Syndromes of head and neck region associated with gingival findings

Manjeeta Mahesh Sinai Dhume and Clarence Pascoal Dias

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Abstract
The part of the oral mucosa that covers the alveolar processes of the jaws and also surrounds the neck of the teeth is known as gingiva. The word syndrome is derived from the Greek syn (together) and dromos (running) and refers to a ‘running together’ or concurrence of symptoms. Even after taking into account local inflammatory conditions and drug use, occasional instances with a syndromic origin have been recorded. Present review tries to combine the relevant features of syndromes associated with gingival findings into a systemic review.

Keywords: Syndromes, head and neck, gingiva, gingival enlargement

Introduction
In genetics, ‘syndrome’ refers to a pattern of multiple malformations that are thought to be pathogenetically related [1]. Cohen & Kreiborg, who stated that in medical genetics, Multiple abnormalities that arise in embryonically disjointed regions are known as a syndrome [2]. Head and neck syndromes represent a complete set of anomalies that involve signs and symptoms associated with various other systems in human body along with distinct head and neck features.

Syndromes involving the gingiva are as follows [3]

1. Syndromes associated with gingival enlargement
Gingival enlargement or gingival overgrowth, a common trait of gingival disease, is characterized by an increase in the size of gingiva. This group includes syndromes as follows along with relevant findings of each one of them as follows:

a. Cowden’s syndrome/Cowden disease/Multiple hamartoma syndrome
It is associated with mutations in the PTEN gene on chromosome arm 10q [4]. Multiple papules on the gingiva has been noted giving an appearance of a cobblestone pattern. Other findings include nose, lips and ears showing popular lesions, periodontitis, gross dental caries, thyroid adenoma and gastrointestinal hamartomas [5].

b. Sturge-Weber syndrome
Caused by a mutation in the GNAQ gene. Gingival lesions vary from slight vascular enlargement to massive gingival growths [6]. Other intraoral findings include the buccal mucosa, palate, tongue, the floor of mouth, gingiva, and lips showing angiomatosis which may show purplish-red discoloration [7]. Other extraoral findings characteristic port wine stains-confined to skin supplied by trigeminal nerve along with brain calcifications, ocular disorders, hemiplegia and epilepsy.

This syndrome is associated with mutations in AGGF1 (Angiogenic Growth Factor 1). Intraoral gingival findings include capillary hemangiomas, vascular hypertrophy, gingival fibroma, fibromatosis, and hyperplasia. There is also unilateral increase in size of periodontal tissues [8]. Other intraoral findings include capillary hemangiomas on tongue, unilateral macroglossia, increase in size of fungiform papillae, unilateral increase in size of the lips, hyperplastic tissue responses on cheeks, tooth malformation which includes diastema formation. Delayed exfoliation of primary teeth along with premature eruption
of teeth on affected side and early mineralization of roots on affected side [8].

d. **Hurler’s syndrome**
This syndrome is characterized by anterior region showing gingival overgrowth with hyperplastic gingiva. There is also enlargement of tongue, shortening and widening of mandible, areas of bone destruction in jaws, high-arched palate, localized dentigerous cyst-like radiolucencies [19].

e. **Ellis–Creved syndrome**
Ellis–Creved syndrome is characterized by mutation in EVC and EVC2 gene [10]. Characteristic features include upper lip fused to the gingiva with disappearance of mucobuccal fold, absence of sulcus, partial hare lip, preanal eruption of the teeth, conical teeth, hypoplasia of enamel and hypodontia [10]. Extraoral findings include dwarfism and finger nail abnormalities.

f. **Robinow syndrome / Fetal face syndrome**
This syndrome is commonly associated with mutations in ROR2 gene on chromosome 9q22 [11]. Gingival enlargement along with upper lip with inverted V appearance, midline clefting of lower lip, malposition of primary and permanent teeth and ankyloglossia is noted.

g. **Oro-facial-digital syndrome type 1**
This syndrome is associated with mutations OFDI gene (CXORF5) [12]. This syndrome is characterized by numerous hyperplastic fibrous bands traversing the gingivalabial and gingivobuccal folds. Also gingivitis or gingival recession is noted in these patients. Other findings include thickened alveolar ridges and abnormal dentition, cleft palate, lingual hemartomas and ankyloglossia [12]. Patients might also show learning disabilities and polycystic kidneys.

h. **Goltz syndrome**
Goltz syndrome is associated with mutations in PORCN gene [13]. Intraoral findings include papillomas of gingiva, oral mucosa, skin and nails. Papillary gingival hyperplasia is noted. Few patients present with abnormalities of the extremities, telangiectasia and pigmentation of skin.

i. **Prune-belly syndrome**
This syndrome is characterized by microdeletion in relationship to hepatocyte nuclear factor-1-beta gene at 17q12 [14]. Gingival fibromatosis along with absence of abdominal muscles, abnormalities of urinary tract, cryptorchidism and facial dimorphism is noted.

j. **Sweet syndrome**
Intraoral features include gingival fibromatosis and hyperplasia along with necrotizing ulcerative periodontitis. Some of these patients show edematous and aphthous lesions of the upper aero-digestive tract in the mouth and pharynx [15]. Other symptoms, which include fever, myositis, neutrophilia, along with tender erythematous skin is noted. Köbner Phenomenon-‘specific’ skin lesions at sites of minor cutaneous trauma are also seen in such patients.

k. **Bourneville–Pringle syndrome/Tuberous sclerosis**
This syndrome is characterized by mutations of the TSC1 (also called hamartin) and / or the mutations of TSC2 (also called tuberin) genes [16]. Poplar fibrous enlargement of gingiva, especially in the anterior region and cheek mucosa, dental enamel pits, intraoral fibromas are findings in such patients.

l. **Cantu syndrome/ Osteochondrodysplasia with hypertrichosis**
This syndrome is represented by gain-of-function (GoF) of pathogenic variants in ABCC9 [17]. Intraoral findings include gingival enlargement/hypertrrophy, macroglossia, prominent mouth, generalized hypertrichosis and thick lips. Other relevant extra oral findings include skeletal abnormalities, osteoporosis, cardiomegaly, coarse facial features and epicanthal folds.

m. **Patterson–Davis syndrome**
This syndrome is associated with mutations in the insulin receptor gene (INSR; 19p13.3–p13.2) [18]. Gingival hypertrophy along with thick lips is noted in these patients. Marked facial hirsutism with unusual facies and insulin resistance is noted in this syndromic patient.

n. **Apert syndrome/ Acrocephalosyndactyly**
Apert syndrome is associated with mutation of fibroblast growth factor receptor-2 (FGFR-2) on chromosome 10q [19]. Intraoral findings include lateral palatal swellings, which gives appearance of apparent increase in size of gingiva with sagittal narrow palate, lateral palatal swellings with prominent central fissure, maxillary arch is V shaped, severe dental crowding and delayed tooth eruption and posterior slanting maxilla giving rise to class III malocclusion [19].

o. **Syndrome of hemimaxillary enlargement, asymmetry of the face, tooth abnormalities, and skin findings (HATS)**
This syndrome is associated with gingival thickening of the affected side along with delayed eruption of the teeth and unilateral abnormalities of the face involving the bones, teeth, gums, and skin [20].

2. **Gingival fibromatosis**
Gingival fibromatosis (GF) is characterized by abnormal, localized, or diffuse development of the gingiva. The illness can manifest as a non-syndromic hereditary gingival fibromatosis (HGF) or as a symptom of a syndrome, and it may be caused by hereditary causes. The clinical presentation of GF appears to be influenced by an excessive buildup of extracellular matrix (ECM) components, although the underlying molecular pathways are yet unknown. The syndromes associated with GF are described as follows: (Table 1)

3. **Syndromes associated with gingival bleeding**
Gingival bleeding (GB) is a common sign of gingival inflammation, which indicates the presence of periodontal diseases. GB is a reversible gingival inflammation brought on by the buildup of dental plaque. Various syndromes associated with gingival bleeding are tabulated in table 2. (Table 2)

**Management**
Because different gingival findings may be the first observable symptom of an undiagnosed genetic disorder and/or a sign of how that disorder is progressing, oral health professionals need to gain the necessary knowledge and be aware of the uncommon situations in which these diseases may occur.

The examination of gingival enlargement in patients with syndromes mostly shows two components of the overgrown tissues which are either fibrotic or inflammatory [32]. The clinician should give biofilm control priority while treating gingival enlargement since it is a necessary step. Evidence suggests that proper oral hygiene, chemotherapeutic drugs, and routine professional biofilm removal reduce the degree of gingival enlargement and enhance overall gingival

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health, even though the precise role played by bacterial biofilm is not entirely known [33, 34]. The development of pseudo-pockets and an abundance of biofilm are linked to the existence of enlarged gingival tissue, which may cause periodontitis. Therefore, careful biofilm management supports the maintenance of attachment levels. In addition, in cases where gingival enlargement was surgically addressed, proper biofilm control may aid in preventing its recurrence. Even after careful evaluation of the first two methods, gingival enlargement still occurs in many people. In these cases, surgical gingival expansion excision must be taken into consideration [35].

Before beginning periodontal therapy in patients who have a higher tendency to bleed from the gingiva, the patient's blood profile, including bleeding and clotting times and platelet count, should be reviewed. The hematologist should also be consulted. Leukemic gingival hypertrophy is frequently linked to spontaneous gingival bleeding. After the acute symptoms have subsided, the gingival expansion needs to be corrected. Controlling the inflammatory component of the enlargement is made easier by eliminating local irritants. To do it, scaling and root planning are used. The patient is given oral hygiene instructions for preventing biofilm as part of the initial therapy procedures, which also include conducting superficial scaling and gently removing all loose debris with cotton pellets. Chlorhexidine mouthrinses should be used every day as part of this hygiene. For these people, oral hygiene practices are crucial. At future visits, definitive scaling and root planning are performed under local anesthetic (if necessary). If hemostasis is difficult to achieve, treatment sessions are limited to a small portion of the mouth. To lower the chance of infection, antibiotics are given systemically the evening before and for a week following each treatment [35]. In cases where gingival hypertrophy was surgically addressed, recurrence is a possibility. The difficulties with postsurgical dental care are the main reason for the return of gingival expansion. Careful home care is recommended, including use of a soft postoperative brush and chlorhexidine gluconate rinses. Additionally, regular expert cleanings might lessen the frequency of recurrence [36].

Table 1: Syndromes associated with gingival fibromatosis

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Inheritance pattern</th>
<th>Extra oral findings</th>
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<tr>
<td>Jones syndrome, Jones–Hartsfield syndrome</td>
<td>Autosomal Dominant [21]</td>
<td>-Hearing loss</td>
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<tr>
<td>Ramon syndrome</td>
<td>Autosomal dominant [22]</td>
<td>-Cherubism</td>
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<tr>
<td>Cornelia de Lange syndrome</td>
<td></td>
<td>-Primordial growth deficiency</td>
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<tr>
<td>Cross syndrome</td>
<td>Autosomal Recessive</td>
<td>-Microphthalmia</td>
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<tr>
<td>Gingival fibromatosis with Murray syndrome (Murray–Puretic–Drescher syndrome, juvenile hyaline fibromatosis)</td>
<td>Mutations in capillary morphogenesis protein-2 (CMG-2 gene)</td>
<td>Nodular, papular skin lesions</td>
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<td>Ambras syndrome</td>
<td></td>
<td>-Extreme hypertrichosis involving the shoulders, face, nose, and ears [24]</td>
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<tr>
<td>Rutherford syndrome</td>
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<td>-Delayed tooth eruption</td>
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Table 2: Syndromes associated with gingival bleeding

<table>
<thead>
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<th>Syndromes</th>
<th>Genetics</th>
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<tbody>
<tr>
<td>Shwachman–Diamond syndrome</td>
<td>SBDS gene is located at chromosome 7q11 [26]</td>
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<tr>
<td>Myelodysplastic syndrome (MDS)</td>
<td></td>
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<tr>
<td>Hemorrhagic lupus anticoagulant syndrome</td>
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<tr>
<td>Craniofacial arterovenous menetameric (CAMS) syndrome</td>
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<tr>
<td>Epstein syndrome</td>
<td>Mutations affecting the myosin heavy chain (MYH-9) gene [28],</td>
</tr>
<tr>
<td>Osler–Rendu–Weber Syndrome (Hereditary hemorrhagic telangiectasia)</td>
<td></td>
</tr>
<tr>
<td>Asthenia–polyarthritus, Edema, fever and hemorrhagic syndrome</td>
<td></td>
</tr>
<tr>
<td>Bernard–Soulier syndrome</td>
<td>Genetic abnormalities in the function of the GPIb-V-IX complex,</td>
</tr>
<tr>
<td></td>
<td>which is required to bind von-Willebrand factor IX [29],</td>
</tr>
<tr>
<td>Von Willbrand-like syndrome</td>
<td>Dectect of Von Willebrand Factor (VWF) at chromosome 12p13.2 [30],</td>
</tr>
<tr>
<td>Sheehan’s syndrome (Post-partum pituitary necrosis) [31]</td>
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Conclusion
The patient's main worry is gingival enlargement because it compromises both function and aesthetics. In cases of excessive enlargement, an appropriately scheduled surgical treatment to reduce the tissue to a normal contour will offer the greatest benefit to the patient, minimizing the number of clinical visits required and enhancing the quality of life for the patient.

References