Dental Findings and Treatment in Consanguinity Associated Congenital Chronic Familial Neutropenia

Nurcan Buduneli* / Dilsah Cogulu** / Levent Kardesler*** / Necil Kütükçüler*****

The purpose of this report is to describe dental findings and treatment of an 11-year old male patient and a 5-year old female patient, children of first cousins, suffering from severe benign congenital chronic familial neutropenia. This case report emphazises the importance of differential diagnosis of immunodeficiencies including congenital chronic familial neutropenia in the background of severe periodontal diseases and/or diffuse carious lesions in children.
Key words: *congenital chronic familial neutropenia, dental treatment, neutrophil defects, immunodeficiency*
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INTRODUCTION

A number of systemic factors have been documented as being capable of affecting the periodontium and/or treatment of periodontal diseases. Severe periodontal disease in children is frequently associated with congenital defects of haematological and/or immunological origin. Papillon-Lefevre syndrome, Langerhans cell histiocytosis, Chediak-Higashi syndrome, hypophosphatasia, neutropenia, and especially leukocyte adhesion defects are well known to be among these systemic conditions.[1-3] There is sufficient evidence that phagocytic cells, mainly polymorphonuclear neutrophils, are important in maintaining periodontal health. Besides adhesion, chemotaxis, and phagocytic functions, defects may be present in the killing mechanisms of neutrophils reducing the host response and predisposing to recurrent severe bacterial and fungal infections.[2] In addition to bacterial and fungal infections, progressive periodontitis frequently develops in patients with chronic neutropenia who survive infancy.[3]

Neutropenia is defined as a peripheral blood absolute neutrophil count (ANC) of less than 1500/ml.[4] Several factors may cause neutropenia, including decreased bone marrow production, increased destruction by immune mechanisms and increased clearance by reticuloendothelial system. Most patients have secondary neutropenia caused by infections, drugs, malignancy or hypersplenism. Congenital neutropenias are relatively uncommon. Severe congenital neutropenia which is an inborn defect characterized by a neutrophil cell-line specific impairment was defined by Kostmann.[5] Severe congenital neutropenia (Kostmann syndrome) is caused by a defect in the maturation process of neutrophilic precursors at the myeloid stage in bone marrow and life-threatening pyogenic infections in the respiratory and gastrointestinal tract, genitourinary system, and skin are frequently observed. The estimated frequency of this disorder is approximately one to two cases per million with equal distribution for gender.[6] Other than Kostmann syndrome, there are a few more forms of congenital neutropenia such as "congenital chronic familial neutropenia".

All patients with severe neutropenia (ANC below 500 cells/ml) have to take antimicrobial and antifungal prophylactic treatments throughout their lifetime. Main components of this treatment are oral trimethoprim-sulphamethoxazole (TMP-SMX) and itraconazole in prophylactic doses. However, management of neutropenia includes use of recombinant human granulocyte colony-stimulating factor (rhG-CSF), a glycoprotein which stimulates the survival, proliferation, differentiation, and function of neutrophil granulocyte progenitor cells and mature neutrophils. The recombinant protein resembles the natural factor, releasing the neutrophil reservoirs from the bone marrow to the peripheral bloodstream, thus elevating the neutrophil count 10 to 12-fold. Treatment with rhG-CSF prolongs life expectancy of congenital neutropenia patients and often reduces significantly the severity of gingivitis, periodontitis, and oral ulcerations.[7-9]

Various oral features including gingival inflammation, gingival recession, tooth mobility, alveolar bone loss and early tooth loss that may affect both primary and permanent dentitions are frequently encountered in neutropenia.[7] Neutropenic ulceration is also common and may develop as the only major clinical manifestation.[10]

The purpose of this report is to describe dental findings and treatment of an 11-year old male and a 5-year old female patient, children of first cousins, suffering from congenital chronic familial neutropenia.

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CASE DESCRIPTIONS

Case 1

An 11-year old Caucasian male patient was referred by his Pediatrician to the Periodontology Department, School of Dentistry, Ege University. At his initial dental examination severe gingival inflammation and pronounced marginal erythema were observed (Figure 1a). Furcation lesions and alveolar bone loss were detected in the mandibular first molar teeth (Figure 1b). According to the clinical and radiological evaluations, the periodontal diagnosis was localized periodontitis with generalized gingivitis. No carious lesions were detected. His dental and medical history was remarkable with recurrent severe infections. In his family background, consanguinity as first cousins existed between his parents and he was the only child of the family. None of his parents had a specific disease. His past history revealed abscess, granuloma formations in his lower extremities, and twice a diagnosis of pneumonia, anti-tuberculosis treatment and hospitalization three times.

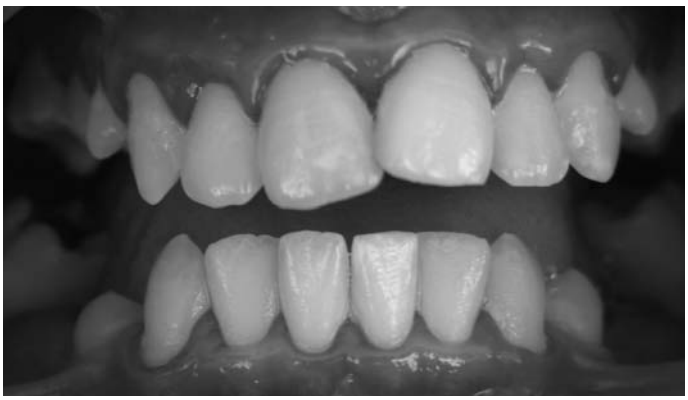

FIGURE 1a: Oral findings in the 11-year old boy suffering from congenital chronic familial neutropenia. Note the severe gingival inflammation.

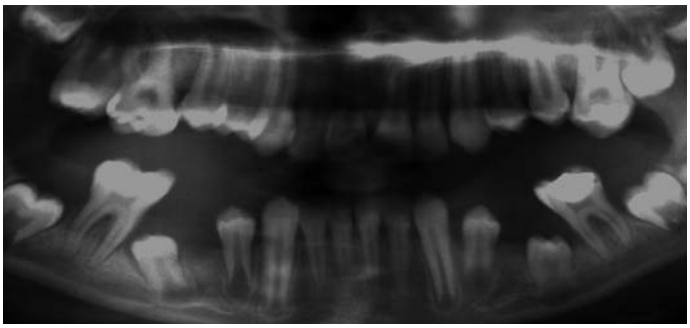

FIGURE 1b: Panoramic radiograph of the male patient. Note the furcation lesions and alveolar bone loss in the mandibular first molars.

Case 2

A 5-year old Caucasian female patient with signs of severe gingival inflammation and recurrent oral ulceration was also referred by the same Pediatrician. These two patients were children of first cousins. At her initial dental examination, all of the primary teeth were present and the first permanent molars were erupting (Figure. 2a). There was a deep ulceration on her tongue approximately 10 mm in diameter (Figure 2b). Panoramic and periapical radiographs revealed carious lesions in 16 primary teeth. On the other hand, no sign of alveolar bone loss was present (Figure 2c) and the periodontal diagnosis was gingivitis. She was the only child of her family and her parents were systemically healthy.

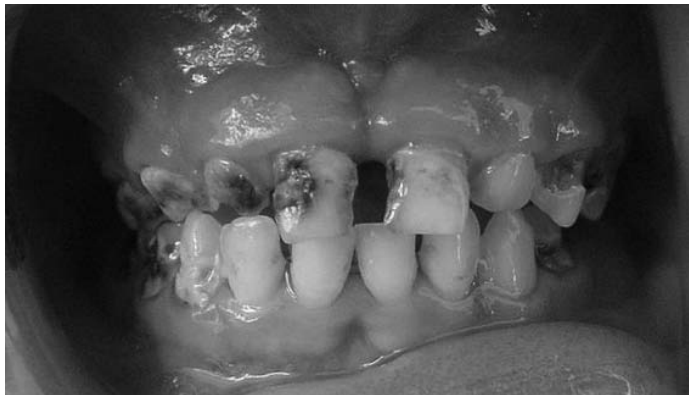

FIGURE 2a: Oral findings in the 5-year old female patient. Mild gingivitis and generalised carious lesions were evident.

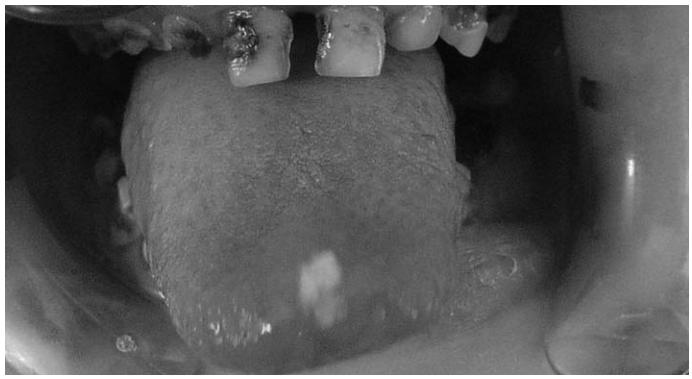

FIGURE 2b: Ulcer on the tongue.

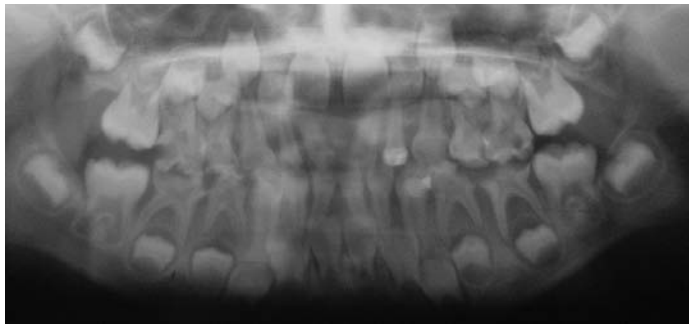

FIGURE 2c: Panoramic radiograph of the female patient. No sign of alveolar bone resorption was evident.

Complete oral examination was undertaken in both children and plaque index (PI)[11], papilla bleeding index (PBI)[12], probing depth (PPD) were recorded at six sites per tooth (Table 1).

The haematological findings of both children are outlined in Table 2. Differential diagnosis for various phagocytic disorders was performed. Leukocyte adhesion deficiency was ruled out, because CD11a and CD18 on neutrophils were normal in both patients. Papillon-Lefevre syndrome was also ruled out, as the patients presented no evidence of hyperkeratosis on their hands, elbows, knees, or feet. On the basis of the children's past history, family history, clinical investigations, bone marrow aspiration findings and ANC in peripheral blood, the patients were diagnosed as having congenital chronic familial neutropenia. Kostmann syndrome was excluded, because of late onset of infections, and consanguinity between the patients. The infections observed in these patients were not so severe and there was still no need for G-CSF therapy. Both of the patients

TABLE 1: Mean values of clinical measurements

	PI (0-3)	PD (range)	PBI (0-4)
Male patient	1.9	3.05 (2-5)	3.1
Female patient	2.1	2.13 (2-4)	2.7

PI: Plaque Index; PD: Probing pocket depth (mm); PBI: Papilla Bleeding Index

TABLE 2: Results of blood tests

	Male patient	Female patient
WBC	5,720 / mm^3	3,460 / mm^3
RBC	4,440,000/ mm^3	4,200,000/ mm^3
Hb	11,7 g / dl	10,5 g / dl
Hct	34,6 %	31,1 %
Neutrophils	4 %	2 %
ANC	208/µl	68/µl
Lymphocytes	68 %	76 %
Monocytes	22 %	18 %
Eosinophiles	6 %	4 %
Bone marrow aspiration	Myelopoiesis is left-shifted, rarely mature segmented neutrophils, no increase in blasts	Myelopoiesis is left-shifted, hyper-cellular, myelocytes were mostly promyelocytes, lymphoid cell lines 15 %, monocytic cell lines 10 %

WBC: white blood cells; RBC: red blood cells; Hb: haemoglobin; Hct: haemotocrit; MCV: mean corpuscular volume; ANC: absolute neutrophil count.

were registered to SCNIR (Severe Chronic Neutropenia International Registry) coordinated by EWOG MDS (European Working Group on Myelodysplastic Syndromes in Childhood, Freiburg, Germany) and after examination of their peripheral blood and bone marrow aspiration smears, experts in EWOG MDS confirmed the diagnoses as "congenital chronic familial neutropenia". Trimethoprim-sulfamethoxazole (TMP-SMX) with a daily dosage of 2 mg/kg TMP and flucanasole with a dosage of 1-2 mg/kg were administered as prophylactic treatment.

In the male patient, periodontal treatment including oral hygiene instructions, scaling and root planing was performed. The female patient received scaling as initial periodontal therapy. Considering the continuing development of the jaws, carious teeth were restored with compomer, whereas teeth with poor prognosis (tooth numbers; 53, 54, 55, 64, 65, 74, 75, 84, 85) were extracted and space maintainers in the form of removable partial prosthesis were constructed for upper and lower jaws. The two children and their mothers were instructed on improving oral hygiene and sucrose intake was limited for prevention of caries.

In order to be able to determine any further dental-periodontal pathology in the permanent dentition, a close monitoring of both patients from a dental point of view was considered to be mandatory. Topical fluoride was applied and the patients were scheduled for regular fluoride applications every 6-months. Both patients are now on a regular maintenance program with one-month intervals. Six-month follow-up of the patients revealed good maintenance (Figure 3a, b).

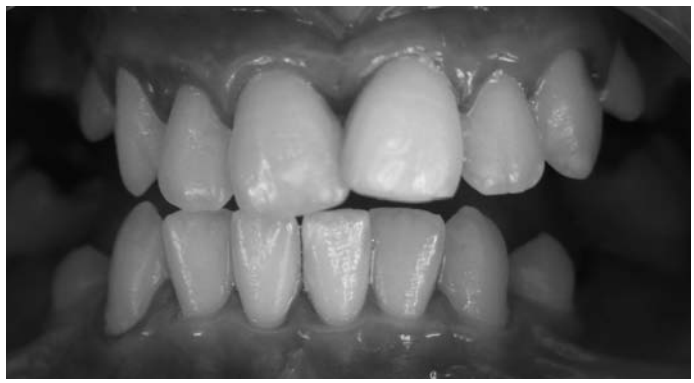

FIGURE 3a: Oral findings of the male patient 6 months after the completion of periodontal treatment.

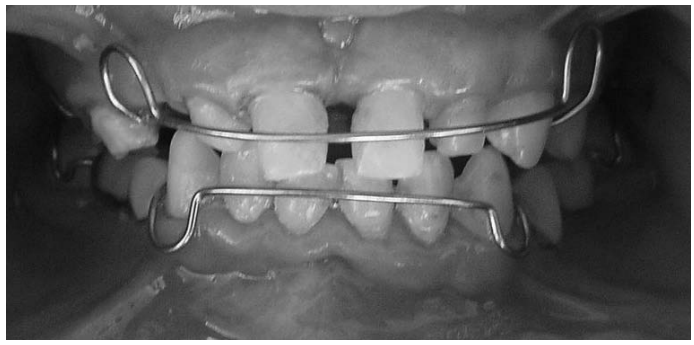

FIGURE 3b: Oral findings of the female patient 6 months after completion of periodontal treatment, compomer restorations, tooth extractions and application of space maintainers.

DISCUSSION

Polymorphonuclear leukocytes (PMNLs) are produced in the bone marrow, complete their maturation, and sway to systemic circulation. PMNLs are present in gingival connective tissue, junctional epithelium, and gingival sulcus forming the first line of host response to the pathogens in microbial dental plaque. Prevalence of periodontitis under the age of 15 varies in different populations from 0.1% to 11%[1] and periodontitis is among the most typical infections in neutropenic patients together with otitis media, cutaneous cellulitis and abscess, furunculitis, pneumonia, respiratory infections, and stomatitis.[13] Leukocyte abnormalities are highly prevalent in children with severe oral diseases like periodontitis and a history of recurrent infections due to an impaired host response. Defraia and Marinelli[14] reported severe periodontal pathology similar to aggressive periodontitis in the primary dentition as a characteristic finding in Kostmann syndrome. Congenital neutropenia affecting <0.01 % of the population is often associated with recurrent upper and lower respiratory tract infections, oral ulcers and stomatitis and sometimes with infantile osteoporosis and bone fractures.[15] Nonetheless, the exact pathogenic mechanisms remain unclear.

Our present cases were children of first cousins where consanguinity between parents is among the major risk factors in the aetiology of immunodeficiencies like congenital chronic neutropenias since these diseases are genetically transmitted. Therefore, informing the society about these severe diseases and discouraging consanguineous marriages is extremely important.

Dental findings like severe periodontitis may sometimes be the pioneering sign of severe neutropenia. Accordingly, Hakkı *et al.*[16] reported two siblings with severe periodontitis who were subsequently diagnosed with severe congenital neutropenia and emphasized the role of periodontists in the diagnosis of diseases linked with neutrophil and other systemic disorders. The authors also stressed on the importance of reducing microbial dental plaque accumulation in patients with haematological and genetic disorders. The therapeutic goal in the patient with contributing systemic factors is to achieve a degree of periodontal health consistent with the patient's overall health status. The treatment outcome of periodontal therapy may be directly affected by the control of the systemic condition. Previous reports have demonstrated that patients with mild to severe neutropenia respond well to periodontal treatment.[9,17]

Due to the number of teeth involved and the age of onset, our male patient was diagnosed as having localized periodontitis with generalized gingivitis, whereas our female patient was diagnosed as having solely generalized gingivitis. Medical tests revealed the only immunodeficiency sign as the extremely low number of neutrophils. Their oral and dental symptoms were highly recovered after periodontal treatment although they have not received G-CSF therapy. Yamalık *et al.*[18] documented a case of congenital neutropenia in which thorough scaling and oral hygiene procedures resulted in a resolution of gingival inflammation. Furthermore, Goultschin *et al.* 9 and Tözüm *et al.*[19] reported that regular follow-up visits resulting in improved plaque control could improve not only the dental health but also the systemic condition without application of G-CSF. Our present cases responded well to the non-surgical periodontal treatment and therefore, provide further support for the findings reported previously.

In conclusion, we suggest that congenital neutropenias such as congenital chronic familial neutropenia should be included among the systemic conditions associated with periodontitis and/or generalized carious lesions in children and have to be considered for differential diagnosis. Idiopathic localized aggressive periodontitis cases have been reported in the literature and the present report suggests that congenital chronic familial neutropenia should be searched in the background of such cases.

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