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Review Article

Early Tooth Loss Related to Medical Syndromes: Review of More Than 20 Entities

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Abstract

Teeth play various significant roles in the oral cavity. Tooth loss can result in disturbance in normal functions of the oral cavity and masticatory system. Teeth also play a crucial role in the facial aesthetics, and edentulism could have undesirable emotional impacts on the level of one's self-confidence. Early tooth loss is defined as the loss of teeth prior to the normal expected period of time. Factors that could lead to edentulism could be divided in two groups: local and systemic factors. Local factors such as poor oral hygiene or structural defects in the teeth could increase the incidence of caries, and eventually, if not restored, these caries make the teeth unable to remain in the oral cavity. Poor oral hygiene also increases the risk of periodontal disease, which affects the supporting tissues of the teeth. Some systemic diseases such as diabetes, Sjogren's syndrome, hypophosphatasia, etc. could also have unfavorable impacts on the oral cavity and teeth, and make them susceptible to exfoliation. In this review article, we have tried to concentrate on a number of medical syndromes as a systemic cause of early tooth loss in order to enlighten the vision of physicians and dentists into this important aspect of adversities that these syndromes could result in.

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Introduction

Teeth play a crucial role in the oral cavity. They contribute in the process of mastication, speech, and maintaining the facial aesthetic. Edentulism can result in the disturbance in daily-living activities such as adequately chewing as well as leading to emotional problems (1, 2). Loss of self-confidence and concerning about appearance and self-image are the emotional impacts of tooth loss (3). Early tooth loss or premature exfoliation of teeth is defined as loss of tooth in the oral cavity prior to the normal expected period of time. Since there are no references to address the exact natural expected age for the loss of permanent dentition, early tooth loss is a relative term. There are both local and systemic factors that could result in such phenomenon. Poor oral hygiene could cause caries and periodontal diseases leading to the loss of teeth (4, 5). Additionally, there are a number of systemic diseases such as diabetes, hyphophpsphatasia, leukemia, hyperthyroidism and etc. whose effects on the oral cavity could make the teeth susceptible to exfoliation (6). They could increase the risk of caries as a result of interrupting the normal function of salivary glands, or affect the periodontal tissues, which support the teeth (7). The impact of systemic diseases on periodontal tissues could be categorized into two groups. Some systemic diseases undermine tooth supporting bone and fibers such as Langerhan's cell disease and Ehlers-Danlus syndrome, while others make the oral cavity prone to periodontal infections such as Down's syndrome (6). In this review, we aim to focus on these syndromes, their etiology, their general and specifically, oral manifestations, and the possible pathogenesis process that could lead to edentulism.

Methods of Literature Search

A web-based literature search using the advanced features of various databases such as PubMed, PubMed Central, Medline Plus, Medknow, Wiley online library, Elsevier, Google Scholar, Directory of Open Access Journals (DOAJ) was performed. The main keywords in this search were early tooth loss, tooth mobility, tooth loosening, tooth exfoliation, and medical syndrome. The search was accomplished in 2016 and was restricted only to English-language published articles in both medical and dental journals over the last 50 years. A total number of 547 articles were screened, and 72 articles were opted after provisional assessment of the titles and abstracts by two reviewers for this paper. Among these articles, 59 were available for us including 16 reviews and meta-analyses, 21 case reports, and 22 original papers regarding syndromes that cause early tooth loss. Eighty five percent of the articles were published after 1990.

Medical Syndromes

ADULT syndrome (Acro- Dermato- Ungual-Lacrimal-Tooth syndrome)

An autosomal dominant condition on the basis of its most common symptoms in the affected patients is called ADULT syndrome (acro-dermato-ungual-lacrimal-tooth syndrome. (8-10). It is a result of missense mutation in the DNA binding domain of p63 geneI (9). The manifestations in this disorder include ectrodatyly, syndactyly, dysplasia of finger and toe nails, hypoplastic breasts and nipples, extensive freckling, lacrimal duct atresia, frontal alopecia, primary hypodontia, sparse hair and thin skin, onychodysplasia (8-10). Hypodontia is another common

feature of this syndrome that is suggested to be as a result of weak fixation at the beginning of adolescence (8, 10).

Chediak-Higashi syndrome

Chediak-Higashi (C-HS) is a rare genetically immunodeficient disorder with autosomal recessive transmission (6, 11, 12). This disease is caused by defective granulations in whole leukocyte population, precursory cells, promyelocytes, myelocyteds, melanocytes and neurological cells, and in the bone marrow (6, 11). The major manifestations of this syndrome include oculocutaneous albinism that usually involves the hair, the skin, and the eye with photophobia and nystagmus, peripheral neurologic defects, an unusual susceptibility to bacterial and viral infections, chronic recurrent infection with serious acute inflammatory periods, qualitative alteration of blood leukocyte function, neutropenia, and reduced chemotaxis. Massive and hemorrhagic inflammatory response of the marginal gingiva, ulcerative lesions of the gingiva, generalized tooth mobility, and early teeth exfoliation due to alveolar bone atrophy are the oral features of Chediak-Higashj syndrome(6, 11, 12). This disorder has two phases: chronic phase, and accelerated phase. The accelerated phase is suggested to be initiated by a viral cause and is characterized by the lymphohistiocytic infiltration of the liver, the spleen, the lymph nodes, and the bone marrow, leading to fever, hepatosplenomegaly, lymphadenopathy, abnormal liver function tests, pancytopenia, and infiltration of the central nervous system (12).

Coffin-Lowry syndrome

Coffin-Lowry syndrome is a genetic disorder with x-linked inheritance that is caused by heterogenous loss-of-function mutations in the hRSK2 gen on Xp22 (6, 13). Prevalence of this syndrome is estimated to be in a rate of 1:50,000 to 1:100,000 (13). Newborn male indicates hypotonia and hyperlaxity of joints, broad tapering fingers, hypertelorism, frontal bossing, thick and protruded lips (13). Microcephaly, mental retardation, growth delay, and sensorineural hearing loss are other features of this syndrome (6,13). Manifestations of Coffin-Lowry syndrome in an adult male are prominent forehead, orbital hypertelorism, downward-slanting palpebral fissures, epicanthic folds, large and prominent ears, thick everted lips, and a thick nasal septum with anteverted nares (13). Heterozygote females show the clinical features more variable and less severe (6). High narrow palate, midline lingula furrow, hypodontia, and peg shaped incisors are the oral findings (13). Hypodontia in this syndrome as reported in several articles may be related to premature exfoliation of teeth rather than a lack of tooth formation or eruption (6,14). Premature tooth loss in Coffin-Lowry patients is likely to be a result of severe bone loss (14).

Cohen syndrome

Cohen syndrome is an inheritable disorder with an autosomal recessive mode of transmission (15, 16). It is a result of the mutation in a gene that was mapped to chromosome 8 in 1994 (15). The clinical manifestation of this disease are obesity, mental retardation, microcephaly, wave-shaped lid openings of the eyes, antimongoloid and down slanting eyebrows, thick eyelids, short philtrum, slender hands, fingers, feet and toes, hyper mobile joints, hypotonia, ophtalmological findings such as myopia and chorioretinal dystrophy, and typical cranofacial appearance that includes high nasal bridge, open mouth, and large prominent incisors (15,16). Neutropenia is also another important feature in Cohen syndrome patients (15). Neutrophils play a key role in the defense against periodontal pathogens; therefore, patients with Cohen syndrome show a high susceptibility to periodontal disease that could vary from gingivitis to generalized bone loss, marked tooth mobility, and tooth loss in these patients (15). Alaluusua et al. reported early periodontal breakdown as a clinical feature of Cohen syndrome for the first time (15).

Down's syndrome

Down's syndrome, firstly described as the "Mongolism type of idiocy" is a disorder caused by a chromosomal aberration that results in a trisomy in the twenty-first chromosome (17). In addition to mental disability, up slanting palpebral fissures, flat facial profile, hypotonia, joint hyperflexiblity, and excess nuchal skin are the manifestations of this syndrome (6). One in 600 to 1 in 1,000 newborns in the general population are estimated to be affected by this disorder (18). Patients with Down's syndrome are more susceptible to infection. Several studies emphasize on the high prevalence of advanced periodontal disease in these patients (17).These patients show more extensive gingivitis at an earlier age followed by generalized periodontal breakdown in early adulthood (18). This phenomenon is considered to be a result of multiple factors such as immunological deficiency, poor oral hygiene, fragile periodontal tissues, early senescence, and poor masticatory function. The mental retardation in patients with Down's syndrome is a significant factor that determines oral hygiene and plays an important role in periodontal health as well as bacterial ecology (18). According to studies, there is no significant bacterial profile difference in Down's syndrome patients and non-down's syndrome patients (18). Defects or dysfunction in leukocytes as an important host defense in the periodontal barrier are identified in patients with Down's syndrome. The rapid periodontal progression is related to defective neutrophil function such as chemotaxis and phagocytosis (17). It is said that 60% to 100% of young adults under 30 years with Down's syndrome are reported to have advanced periodontal disease that can lead to early loss of permanent teeth (6, 17).

Dyskeratosis Congenita Syndrome

Dyskeratosis congenita is a rare inherited variant of ectodermal dysplasia firstly described in 1910 by Zinsser that affects skin, nails, and mucous membrane (19). This syndrome is characterized by the triad of reticular pigmentation of the skin, dystrophic nails, and leukoplakia and is often associated with pancytopenia (19, 20). It is more prevalent in males and the mode of inheritance controversially is reported to be X-linked, autosomal dominant or autosomal recessive transmission (19, 20). Dyskeratosis congenita is a bone marrow failure syndrome that has been established as a multi-system disorder in which affected patients usually develop single or pancytopenia, abnormalities of the eye, lacrimal duct stenosis, pulmonary fibrosis, and malignancies such as

squamous cell carcinoma (19). Generalized growth retardation, atrophic and teleangiectatic skin, hematopoietic abnormalities such as anemia, thrombocytopenia, and ultimately pancytopenia, mental retardation, small sella turcica, dysphagia, transparent tympanic membrane, deafness, epiphora, urethral anomalies, small testes, hyperhydrosis of the palms and soles hepatic abnormality, signet carcinoma, atrophy of the frontal lobes, excessive intracranial calcifications, and increased risk of hemorrhage and infections are the general manifestations of dyskeratosis congenita syndrome (19, 20). Oral and dental findings include leukoplakia that is the most frequent change in the oral mucosa, erythema on either buccal mucosa or tongue, which is the result of superficial epithelium atrophy without the disruption of underlying connective tissue, brown pigmentation of the tongue, taurodontism, thin enamel structure, hypodontia, tendency to decay, short-blunted tooth roots, gingival bleeding, gingival inflammation, destruction of the alveolar margin, severe alveolar bone loss resembling juvenile periodontitis, and tooth hypermobility and loss (19, 20). Since this syndrome causes anomalies in several ectodermally derived structure, the possibility of the involvement of the dental organ, epithelial attachment, etc., could be considered (20).

Ehler's-Danlos syndromes

Edhers-Danlos syndromes are a large group of heritable connective tissue disorders that alter the biosynthesis of collagen molecules. The main characteristics of these syndromes are joint hypermobiility, skin hyperextensibility, and tissue fragility (21). Clinical manifestations of these syndromes differ depending upon the type of collagen that is affected (22). Genetic defects, which result in EDS cause errors in the synthesis or processing of collagen type I, III or IV (21). According to last studies, there are 6 types of Ehler's-Danlos syndromes (22). In terms of epidemiology, although there is not an agreement on the prevalence of different types of EDS, the overall prevalence for classical EDS type is 1:10000-20000, and for vascular EDS type is 1-100000 according to most reports (21). Skin hyperextensibility, generalized joint hypermobility, easy bruising, tissue fragility, mitral valve prolapse, proximal aorta dilation, and chronic joint and limb pain are the common clinical features among various types of EDS (21). Oral manifestations of EDS are fibrinoid deposits, bleeding, mucosal ulceration and fragility, teeth mobility, irregularity in the placement of the teeth due to anodontia, multiple supernumerary teeth, dentin structural irregularity, root anomalies, pulpal anomalies, dysfunction in tempromandibular joint (TMJ), absence of inferior labial or lingual frena, high arched palate (21, 22). Early onset periodontitis is also a frequent oral manifestation report of EDS (22). Studies indicate that rapid periodontal breakdown occur in EDS patients as a result of decreased resistance to mechanical or bacterial assaults and/or deficiency in healing and restitutional capacities (21). In EDS patients who indicate periodontitis, affected type I, III, V collagen become more soluble, and their type ratios also change. This results in an increased amount of type V collagen and the advent of a new, unstable collagen: Type I trimer (21, 22). The integrity of periodontal tissues is also undermined by the defective type III collagen (6). Poor oral hygiene is another finding in EDS patients that lead to a high DMF-s score. This is mostly because of limb pain accompanied with restraint joint mobility that result in improper brushing (22). Therefore, poor oral hygiene can be another factor that makes EDS patients prone to periodontal disease.

Ellis-Van Creveld syndrome

Ellis-Van Creveld (EVC) syndrome is a rare autosomal recessive skeletal dysplasia that is characterized by short limbs, short ribs, postaxial polydactyly, and dysplastic teeth and nails (23, 24). It is one of the conditions which belongs to the short rib-polydactyly group (23). EVC syndrome seems to be more common among the Amish community although the exact prevalence remains unknown (23, 24). Mutations of the EVC1 and EVC2 genes on chromosome 4p16 are considered to be the causative of this disease (23). Prenatal abnormalities include narrow thorax, marked shortening of the long bones, hexadactyly of hands and feet, and cardiac defects (23). Cardinal features after birth are disproportionate small stature, shortening of the middle and distal phalanges, polydactyly affecting hands, and occasionally, the feet, brachydactyly, fusion of the capitate and hamate, genuvalgum, distal limb shortening, hidrotic ectodermal dysplasia mainly affecting nails, hair, and teeth, genitourinary anomalies such as epispadias and hypospadias, congenital heart malformations in 50-60% of the patients compromising of single atrium, defects of the mitral and tricuspid valves, patent ductus, ventricular septal defect, atrial septal defect, and hypoplastic left heart syndrome (23, 24). Oral manifestations include malocclusions, labiogingival adherenes, gingival hypertrophy, labiogingival frenulum hypertrophy, accessory labiogingival frenula, serrated incisal margins, dental transposition, diastema, conical teeth, enamel hypoplasia, and hypodontia. (23) Premature eruption and exfoliation of the teeth are also a common finding in patients with Ellis-Van Creveld syndrome (23, 24).

Hadju-Cheney syndrome

Hadju-cheney syndrome or acro-osteolysis is a rare genetic disorder associated with bone metabolism and is characterized by spinal, cranial, and facial bone abnormalities accompanied by progressive resorption of the distal phalangian bones (25, 26). This alteration in the bone metabolism is attributed to an abnormality of a structural protein (25). The most likely pattern of transmission is autosomal dominant (6, 25, 26). The main clinical manifestations of HCS are short stature, scoliosis and kyphosis, the elongation of the skull, small chin, clubbing of the fingers, coarse hair and thick eyebrows (6, 25,26). The short stature is the result of both diminished growth in early life and loss of height in adulthood due to vertebral compression (26). Radiographic findings include the enlarged sella turcica, wormian bones, persistent wide cranial sutures, absence of the frontal and maxillary sinuses, and osteolysis of the distal phalanges (25 ,26). Headache, joint laxity, fractures of long bones, valgus deformity of the knee, spondylolisthesis, high arched palate, hirsutism, and recurrent infections also may occasionally occur in patients with Hadju-Cheney syndrome (26). Chiari malformation

with an obstruction of celebrospinal fluid flow and cervicothorasic syringomyelia are the outcome of progressive platybasia in some cases (26). Progressive basilar invagination also results in associated neurologic abnormalities, such as optic nerve head swelling and mild optic neuropathy (25). Oral findings in HCS patients include premature exfoliation of teeth, dental maleruption and malocclusion, increased tooth mobility, impaction of teeth, hypoplastic dental roots, atrophy of the alveolar process, and structural changes in the dentin and cementum of the teeth (25, 26). Rapidly progressive periodontitis, insufficient attached gingiva can lead to mobility and early tooth loss in HCS patients (25).

Haim-Munk syndrome

Haim-Munk syndrome is one of the inherited disorders that is included in palmoplantar keratoderma (PPK), which is a heterogenous condition characterized by hyperkeratosis and erythema of the palms and soles (27, 28). It is a rare autosomal recessive type IV PPK with the presence of early onset periodontitis (27-29). Patients with Haim-Munk syndrome also demonstrate hypertrophy and curving of the nails (onychogryphosis) , flat foot (pes planus), extreme length and slenderness of fingers and toes (arachnoductyly), osteolysis involving the distal phalanges of fingers and toes (acroosteolysis), psoriasiform plaques on the face, trunk, and extremities, recurrent episodes of the skin and soft tissue infections, athralgia, loss of medial longitudinal arches of the feet, dry skin, and transverse grooving and slight pitting of the nails (27, 29). Consanguineous marriage in the familial history of the affected patients is a common report (1,3). This disease is a result of mutations of the Cathepsin C gene (27-29). It has been shown that Cathepsin C is expressed in the junctional epithelium, which is attached to the teeth and surrounds them, and is the site of inflammation and destruction in Haim-Munk syndrome (27). Therefore, an increased susceptibility to severe periodontal disease in Haim-Munk syndrome is the outcome of changes in the Cathepsin C protein (27). Gums are edematous, friable, and receding (27-29) severe vertical and horizontal bone loss is found in the intra oral examination (27-29).The early onset periodontitis affects both deciduous and permanent dentition leading the patients to become edentulous by the age of 20 years (27).

Hand-Schuller-Christian syndrome

Hand-Schuller-Christian syndrome is one of the triple conditions that are included in histiocytosis X or langerhan's cell disease. The other two types of histiocytosis X are eosinophilic granuloma and letter-siwe disease (6, 30, 31). This disease is characterized by a monoclonal proliferation of large mononulear cells accompanied by a prominent eosinophil infiltrate (30, 31). Hand-Schuller-Christian syndrome is the chronic disseminated form of langerhan's cell disease that manifests a classic triad of skull lesions, exophtalmous, and diabetes insipidus, and is primarily seen in infants and children and is rarely found in young adults (30, 31). It is suggested that this disease is a result of immunologic dysregulations that causes the accumulation of langerhan's cells (30). The incidence of this disease is 0.18 in 1,00,000 with approximately 30% cases occurring in adults (30). Skull is the most common site of lytic lesions and is usually associated with soft tissue swelling, tenderness, and facial asymmetry. Femur, ribs, vertebrae, and pelvis are other bones that are frequently involved (30, 31). Retarded growth and otitis media are also another manifestation of this syndrome (30). Slight lymph node enlargement, splenomegaly, blue sclerae, cutaneous or mucosal "xanthomata", mental retardation, and hypogenitalism are the features that are occasionally found in patients suffering from this syndrome (31). Oral findings are sore mouth, halitosis, gingivitis, unpleasant taste, loose teeth, and failure of extracted tooth socket to heal (30, 31). Loss of supporting alveolar bone mimicking severe periodontitis is the cause of teeth to become loosened and early exfoliated (30, 31). Radiographic findings reveal that bone lesions are sharply outlined and scooped out and extensive bone loss in the alveolar region makes teeth appear as they are "floating in air" (6, 30).

Kindler's syndrome

Firstly described by Theresa Kindler in 1954, Kindler's syndrome is a rare dominantly inherited disorder with cutaneous manifestations of epidermolysis bullosa and poikiloderma congenitale associated with extreme photo sensitivity (32). Trauma- induced blistering lesions and photo sensitivity exist early in life and improves with age, and generalized poikilodermatous changes and cutaneous atrophy start to appear later in life (33). The histopathology of the Kindler's syndrome has not yet well determined (32). R. C. Sharma and associates reported some other manifestations of this syndrome that included chronic simple conjunctivitis, multiple nebular corneal opacities, thickened corneal nerve, and skeletal changes such as dome-shaped skull, bifid fourth rib, missing fifth rib, and short fourth and fifth metacarpals (32). Additionally, loss of mandibular angles, anterior mandible concavity, and restricted mouth opening are the oral findings of this syndrome (32). There are reports of early loss of both deciduous and permanent dentitions as a result of severe periodontitis in patients suffering from Kindler's syndrome (32, 33). Colin B. reported a Kindler's syndrome patient with generalized tooth hypermobility (33). Thin and fragile gingiva with spontaneous bleeding, soft tissue catering, gingival pockets and recessions, extensive bone loss, and advanced loss of periodontal attachment were the other oral findings of the case in Colin B. report (33). He claims that genetic changes in this disease increases the susceptibly to periodontitis, since the plaque index in the patient was approximately low, and the oral hygiene was at an acceptable level (33).

Mac-1, LFA-1 deficiency syndrome

Mac-1, LFA-1 deficiency syndrome is an autosomal recessive disease that causes severe generalized prepubertal periodontitis (G-PP) (34). LFA-1 and Mac-1 are high molecular weight, leukocyte surface glycoproteins that contribute in multiple types of leukocyte adhesion reactions (35). LFA-1 or leukocyte function-associated-1 contributes to adhesion formation between effector and target cells in cytolytic T lymphocyte-mediated killing and in natural killing, and also in T-helper cell responses and the adhesion of B cells, granulocytes, and monocytes (35). Mac-1 is a

molecule on human myeloid cells identical to complement receptor type 3 (CR3), which binds the inactivated form (iC3b) of the third component of complement and mediates adherence and phagocytosis of iC3b-coated particles by granulocytes and monocytes (35). These molecules (Mac-1, LFA-1) also participate in endothelial margination and subsequent infiltration of peripheral blood polymorphonuclear neutrophils and monocytes into extravascular inflammatory sites (34). Manifestations of the Mac-1, LFA-1 deficiency syndrome are recurrent bacterial infection, impaired pus formation, progressive periodontitis, delayed wound healing, persistent granulocytosis, delayed umbilical cord separation, and complex abnormalities of adhesion-dependent leukocyte functions (34, 35). This syndrome is the only disorder causing generalized prepubertal periodontitis (G-PP) for which a molecular pathogenesis basis has been identified (34). Prepubertal periodontitis is a form of periodontitis that its onset is found in children before or at 4 years of age (6). The general form of prepubertal periodontitis cause the gingiva to become fiery red and promotes acute inflammation around all primary teeth (6). Other features of G-PP are rapid bone destruction, marginal proliferation, recession clefting, bleeding, and accumulation of dental plaque (34). Despite localized prepubertal periodontitis that can be treated by dental curettage, an antibiotic therapy, and improved tooth brushing, the generalized form is refractory to antibiotic treatment; therefore, the permanent dentition may be lost (6).

Lowe's syndrome

Lowe's syndrome or oculo-cerebro-renal syndrome, is a congenital disorder firstly described by Lowe in 1952 (36, 37). It is inherited in an X-linked recessive fashion and affects the nervous, ocular, and renal system (36, 37). Mutations in the gene encoding the enzyme inositol polyphosphate 5-phosphatase are responsible for this disease (37). Patients' manifestations of this syndrome include general growth retardation, low weight, shortness of height, hypotonic musculature, areflexia, non-tender joint, subcutaneous nodules, rickets, mental retardation, congenital cataract, and glaucoma (36, 37). There is a higher risk of hemorrhage in Lowe's syndrome patients due to defects in platelet functions (37). Patients usually demonstrate major ophthalmic problems such as congenital cataract at the first phase, slowly progressive renal tubular dysfunction characterized by proteinuria, generalized aminoacidurea, carnitine wasting, and phosphoruria at the second phase, and progressive renal failure and less severe metabolic problems at the third phase of this disease (36). Females are usually carriers of this syndrome and are identified by characteristic lens opacities (36). Tsai et al. reported the oral manifestation of this disease. They found evidence of taurodontism and considerable bone loss around all teeth, which resulted in all the teeth becoming mobile (36). They claimed that periodontal problem that leads to early tooth loss in Lowe's syndrome patients is the outcome of mental retardation that interferes with the patient's ability to achieve acceptable oral hygiene. They suggested that dental care must focus on the prevention in these patients (36).

Lymphoma syndrome

Lymphoma syndrome is one of the most frequent malignancies affecting the jaws in children in tropical Africa (38-40). This syndrome is caused by a multicentric tumour occurring in certain characteristic situations (38). This tumor as a malignant lymphoma, arises from a primitive mesenchymal cell (38). It affects children of both sexes in Africa mostly between the ages of 2-5 years (38, 40). This syndrome is occasionally found in cases below 2 and above 14 years old (38, 40). Deposits of the tumor are found in the jaws, long bones, kidneys, liver, thyroid, heart, stomach, ovaries, salivary glands, intestines, and breast and testis (38-40). Loosening of the teeth is the first evidence of the jaw tumors (38-40). Teeth become displaced and eventually fall out as a result of rapid growth of the tumor (38, 39). Palplegia due to deposition of the tumor within the extradural space in the spinal canal is also another manifestation of this syndrome (38, 39).

Marfan's syndrome

Marfan's syndrome is a genetic disorder with autosomal recessive inheritance (41). It involves the skeletal, cardiovascular, ocular, pulmunary systems, and also the skin and muscles (42). The frequency of this disease is estimated to be 2 to 3 per 100.000 (42). The etiology of this disease is the mutations in the fibrillin-1 gene that is mapped on chromosome 15 (41, 42). Fibrillin-1 glygoprotein is a major component of connective tissue microfibrils and can be found in various tissues such as suspensory ligaments of the lens, blood vessel walls, the skin, and connective tissues (42). Pectus carinatum, reduced extension at the elbows, joint hypermobility, dilatation of the ascending aorta, mitral valve prolapse, apical blebs, lumbosacral dural ectasia, ectopia lentis, high arched palate, and concave anterior chest are features that could be found in Marfan's syndrome patients (41,42). Severe periodontitis has also been described as an important manifestation of Marfan's syndrome in several reports (42-44). Periodontitis is a bacterial-plaque-induced disease that contributes to the destruction of tooth-supporting tissues such as bone, gingiva, and periodontal ligaments (42). The alteration in the synthesis of the fibrillin-1 glygoprotein in Marfan's syndrome would also cause defects in the periodontal ligaments (43). This makes the connective tissue of periodontal ligaments more susceptible to break down in accordance to the presence of bacterial plaque (42, 43). Therefore, vertical and horizontal bone resorption and dental hypermobility could occur that may lead to tooth loss (43).

Metabolic syndrome

Metabolic syndrome or "syndrome X" is a mixture of multi-systemic condition that includes obesity, insulin resistance, hypertension, and atherogenic dyslipidemia associated with a strong risk of developing diabetes and cardiovascular diseases (45, 46). It is estimated to have a prevalence of 17-30% in the general population (46). The etiology of this disease is not yet well determined; however, environmental factors such as excessive calorie consumption, sedentary lifestyle, and genetic factors produce this syndrome (45). Despite the contradictory beliefs about the association between metabolic syndrome and periodontal disease, many

reports support the existence of such association (45). This association may be contributed to either shared risk factors such as genetic variants, health behavior factors such as smoking and diet, and socioeconomic factors, or pathogenic factors such as systemic release of periodontal bacteria, release of inflammatory cytokine by periodontal tissue, oxidative stress, proatherogenic lipoproteins, abdominal obesity, and cross-reactivity and molecular mimicry (46). Nibali et al. claimed that subjects with Metabolic syndrome are nearly twice as likely to have periodontitis and its consequences such as early loss of teeth as the rest of the population (46).

Numb chin syndrome

Numb chin syndrome (NBS) or mental neuropathy is a sensory neuropathy characterized by numbness of the chin in the distribution of the mental nerve and the branches of the mandibular division of the trigeminal nerve (47, 48). Breast cancer, lymphoma, leukemia, lung cancer, prostate cancer, and head and neck cancers are the most common causes if the numb chin syndrome (47, 48). This syndrome could be the first manifestation of the metastasis of an underlying cancer (1). Compression of the mandibular nerve by a tumor mass or leptomeningeal invasion may cause NCS (48). Unilateral numbness of the skin of the chin, lip, and the gingiva, pain and swelling, hyposthesia and anesthesia over the chin, lip, and gingiva are the signs and symptoms of NBS. Percussion-induced pain and tooth loosening also may occur in cases of infiltration of the mandibular canal with cancerous cells (47, 48).

Oculodentodigital syndrome

Oculodentodigital syndrome (ODD) is a genetic disorder which causes developmental anomalies in the face eyes, limbs, and dentition (49, 50). It is inherited by an autosomal dominant mode of transmission and has high penetrance and variable expression (49, 50). Patients exhibit a long, narrow nose with hypoplastic alae, thin anteverted nostrils, and a prominent nasal bridge, short palpebral fissures, and bilateral microcornea often with iris anomalies (49, 50). Secondary glucoma may also be found in a number of patients (49). Bilateral type III syndactyly of the fourth and fifth fingers is the characteristic digital malformation (49, 50). Involvement of the third finger associated with campodactyly is also a common finding (49). Cleft plate, microdontia, and enamel hypoplasia, multiple caries, and early tooth loss that involve both dentitions are the oral features of this syndrome (49, 50). Less common manifestations are thin, sparse hair, conductive deafness, spastic paraparesis or lower limb weakness (49). The underlying causes of this syndrome are the mutations in GJA1 that encodes the gap junction protein connexin 43 (49, 50).

Papillon-Lefevre syndrome

The syndrome of hyperkeratosis of the palms and soles, and early loss of deciduous and permanent teeth was firstly described by Papillon and Lefevre in 1924 (51). It is a rare genetic disorder that is being inherited by an autosomal-recessive pattern (52). In the term of frequency, it is found in one or four cases per million (52). The manifestations of this syndrome generally appear in the first years of life according to most reports (51-53). The most frequent finding of this syndrome is the hyperkeratosis of the palms and soles (51). The initiation of the skin manifestation usually occurs at the same time when periodontal involvement is observed. Eczema and erythema of the face, sacral and gluteal region may be other cutaneous manifestations (51). In addition, hyperkeratotic regions may be found in the elbows, knees, and the trunk (52). Other findings in this syndrome include high blood pressure, a high blood sugar curve, systolic murmur, elevated hemoglobin, retardation of skeletal maturation, generalized osteoprosis, diffuse swelling of the thyroid, and microphtalmia (51). As mentioned earlier, periodontal destruction is another important manifestation of papillon-lefevre syndrome that leads to loosening and early shedding of both dentitions. The genetic track of the syndrome shows some mutations in a gene in chromosome 11q14 (2). This gene, which is responsible for papillone-lefevre syndrome is identified as the *Cathepsin C* gene (52). Cathepsin C is one of the components in the processing of serin proteases such as neutrophil-derived cathepsin G or neutrophil elastase. Mutations in the Catepsin C gene lead to reduction in the activity of the enzymes and disturbance in function and stability of the polymorphonuclear leukocyte (PMN)-derived proteases. Therefore, the innate immune system also gets affected as a consequence (52). As the hyperkeratosis of the skin begins, pathologic changes in the gingiva appear: the gingiva become red, swollen, boggy, and bleed easily. Destruction of the alveolar bone begins as soon as the last deciduous molars erupt. It is accompanied with deep periodontal pockets and pus exudation. Alveolar bone atrophy leads to premature loosening and loss of deciduous teeth. After the shedding of primary teeth, the gingiva resumes to its normal condition. However, the same process repeats simultaneously by the beginning of the eruption of permanent teeth, and the signs and symptoms are usually more noticeable. Patients usually become completely edentulous by the age of sixteen (51).

Rieger syndrome

The Rieger syndrome is a genetic disease with an autosomal dominant pattern that leads to development in the anterior segment of the eye (54). It is estimated that the overall frequency of this syndrome is 1 per 200,000 (55). A defect in the developmental process of neural crest is considered to be the source of the various anomalies in this syndrome (55). Mutations in the chromosomes 4q25 and 13q14 are discovered to be the etiology of the Rieger syndrome (55). These mutations result in disturbance in the development of the tissues that originate from the neural crest (56). The ocular manifestation includes a triad of features: hypoplasia of the iris, anterior synechiae (iridiocorneal adhession), and a prominent, anteriorly displaced Schwalbe's line. Hypoplasia of the maxialla, which results in a mild prognathic profile, shorened philtrum, a pronounced lower lip, a receeding upper lip, and also hypertelorism are the craniofacial features of this syndrome. One of the most frequent systemic anomalies is the defect in the involution of the periumblical skin. Additionally, other manifestations of the Rieger syndrome that include dental anomalies are oligodontia in both primary and permanent dentitions, microdontia, enamel hypoplasia, conical-shaped teeth,

delayed eruption and shortened roots (56). There is evidence of early tooth loss in Rieger syndrome patients secondary to the decay promoted by the dental hypoplasia and abnormal tooth enamel characteristic of this disorder (55). Many of the Rieger syndrome patients suffer from juvenile glaucoma as a result of ocular anetrior segment dysgenesis that can lead to deterioration of the optic nerve and blindness (55, 56).

Singleton-Merten sydrome

Singleton-Merten syndrome firstly described by Singleton and Merten in 1973 is an autosomal dominant multi-systemic condition that exhibits skeletal deformities (6, 57). The core features of this disorder include marked aortic calcification, cardiac arrhythmia, osteopenia, wide medullary cavities in phalanges, acro-osteolysis, subungal calcification, tendon rupture, subluxation of the joints, thick neurocranium, glucoma scoliosis, short stature, hypotonia psoriasis, primary infertility, and unusual face indicating a high anterior hair line, broad forehead, mild ptosis, smooth philtrum, and thin upper vermilion (6, 57). Anomalies found in the oral cavity are delayed eruption and immature root formation of primarily anterior teeth and early loss of permanent teeth (6, 57). Premature loss of the teeth is the result of a combination of caries and a process of both dental roots and alveolar bone (57). The cause and pathogenesis of this disturbance in calcium metabolism that causes increased calcification in some areas (aorta, heart valve, and cranium) and decreased calcification elsewhere (phalanges, osteopenia, teeth) still remain unknown (57).

Sjogren syndrome

Sjogren's syndrome is considered as a prevalent systemic autoimmune disease (58). Primary Sjogren's syndrome with no other autoimmune disease association, and secondary Sjogren's syndrome, which is accompanied with other autoimmune diseases are two identified types of Sjogren disease (58). In primary SS, there is only the participation of salivary and lacrimal glands, while in secondary SS, another autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, and others are found along with the disease (7). A progressive lymphocytic infiltration of the lacrimal and salivary glands, with the activation of the polyclonal B lymphocyte and production of the autoantibody, in particular, antinuclear antibodies (ANA), autoantibodies to SS-A (Ro) or SS-B (La) antigen, and rheumatoid factor are involved in this immune disorder disease (59). Sjogren syndrome is a common autoimmune disease with the prevalence of 1% in the population; women are nine times more susceptible to this disease due to statistical findings (7). In addition to the typical presence of "sicca complex" of dry eyes and dry mouth, the involvement of exocrine glands of the skin, pancreas, vagina, respiratory, and gastrointestinal systems are observed in Sjogren's syndrome (59). Saliva is an important component of the oral structure. The secretion of saliva decreases by the irreversible replacement of glandular paranchyma by the lymphocytic infiltration and other immune factors (59). This phenomenon can lead to xerostomia. Xerostomia is the decrease in the flow of saliva to less than 50%. Subsequent to xerostomia, oral manifestations are dry and cracked lips, mucosal soreness, tongue depapilation, decrease in secretory IgA, difficulty in swallowing, severe and progressive tooth decay, and oral infections (7). There are some studies, which report some oral clinical features as a result of salivary gland dysfunction such as sialochemistry alterations, non-dry mouth accompanied salivary gland swelling, and early dental loss. Long-term hyposalivation results in an increase in caries activity, and early tooth loss occurs as a complication in SS patients (59). However, biochemical changes, which alter PH and buffer capacity of the saliva primarily to xerostomia, also increase caries activity (59). Low salivary flow increases the dental plaque formation. Although there are some studies that suggest higher periodontal disease risk in SS patients, other studies decline any increase in the risk of periodontal disease in these patients and suggest the predominant presence of cariogenic pathogens instead of perio-pathogens (7).

Conclusion

Early loss of teeth causes masticatory problems as well as impairment of the patient's psychological status and quality of life. Therefore, it would appear to be prudent for physicians and dental practitioners to recognize diseases associated with tooth loss in order to provide timely and appropriate measures in terms of prevention and therapeutic aspects.

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