcinoma, salivary gland adenocarcinoma, melanoma, adenoma and mucoepidermoid carcinoma [24].

The differential diagnosis also should be made with certain drugs such as antihypertensives, immunosuppressants, anticonvulsants, antibiotics and oral contraceptives [24].

Another group of lesions to be considered are granulomatous lesions, including systemic diseases such as sarcoidosis, Crohn's disease and tuberculosis [24].

Although leukemia is a malignant disease, uncontrolled proliferation can occur, which in some cases may produce lesions resembling HGF [24].

Treatment

The treatment of HGF consists of surgical excision of the hyperplastic tissue to restore the gingival contours, external or internal bevel gingivectomy in association with gingivoplasty, an apically-positioned flap, electrosurgery, or carbon dioxide laser.

The advantages of CO_2 laser in comparison to the conservative or surgical methods consist of limitations in bleeding, pain, and treatment duration, as well as allowing treatment of all quadrants in one visit with minimal discomfort, which is an important consideration in children's therapy.

Treatment depends on the severity of enlargement and shows varying degrees of success. When the enlargement is minimal, thorough gingivectomy and home care might be all that is required to maintain good appearance. The patients receive a conservative treatment that consists of quadrant by-quadrant internal bevel gingivectomy in association with gingivoplasty, followed by 0.12% chlorhexidine oral rinse twice a day for 2 weeks after each surgery. The interval between surgeries is 2 - 3 months. Although recurrence is unpredictable, it is most often seen in children and teenagers, rather than adults. It has been demonstrated that recurrence is faster in areas with dental plaque accumulation. Normally recurrence is minimal or delayed if good oral hygiene is achieved by a combination of monthly examinations with professional cleaning and oral hygiene instructions [25].

Although there is general consensus on the modality of treatment for HGF patients, there are controversies as to the exact period in which it should be accomplished. According to several authors, the best time is when all of the permanent dentition has erupted, because the risk of recurrence is greater before eruption.

However, in some cases, a delay in the surgical treatment might cause significant consequences for the patient, such as primary dentition retention with delay in the eruption of the permanent teeth, difficulties in mastication and phonation, malpositioned teeth, aesthetic effects, and psychological problems for the patients and relatives.

Disease recurrence

In the systematic review of Boutiou., *et al.* recurrence after surgical treatment was observed in 33.85% of the children within a median time period of 12 months; while after 3 years from surgery less than 50% of operated patients result free from relapse [5]. However, the recurrence rate is difficult to predict and to determine. It is therefore essential to follow-up patients over time [6].

Conclusion

HGF is an uncommon condition that causes enlargement of the gingival tissues affecting the maxilla or mandible in a generalized or localized form. It can occur in isolation or as part of a syndrome. Its diagnosis is based on clinical observation, family history and histological analysis. Although the prediction of recurrence after surgical treatment is difficult to estimate, it is sometimes necessary to prevent patient discomfort.

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