Syndromes with Unusual Dental Findings or Gingival Components

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Papillon-Lefevre syndrome

Key points
- Periodontal disease associated with Papillon-Lefevre syndrome (PLS) affects the primary and permanent dentition.
- Keratosis of the palms and soles and the dorsal surfaces and other skin sites are characteristic components of the syndrome.
- Cathepsin C gene mutations result in a gene product that does not have functional cathepsin C (CTSC) activity.
- PLS and Haim-Munk syndrome (HMS) are allelic variants of cathepsin C gene mutations.

Genetics

Papillon-Lefevre syndrome (PLS) is an autosomal-recessive disorder caused by mutations on the cathepsin C gene. The cathepsin C (CTSC) gene mutations have been mapped to 11q14.1-14.3. Heterozygous carriers of the mutation do not have clinical manifestations of the disease. CTSC is a lysosomal protease and functions as an activator of neutrophil serine proteases. Defective CTSC function likely impairs microbial degradation, cytokine pathways, neutrophil recruitment, and macrophage dysfunction. Also, impaired natural killer cell cytotoxicity is noted in PLS. Haim-Munk syndrome and perhaps aggressive prepubertal periodontitis are similar to PLS in that they too demonstrate inactivation of CTSC. A late onset variant of PLS without alteration of the CTSC gene has been described, but this clinical situation is likely due to another genetic cause.

Clinical features

The syndrome was first described by Papillon and Lefevre in 1924. The clinical findings associated with PLS include palmoplantar erythema and hyperkeratosis, and severe periodontitis that affects both the primary and the permanent dentitions (Figs. 1 and 2). Haim-Munk syndrome, described in 1965, has in addition to the findings that characterize PLS, atrophic changes to the nails, and finger findings of acro-osteolysis and clawlike volar curves noted radiographically. Susceptibility to infection has been described in these hereditary forms of palmoplantar keratoses. Tooth loss is preceded by gingival inflammation and subsequent periodontal bone loss and tooth mobility; Aggregatibacter actinomycetemcomitans (AA) is an identified pathogen in PLS. Tooth loss follows the pattern of eruption, incisors lost first, and then the more posterior dentition. Both primary and permanent dentition are affected. The permanent dentition is often lost in the teenage or early adult years. Upon tooth loss, the alveolar mucosa is normal in appearance. Gorlin reported calcified falx and choroid plexus in PLS.

Differential diagnosis

All forms of aggressive periodontitis should be included in the differential. These forms of aggressive periodontitis include syndromes associated with decreased number of neutrophils, including the various types of severe congenital neutropenia syndromes, cyclic neutropenia, bone marrow failure syndromes, as well as syndromes with abnormal neutrophil function, such as Chediak-Higashi syndrome, and leukocyte adhesion deficiency types 1 and 2. In addition, syndromes of metabolic or structural defects, such as Kindler syndrome, Ehlers-Danlos syndrome type IV and VIII, hypophosphatasia, and hypotrichosis-osteolysis-periodontitis-palmoplantar keratoderma syndrome should also be included in the differential.

Treatment considerations

Careful attention to oral hygiene and periodontal care are essential; however, disease is progressive even with conventional approaches to periodontal disease. It has been recommended that compromised primary teeth should be extracted 6 months before eruption of the permanent teeth. 

KEYWORDS
- Papillon-Lefevre syndrome • Hereditary gingival fibromatosis type 1 • Klippel-Feil syndrome
- Oral-facial-digital syndrome type I • Oligodontia • Taurodontism

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dentition. Ishikawa reported suspect bacterial pathogens, including AA and a benefit of extraction of the primary dentition, but the permanent dentition status was followed only for several years. Antimicrobial therapy has been tried, including amoxicillin and metronidazole regimens for periodontal disease as well as treatment with retinoids for dermatologic manifestations. Retinoids have not consistently proved effective for periodontal disease. Various studies of implant placement in the PLS patient have been described, yet too few to form solid recommendations.

Hereditary gingival fibromatosis type 1

Key points

- Hereditary gingival fibromatosis type 1 (HGF1) is a benign progressive fibrous gingival enlargement.
- HGF1 is the result of a mutation in the SOS1 gene on chromosome 2p21.
- HGF1 severity is variable among affected individuals; severe forms can impede tooth eruption.
- Gingival fibromatosis is a feature of many syndromes.
- Gingival hyperplasia related to medications (anticonvulsants, calcium channel blockers, and cyclosporine) can clinically simulate HGF1.
- HGF1 treatment consists of gingivectomy; timing of the procedure is controversial.

Genetics

Hereditary gingival fibromatosis 1 (GINGF1) is an autosomal-dominant form of gingival overgrowth caused by a heterozygous frameshift mutation in the SOS1 gene on chromosome 2p21. Additional forms of HGF (GINGF2, GINGF3, and GINGF4) have been mapped to other chromosome loci. A less common autosomal-recessive form and sporadic cases of HGF are recognized. Mutation on the SOS1 gene has also been reported in Noonan syndrome. The exact mechanism by which the SOS1 gene mutation results in the gingival overgrowth is not currently known.

Clinical features

HGF1 is characterized by slowly progressive fibrous overgrowth of the gingival tissues of the maxilla and mandible (Fig. 3). Typically, the overgrowth is nonhemorrhagic and the affected tissues are firm and of normal color, but secondary inflammatory changes can occur. The condition manifests at the time of eruption of the primary or permanent dentition, and the degree of gingival overgrowth can be variable. Delayed tooth eruption may occur. This phenomenon is referred to as variable expressivity. Thus, members of an affected family may demonstrate varying degrees of severity of the gingival overgrowth. Severe cases may completely cover the dentition. A kindred with HGF and associated hypertrichosis has been described. The clinical presentation of HGF1 may be indistinguishable from syndromes that may have gingival overgrowth as a component of the disease and gingival overgrowth secondary to particular medications known to cause gingival hyperplasia. The histopathology of HGF1 is characterized by abundant collagen with interspersed spindle-shaped fibroblasts, typically without an inflammatory component, but a chronic inflammatory component consisting of plasma cells and lymphocytes may be a secondary finding. The surface stratified squamous epithelium often exhibits elongation of the rete pegs into the underlying collagenous stroma. The histopathology is nonspecific and similar to the pathologic abnormality noted in syndrome-related and medication-related gingival overgrowths.

Differential diagnosis

A comprehensive review of syndromes that may have gingival fibromatosis has been published by Hart and colleagues. These syndromes include but are not limited to Jones syndrome (gingival fibromatosis with progressive deafness), gingival fibromatosis with hypertrichosis, gingival fibromatosis with distinctive facies, Ramon syndrome, Zimmerman-Laband
syndrome, juvenile hyaline fibromatosis, Cross syndrome, and Rutherfurd syndrome. Katz and colleagues reported a case of gingival fibromatosis and associated supernumerary tooth, chest deformity, auricular cartilage deformation, joint laxity, and undescended testes. Wynne and colleagues reported HGF with associated hearing loss and supernumerary teeth. Medication-related gingival hyperplasia also enters into the differential diagnosis. Anticonvulsant medications, calcium channel blockers, and the immunosuppressive medication cyclosporine, as well as oral contraceptives, can result in gingival overgrowth. The diagnosis of HGF requires an adequate history and clinical examination with the exclusion of the aforementioned related conditions.

Treatment considerations

Gingivectomy is the recommended treatment. It has been suggested that this is best accomplished after the permanent teeth have erupted. However, severe cases of HGF may require gingivectomy to allow the dentition to erupt when the gingival overgrowth is thought to be responsible for lack of anticipated tooth eruption. Repeated debulking of the affected gingival tissues may be necessary.

Klippel-Feil syndrome

Genetics

Most cases of Klippel-Feil syndrome (KFS) occur sporadically. KFS1 is autosomal-dominant, caused by a mutation in the GDF6 gene on chromosome 17q21, and KFS3 is autosomal-dominant, caused by a mutation in the GDF3 gene on chromosome 12p13. The GDF6 and GDF3 genes code for proteins in the bone morphogenic protein family. The GDF6 gene codes for a protein that is involved in bone growth, boundaries between bones, and vertebral formation. Thus, a reduction in functional protein likely leads to the incomplete separation of vertebrae that characterizes the syndrome. The GDF3 protein is involved in bone development also, but the exact function is unclear.

Clinical features

KFS has variable clinical presentations but is characterized by defective formation or segmentation of the cervical spine, short webbed neck, limited range of motion of the neck with a decrease in lateral bend and rotation, and low posterior hairline. Klippel and Feil, in 1912, first described this syndrome reporting massive fusion of the cervical and thoracic vertebrae in a 46-year-old man. Clarke in 1998 reported follow-up data of a family with KFS, the new proband had separation of the C2-3 vertebrae at 10 weeks of age, but showed progressive ossification with complete fusion of C2-3 at 4 years of age. They concluded that fusion is postnatal. Congenital scoliosis has been reported in more than 50% of patients and rib abnormalities in 30% of patients. Cervical ribs have also been reported. Laryngeal cartilage malformations resulting in vocal impairment has been described, as well as conductive, sensorineural, or mixed-type hearing loss. Sprengel deformity is identified in about 30% of affected individuals. Sprengel deformity is related to limb bud formation and characterized by upward displacement of the scapula. The deformity may be minimal with no restriction in motion to severe mobility restrictions. Thompson and colleagues reported on 6 family members with autosomal-dominant KFS; 4 of the 6 had cleft palate. Multiple jaw cysts in a patient with KFS were reported by Eisenbud and colleagues. Additional findings reported in KFS include facial asymmetry, hemifacial microsomia, synkinesia, torticollis, renal anomalies, cardiovascular abnormalities, upper extremity anomalies, cranial nerve abnormalities, and ear defects (Figs. 4 and 5).

Differential diagnosis

KFS should be considered when one or more of the following is encountered: cleft palate, torticollis, neural tube defects, scoliosis, Sprengel deformity, neck pain, instability of the upper cervical spine, cranial or cervical nerve palsies, and laryngeal cartilage anomalies.
Treatment considerations

Fusion of cervical vertebrae places these patients at risk for cervical cord syndrome. Cord impairment can occur after even mild trauma. Special attention to the cervical spine deformity that characterizes KFS is of importance to the surgeon, anesthesiologist, and operating room, radiology, and emergency medicine personnel caring for these patients. This special attention to the cervical spine deformity is emphasized in the context of radiology assessment protocols, craniofacial trauma, or surgeries such as cleft, orthognathic, dentoalveolar, neurosurgical, orthopedic, or other surgical or endoscopic procedures that may affect the stabilization and positioning of the cervical spine. Modified activities, bracing, or traction may be used to treat symptoms related to KFS.

Oral-facial-digital syndrome type I

Key points

- Oral-facial-digital syndrome type I (OFD1) is characterized at birth based on the identification of characteristic oral, facial, and digital findings.
- Some cases of OFD1 are diagnosed only after the identification of polycystic kidney disease in late childhood or adulthood.
- Oral findings associated with the syndrome include various clefts, bifid or lobed tongue with nodular hamartomatous growths, hypodontia or supernumerary teeth, and accessory hyperplastic frenula.
- Facial findings include hypertelorism, broad nasal bridge, and ala hypoplasia, with facial asymmetry and micrognathia.
- The most common finger findings are brachydactyly, syndactyly, and clinodactyly; toe anomalies are less common.
- There are multiple OFD syndrome types often with overlapping clinical features with different inheritance patterns than OFD1.

Genetics

Oral-facial-digital syndrome I (OFD1) is characterized by an X-linked dominant mode of inheritance with lethality in male patients. Approximately 25% of female patients diagnosed with the condition have an affected mother. The condition is highly penetrant and exhibits variable clinical expressivity. The OFD1 gene, Cxof5 (Xp22.2022.3), is expressed in adult tissues. Several different mutations in the gene have been defined. The gene encodes OFD1 protein, is centrosomal, and localizes to the basal body of primary cilia. OFD1 belongs to a group of diseases characterized by cilia dysfunction and is classified as a ciliopathy. The protein is widely expressed in the early stages of development in all the tissues affected by the syndrome. There are several other OFD syndromes that have overlapping clinical features with OFD1.

Clinical features

Oral findings associated with OFD1 include pseudocleft of the midline of the upper lip, bifid or lobulated tongue, nodular hamartomatous lipoma-like masses of the tongue, hyperplastic accessory frenula, submucosal clefting, cleft palate...
or cleft uvula, hypodontia (especially the lower lateral incisors), or supernumerary teeth. Facial findings include micrognathia, facial asymmetry, broad nasal bridge, hypertelorism, and nasal ala hypoplasia. Abnormalities of the digits include brachydactyly, syndactyly, clinodactyly, and less commonly, polydactyly. The fingers are more frequently affected than the toes. Brain abnormalities include agenesis of the corpus callosum, cerebellar abnormalities, arachnoid cysts, and other central nervous system malformations. Fifty percent of individuals have some degree of intellectual disability. Polycystic kidney disease is present in 50% of affected individuals, usually diagnosed no earlier than late childhood. Some have cysts of the liver, pancreas, and ovary. Milia of the skin are usually present at birth but can undergo resolution with resultant pitting scars (Figs. 6 and 7).

Differential diagnosis

The differential diagnosis includes other OFD syndrome types, and conditions characterized by cystic renal disease. The clinical features listed above can overlap with other OFD syndromes but the X-linked dominant inheritance pattern, male lethality, and the presence of cystic kidney disease aid in separating OFD1 from these other forms.

Treatment considerations

Surgical corrections of cleft lip or palate are indicated. Removal of tongue nodules may be necessary because of the size of these hamartomatous growths. Orthodontia and correction of malocclusion is needed. Surgical intervention for ankyloglossia, if severe, may be warranted, and referral to speech pathology if indicated. Affected individuals should have a hearing evaluation. Monitoring of the patient for polycystic kidney disease is required.

Oligodontia

Genetics

Autosomal-dominant, autosomal-recessive, and X-linked inheritance occurs. Transcription factor gene mutations have
been identified in the following syndromes: oligodontia cleft palate MSX1, Witkop MSX1, Wolf-Hirschhorn MSX1, oligodontia PAX9, Axenfeld-Rieger types PITX1, FOXC1, cleft palate, and ankyloglossia TBX22. WNT signaling pathway gene mutations have been identified in oligodontia colorectal neoplasia AXIN2. Also, gene mutations that affect the TNF/NF-κB signaling pathway have been described in several of the hypohidrotic ectodermal dysplasia syndromes with EDA, EDAR, EDARADD gene mutations identified. Disruption of this signaling pathway also includes but is not limited to incotinieta pigmenti, Ellis van Crevel, Van der Woude, Williams, and oculodentodigital syndromes. Tooth agenesis may also occur with disruption of the transforming growth factor-β, fibroblastic growth factor, and Sonic Hedge Hog pathways.

Clinical features

Tooth agenesis (excluding third molars, typically bilateral and symmetric such as the maxillary lateral incisors or premolar dentition, or single tooth agenesis) has been estimated to occur in up to 20% of the population. The absence of more than 6 teeth (oligodontia) is less common. Tooth agenesis is associated with numerous syndromes, and nonsyndromic forms that are either familial or sporadic have been described. The gene involved in cases of tooth agenesis often defines which teeth are missing. For example, MSX1 associated tooth agenesis typically affects the maxillary first premolars and PAX9-associated tooth agenesis is most frequently associated with the absence of the maxillary and mandibular second molars. Alveolar bone hypotrophy is noted in the absence of teeth (Fig. 8).
Differential diagnosis

The absence of teeth especially when multiple and symmetric should prompt consideration for a familial occurrence and possible association of syndromic features for which hypodontia and oligodontia may be a component. Other potential causes of tooth agenesis include systemic or external influences that could adversely affect tooth formation, such as infection, radiation, chemotherapeutics, and other environmental factors.

Treatment considerations

Radiographic imaging is needed to confirm the absence of teeth. Prosthetic rehabilitation with partial dentures, full dentures, overdentures, or implant placement is recommended. The adequacy of alveolar bone height may be problematic, and augmentation of the affected segments may be required. Syndromic oligodontia may have additional considerations based on the specific syndrome.

Taurodontism

Key points

- Taurodont teeth have pulp chambers with a greater apical occlusal height than normal teeth, with the bifurcation or trifurcation of a molar displaced apically.
- The distance from the bifurcation or trifurcation to the cementoenamel junction is greater than the occlusal cervical distance.
- Taurodont teeth lack constriction at the cementoenamel junction.
- Hypotaurodontism, mesotaurodontism, and hypertaurodontism are subclasses of the condition.
- The molars are the most commonly affected.
- Failure of the Hertwig epithelial root sheath diaphragm to invaginate at the proper horizontal level has been suggested as the developmental putative cause.
- Taurodontism can occur as an isolated phenomenon or in association with various syndromes.

Genetics

Taurodontism is rare, with prevalence in the primary dentition of Japanese children reported to be 0.54%, and 5.6% in the permanent dentition of Israeli adults. Other studies have described a prevalence of 2.0% in Caucasian adults. The second and third mandibular molars are the most commonly involved teeth. Taurodontism has been described in several syndromes including amelogenesis imperfecta type IV and type IC, distalless homeobox 3, simultaneously occurring taurodontism, microdontia, and dens invaginatus, trichdentoosseous syndrome, oculodentodigital dysplasia, dentin dysplasia type I, scanty hair-oligodontia-taurodontia syndrome, cranioectodermal dysplasia 4, hypohidrotic X-linked ectodermal dysplasia 1, otodental dysplasia, failure of primary tooth eruption, familial tumoral calcinosis hypophosphatemic syndrome, Barber-Say syndrome, Ackerman syndrome, X-chromosome aneuploidy including Klinefelter syndrome, trisomy 21, and cleft lip and palate subphenotypes. Autosomal-dominant, autosomal-recessive, and x-linked recessive inheritance patterns are noted depending on the specific syndrome association.

Clinical features

Taurodontism is a condition affecting the teeth, usually the molars, with pulp chambers enlarged in the vertical dimension with resultant apical displacement of the bifurcation or trifurcation of the tooth root. The condition is recognized on dental radiographs or extracted teeth with root morphology, suggesting the diagnosis and confirmed with radiographic findings. There are varying degrees of severity of this defect and the subclassification scheme of hypotaurodontism (mild), mesotaurodontism (moderate), and hypertaurodontism (severe) has been suggested (Figs. 9 and 10). Diagnosis of taurodontism in the nonmolar dentition is difficult and controversial; computed tomography may help with this diagnostic difficulty, but should be reserved for an affected tooth needing endodontic management. It has been described as an isolated finding, as a familial trait, as well as in geographic and ethnic groups including Eskimos and Aleuts, and fossil remains of early man, and has been associated with syndromes.

Differential diagnosis

Other conditions with enlarged pulp chambers, such as Vitamin D-resistant rickets, hypophosphatemia, shell teeth, regional odontodysplasia, and internal resorption, should be included in the differential. Attention to the radiographic or clinical shape of the tooth root and cementoenamel junction morphology should be helpful in defining taurodontism, although the definition can in some cases be arbitrary.

Treatment considerations

Taurodontism cannot be prevented and no treatment is required. The identification of the condition mandates a need for selected dental radiographs of family members to survey
for taurodontism, and the need to exclude specific syndromes associated with taurodontism as listed above.

**Recommended readings**

### Papillon-Lefevre syndrome (PLS)


### Hereditary gingival fibromatosis type 1 (HGF1, GINGF1)


### Klippel-Feil syndrome (KFS)


Available at: http://www.omim.org/118100klippel-feil.


Oral-facial-digital syndrome type I (OFD1)

Available at: http://www.omim.org/OFD1.

Oligodontia

Available at: http://omim.org/oligodontia.

Taurodontism