



Christine Casey

Tony Brooke, Rebecca Davies and Deborah Franklin

Case Report of a Family with Benign Familial Neutropenia and the Implications for the General Dental Practitioner

Abstract: Benign familial neutropenia (BFN) is a condition where there is a decrease in circulating neutrophils in the blood and patients suffer from oral manifestations which include: persistent periodontal disease, recurrent neutropenic ulceration and candidal infections. This report discusses a family affected by BFN and the effects on their oral health.

Clinical Relevance: Benign familial neutropenia is a rare condition and this article aims to raise awareness among general dental practitioners so that prompt referral and management in secondary care can be arranged.

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The different types of neutropenia can be divided up into the following groups:

- Neutropenias present at birth: severe congenital neutropenia and cyclic neutropenia;
- Metabolic diseases associated with neutropenia: glycogen storage disease type 1b;
- Neutropenias that are acquired during life: idiopathic and autoimmune neutropenias.

The incidence of BFN is thought to be around 3-4 cases per million per year. The incidence of drug-induced neutropenia for comparison is about one case per

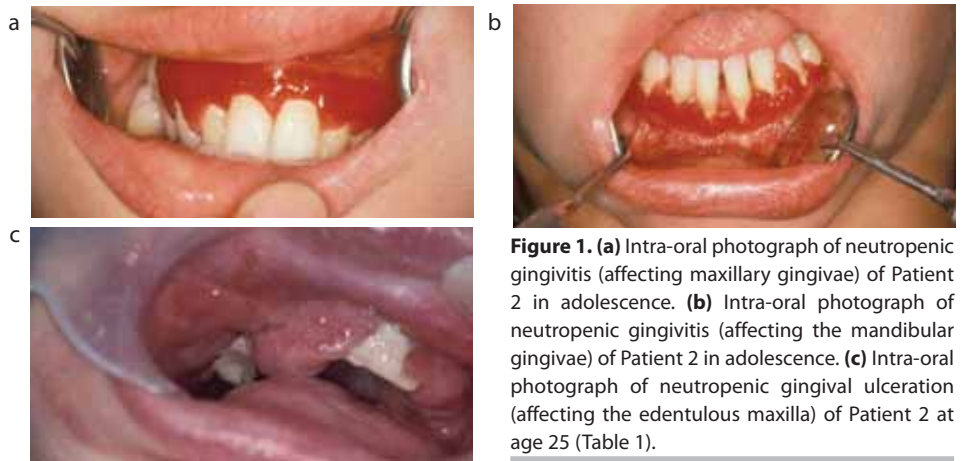


Figure 1. (a) Intra-oral photograph of neutropenic gingivitis (affecting maxillary gingivae) of Patient 2 in adolescence. (b) Intra-oral photograph of neutropenic gingivitis (affecting the mandibular gingivae) of Patient 2 in adolescence. (c) Intra-oral photograph of neutropenic gingival ulceration (affecting the edentulous maxilla) of Patient 2 at age 25 (Table 1).

Christine Casey, Senior House Officer, Department of Child Dental Health, **Tony Brooke**, Associate Specialist, Department of Oral Medicine, **Rebecca Davies**, Specialist Registrar in Maxillofacial Radiology and **Deborah Franklin**, Consultant in Paediatric Dentistry, Department of Child Dental Health, Bristol Dental Hospital, Lower Maudlin Street, Bristol BS1 2LY, UK.

million per year.¹

Neutropenias are defined by an acute or chronic decrease in the peripheral blood neutrophil count, resulting in the individual being more susceptible to opportunistic infections. These may not last long in nature, when treated early and controlled by the appropriate antimicrobial or antifungal therapy, however, if the neutropenia is profound and there is a delay in the acute management of these infective

episodes, then the patient faces a possible life-threatening situation.

The oral manifestations of neutropenias include:

- Mucosal ulceration;
- Angular stomatitis;
- Increased susceptibility to periodontal disease; and
- Early tooth loss (Figure 1).

The mucosal tissues are affected by characteristic neutropenic ulcers

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex	Female	Female	Male	Male	Female
Age	48	25	19	6	4
Relationship	Mother of Cases 2 and 3	Mother of Cases 4 and 5	Brother of Case 2	Son of Case 2	Daughter of Case 2
Medical History	BFN	BFN	BFN,	BFN , Subaortic stenosis	BFN
Complaints	Poor fit of dentures	Mouth ulcers, poor fit of dentures	Mouth ulcers, mobile teeth, bleeding gums	Mouth ulcers, stained teeth, red gums	Mouth ulcers, red gums
Main Problems	Denture retention	Neutropenic ulceration	Severe periodontitis Neutropenic ulceration	Neutropenic ulceration Severe periodontitis	Severe periodontitis
Dental State	Edentulous	Edentulous	Dentate (with the exception of 6s)	Mixed dentition (6s are erupted)	Deciduous dentition
Differential Diagnosis	N/A	Juvenile Periodontitis, Papillon-Lefevre syndrome and Haim- Munk syndrome (the periodontal disease is less severe than in Papillon-Lefevre) ⁴			
Treatment Modalities	Full clearance age 14	Full clearance age 15	Intensive oral hygiene support	Oral hygiene support	G-CSF (granulocyte-colony stimulating factor), oral hygiene support
Treatment Plan	Complete dentures	Complete dentures	Periodontal treatment	Periodontal treatment	G-CSF
Radiographs	N/A	DPT age 10 DPT age 13 DPT age 14	DPT age 15 DPT age 20	Lateral Obliques age 4	Lateral Obliques age 3
Radiographic Findings	N/A	Bone loss in all quadrants. Furcation involvement in the molar region, bone loss in the anterior dentition ranging from 40–80%.	Generalized horizontal bone loss, abnormal for this age. Bone loss is seen in the second molars (greater than 50%) and furcation involvement present in all quadrants.	Shows evidence of periodontal bone loss posteriorly with furcation involvement seen in the primary molars.	Pronounced bone loss posteriorly in all quadrants with furcation involvement in the primary molars.
Conclusions	Early tooth loss precipitated by periodontal disease	Consistent with the differential diagnosis above and support a diagnosis of chronic familial neutropenia.	Progressive advanced periodontal bone loss in the incisor/ molar regions. Features consistent with chronic familial neutropenia.	Consistent with the differential diagnosis above and supports a diagnosis of chronic familial neutropenia.	Consistent with the differential diagnosis above and supports a diagnosis of chronic familial neutropenia.

Table 1. Family with benign familial neutropenia.

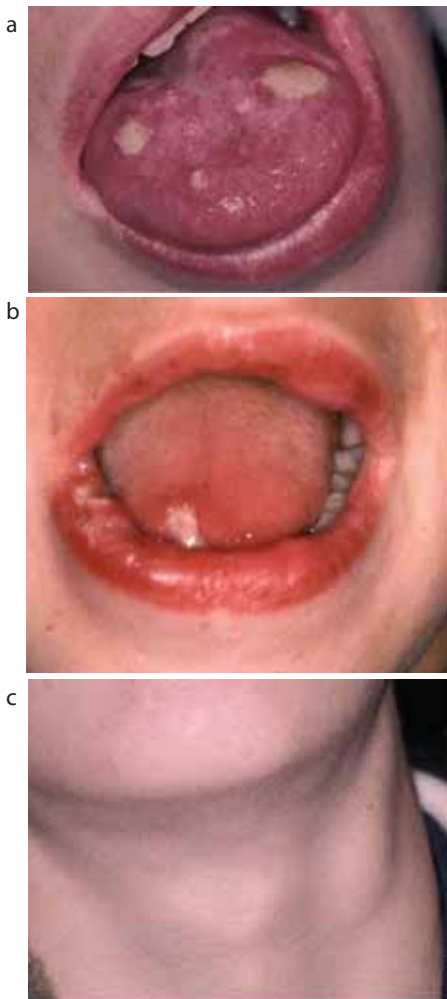


Figure 2. (a) Intra-oral photograph with neutropenic ulcers on tongue and lips of Patient 3. (b) Intra-oral photograph of neutropenic ulceration on the tongue of Patient 3. (c) Cervical lymphadenopathy secondary to neutropenic ulcers on tongue of Patient 3 (Table 1).

on the tongue and lips and cervical lymphadenopathy secondary to the ulceration (Figure 2). The neutropenic gingivitis is seen in its earliest manifestation in children affected by BFN (Figures 3 and 4). There can also be systemic manifestations which can include recurrent chest infections and skin infections. These manifestations can be seen either together or independently of each other.²

There have been a number of case reports on cyclic neutropenia and its effects on oral health but very few of benign familial neutropenia³ (Table 1).

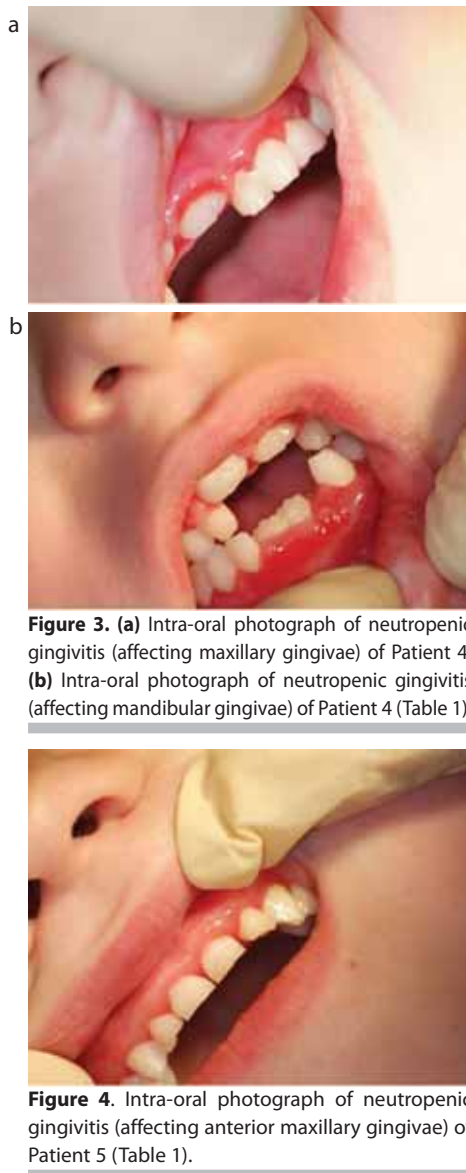


Figure 3. (a) Intra-oral photograph of neutropenic gingivitis (affecting maxillary gingivae) of Patient 4. (b) Intra-oral photograph of neutropenic gingivitis (affecting mandibular gingivae) of Patient 4 (Table 1).

Figure 4. Intra-oral photograph of neutropenic gingivitis (affecting anterior maxillary gingivae) of Patient 5 (Table 1).

Discussion

There are many causes of neutropenia, with drug-induced and autoimmune being the most commonly recognized. Primary neutropenias are uncommon and the benign familial variety is recognized as an autosomal dominant disorder. It is thought to be observed more commonly in Afro Caribbeans, West Indians, Arab Jordanians and in groups within the Jewish population.⁴ In our case study, all the patients were Caucasian. There is a paper describing severe congenital neutropenia, also known as Kostmann syndrome, which is reported as an autosomal recessive

disease of neutrophil production.⁵

Benign familial neutropenia is characterized by a low total leukocyte count, consistent neutropenia and a relative monocytosis, and lymphocytosis with occasional eosinophilia.⁶ There is no sign of anaemia or thrombocytopenia.² The oral symptoms are also persistent, unlike those seen in cyclic neutropenia which present in episodes. The condition predisposes to bacterial infections of the mucosal and skin surfaces, with the risk of infection said to be more likely when the neutrophil count falls below $0.5 \times 10^9 / \text{mm}^3$.^{3,2}

There has been some work which examined neutrophil function in patients with periodontal disease of differing severity.⁷ The neutrophil levels were obtained from heparinized peripheral blood. The results showed that neutrophil phagocytosis in rapidly progressing periodontitis was depressed. Neutrophil abnormalities may lead to a decreased resistance to periodontal infections. If a patient presents with low neutrophil counts, then this suggests that his/her resistance to periodontal disease will be low, as seen in the above cases. Furthermore, other studies have shown that normal levels of neutrophils collected in sites of disease are either exhausted by the numbers of bacteria, or are inhibited by bacteria.⁸ In cases where neutrophil numbers are reduced in the first place, resistance to disease is unlikely.

The patients affected by this condition have a good prognosis, in general requiring prompt treatment of infections and frequent professional hygiene therapy. This can sometimes prove difficult to maintain, with the background of systemic illness of some patients and the lack of compliance with numerous dental appointments. Those with very severe neutropenias can be prescribed steroid therapy over short periods of time. The affected individuals have a normal life expectancy.⁶ Some patients can be asymptomatic in terms of their oral health but most suffer with the characteristic oral conditions.⁵ There appears to be so little data on their condition that it is unclear, whether topical or systemic, antibiotic therapy might work well as an adjunct to excellent oral hygiene.¹ It was concluded in one article of long-term follow-up of three siblings that scaling, surgery and the

use of topical antimicrobial agents may be successful, therefore not making them candidates for full mouth extraction.⁷

There has been some encouraging news that it may be possible to use G-CSF (granulocyte-colony stimulating factor) to treat oral mucosal conditions, but this remains to be established.⁹ It is hoped that the use of G-CSF alongside oral hygiene care regimes will be an established treatment plan in the future for those suffering with chronic severe neutropenia and thus benign familial neutropenia.¹⁰ An ideal treatment regime has been suggested in the meantime which includes:

- Prevention and control of infection;
- Daily applications of 0.4% stannous fluoride gel;
- Periodontal therapy;
- Diet advice; and
- A rinse with a phenolated antiseptic mouthwash prior to soft tissue dental manipulations.¹¹

This paper suggests that periodontal therapy should be palliative and that surgery is contra-indicated. This is owing to the high risk of postoperative infection. If surgery is indicated, then it is suggested that it should be done in hospital with the use of adjunctive antibiotics, and that wound healing will progress even with low/absent neutrophils, as long as infection is prevented.¹¹ This contradicts Kirstila *et al* who suggested that surgery is a perfectly reasonable option to prevent loss of teeth.⁹

Advice for General Dental Practitioners

It is important with all presenting conditions that a wide provisional diagnosis list is drawn up and that any unusual presentations are referred promptly for opinion and/or management. In these particular circumstances, the importance of taking a sound family history when presented with such cases is the key to competent management.

Conclusion

It is hoped that this case report will underline the importance of the joint role of the medical and dental professions in providing care and the roles within the dental profession of the paediatric dentists and periodontologists in stabilizing/ maintaining the oral health of this group of patients.

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Cochrane Synopses

PIT AND FISSURE SEALANTS VERSUS FLUORIDE VARNISHES FOR PREVENTING DENTAL DECAY IN CHILDREN AND ADOLESCENTS

(NO CHANGE TO CONCLUSIONS)

Hiiri A, Ahovuo-Saloranta A, Nordblad A, Mäkelä M. Pit and fissure sealants versus fluoride varnishes for preventing dental decay in children and adolescents. Cochrane Database of Systematic Reviews 2010, Issue 3. Art. No.: CD003067. DOI: 10.1002/14651858.CD003067.pub3

‘Dental sealants reduce more tooth decay in the grooves of back teeth in children than fluoride varnish application but the number of studies supporting this evidence is very low. Therefore, more high

quality research is needed.

Sealants are coatings applied by the dentist or by another person in dental care on the grooves of back teeth. These coatings are intended to prevent decay in the grooves of back teeth.

Fluoride varnishes are sticky pastes that are professionally applied on teeth at a frequency of two to four times a year.’

INTERVENTIONS FOR REPLACING MISSING TEETH: ANTIBIOTICS AT DENTAL IMPLANT PLACEMENT TO PREVENT COMPLICATIONS

(NO CHANGE TO CONCLUSIONS)

Eposito M, Worthington HV, Loli V, Coulthard P, Grusovin MG. Interventions for replacing missing teeth: antibiotics at dental

implant placement to prevent complications. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD004152. DOI: 10.1002/14651858.CD004152.pub3.

‘Missing teeth can sometimes be replaced with dental implants to which a crown, bridge or denture can be attached. Bacteria introduced during placement of implants can lead to infection and sometimes implant failure. It appears that the oral administration of 2 grams of amoxicillin 1 hour before placement of dental implants is effective in reducing implant failures. More specifically, giving antibiotics to 33 patients will avoid one patient experiencing early implant losses. It is still unclear whether postoperative antibiotics are of any additional benefits.’