Aggressive forms of periodontitis secondary to systemic disorders

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A compromised host immune response is an important risk factor in the pathogenesis of severe forms of periodontitis (90). Certain systemic disorders may compromise the host immune system and these disorders are often associated with destructive periodontal disease (29). Neutrophils are important immune defense cells that play a significant role in controlling the spread of microbial plaque infections in the dentogingival region. Neutrophils are the first immune cells to arrive at affected gingival sites. They exit the blood vessels in the gingival connective tissues, cross the junctional epithelium, move into the gingival sulcus/pocket and form a live defense barrier between the microbial infection and the periodontal tissues. Individuals with altered neutrophil function or counts are unable to mount a successful neutrophil defense barrier against microbial plaque infections in the dentogingival region and are more susceptible to periodontal disease. Many systemic diseases can alter neutrophil function and/or counts. Individuals affected with these diseases tend to develop acute and aggressive forms of periodontitis that often lead to early tooth loss (29).

Approximately three decades ago ‘prepubertal periodontitis’ was defined as a unique clinical entity with an onset during or immediately after eruption of the primary teeth, leading to early exfoliation of some or all of the primary teeth (67). Destructive periodontitis resulting in the early loss of teeth in prepubertal children is very rare. However, for the affected children, the loss of teeth at an early age could be devastating and may significantly influence their quality of life (109).

According to the 1999 American Academy of Periodontology’s classification of periodontal diseases, aggressive forms of periodontal diseases secondary to a systemic condition are termed ‘periodontitis as a manifestation of systemic disease’ (12). More recent studies suggest that prepubertal children with severe periodontitis are often diagnosed with certain systemic disorders, usually involving a compromised host response to bacterial infections. However, a systemic disorder is not invariably ascertained, either because it is incipient or for other reasons. Hence, at present the classification of prepubertal periodontitis is not recommended, and the classification of periodontitis as a manifestation of systemic disease is used instead. This article will review relevant major systemic diseases with a focus on disorders that are associated with defects in the mineralization of bone and dental tissues and with alterations in either neutrophil counts (quantitative disorders) or neutrophil function (qualitative disorders).

Hypophosphatasia

Hypophosphatasia is a genetic disorder characterized by defective mineralization of bone and teeth and a deficiency of tissue-nonspecific alkaline phosphatase activity. Tissue-nonspecific alkaline phosphatase is involved in collagen and calcium binding and also hydrolyzes inorganic pyrophosphate, which is a potent natural inhibitor of hydroxyapatite crystal growth (93). Therefore, a deficiency in tissue-nonspecific alkaline phosphatase leads to the accumulation of extracellular pyrophosphate, and this causes inhibition of skeletal and dental mineralization (35, 70, 108).

The clinical expression of hypophosphatasia is highly variable and ranges widely in severity. In the severe form the bone does not mineralize, resulting in stillbirth. Early loss of teeth is common to most forms of hypophosphatasia. Clinical signs of the childhood form include early exfoliation of the primary teeth, skeletal deformities, short stature, waddling gait, bone pain and fractures. The adult form is usually recognized in middle age and presents as foot...
pain, stress fracture of the metatarsals and dental abnormalities (107). Chondrocalcinosis and osteoarthropathy may develop with age. In the mild form of the disease, loss of teeth and/ or severe dental caries are the only manifestations, with no systemic symptoms (22). This latter form was termed odontohypophosphatasia and it shows only mildly reduced serum alkaline phosphatase levels, whereas in the more severe forms there is pronounced reduction or complete lack of tissue-nonspecific alkaline phosphatase. Osteomalacia distinguishes adult hypophosphatasia from odontohypophosphatasia.

The prevalence of hypophosphatasia varies depending on the form of the disease and the population studied. The prevalence of the severe form, which includes the perinatal and infantile forms, is estimated to be 1 / 100,000 in Canada (36) and 1 / 300,000 in France (63). However, the prevalence of the mild/moderate forms of hypophosphatasia, which includes childhood, adult and odontohypophosphatasia forms, is thought to be much higher and was estimated to be 1 / 6,370 among the European population (63).

Hypophosphatasia is caused by more than 200 distinct mutations in the ALPL gene (62). Both autosomal-recessive and autosomal-dominant transmission have been shown in patients with mild or moderate forms of hypophosphatasia. The diagnosis of this disease is usually based on clinical examination and laboratory assays, and, more recently, DNA sequencing of the causative gene has been performed to further verify the diagnosis.

Patients with hypophosphatasia do not show increased gingival inflammation or periodontitis (106) and their immune response to infections is not defective. However, they have various dental deformities, including thin dentin, hypocalcified enamel, large-diameter dentinal tubules, and enlarged pulp chamber and root canals. Furthermore, the dental cementum is absent, hypocalcified or dysplastic (101). For this reason the roots of the teeth in these patients are not adequately anchored to the alveolar bone via the periodontal ligament and the teeth are lost prematurely.

**Diseases associated with neutrophil disorders**

Neutrophils form the major part of leukocytes in humans and are an essential component of the innate immune system. These cells are the first line of defense against infection, and they have a short lifespan (69). Hence, a significant decrease in the number of neutrophils may compromise the host’s response to infection, and as such is an important etiological factor for certain forms of periodontal diseases (76, 81).

**Quantitative neutrophil disorders**

**Familial and cyclic neutropenia**

Cyclic neutropenia is a rare genetic disorder characterized by a cyclical decrease in the number of circulating neutrophils. The decrease in the number of circulating neutrophils tends to occur every 3 weeks and lasts for 3–6 days at a time. The decrease in the number of circulating neutrophils is caused by changes in the rates of cell production in the bone marrow. The condition is caused by mutations in the gene that encodes neutrophil elastase (10, 104). In humans, neutrophil elastase is encoded by the ELA2 gene, and mutations in this gene may impede neutrophil maturation. The mutations are passed down through family members by autosomal-dominant inheritance, and therefore the condition tends to affect several members of the same family.

The neutropenic phase is characteristically associated with clinical symptoms such as recurrent fever, malaise, headaches, anorexia, pharyngitis, ulcers of the oral mucous membrane and gingival inflammation (27). Several reports in the literature indicate that affected individuals tend to have periodontal problems. The importance of regular oral hygiene, removal of subgingival plaque and calculus and periodic professional tooth cleaning are indicated to control the progression of periodontal disease in affected individuals (65). Local antibiotic application in periodontal pockets was recommended, in a case report (65), to help manage the periodontal problems during neutropenic periods. Treatment with recombinant granulocyte colony-stimulating factor has been shown to result in resolution of the oral ulcerations and of other clinical symptoms (68), and a combination treatment using granulocyte colony-stimulating factor and nonsurgical periodontal therapy may lead to an improvement of the periodontal condition of the affected patients (58).

**Infantile genetic agranulocytosis**

Infantile genetic agranulocytosis is a rare autosomal-recessive disease caused by a defect in the granulocyte colony-stimulating factor receptor (39). Granulocyte colony-stimulating factor receptor stimulates the bone marrow to produce granulocytes
and stem cells, and also stimulates the bone marrow to release these cells into the bloodstream. In addition, granulocyte colony-stimulating factor also stimulates the survival, proliferation, differentiation and function of neutrophil precursors and mature neutrophils (52). As a result, children born with defects in granulocyte colony-stimulating factor receptor cannot make neutrophils and are therefore susceptible to infections, including periodontal diseases.

There are only a few studies describing the oral and periodontal status of subjects affected with infantile genetic agranulocytosis, and some of the reported findings include a generalized gingival inflammation characterized by red spongy gingiva, increased probing depth, gingival bleeding on probing and severe alveolar bone loss (11, 23, 30). A case report implicates herpes viruses in the pathogenesis of the periodontal defects associated with the condition (112). It has been suggested that a therapeutic regimen consisting of scaling and root planing, soft-tissue curettage and the use of selected antimicrobial agents could be successful in the resolution of periodontal infection in subjects inflicted with this syndrome (77).

**Glycogen storage diseases**

Glycogen is an energy storage molecule. Glycogen storage diseases are rare metabolic disorders involving glycogen synthesis or storage, and these diseases cause the body to either not be able to make enough glucose, or not be able to use glucose as a form of energy (42). There are 11 known types of glycogen storage diseases. Type 1 glycogen storage disease accounts for about 25% of all cases diagnosed in the USA and Europe and has an estimated incidence of about 1/100,000 live births. The two most frequent symptoms of the disease include enlarged liver and hypoglycemia. There are two different subtypes of type 1 glycogen storage disease: type 1a and type 1b. Glycogen storage disease type 1b is an autosomal-recessive disease caused by a deficiency of microsomal glucose-6-phosphate translocase. Glucose-6-phosphate translocase transports glucose-6-phosphate from the cytoplasm to the lumen of the endoplasmic reticulum where the enzyme glucose-6-phosphatase converts glucose-6-phosphate into glucose. The gene that codes for glucose-6-phosphate translocase is called *SLC37A4* and is located on chromosome 11q23.3. In glycogen storage disease type 1b the *SLC37A4* gene is mutated and this results in a deficiency in glucose-6-phosphate translocase.

Patients with glycogen storage disease type 1b have neutropenia accompanied by progressive defects of neutrophil functions, such as chemotaxis and respiratory burst. Overexpression of proapoptotic proteins may accelerate the apoptosis of neutrophils in patients with glycogen storage disease type 1b. The underlying cause of neutrophil dysfunction in glycogen storage disease type 1b is endoplasmic reticulum stress generated by disruption of endogenous glucose production. It has also been suggested that glucose-6-phosphate translocase deficiency may result in a redox shift toward oxidizing conditions in the endoplasmic reticulum lumen of neutrophils in glycogen storage disease type 1b. Patients with glycogen storage disease type 1b are susceptible to a variety of infections, including periodontal infections. Patients showing aggressive forms of periodontal breakdown have been reported in the dental literature (18, 71).

**Cohen syndrome**

Cohen syndrome is a rare genetic disorder with an autosomal-recessive mode of transmission. The disease is characterized by intellectual disability, developmental delay and a unique physical appearance including narrow hands and feet with long, slender fingers (34). Most affected individuals have truncal obesity (deposition of fat around the midsection of the body) and prominent upper central incisors. The etiology of this disease is mutations in the *VPS13B* gene (frequently called the *COH1* gene). The *VPS13B* gene is located on the long (q) arm of chromosome 8 at position 22.2. The exact function of the protein expressed by this gene is not known, but it is believed to be involved in protein sorting and transportation inside the cell. Almost all affected individuals have abnormally low counts of white blood cells (granulocytopenia), and the neutrophil is the cell type particularly affected (neutropenia). Because of the low white-blood-cell counts, affected individuals are susceptible to infections, including periodontitis (5).

**Qualitative neutrophil disorders**

**Leukocyte adhesion deficiency syndrome**

Leukocyte adhesion deficiency syndrome is a rare immunodeficiency disorder inherited in an autosomal-recessive trait and characterized by defects in adhesion receptors of the white blood cells (33). There are three main types of leukocyte adhesion deficiency syndrome. Type I involves a deficiency in membrane integrins, type II involves a defect in the expression of ligands for selectins, and type III encompasses other variants of leukocyte adhesion
deficiency syndrome and may include platelet aggregation abnormalities. Type I is the most common form of the disease, whereas types II and III are extremely rare.

Integrins are integral cell-surface proteins composed of an alpha chain and a beta chain. Integrins are involved in cell adhesion as well as in cell-surface-mediated signaling. In humans, the integrin beta-2 gene (ITGB2), on the long arm of chromosome 21, encodes integrin beta-2 protein (CD18). Integrin beta-2 combines with various alpha-chain partners to form various integrins. CD18 paired with CD11a forms lymphocyte function-associated antigen-1; CD18 paired with CD11b forms macrophage antigen-1; and CD18 paired with CD11c forms the p150,95 protein. Lymphocyte function-associated antigen-1 is expressed on the surface of lymphocytes and is involved in lymphocyte trafficking, antigen presentation and cytotoxic T-cell activity. Macrophage antigen-1 and p150,95 are expressed on leukocytes and are involved in the adhesion of leukocytes to endothelial cells (88).

A mutation in the ITGB2 gene results in a non-functioning leukocyte cell-adhesion molecule. The affected neutrophils have migration and phagocytic abnormalities. Thus, they cannot mount a successful defense response against microbial infections. Affected individuals are susceptible to infection, including periodontal infections.

Patients with leukocyte adhesion deficiency syndrome often show severe gingival inflammation and rapidly progressive periodontal destruction around the primary and permanent teeth, usually resulting in the early loss of the affected teeth (26). Other oral manifestations may include acute gingival lesions, gingival enlargement, recession, tooth mobility and pathologic migration. The management of the aggressive periodontal disease associated with leukocyte adhesion deficiency syndrome is very challenging and is often unsuccessful in arresting the progression of periodontal tissue loss (19).

**Chediak–Higashi syndrome**

Chediak–Higashi syndrome is a rare autosomal-recessive genetic disorder of granule morphology and function affecting multiple organ systems (105). It is clinically characterized by partial albinism, frequent infections and an accelerated lymphohistiocytic phase (14). The pathological hallmark of Chediak–Higashi syndrome is the presence, in all white blood cells and in certain other cell types, of massive lysosomal inclusions in the cytoplasm of the cells. The defect is secondary to a mutation of a lysosomal trafficking regulator protein (105). Clinical reports have identified mutations throughout the CHS1 /LYST gene, and the nature of these mutations can be a predictor of the severity of the disease (45). These mutations result in the impaired function of multiple body cells and systems. Subjects with Chediak–Higashi syndrome have immune-system abnormalities, recurrent infections, bleeding abnormalities and muscle weakness. Progressive damage to the peripheral nervous system, partial albinism and sensitivity to light are associated with the disease. In addition, subjects with Chediak–Higashi syndrome tend to have slight cognitive deficits. The disease is lethal, and life expectancy is usually short, with the majority of patients dying in childhood. Fatality is associated with infections and lymphoproliferative disorders in multiple organs (43). Treatment with bone marrow transplantation may be helpful in correcting neutrophil dysfunction in some patients (1, 96).

Chediak–Higashi syndrome is associated with significant periodontal symptoms, including profound gingival inflammation, deep probing depth generalized to most of the dentition (Fig. 1) and severe alveolar bone loss (13, 46) (Fig. 2). The management of the periodontal component of the disease is very challenging, and both successful (13) and unsuccessful (31, 83) results have been reported in the literature. The response to treatment may be related to the severity of the Chediak–Higashi syndrome. Early reports did not specifically address recommended periodontal management and possible bleeding complications. In a recent study, Khocht et al. (46) described a severe case of Chediak–Higashi syndrome.
syndrome and recommended the extraction of periodontally compromised teeth and the fabrication of dentures to avoid significant oral infections that may impact on the systemic health of these patients.

**Papillon–Lefèvre syndrome**

Papillon–Lefèvre syndrome is a rare genetic disorder characterized by hyperkeratosis of the palms, the soles of the feet, the elbows, the knees and other organs (Fig. 3), and, in addition, shows a rapidly progressive, severe periodontitis that leads to early loss of the primary and permanent teeth (6, 28) (Fig. 4). The disease is inherited as an autosomal-recessive trait. A loss-of-function mutation affecting the cathepsin-C gene \((CTSC)\) on chromosome 11q14.1-q14.3 has been associated with the disease. Cathepsin-C is expressed by epithelial cells and immune cells, such as leukocytes and macrophages. Cathepsin-C functions as a key enzyme in the activation of granule serine proteases (e.g. elastase), the activation of granzymes and the regulation of epithelial morphogenesis. The prevalence of the syndrome in the general population is 1–3 per million, with no sex or race preference. The skin symptoms vary greatly. In some affected individuals the hyper-

keratotic skin lesions are dramatic, whereas in others they are hardly visible or almost missing.

The periodontal manifestations include gingival inflammation, increased probing depth and advanced radiographic alveolar bone loss (Fig. 5). Typically, the affected individuals lose their teeth early in life and eventually become edentulous with significant ridge resorption. Immunohistological examination of the gingival tissues shows a massive inflammatory infiltrate dominated by plasma cells (47). Lundgren et al. (57) reported impaired salivary secretions and somewhat altered salivary gland function in children and young adults affected with Papillon–Lefèvre syndrome.

Several studies have investigated the pathogenesis of periodontitis in individuals affected with Papillon–Lefèvre syndrome. Impaired neutrophil functions, including chemotaxis, phagocytosis and bacterial killing, were reported by some authors (53, 102). Severe depressed natural killer cell cytotoxicity has also been reported in affected individuals (54). There are also reports of increased levels of interleukin-1beta
and matrix metalloproteinase-8 in gingival crevicular fluid (98), and atypical activity of the plasminogen activating system with a disturbed epithelial function in the gingival tissues of affected individuals (99). It has been suggested that the periodontal destruction seen in individuals with Papillon–Lefèvre syndrome might be attributed to a defect in the epithelial barrier defense system.

The subgingival microbial profile of subjects with Papillon–Lefèvre syndrome has been investigated. Studies using bacterial culture or DNA probes showed that the subgingival microbial profile in individuals with Papillon–Lefèvre syndrome closely resembled a profile characteristic of deep pockets in patients with chronic periodontitis (47, 56, 75, 103). On the other hand, Albandar et al. (6) conducted a comprehensive analysis of the subgingival microbiota in subjects with Papillon–Lefèvre syndrome using 16S ribosomal RNA clonal analysis and the 16S ribosomal RNA-based Human Oral Microbe Identification Microarray and concluded that the subgingival microbiota in these patients is diverse and comprises periodontal pathogens commonly associated with chronic and aggressive periodontitis as well as opportunistic pathogens, the most prevalent of which included Gemella morbillorum, G. haemolysans, Granulicatella adiacens, Lachnospiraceae, Parvimonas micra, Selenomonas noxia and Veillonella parvula. Velasco et al. (103) reported the presence of cytomegalovirus and Epstein–Barr virus type 1 in the subgingival sample of a patient with Papillon–Lefèvre syndrome and hypothesized that viruses, in concert with subgingival periodontopathic bacteria, may contribute to the development of periodontitis in Papillon–Lefèvre syndrome-affected individuals.

The treatment of periodontitis and the control of periodontal tissue loss in Papillon–Lefèvre syndrome are difficult, and most previous studies have consistently shown that the early loss of primary and permanent teeth is inevitable. However, some recent reports suggest that it is possible to control periodontal disease in individuals with Papillon–Lefèvre syndrome by combining antibiotic therapy with conventional periodontal therapy, including mechanical debridement and surgical pocket reduction (3, 55, 66). A long-term follow-up case report showed a successful outcome following a multidisciplinary treatment approach consisting of extraction of periodontally involved teeth, rehabilitation of the edentulous region with temporary dentures, a guided bone-regenerative procedure to augment lost alveolar bone and construction of dental implants, together with a meticulous oral hygiene regimen by the patient (95). Also, full-mouth rehabilitation of the missing dentition in a patient with Papillon–Lefèvre syndrome using fixed prostheses supported by osseointegrated dental implants has been reported (2).

**Down syndrome**

Down syndrome is more common than other genetic disorders, with an incidence of about 1 per 800–1,000 births (82, 84). The disease is characterized by the presence of an extra copy of chromosome 21. The most common manifestations of the syndrome include a characteristic physical appearance and varied mental and physical disorders (59), including congenital heart disease, thyroid dysfunction, Alzheimer disease and alteration of the immune system, including granulocyte/monocyte cell dysfunction (21, 50, 59).

Periodontal disease is a common manifestation among subjects with Down syndrome, with an estimated prevalence of 58–96% in patients under 35 years of age, and periodontitis is more severe in these subjects than in persons who do not have Down syndrome (60). The disease starts early in life, progresses with age and eventually leads to tooth loss (37, 100). Periodontal disease adversely impacts on the quality of life of subjects with Down syndrome (9).

The factors contributing to the increased prevalence and severity of periodontitis in individuals with Down syndrome have been studied extensively. Studies show that individuals with Down syndrome have difficulty maintaining adequate oral hygiene and thus tend to harbor high levels of supragingival dental plaque (25, 46, 78). In addition, following oral hygiene instructions, individuals with Down syndrome continue to show reduced ability to achieve adequate plaque control (79) (Fig. 6). It has often been surmised that mental disability associated with Down syndrome is an important factor in the reduced ability of patients to maintain adequate oral hygiene and leads to an increased susceptibility to periodontitis (32, 60). Khocht et al. (46) recently used a multivariate model that included assessment of mental disability and traditional risk factors of periodontitis, and showed that loss of periodontal attachment in individuals with Down syndrome was not associated with mental disability.

It is well documented that Down syndrome is associated with immune deficiencies and host response impairment (50, 72, 73). Infections, and respiratory infections in particular, are an important cause of mortality in Down syndrome (20, 94). The most likely reason for this increased susceptibility to
infection and reduced immunity in individuals with Down syndrome is the increased dosage of protein products encoded by chromosome 21, which are likely to result from an increased amount of protein products encoded by chromosome 21 (there are three copies of this chromosome in subjects with Down syndrome), which are likely to result from the increased transcription of one or more of the approximately 310 genes present on this chromosome, and a complex genetic interplay caused by increased copies of many of these genes leading to the diverse Down syndrome phenotypes (51). Several proteins important in immune function are encoded by genes present on chromosome 21 (38), including superoxide dismutase, nicotinamide adenine dinucleotide phosphate (NADPH)-dependent carbonyl reductase and integrin beta-2 (CD18). Increased production of superoxide dismutase and of NADPH are associated with increased oxidative stress and tissue injury (4, 89). Aberrant expression of CD18 integrin on immune-cell surfaces in Down syndrome may be associated with altered lymphocyte function (50, 91, 92). The interleukin-10 receptor beta subunit component of the interleukin-10 receptor (involved in the resolution of inflammation) is encoded by chromosome 21, and its function may be altered in Down syndrome (40). In addition, it seems that interleukin-1 is up-regulated indirectly by some chromosome 21-based genes (64). Interleukin-1 is an important inflammatory mediator, and its increased production may be associated with brain tissue damage (64).

Periodontitis is initiated by bacterial infection, and the impaired immune response to infections in individuals with Down syndrome may be the primary contributing factor to the increased susceptibility of these individuals to periodontal destruction. It is likely that the compromised host response makes it easier for virulent periodontopathic microbial species to colonize the subgingival sites, and consequently if these bacteria remain unchallenged an intense inflammatory reaction could be induced within the periodontal tissues. The increased periodontal inflammation would lead to elevated production of degrading enzymes and alter bone remodeling. The end result of these inflammatory-induced changes would be the loss and destruction of the periodontium, and eventually tooth loss (Fig. 7). Several studies have investigated the microbiological, host response and inflammatory aspects in Down syndrome. These are discussed below.

**Microbiological findings**

Barr-Agholme et al. (15) reported increased frequency of detecting *Aggregatibacter actinomycetemcomitans*, *Capnocytophaga* and *Porphyromonas gingivalis* in the subgingival plaque of adolescents.
with Down syndrome. *A. actinomycetemcomitans* was detected in 35% of subjects with Down syndrome compared with 5% of healthy, age- and sex-matched controls. The authors suggested that this increased frequency of *A. actinomycetemcomitans* indicated an altered microbial composition in the subgingival plaque of subjects with Down syndrome compared with healthy controls.

Amano et al. (8) detected various periodontal disease-causing bacteria in very young subjects with Down syndrome and suggested that periodontopathic bacteria could colonize the teeth of these patients at a very early age. Periodontal pathogens in the subgingival plaque of subjects with Down syndrome were detected with far greater frequency than in age-matched controls, and this may explain the intense gingival inflammation in these individuals. The authors concluded that certain periodontal pathogens, particularly *P. gingivalis*, play a key role in the initiation of gingival inflammation.

Sakellari et al. (78) assessed clinical periodontal parameters in 70 subjects with Down syndrome and in 121 age-matched healthy controls, collected subgingival plaque samples from the Ramfjord teeth and assessed the presence of 14 bacterial species using ‘checkerboard’ DNA–DNA hybridization. The study reported that important periodontal pathogens colonize subjects with Down syndrome earlier, and at higher levels, compared with age-matched healthy individuals. Reuland-Bosma et al. (74) compared the subgingival microflora in adult subjects with Down syndrome with that in other individuals with intellectual disabilities. Despite advanced periodontitis in subjects with Down syndrome, no differences in the prevalence of distinct suspected periodontopathic bacteria were established, and the authors conclude that host factors are the most likely explanation for the advanced periodontal disease associated with subjects with Down syndrome.

Amano et al. (7) sampled subgingival plaque from 67 young adults with Down syndrome and 41 age-matched systemically healthy individuals with mental disabilities. The prevalence of *A. actinomycetemcomitans*, *P. gingivalis*, *Tannerella forsythia* (previously known as *Bacteroides forsythus*), *Trepomonema denticola*, *Prevotella intermedia*, *P. nigrescens*, *Capnocytophaga ochracea*, *C. sputigena*, *Campylobacter rectus* and *Eikenella corrodens* were investigated in subgingival plaque samples using the PCR. The authors found no significant differences in the bacterial profiles between the groups.

The cited microbiological studies indicate early colonization of important periodontal pathogens in children and adolescents with Down syndrome. However, the microbial subgingival profile of adults with Down syndrome is not different from that of matched non-Down-syndrome individuals. Despite the lack of differences in microbial profiles, adults with Down syndrome still show greater loss of periodontal attachment than do adults who do not have Down syndrome (7, 74). This suggests that the host response to the same bacteria is different between individuals with Down syndrome and those who do not have Down syndrome.

**Immune response**

Significant evidence exists suggesting that subjects with Down syndrome have an impaired immune response to infection (50). Studies investigated the hypotheses that the immune/inflammatory response in Down syndrome is either defective or more intense, resulting in greater periodontal tissue damage. Various studies investigated different components of the immune system in relation to periodontitis in subjects with Down syndrome, with more focus on neutrophil function, the gingival immune cellular response and antibody production against periodontopathic bacteria.

**Neutrophil function.** Studies uncovered a defective neutrophil chemotaxis in subjects with Down syndrome, leading to a significantly lower chemotaxis compared with healthy controls (44). As neutrophils are the main cells involved in the first line of host defense against invasion with bacteria, defective neutrophil chemotaxis can lead to significant tissue loss and to the progression of periodontitis. Additionally, it has been found that significant correlations exist between the amount of bone loss and the age and chemotactic index, suggesting that the rate of periodontal destruction in these subjects is dependent on the degree of the chemotaxis defect. A study assessed the clinical periodontal parameters, chemotaxis and random migration of neutrophils in 15 subjects with Down syndrome and in 15 healthy subjects and found more severe gingival inflammation, and a significantly decreased random migration and chemotaxis of neutrophils, in the subjects with Down syndrome compared with the control group (111).

A study of the effectiveness of surgical and nonsurgical periodontal therapies, and the neutrophil chemotaxis status and functions in relation to treatment, were investigated in a group of 14 subjects with Down syndrome, 14–30 years of age (113). Surgical and nonsurgical periodontal therapies were
compared in a split-mouth design, and clinical periodontal parameters were recorded at baseline, and 6 months, and 1 year post-treatment. Neutrophil chemotaxis, phagocytic activity and production of superoxide anion were compared between the 14 subjects with Down syndrome and nine healthy controls, 24–28 years of age. The results showed that both surgical and nonsurgical therapies contributed to a significant improvement in all clinical parameters compared with baseline values. Furthermore, neutrophil chemotaxis, phagocytic activity and production of superoxide anion decreased significantly following treatment in the subjects with Down syndrome, suggesting that neutrophil impairment may not affect the clinical response to therapy (113).

These studies suggest that deficient neutrophil chemotaxis is a common finding in subjects with Down syndrome and that this defect may be secondary to increased oxidative stress associated with trisomy of chromosome 21 (4). The oxidative stress may impair internal cell functions and disrupt chemotaxis. It has been shown that reduced chemotaxis is positively correlated with the severity of periodontitis (44). Moreover, there is some evidence that, despite the reduced neutrophil chemotaxis, periodontal therapy aiming to reduce plaque and correct periodontal architecture may improve the periodontal health in subjects with Down syndrome (113).

**Gingival cellular immune response.** Assessment of the composition of mononuclear cells in the gingival inflammatory infiltrate in chronic periodontitis showed that, compared with non-Down syndrome controls, subjects with Down syndrome had a higher number of cellular infiltrate, increased numbers of CD22+ cells (B lymphocytes), CD3+ cells, CD4+ cells, CD8+ cells and CD11+ cells (macrophages), and a significantly higher CD4+ /CD8+ cell ratio (85). This indicates that subjects with Down syndrome may have a more pronounced and altered gingival cellular immune response when compared with controls, and this immune profile may be associated with the increased tissue destruction in Down syndrome.

Variations in the expression of HLA class II antigens on antigen-presenting cells seem to play an important role in immune regulation. It has been shown that there is an increased frequency of HLA class II antigens in the gingival tissues of subjects with Down syndrome and chronic periodontitis compared with periodontitis patients who do not have Down syndrome, and there were also significantly higher numbers of CD1a+ cells, ratios of HLA-DR+ /CD1a+ cells, and HLA-DP+ /CD1a+ cells (86). The authors concluded that there is a highly activated immune response in subjects with Down syndrome.

Further analysis to characterize the distribution of T-cell-receptor gamma/delta-expressing lymphocytes in gingival tissues of individuals with Down syndrome showed that the percentage of these cells is <1% (87). It was suggested that a defect in the proliferative response of these cells might account for their reduced numbers (82). The gamma/delta T-lymphocytes usually reside within epithelial tissues and encounter antigens on the surface of epithelial cells. They bind to antigens that are intact proteins and to antigens that are not presented within class I or class II histocompatibility molecules. The low numbers of gamma/delta T-lymphocytes in the gingival tissues of individuals with Down syndrome might be a factor in their increased susceptibility to periodontal infections.

The results of these studies suggest presence of a high level of a variety of immune cells within the gingival tissues of subjects with Down syndrome and periodontitis. An increased production of HLA class II antigens on the surfaces of antigen-producing cells suggests that the cells are locally engaged in specific immune responses, and the low presence of gamma/delta T-lymphocytes may increase the vulnerability of subjects with Down syndrome to microbial noxious agents.

**Antibody/immunoglobulin production.** Several studies have investigated the level of specific antibodies to periodontopathic bacteria in serum and saliva. The serum antibody titers to *A. actinomycetemcomitans* were assessed in 11 subjects with Down syndrome and periodontitis, in five subjects with Down syndrome and gingivitis and in 10 non-Down-syndrome healthy controls (80). Significant differences were found between the groups (*P* = 0.05), with the group of subjects with Down syndrome and periodontitis having the highest antibody response, followed by the subjects with Down syndrome and gingivitis and then by the controls. A study examined 75 subjects (2–18 years of age) with Down syndrome, and assessed their gingival health using a modified gingival inflammation index and their serum antibody titers to periodontal bacteria using a micro-ELISA (61). It was found that the average antibody titers to *A. actinomycetemcomitans, Streptococcus mitis* and *Fusobacterium nucleatum* exceeded those of the normal adult reference serum pool. In addition, IgG titers to *P. gingivalis, A. actinomycetemcomitans, F. nucleatum, Selenomonas sputigera* and *S. mitis* correlated significantly with gingival inflammation. It may be inferred from these two
studies that the humoral immune response against periodontopathic bacteria is not impaired in individuals with Down syndrome.

Barr-Agholme et al. (16) investigated the clinical periodontal conditions and salivary immunoglobulins in Down syndrome and found an altered distribution of IgG subclasses in saliva, with an increased amount of IgG1 compared with controls. This is in agreement with other studies showing increased salivary IgG1 in subjects with Down syndrome (50). In contrast, the proportion of salivary IgG2, IgG3 and IgG4 subclasses is not increased in Down syndrome. It is also noted that the level of secretory IgA is increased in subjects with Down syndrome who have alveolar bone loss compared with those without bone loss.

Chaushu et al. (24) assessed age-related changes in the salivary-specific humoral immune response in a young group (mean age = 23 years) and an older group (mean age = 52 years) of individuals with Down syndrome and compared these with the same changes in two age-matched groups of healthy controls. The levels of total IgA and of specific antibodies to three common oral pathogens – P. gingivalis, A. actinomycetemcomitans and Streptococcus mutans – were analyzed. Compared with young controls, the median secretion rates of the specific antibodies of young individuals with Down syndrome were 70–77% lower in whole saliva and 34–60% lower in parotid saliva. In the older age group the secretion rates of subjects with Down syndrome were 77–100% lower in whole saliva and 75–88% lower in parotid saliva.

Hence, these studies show inconsistent antibody responses in saliva and serum in individuals with Down syndrome. While the salivary antibody response was low, the serum antibody response to several periodontopathic bacteria was elevated. The low salivary antibody response to bacteria is associated with decreased salivary flow in individuals with Down syndrome, and this may facilitate the colonization of periodontal pathogens. The elevated serum antibody titers corroborate the increased gingival immune cellular activity described previously in subjects with Down syndrome. It demonstrates that Down syndrome individuals, despite known immune deficiencies, are capable of mounting a specific humoral immune response. Such antibodies would find their way into the gingival tissues and gingival fluid and help to contain the microbial damage. Increased antibody levels in gingival tissues may also accentuate the gingival inflammatory response through complement activation and thus contribute to tissue loss.

Inflammatory response

Inflammatory response studies focused on inflammatory mediators and degrading enzymes in the gingival crevicular fluid of subjects with Down syndrome. One study found that the mean level of prostaglandin E2 in gingival crevicular fluid was significantly higher in subjects with Down syndrome compared with controls (17), suggesting an alteration in arachidonic acid metabolism in subjects with Down syndrome. However, the mean level of interleukin-1beta in the gingival crevicular fluid was not significantly elevated in subjects with Down syndrome, although gingival inflammation was more severe in the Down syndrome group than in the controls. It has been reported that prostaglandin E2 down-regulates the production of interleukin-1beta (49), and this may explain the lack of difference in the level of interleukin-1beta between the groups. This issue has not been thoroughly studied and therefore further investigation is warranted.

Another study assessed the levels of prostaglandin E2, leukotriene B4 and matrix metalloproteinase-9 in gingival crevicular fluid in 18 subjects with Down syndrome and in 14 controls, matched for age and degree of gingival inflammation (97). The results showed that the mean levels of prostaglandin E2, leukotriene B4 and matrix metalloproteinase-9 were statistically significantly higher in the gingival crevicular fluid from subjects with Down syndrome compared with that from controls. Furthermore, the correlation coefficients for leukotriene B4 to bleeding on probing, and to probing depth, respectively, as well as for matrix metalloproteinase-9 to bleeding on probing, differed significantly between the Down syndrome group and the control group. These results may indicate an altered host response in periodontal tissue in Down syndrome.

Among studies investigating tissue-degrading enzymes, Halinen et al. (41) characterized the periodontal status of nine children with Down syndrome, 9–17 years of age, relative to their age-matched systemically and periodontally healthy controls. They assessed clinical periodontal parameters and the collagenase and gelatinase activities in gingival crevicular fluid and saliva samples. Compared with controls, the endogenously active collagenase and total collagenase activities were slightly higher, and salivary collagenase was high, in children with Down syndrome but of the same matrix metalloproteinase-8 type as in the saliva of the controls.

Komatsu et al. (48) examined the level and the enzyme activity of matrix metalloproteinase-2 in the
gingival tissues and reported a significantly higher production of matrix metalloproteinase-2 in cultured gingival fibroblasts of subjects with Down syndrome compared with controls. In addition, markedly different levels of expression of membrane-type I matrix metalloproteinases and matrix metalloproteinase-2 mRNAs were observed in cultured fibroblasts from subjects with Down syndrome compared with cultured fibroblasts from controls. This may indicate that the increased amount of active matrix metalloproteinase-2 produced in Down syndrome could be linked to the simultaneous expression of membrane-type I matrix metalloproteinases, which could also be a marker of periodontal disease that is seen in a majority of subjects with Down syndrome.

Yamazaki-Kubota et al. (110) investigated the levels of matrix metalloproteinase-2 and matrix metalloproteinase-8 in gingival crevicular fluid and the detection of periodontopathic bacteria in subgingival plaque. The concentrations of the matrix metalloproteinases were evaluated using ELISAs, and the periodontopathic bacteria were detected using the PCR. The levels of matrix metalloproteinase-2 and matrix metalloproteinase-8 were higher in subjects with Down syndrome than in healthy controls, and increases in the matrix metalloproteinase levels were observed in the gingival crevicular fluid from patients with good oral hygiene and absence of bleeding on probing. Also, the numbers of periodontopathic bacteria detected in subjects with Down syndrome were higher than the numbers of such bacteria in healthy controls. Surprisingly, the matrix metalloproteinase-2 levels in sites harboring *P. gingivalis* or *A. actinomycetemcomitans* were lower than in sites without these microorganisms.

The cited studies indicate increased matrix metalloproteinase activity in the gingival tissues of individuals with Down syndrome. The presence of matrix metalloproteinase-8 suggests that neutrophils, in their frustration to reach their target pathogens, release their enzymes extracellularly. Matrix metalloproteinases are involved in the breakdown of the extracellular matrix, and their increased activity in the gingival tissues of individuals with Down syndrome explains the gingival tissue loss and associated clinical parameters, such as increased probing depth and loss of attachment. In addition, the increased level of prostaglandin E₂, in combination with the increased activity of matrix metalloproteinase-9, suggests a higher level of osteoclastic activity and explains the increased susceptibility to periodontal disease in Down syndrome.

In reviewing the presented evidence, it seems that a combination of factors, including early microbial colonization, altered immune functions and increased gingival inflammation, contribute to the increased susceptibility to periodontitis in individuals with Down syndrome.

### Summary and concluding remarks

This report reviewed a selected group of systemic disorders involving the mineralization of bone and dental tissues, or affecting neutrophil counts or function and their impact on the periodontium. Aggressive forms of periodontitis almost always accompany these systemic diseases. When dealing with or suspecting these disorders, it is recommended to establish a differential diagnosis and attempt to identify the underlying causal factors. Proper diagnosis is a prerequisite for proper management of the periodontal problem. To establish a diagnosis it is important to review the medical history, family history, laboratory findings of neutrophil counts and functions, and total serum alkaline phosphatase activity, and to consult with other medical specialists. In certain cases molecular genetic testing may be indicated and may help validate a clinical diagnosis. In most of these diseases controlling the progression of periodontal disease is very challenging. Controlling the supragingival dental plaque and combining antimicrobial therapy with conventional periodontal therapy may help in some situations. Future advances in research, including gene targeting and the resolution of enzyme deficiencies, may bring about remedies of the underlying genetic defects, and such treatments may significantly improve the outcome of periodontal treatment in these patients.

### References

Syndromic aggressive periodontal disease


