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Review Article

NEUTROPENIA ASSOCIATED PERIODONTAL DISEASES- A REVIEW

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ABSTRACT

Neutropenia is a group of diseases that have a common feature of decrease in the number of neutrophils, resulting in the diminished ability to ward off infections and in certain cases death. Neutropenia can be caused by many genetic and systemic factors and also accompanied by many syndromes. In general defect in neutrophils can cause periodontal disease by altering the capacity to resist infections by dental plaque, resulting in bone loss and loss of teeth prematurely.. The dentists and in particular Periodontist should know the disorders that can affect the periodontium and cause bone loss so as to treat them appropriately. The response to treatment is not always good and the progression of periodontal disease is inevitable despite adequate maintenance treatment.

Key Words- Neutropenia, periodontal disease, syndromes, genetic conditions, systemic conditions, bone loss.

INTRODUCTION

Neutropenia is a decrease in the Absolute Neutrophil Count (ANC) to below normal levels. The ANC is determined by multiplying the total white blood cell count by the percentage of segmented and band forms.[1] The ANC varies widely in healthy individuals like exercise, emotional state, time of the day. Neutropenia may be chronic or cyclic, severe or benign, and can be divided into three categories depending on the absolute neutrophil count (ANC). An absolute neutrophil count below 2000/mm^2 and above 1000/mm^2 is considered mild form, and between 500-1000/mm^2 is moderate and below 500/mm^2 are severe neutropenia.[16] Neutropenia is often caused by medications, chemotherapy or recurrent illness and can also be inherited.[2]

Neutropenic patients are usually infected by endogenous organisms. In general patients with severe chronic neutropenia have less serious infections than patients with the same degree of neutropenia due to immunosuppressive drugs and cancer chemotherapy. These patients usually present with stomatitis, gingivitis, perirectal inflammation or cellulitis, abscess, pneumonia, and septicaemia. Fever is the common symptom and the patients are prone to parasitic, viral or fungal infections.

Neutropenia has many causes, it can be divided into

Intrinsic disorders of proliferation and maturation of myeloid and stem cells

Secondary neutropenia caused by factors by factors extrinsic to marrow myeloid cells

Syndromes associated with neutropenia

Neutropenia is life threatening and infections are difficult to manage. Patients with neutropenia exhibit variety of periodontal manifestations. In severe forms occurs mostly in drug induced forms, there is severe ulcerations with necrosis of marginal gingiva, bleeding and also involvement of attached gingiva.[30] The ulcerated areas exhibit little or no PMN infiltration. The gingival is oedematous, hyperaemic, hyperplastic with areas of partial desquamation. These conditions are accompanied with deep pockets and extensive generalised periodontal destruction and loss of teeth.[36] This review discusses the conditions which cause neutropenia and the associated periodontal pathologies.

Congenital Agranulocytosis- Congenital agranulocytosis associated with complete absence of peripheral granulocyte but shows increase in Monocytes, basophils, and eosinophils. Some patients have defects in the receptors required for neutrophil growth while some others have mutation in their elastase gene.[8,32] Nearly all patients with agranulocytosis have frequent infectious diseases of the skin, oral mucosa, gastrointestinal and genitourinary tracts and succumb early in life. The mucosa exhibits isolated necrotic patches that are black and grey and are sharply demarcated from the surrounding uninvolved areas.[2] The gingival margin may or may not be involved and unless the neutrophil count is appropriately corrected, the patients will develop periodontitis.[17]

Severe congenital neutropenia(SCN) or infantile genetic agranulocytosis or Kostmann syndrome(IGA)- In SCN or IGA there is a decrease in the presence of Neutrophils and predisposes the patients to bacterial and fungal infections in childhood due to altered defence capacity and transmitted as **autosomal dominant and autosomal recessive** disorder. The ANC at diagnosis is usually less than 0.2 x 109/L. Blood Monocytes are frequently three to four time normal, platelets are moderately increased and there is a mild anaemia. Also there a decrease in the production of granulocyte colony stimulating factor[10] associated with the disease. Early age periodontitis with gingival inflammation, aggressive periodontal destruction, enlarged gingiva, pockets and mobility due to altered host defence capacity are commonly found in this condition.[2,32] This is similar to prepubertal or rapidly progressing periodontitis with premature loss of deciduous teeth.[10,12,33]

Cyclic Neutropenia- Patients with cyclic neutropenia have a defect in their pluripotent stem cell maturation process as a result of accelerated apoptosis of marrow precursors and is an **autosomal dominant** genetically transmitted disorder. These are cyclical episodes lasting 3-6 days where neutrophil counts are reduced. The peripheral blood neutrophil counts oscillate between approximately 0.1x 109/L and1.5 x109/L every 21 day. These episodes are accompanied by malaise, anorexia, fever, lymphadenopathy, and ulcerations of the mucous membrane in the mouth and gastrointestinal tract and can cause bacterial sepsis or pneumonia. In addition to idiopathic cyclic neutropenia there are neutropenias induced by pharmaceutical agent and chemotherapy. The cyclic neutropenia levels have been associated with inflamed gingiva, gingival ulceration, periodontal attachment loss and severe periodontal bone loss. [8] Red hyperplasic oedematous gingivitis involving both the marginal and attached gingiva which bleeds easily is a common finding .[13,14]

Familial Neutropenia- Familial neutropenia is inherited as an **autosomal dominant** trait. Neutrophils are not released regularly from the marrow. A slight monocytosis occurs with neutropenia. There is susceptibility to systemic infections and vary with neutrophil count. The gingiva is fiery red, oedematous with ulceration and attachment and bone loss are common features.[16]

Leukocyte Adhesion deficiency(LAD) syndrome -Leukocyte adhesion deficiency is a group of disorders that is **autosomal recessive** and have cell surface receptor defects on neutrophils, Monocytes and lymphocytes. These are inherited defects and show defects in adhesion molecules β2 integrins resulting in the defect in adhesion functions and the ability of neutrophils to emigrate even in the presence of chemotactic factors. There is also a defect in the ability to process opsonised particles.[12,29] LAD is associated with systemic infections especially staphylococcal and gram negative bacterial infections. These patients have neutrophilia with rapidly progressing periodontal disease with acute inflammation and proliferation of the gingival tissues with significant bone loss and eventually tooth loss.[23] In the mild cases of LAD periodontal disease may be the presenting factor and is refractory.

Lazy Leukocyte syndrome- Lazy leukocyte syndrome is characterised by susceptibility to sever periodontal infections, neutropenia, defective, chemotactic response to neutrophils and abnormal inflammatory response. The syndrome is characterised by recurrent stomatitis, otitis, and low-grade fevers, normal humoral and cellular immunity, severe peripheral neutropenia, normal numbers of mature, morphologically normal neutrophils in the bone-marrow, poor peripheral blood leukocyte response to chemical or inflammatory stimulation, poor neutrophil chemotaxis, and severely impaired random mobility of neutrophils.[24,25] Patients diagnosed with Lazy leukocyte syndrome have severe oral stomatitis, recurrent infections of the buccal mucosa and tongue, severe gingivitis and periodontal disease and advanced alveolar bone loss and loss of teeth.[26]

Glycogen storage disease- This is a metabolic disease with recurrent infections and neutropenia has severe prognosis. It is and **autosomal recessive** trait. Classic von Gierke glycogen storage disease (GSD1a and GSD1b) causes massive enlargement of the liver and kidney and growth retardation with doll face. There is a defect in the microsomal glucose 6 phosphate translocase and associated with neutropenia and neutrophil dysfunction. Absence of the translocase therefore results in an inability to liberate glucose from the deficient substrate, glucose-6-phosphate leading to hypoglycaemia and hepatomegaly.[11] The blood neutrophils have reduced oxidative burst activity and defective chemotaxis. Early onset gingivitis leading to severe periodontitis and loss of alveolar bone and tooth migration are the common findings. The mucosal lesions present as deep irregular recurrent ulcers covered by pseudomembrane, and recurrent oral infections may occur.[12]

Shwachman- Diamond syndrome- Although neutropenia is the most common presenting haematological feature, there is also a greatly increased risk of developing acute leukaemia later in life. Other organs which can be affected include the skeleton (metaphyseal dysostosis, epiphyseal dysplasia), teeth and oral cavity, liver, heart, kidneys, and skin. Mucositis and periodontal infections are frequently seen in individuals who are profoundly and persistently neutropenic.[6,18] However, there is an increased incidence of tooth enamel defects (dental dysplasia) in children with SDS, including hypomaturation, hypocalcification, and hypolasia.[31]

Chediak- Higashi syndrome- Chediak- Higashi syndrome is a rare, often fatal, **autosomal recessive** that mostly affects melanocytes, platelets and phagocytes. This disorder presents variable oculocutaneous albinism, strabismus, nystagmus, and infections involving respiratory tract and skin. The leucocytes presents abnormal giant lysosomal granule that can fuse with the phagosome but unable to release their contents.[19,30]Patients are mildly neutrophilic with defective intracellular killing and chemotaxis. In addition the patients with this disease have impaired natural killer cell function, multiple recurrent bacterial infections and periodontal disease.[20] The periodontal condition in Chediak- Higashi syndrome manifests as severe gingivitis, early onset periodontitis with marked mobility of teeth and premature exfoliation in both dentitions. The bone destruction may be localized or generalized and are related to gingival inflammation with rapidly progressing disease and refractory to treatment.[21]The anaerobic flora with predominant spirochetes with severe inflammation and purulent exudates with high proteolytic activity and which facilitates bacterial adherence are the common features.

Hyper IgM syndrome is a family of genetic disorders in which the level of Immunoglobulin M (IgM) antibodies is relatively high. The most common type is a result of a defect in a Th2 cell protein (CD40 ligand)). The disorder causes immunodeficiencies, including a higher than normal susceptibility to various types of infections. Individuals with hyper-IgM syndrome typically also have a low number of neutrophils and platelets. In people with hyper IgM syndromes, the B cells keep making IgM antibodies because they can't switch to a different kind of antibody.[35] This results in an overproduction of IgM antibodies and an underproduction of all other types, IgA, IgG, and IgE. Recurring upper and lower respiratory infections, enlarged tonsils, liver, and spleen, chronic diarrhoea, and an increased risk of unusual or "opportunistic" infections and non-Hodgkins lymphoma oral and anal ulcers, and periodontitis are the common presentations of this disorder.[8,27]

Hermansky-Pudlak syndrome (HPS)- Hermansky-Pudlak syndrome (HPS) is a rare group of **autosomal recessive** diseases whose manifestations include oculocutaneous albinism, bleeding, and lysosomal ceroid storage. Its etiology has been related to defects in 7 genes. The type of albinism associated with Hermansky-Pudlak syndrome is a tyrosinase-positive form. Secondary to the albinism that results from Hermansky-Pudlak syndrome, visual defects, including photophobia, strabismus, and nystagmus occur. The bleeding problems of Hermansky-Pudlak syndrome result from platelet dysfunction and manifest with easy bruisability, nose bleeds, and extended bleeding times. Gingival bleeding, varying degrees of gingivitis and periodontitis are described.[20, 26]

Griscelli syndrome type 2 -Griscelli syndrome type 2 (also known as "Partial albinism with immunodeficiency") is a rare **autosomal recessive** syndrome characterized by variable pigmentary dilution, hair with silvery metallic sheen, frequent pyogenic infections, neutropenia, and thrombocytopenia. Affected individuals typically have delayed development, intellectual disability, seizures, weak muscle tone (hypotonia), and eye and vision abnormalities. These individuals are prone to recurrent infections due to defective immune system. They also develop hemophagocytic lymphohistiocytosis (HLH), in which the immune system produces too many activated immune cells called T-lymphocytes and macrophages (histiocytes). Overactivity of these cells can damage organs and tissues throughout the body, causing life-threatening complications if the condition is untreated.[23] Severe gingivitis leading on to periodontitis at young age and even total extraction has been reported.[26]

Wiskott-Aldrich syndrome(WAS) – This is an **X linked recessive disorder** of lymphocytes presents with thrombocytopenia, rarely neutropenia, defective cellular and humoral function and eczema.[8] IgM levels are reduced, Ig A and IgE are elevated and IgG levels can be normal, reduced or elevated. The classic form of WAS has a characteristic pattern of findings that include an increased tendency to bleed caused by a reduced number of platelets, bloody diarrhoea, recurrent bacterial, viral and fungal infections and eczema of the skin. The WAS is caused by mutations in the gene which produce a protein named the Wiskott - Aldrich syndrome Protein (WASP). Only boys are affected with this disease. There is mild to severe periodontitis with attachment and bone loss, can also cause Candidiasis, Herpes and ulcers.[7]

XL-dyskeratosis congenital (Hoyeraal- Hreidarsson syndrome) This disorder is an **autosomal dominant** caused by mutation of TINF2gene (604319) on chromosome 14q12. Dyskeratosis congenita (DC), a telomere biology disorder, is characterized by a classic triad of dysplastic nails, lacy reticular pigmentation of the upper chest and/or neck, and oral leukoplakia. People with DC are at increased risk for progressive bone marrow failure, myelodysplastic syndrome or acute myelogenous leukemia, solid tumors (usually squamous cell carcinoma of the head/neck or anogenital cancer), and pulmonary fibrosis. Other findings can include eye abnormalities, and dental abnormalities (caries, periodontal disease, taurodauntism). All the DKC patients had severe disease, with variable features of aplastic anemia, developmental delay, short stature, retinopathy, microcephaly, osteoporosis, cerebellar hypoplasia, alopecia, intracranial calcification, and tooth loss.[25]

Barth syndrome Barth syndrome (BTHS), also known as 3-Methylglutaconic aciduria type II, is an **X-linked** genetic disorder. The disorder, which affects multiple body systems, is found exclusively in males. Though not always present, the cardinal characteristics of this multi-system disorder including cardiomyopathy, neutropenia (chronic, cyclic or intermittent) underdeveloped skeletal musculature and muscle weakness, growth delay, exercise intolerance, cardiolipin abnormalities and 3-methylglutaconic aciduria. For many patients with cyclical neutropenia, there is a predictable pattern of oral ulcers, cervical lymphadenopathy (swollen lymph nodes in the neck) and painful gingivitis about every three weeks, coinciding with the low point in the neutropenic cycle. Gingivitis, periodontal disease, and the loss of permanent teeth are common problems across the spectrum of neutropenic syndromes.[26] Most patients with an absolute neutrophil count (ANC) persistently less than 500 have problems with gingivitis and increased periodontal disease, despite good efforts at oral hygiene.[34]

Cohen syndrome-Most studies have shown an **autosomal recessive** mode of inheritance in Cohen syndrome, but autosomal dominant is also possible. Cohen syndrome is characterised by obesity, hypotonia, mental retardation, narrow hands and feet, ocular abnormalities, and characteristic faces consisting of maxillary hypoplasia, open mouth, prominent central incisors, prominent palpebral fissures. Chronic neutropenia have been observed in most of the cases and resultant destructive periodontal disease has been reported with early tooth loss.[28]

Ataxia telengiectasia, ataxia- like syndrome, Nijmegen breakage syndrome, Bloom syndrome- Ataxia telangiectasia (A-T) (also referred to as Louis–Bar syndrome) is a rare, neurodegenerative, inherited in an **autosomal recessive pattern**, the disease causing severe disability. Mutations in the ATM gene cause ataxia-telangiectasia.[29] The ATM gene provides instructions for making a protein that helps control cell division and is involved in DNA repair which plays an important role in the development and activity of body systems, including the nervous system and immune system. Some have an increased number of respiratory tract infections and telangiectasia of the bulbar conjunctive, ears, nose, perioral

area and other skin surfaces. The immune system problems are caused by abnormalities in T cells and B cells. As a result, people with ataxia telangiectasia are more likely to get bacterial, fungal and viral infections. There have been reports of mild to severe gingivitis and periodontitis, also necrotising periodontitis has been reported.[7,8]

DiGeorge syndrome - 22q11.2 deletion syndrome which has several presentations including DiGeorge syndrome (DGS), DiGeorge anomaly, velo-cardio-facial syndrome, Shprintzen syndrome, conotruncal anomaly face syndrome, Strong syndrome, congenital thymic aplasia, and thymic hypoplasia, is a syndrome caused by the deletion of a small piece of chromosome 22 inherited from a parent as an **autosomal dominant** condition, commonly associated with T-lymphocyte immunodeficiency. B-lymphocyte defects also occur. Variable secondary humoral defects, including hypogammaglobulinemia and selective antibody deficiency, may be present. Various autoimmune diseases, including juvenile rheumatoid arthritis, idiopathic thrombocytopenic purpura, and autoimmune haemolytic anaemia, autoimmune uveitis, and severe eczema are more prevalent.[4] Small teeth with high arched and cleft palate and lips are found. The diminished B and T lymphocytes make them more susceptible to bacterial and fungal infections and hence variable degrees of gingival and periodontal disease.

Other types of neutropenias include chronic idiopathic neutropenia, autoimmune neutropenia, chronic benign neutropenia, as well as others. In addition diseases like Lupus erythematosus in which neutrophils are sequestered in tissue components resulting in reduction in circulating neutrophil count also contributes to rapidly destructive periodontal disease [30]. The other less common neutrophil disorders include myeloperoxidase deficiencies, non specific granulocyte deficiency, Felty syndrome, Cartilage hair hypoplasia, Pearsons syndrome and myelokathexis[22] also reveal the bone loss.

Myeloperoxidase deciency- Deficiency of myeloperoxidase is the most common inherited disorder, with half of them have complete deficiency of myeloperoxidase and the rest have structural or functional defects in the enzyme. Myeloperoxidase is the main component of azurophilic granules which catalyses the function of hypochlorous acid from hydrogen peroxide and chlorine ions. [3]

Non specific granule deficiency- Non specific granule deficiency is a rare but important disorder characterised by recurrent severe infections primarily of skin and lungs. The neutrophils of the affected patients lack specific granules, which have a role in inflammation. Neutrophils with deficiency of specific granules do not migrate normally with atypical nuclear morphology and also lack primary granule defensins and oesinophilic specific granules.[3]

Myelokathexis- Myelokathexis is a rare cause of severe neutropenia and occurs sporadically as an **autosomal dominant** disorder. The total leukocyte count is low, often less than 1.0x109 /L, with a blood neutrophil count less than 0.5 x109 /L. Marrow and blood neutrophils characteristically have very pyknotic nuclei and granulocyte hyperplasia occurs in the marrow.[3] This has been attributed to accelerated apoptosis of marrow neutrophils due to the abnormally decreased expression of the antiapoptopic protein.[3,25]

Felty syndrome (FS)- Felty's syndrome is a rare, potentially serious disorder that is defined by the presence of three conditions: rheumatoid arthritis (ra), an enlarged spleen (splenomegaly) and a decreased white blood cell count (neutropenia), which causes repeated infections. Although some individuals with Felty's syndrome are asymptomatic, others

can develop serious and life-threatening infections. Symptoms of felty's syndrome may include fatigue, fever, weight loss, discoloration of patches of skin, mild hepatomegaly (enlarged liver), lymphadenopathy (swelling of lymph nodes), Sjogren syndrome, vasculitis, lower-extremity ulcers, and other findings.[5] The exact cause is unknown, but several risk factors have been proposed, including autoimmunity. A few familial cases of the condition have been reported.

Schimke immuno-osseous dysplasia is a rare **autosomal-recessive** disease**,** is characterised by multi system medical problems including spondylo epiphyseal dysplasia in utero and post natal growth retardation, protenuria leading to nephrosis and renal failure, mild midfacial dysmorphism, lymphopenia, pancytopenia, defective cellular immunity, recurrent infections and also autoimmune disease.[37,38] Periodontitis is a common occurrence.

Pearson syndrome is a mitochondrial disorder characterized by transfusion-dependent sideroblastic anemia and pancreatic dysfunction resulting in in malabsorption and chronic diarrhoea. The features of this progressive disorder may change over time Pearson syndrome is caused by deletions in mitochondrial DNA[22]. Inheritance is usually sporadic.

Cartilage Hair Hypoplasia- Cartilage-hair hypoplasia is a disorder of bone growth characterized by short stature (dwarfism) with other skeletal abnormalities; fine, sparse hair (hypotrichosis); and abnormal immune system function (immune deficiency) that can lead to recurrent infections. The extent of the immune deficiency in cartilage-hair hypoplasia varies from mild to severe. Affected individuals with severe immune deficiency can develop life-threatening infections. These infections are often caused by common bacteria or viruses, and usually affect the respiratory system, ears, and sinuses.[39] Drugs that causes neutropenia include anticonvulsants- Carbamazepine, Phenytoin, Valproate; Immunosuppressants- Azathioprine, Cyclosporine, Mycophenolate mofetil, Sirolimus, Tacrolimus; Cortocosteroids- Methylprednisolone, Prednisone; Chemotherapy drugs and Immunosuppressants.[1,2]

Treatment In general, the dental treatment consists of scaling, root planning and extraction under corticosteroid and antibiotic cover. The effective way of prevention of oral side effects is an effective oral hygiene program with periodic assessment and regular professional hygiene together with a constant patient motivation for oral hygiene. Patients suffer from frequent periodontal infections in spite of efficient and effective oral hygiene. Invasive dental treatment should be avoided during the neutropenic episodes when oral ulcerations are likely to occur and the immune system is depressed. Twice a day mouth washes are advised to reduce plaque accumulation.

CONCLUSION

Neutropenia conditions can cause periodontal disease by the defective immune system. The various systemic and genetic factors causing this disorder may not be treatable and hence the progress of the periodontal disease is inevitable. The response to treatment is not always good and requires constant supervision and adequate maintenance treatment.

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