

Oral findings and clinical implications of patients with congenital neutropenia: a literature review

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Neutropenia is a granulocyte disorder characterized by a dramatically low number of neutrophils, the most important type of white blood cell. The condition results in susceptibility to severe pyogenic infections. Some people are born with it (congenital neutropenia), and others develop it as young children. The disease is so-called chronic neutropenia when lasting more than two months. This article reviews the definition, clinical properties and common oral manifestations of congenital neutropenia in order to highlight the importance of diagnosis, oral hygiene maintenance and dental treatments.

Key words: congenital neutropenia, dental care, children.

Dentists and dental hygienists play an important role in the early detection of systemic diseases due to initial signs seen in the oral cavity. In cases of abnormal loosening of teeth and periodontal breakdown without an apparent cause, the dental professional should consider the investigation of a variety of differential diagnoses and recommend further investigation¹.

In children, severe periodontitis is often observed as a manifestation of hematologic or genetic disorders, especially with acquired neutropenia, familial and cyclic neutropenia, Papillon-Lefèvre syndrome, Chédiak-Higashi syndrome, and Ehlers-Danlos syndrome^{2,3}. In hematologic disorders, defects in adhesion, chemotaxis, and phagocytic functions, as well as in the killing mechanisms of neutrophils, reduce the host response and predispose the patient to recurrent bacterial and fungal infections⁴. Those patients are at risk for periodontal diseases since there is a body of evidence that phagocytic cells, mainly polymorphonuclear neutrophils, are important in maintaining periodontal health.

Dental Literature To Date

A total of 16 articles were found in PubMed and Medline Databases with the key words “congenital neutropenia and dentistry” between 1976 and 2011⁵⁻¹⁹. Among these, 13 articles

were common in Medline and PubMed and an additional three articles appeared in the PubMed Database. One article is a review article⁸ related with Rothmund-Thomson syndrome, in which neutropenia was observed. Thirteen articles are case reports with 1-3 cases reported. One manuscript is an original study in which immunoassay and immunoblotting in plasma and gingival crevicular fluid were conducted in 14 patients with severe chronic or cyclic neutropenia harboring different genetic backgrounds. There is also a cross-sectional survey regarding the prevalence and severity of oral diseases in patients with Shwachman Diamond syndrome⁹.

Definition And Classification

Neutropenia (or granulocytopenia) is defined as a significant reduction in the absolute neutrophil count (ANC) of circulating neutrophils in the blood, which is calculated by multiplying the total blood cell count by the percentage of neutrophils plus bands noted in the differential cell count²⁰. Based on ANC, the disease has been subclassified as mild (ANC: 1,000 - 1,500/mm³), moderate (ANC: 500 - 1,000/mm³), or severe (ANC: <500/mm³)^{20,21}. The leukopenic pattern was defined as fewer white blood cells²². As for the etiology, several factors are mentioned. Decreased bone marrow production, increased destruction by

immune mechanisms and increased clearance by the reticuloendothelial system are among the causes of neutropenia. Additionally, most patients have secondary neutropenia caused by infections, drugs, malignancy, or hypersplenism²³. A few syndromes, such as Fanconi, Rothmund-Thomson and Shwachman-Diamond syndromes, are also accompanied by neutropenia. Shwachman-Diamond is an autosomal recessive syndrome characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, leukemia predisposition, and skeletal abnormalities. Most people with this syndrome have at least occasional episodes of neutropenia.

When molecular mechanisms are considered, neutropenia has been classified as:

(i) Neutropenia with no extra-hematopoietic manifestations and with normal adaptive immunity (Permanent and cyclic neutropenia, Extracellular granulocyte colony-stimulating factor [G-CSF] receptor defects)

(ii) Congenital neutropenia with extra-hematopoietic manifestations (Neutropenia associated with GFI1 mutations, Permanent congenital neutropenia due to Wiskott-Aldrich syndrome (WAS) gene mutation, neutropenia associated with IRAK 4 mutations)

(iii) Syndromes into disorders of ribosomal dysfunction (Shwachman-Diamond syndrome, Dyskeratosis congenita)

(iv) Disorders of metabolism (Barth syndrome, Glycogen storage disease type 1b, Pearson's syndrome),

(v) Disorders of vesicular transport (Chédiak-Higashi syndrome, Cohen syndrome, Griscelli syndrome, Hermansky-Pudlak syndrome type II, p14 Deficiency), and

(vi) Disorders of immune function (Cartilage-hair hypoplasia, Hyper-immunoglobulin (Ig) M syndrome, Schimke immuno-osseous dysplasia)^{24,25}.

Cyclic (periodic) neutropenia is a rare disease characterized by cyclical depression of the peripheral blood polymorphonuclear leukocyte (PMNL) count at 21-day intervals²⁶⁻²⁸. Although cyclic neutropenia usually manifests initially in infancy or childhood^{28,29}, it may also appear in adulthood³⁰. There may be a familial tendency²⁷. Sex predilection for childhood neutropenia

may be familial, but is generally independent of gender, as shown by one report on cyclic neutropenics with 21 of 39 cases being female³¹.

Congenital neutropenias are relatively uncommon. Severe congenital neutropenia (SCN), a disorder of myelopoiesis, is characterized by an impairment of myeloid differentiation in bone marrow with ANC's <200 cells/4 ml in the blood of affected patients. Described by Kostmann in 1956, SCN is also referred to as Kostmann syndrome³². Patients with SCN experience frequent episodes of fever, pneumonitis, skin infections, and perianal and liver abscesses, usually beginning in early infancy and often leading to fatal infections despite antibiotic therapy^{32,33}.

Neutropenia is called "severe" when neutrophils are below $0.5 \times 10^9/L$ and "chronic" if the condition lasts more than three months, either intermittent or permanent²⁵. Chronic neutropenia is defined as a low ANC for more than three months. When there is no underlying disease to which the neutropenia can be attributed, chronic neutropenia is designated as chronic benign neutropenia.

Medications And Treatment

Various therapeutics, including antimicrobial and antifungal prophylactic treatments, are used in the treatment of severe neutropenia patients throughout their lifetime. Prophylactic antibiotics, corticosteroids, androgens, splenectomy, or cytotoxic therapy have all been recommended³⁴. The ideal prophylactic antimicrobial regimen will be effective against the pathogens most frequently encountered in this setting and well-tolerated. Thus, the best antibiotic is the oral sulfamethoxazole/trimethoprim combination at a daily dose of 50 mg/kg. On the other hand, in chronic neutropenia, the use of this drug may appear paradoxical since it can occasionally cause neutropenia³⁵. Yet, the risk-benefit ratio remains favorable.

Recently, hematopoietic growth factors produced by genetic engineering (recombinant human G-CSF) are considered to be a potential effective therapy for promoting granulopoiesis and in turn elevating the circulating neutrophil count³⁶⁻³⁸. The biological effects of G-CSF are mediated via binding to high-affinity specific receptors mainly on the surface of

neutrophils^{39,40}. The recombinant protein helps in releasing the neutrophil reservoirs from the bone marrow to the peripheral bloodstream; thus, the neutrophil count is elevated 10-12-fold. It is known that a dose of 1-5 $\mu\text{g/kg/d}$ G-CSF has been used (<15 days) in more than a million child and adult cancer patients receiving chemotherapy, with good or excellent tolerability²⁵. Treatment with G-CSF is expected to prolong the life expectancy of congenital neutropenia patients. In addition, the agent significantly reduces the severity of gingivitis, periodontitis, and oral ulcerations¹⁸. Hematopoietic stem cell transplantation (HSCT) can permanently correct the neutropenia, and is the sole option for patients who experience severe infections despite G-CSF therapy²⁵.

Oral Signs, Symptoms And Treatment

The lack of host response in individuals with congenital neutropenia can obstruct the interaction between the host and the microbiotic flora. Thus, the lack of neutrophils increases the risk of infections, as well as of periodontitis⁴¹. It has been reported that periodontitis is the most typical infection in neutropenic patients along with stomatitis, otitis media, cutaneous cellulitis and abscess, furunculosis, pneumonia, and respiratory infections³⁴.

Recurrent, painful oral ulceration and prominent generalized periodontal destruction are common oral features of neutrophil disorders, and they may even be the initial symptoms of the disease^{42,43}. In fact, it has been reported that oral ulceration is the only manifestation in about 20% of patients with cyclic neutropenia⁴⁴. The ulcers may affect any part of the oral mucosa including the tongue and palate. They are similar to major aphthous ulcers, cause distress, and heal with scarring in about 14 days^{45,46}. In cyclic neutropenia, an unusual form of ulcerative gingivitis associated with gingival ecchymoses has also been reported by Wade and Stafford⁴⁵.

Severe and diffuse gingival inflammation, tooth mobility, alveolar bone loss, and early tooth loss in both dentitions are also common features in neutropenia⁴⁷⁻⁴⁹ (Figs. 1, 2). The pattern of breakdown is similar to the prepubertal periodontitis described by Lindhe⁵⁰. In most of



Fig. 1. Intraoral photograph of a patient suffering from chronic neutropenia.

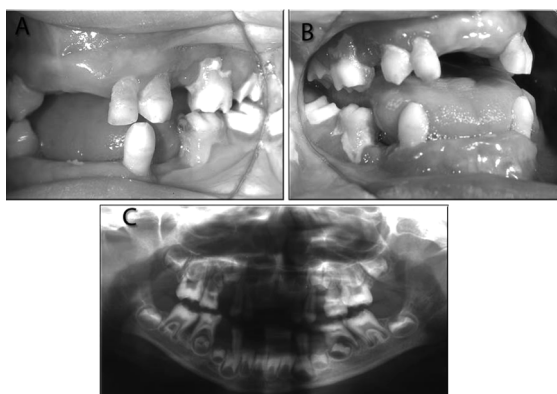


Fig. 2. A-B) Severe attachment loss and moderate amount of dental plaque around the teeth were seen. Note the early loss of multiple primary teeth. C) Panoramic radiograph showing alveolar bone loss affecting nearly all teeth present.

the reported cases, the attached, papillary and marginal gingivae were enlarged, edematous and erythematous, with bleeding on probing. Severe chronic neutropenia causes more destruction in the periodontium. In general, dental treatment consisted of scaling, root planning and extraction under corticosteroid and antibiotic cover. Some authors reported premature eruption of anterior permanent teeth due to extraction of predecessors¹².

The most effective way to prevent oral side effects is an effective oral hygiene program with periodic assessments and regular professional hygiene, together with a constant patient motivation for oral hygiene⁴⁷. Yamalik et al.⁵¹ documented a case of congenital neutropenia in which thorough scaling and oral hygiene procedures resolved the gingival inflammation. Similar to that case, Buduneli et al.¹⁰ reported

another one emphasizing the importance of non-surgical periodontal treatment. Furthermore, Goultschin et al.¹⁷ and Tözüm et al.¹⁴ reported that regular follow-up visits with plaque control could improve not only the dental health but also the systemic condition without application of G-CSF.

On the other hand, although the prognosis and quality of life of patients with congenital neutropenia have been dramatically improved with G-CSF therapy, some patients still suffer from frequent periodontal infections despite efficient and adequate oral hygiene. A recent study demonstrated a correlation between ELANE mutations and periodontitis in patients with severe chronic neutropenia, verifying the view that ELANE mutations are correlated with more severe disease manifestations and a relatively poorer response to G-CSF treatment⁵.

When treating patients with neutropenia, invasive dental treatment should be avoided during the neutropenic episodes when oral ulceration is most likely to occur and defenses are maximally suppressed. Oral surgery should be accompanied by an appropriate bactericidal antibiotic, and in addition, a suitable corticosteroid cover is needed during dental treatment, especially in the management of cyclic neutropenia⁵². In order to reduce dental plaque accumulation and dental caries, rinsing with 0.2% chlorhexidine digluconate twice daily may be recommended⁸⁻¹².

Conclusion

Congenital neutropenias are among the systemic conditions associated with periodontitis, early tooth loss and/or generalized carious lesions in children. In those patients, invasive dental treatment should be postponed during the neutropenic episodes when host defenses are reduced. Oral surgery should be combined with an appropriate bactericidal antibiotic therapy, and with the recent advent of corticosteroid therapy in the management of neutropenia, suitable corticosteroid cover is needed during dental treatment⁵².

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