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Periodontitis as a Clinical Manifestation of Systemic Disease in a Patient with Severe Congenital Neutropenia Treatment, Evolution and Possible Systemic Implication

Paula Riera Sanz*[1], Alejandra Jaque Alquinta[1], Carina Salas Gonzalez[1], Mirta Cavieres Alvarez[2], Gaby Queyrie Henry[1] and Antonio Sanz Ruiz[1]

[1]Department of Periodontology, University of the Andes, Bogotá, Colombia,
[2]Department of Hematology, Luis Calvo Mackenna Children's Hospital, Providencia, Chile

Abstract

Kostmann syndrome is a congenital condition characterized by severe neutropenia. Patients with this condition take a benefit from the use of human recombinant Granulocyte Colony-Stimulating Factor (G-CSF), Neupogen®, which increases the number of neutrophils circulating in the bloodstream. The following clinical case is a 13-year old male patient, with a history of severe generalized Periodontitis, with premature teeth loss due to the disease. Scaling and root planning plus systemic antibiotherapy, was the treatment approach. A significative reduction of tissue inflammation, probing depth, gain of clinical attachment and changes in the microbiota was obtained. Besides the improvement in his oral health his systemic condition also improves, conducting to a reduction of the Neupogen® dose. The treating clinicians believed that the resolution of his periodontal disease diminished the requirement for neutrophils, thus increasing their number in peripheral blood. Further studies are necessary in order to determine whether the improvement in periodontal health restores neutrophil count to values close to normal.

Nowadays, patients with severe congenital neutropenia have a longer life expectancy due to new developments in medicine. However associated complications appeared such as severe periodontal disease. In this clinical case, the proper diagnosis and treatment, was able to recover periodontal health avoiding premature loss of teeth. Additionally, after the periodontal therapy, the neutrophil count was restored the daily dose of the granulocyte colony-stimulating factor was reduced, decreasing the risk of suffering from acute leukemia. The economic cost of the treatment was also reduced.

Keywords: Kostmann syndrome • Severe congenital neutropenia • Periodontal disease • Periodontitis as a manifestation of systemic

Introduction

Kostmann syndrome is a congenital condition which causes a myelodifferentiation alteration in the bone marrow , characterized for a severe neutropenia, with an Absolute Neutrophil Count (ANC) of less than 500 per mm^3 ($<0.5 \times 10^9$/L) [1].

Congenital neutropenia is a specific defect of the neutrophil cell line where granulocytes maturation is arrested in a precocious stage, at the promyelocyte level [2].

This condition make this patients more prone to infections of the respiratory and gastrointestinal tract, ears, skin and genitourinary system.

The treatment of this condition requires the use of Recombinant Granulocyte Colony-Stimulating Factor (rhG-CSF). This medicament stimulates neutrophil production and maturation. It acts through a receptor which binds G-CSF to the cell. This binding induce production of division and maturation signals wich stimulate the releasing of neutrophils from the bone marrow reservoirs to the bloodstream, increasing their count by 10 to 12 times. This treatment extends life expectancy [3].

Patients like this are more susceptible to mouth infections, such as periodontal disease characterized by rapid bone and attachment loss. It is also a common finding, mucosal ulceration and acute gingival inflammation with necrotic areas.

Case Presentation

The patient was born on July 1997 from a full-term pregnancy, he is the third sibling. He did not exhibit morbid syntoms until the age of 10 months, but then he had multiple hospitalizations until the age of two years. In the year 1999, he was admitted in the Luis Calvo Mackenna hospital with an ANC of 236 xmm. Tests were done to discard cyclic neutropenia. On this same year, he began treatment with Neupogen® after the diagnosis of autoimmune neutropenia.

After 2 years, he was diagnosed with Kostmann syndrome, when a bone marrow examination showed the absence of mature forms of the myeloid series and eosinophils. In November 2002 he was registered in the Severe Chronic Neutropenia International Registry, since then he receives Neupogen® 0.2 cc, with a dose of 4 mcg/kg weight/day (colony stimulating factor r-metHUG-CSF), as a treatment. This medicine maintains an ANC above 1500 per mm^3. This treatment decreased the number of infections and hospitalizations.

In September 2002, a bone densitometry test was performed, revealing osteopenia. A calcium supplement treatment was established. His checkups with the endocrinologist were irregular.

In July 2007, bone marrow samples were sent to Germany for molecular studies. A mutation was shown in the Elastase gene (ELA2 Ser 97Leu), this mutation is present in 90% of these patients and confirms the diagnosis of Severe Congenital Neutropenia [4,5].

In 2010, an HLA study was conducted on the patient and his family, but no compatible donor was found for a bone marrow transplant (BMT). He remains

***Address for Correspondence:** Paula Riera Sanz, Department of Periodontology, University of the Andes, Bogotá, Colombia; E-mail: priera@clinicasanz.cl*

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under study in the UTMO transplant unit in search of a compatible donor since he exhibits a mutation of the G-CSF receptor, this being an acquired mutation that is observed in 20% of the patients, 70% of which develop myelodysplasia and leukemia [6].

Monthly blood tests are taken to check his white blood cell level and a bone marrow examination once a year. This cytogenetic test analyzes the bone marrow chromosomes. In most patients with neutropenia, this test is completely normal. Some alterations in the cell chromosomes are not meaningful, but others may indicate progression to leukemia. This is the reason of the yearly bone marrow test [3].

Dental history

Severe gingival inflammation, was reported by his parents, this diminished when he received systemic antibiotherapy. At childhood, he was treated for gingivitis loosing prematurely the deciduous teeth.

Clinical examination 13-year old patient diagnosed with severe congenital neutropenia, “Kostmann syndrome”, was referred from Luis Calvo Mackenna children's hospital for periodontal evaluation and possibilities of treatment to the Sanz´s Clinic in Santiago-Chile.

Clinical showed severe gingival inflammation with increased volume, granulomatous in appearance. Bleeding on probing and spontaneously, teeth migration, mobility, probing depth of 8 to 12 mm, clinical attachment loss, furcation involvement in molars and radiographic bone loss (Figures 1 and 2).

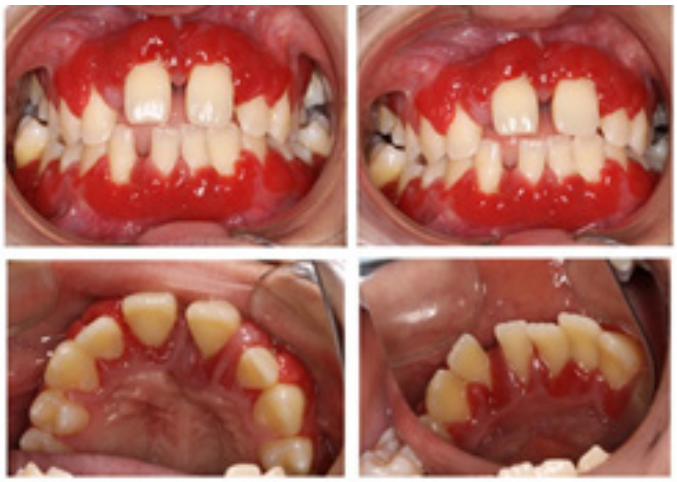

Figure 1. 13-year old patient diagnosed with severe congenital neutropenia.

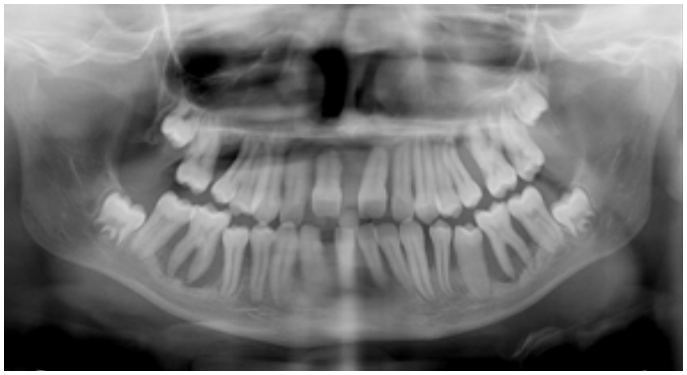

Figure 2. The panoramic X-ray shows teeth 1.8, 2.8, 3.8, 4.8 in evolution, absence of tooth 1.6, generalized advanced horizontal bone loss, furcation involvement in teeth 2.6, 3.6, 4.6, diastemas, root proximity in the area of premolars and canines in the upper maxilla.

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4 microbiological samples were taken from the deepest periodontal pockets. To take these samples, the visible supragingival plaque was removed from the zone with gauze, then a relative isolation was performed with cotton swabs, gently drying with an air syringe and a sterile #35 endodontic paper cone was introduced in the site leaving it for 30 seconds in the pocket. Two of these samples were analyzed by PCR and 2 in culture.

The samples were cold store and sent to the to the microbiology center at the Faculty of Dentistry of the Andes University to perform PCR real time test. The target bacterias were, Porphyromonas gingivalis (Pg), Tannerella forsythia (Tf), Treponema denticola (Td) and Aggregatibacter actinomycetemcomitans (Aa). All of them are the most agressive periodontopathogens.

The PCR reaction employed 9.2 µL DNA template plus 10.8 µL PCR Master Mix; containing 10 µL of Go Taq Green Master Mix (Promega®, USA), 0.4 µL of primer 1 (25 µM) and 0.4 µL of primer 2 (25 µM). Table No. 2 shows the PCR primers used. The final volume of each PCR tube was 20 µL.

The PCR tubes were processed in a Multigene ThermocyclerTM (Labnet®, USA). The PCR schedule consisted of a denaturation cycle for 5 minutes at 94°C and 40 denaturation cycles at 94°C for 30 seconds, annealing at 55ºC for 30 seconds and elongation at 72°C for 45 seconds. Final elongation was at 72°C for 10 minutes and a final cycle at 15°C for 59 minutes.

The samples taken for microbiological cultures were placed in tubes with Stuart medium transport swabs. They were sent to the University Andrés Bello Microbiology Laboratory.The samples were diluted and plated in Blood Agar with Hemin and Menadione, CVE and TSBV media. Then the bacterial colonies were counted and identified by their morphology.

Results

Microbiological results

PCR results

1. Pretreatment: Positive for Aa, Pg, Tf

2. Post treatment: Positive for Tf

Post treatment cultures

TSBV culture count Aa: 533.3 ufc/mL

CVE culture count (Fn): $8.4*10^3$ ufc/mL

TOTAL FLORA Blood count (H-M): $6.5*10^5$ ufc/mL

(50-37-11 (dil 10^2)

Occlusal examination

Study models, were mounted in a Pendant articulator. Premature contacts were observed in teeth 2.6 and 3.6. In Maximun Intercuspation (MIC) the number of oclusal contacts increased. From the premature contacts to MIC, a fulcrum occurs in the first molars with anterior displacement of the mandible that stop in the lateral incisors and canine on the left side. The bilateral TMJ´s are also anteriorly displace (Figure 3) [6] .

Based on the 2017 classification word workshop by the American Academy

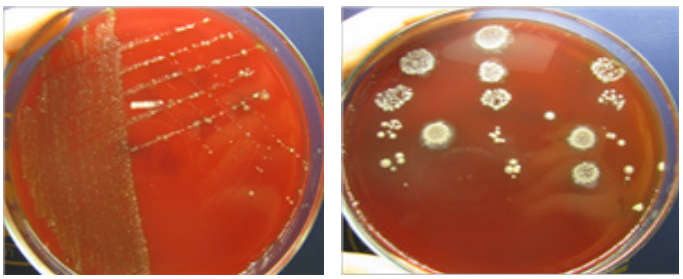

Figure 3. o black pigmented colonies were observed.

of periodontology and European Federation of Periodontology, the diagnosis in this case was "Periodontitis as a manifestation of the systemic severe congenital neutropenia [7].

Systemic phase: Permission from his hematologist was obtained to perform the periodontal treatment with systemic antibiotherapy.

Etiological phase: Education and control of the oral hygiene, which was reinforced each session. Supra and subgingival scaling and crown polishing. Root planning along with the antibiotherapy. Amoxicillin 500 mg plus metronidazole 250 mg every 8 hours by 7 days. Clorhexidine 0.12% twice a day was used as a home care supplement.

Teeth 1.1 and 2.1 dosen´t have bone support were kept in the mouth for aesthetic reasons. They were splinted to the neighboring teeth increasing their stability.

After 4 weeks, a re-evaluation was carried out and new microbiological samples were taken. Aggregatibacter actinomycetemcomitans (Aa), was found. The antibiotherapy strategy was change to an Azithromycin 500 mg once a day during 5 days.

Maintenance phase: Periodontal support therapies were conducted every 30 days, Supra and subgingival scaling and crown polishing was performed.

Corrective phase: Corrective phase: In the first lower molars an endodontics treatment and restauration was done, along with an occlusal adjustment to attain greater stability.

In the anterior upper teeth, aesthetics was improved by slightly closing the space in between them and aligning the teeth. The patient's self-esteem improved significantly, resulting in better compliance and bacterial plaque control.

Microbiological examination

After treatment, we gain stability of the periodontal tissues, characterized by a reduction of inflammation, edema and bleeding (Figure 4 and 5).

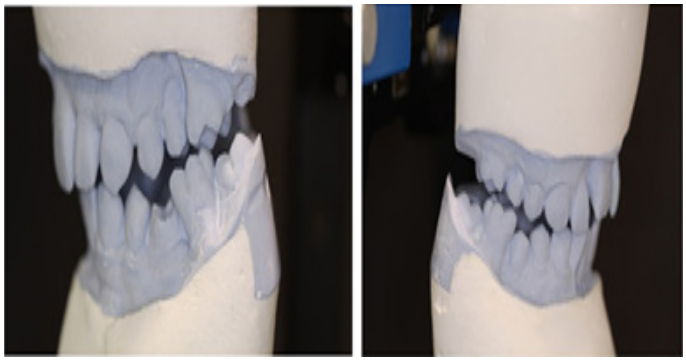

Figure 4. Periodontitis as a manifestation of the systemic severe congenital neutropenia.

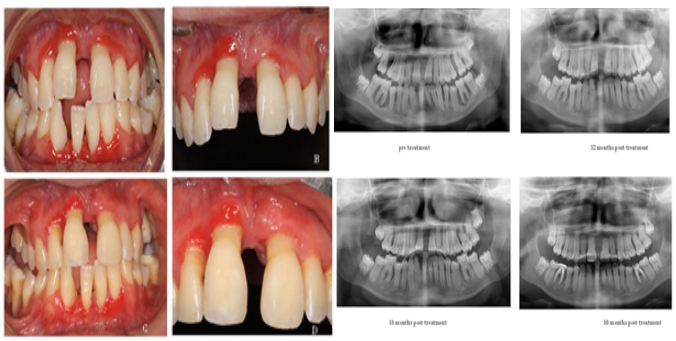

Figure 5. Photo A, and B with 18 months of follow up, C with 24 months follow up, D with 30 months follow up.

Radiographically: Bone gain at the first molar´s and premolar´s. Bone corticalization is observed. After the periodontal therapy an important change was observed in his blood count, the number of segmented neutrophils increased, allowing reducing the daily dose of Neupogen®. Total count of segmented neutrophils ("segs") before and after receiving periodontal therapy (Figure 6).

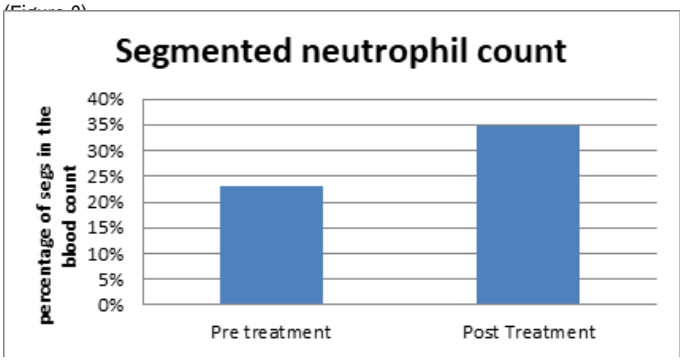

Figure 6. Total count of segmented neutrophils ("segs") before and after receiving periodontal therapy.

Discussion

Patients with neutropenia exhibit a more severe periodontal disease since early childhood [4]. Aggressive forms of periodontal disease, characterized by alveolar bone destruction, clinical attachment loss and teeth loss, have been associated with neutrophil defects [8].

This patient maintained neutrophil levels (ANC) of 500-1000 xmm^5 along with an excellent general health status, but intraorally he had a severe periodontitis. Studies suggest that normal ANC levels are not enough to maintain the oral health in these patients, since neutrophils are the first line of defense [4].

A study of Carlsoon et al. in 2006 found that patients with Kostmann syndrome express a deficiency in the antibacterial peptide LL-37. Bengt-Olof in 2020 found that patients with Kostmann disease, treated with Recombinant Granulocyte Colonystimulating Factor (G-CSF) to normalize their levels of neutrophils, they lack or have very low levels of LL-37 in plasma, saliva and neutrophils. This is a possible explanation about the apparition of the periodontal disease. Even more, Bellanne-Chantelot et al. in 2004 and Ye et al 2011 they found more severe oral diseases in patients with neutropenia who also exhibited mutation in the ELA-2 gene. In this case report the patient also has this mutation and present a severe generalized periodontitis. A study by Germeshausen et al 2013 found that the ELA mutations reduce the elastase activity of neutrophils and its enzymatic activity is significantly lower, in patients with congenital neutropenias.

Belaaouaj et al. in 1998 demonstrated in a study in mice that the elastase deficiency in neutrophils generates lower resistance against gram negative bacteria, but not against gram positive bacteria. This alteration of the neutrophils could explain the presence of a destructive periodontal disease mainly produced by gram negative flora, despite of having an adequate absolute neutrophil count.

This patient presents osteopenia with irregular check-ups with his endocrinologist. Osteoporosis can be seen in children with severe chronic neutropenia, but its cause is still not clear. Changes in the mineral content of the bone possibly represent an additional symptom of the underlying genetic defect [3].

The patient of this report presents osteopenia but his check-ups with his endocrinologist are irregular.

It is believed that the use of G-CSF to treat neutropenia is associated with an increase in bone resorption mediated by the activation of osteoclasts. Osteopenia is associated with a higher risk of bone loss in periodontal disease since bone resumption is higher than bone formation. This happened with this

patient were bone loss was observed in molars and incisors since 2002.

According to Reddy and Morgan 2013, osteopenia is a risk factor for periodontitis and these patients must be more conscious of plaque control and periodontal maintenances.

Another factor that may have influenced the severe bone loss of these teeth is the occlusal factor. This patient shown alterations of the occlusal plane and important premature contacts at the level of the first molars and heavy contacts in the upper incisors. Harrel and Nunn 2009 found that teeth with periodontal disease and premature contacts had a greater probing depth. Branschofsky et al. 2011 demonstrated that patients with premature contacts presented greater attachment loss and a statistically significant relationship between amount of occlusal trauma per patient and severity of the periodontal disease. In the narrative review of the world workshop 2017 they found some association between occlusal trauma and progression of periodontal disease.

Periodontal treatment with scailing and root planing plus systemic antibiotherapy and periodontal maintenance therapy every 30 days obtained excelent results. Reduction of the inflammatory signs, attachment gain and changes in the oral microbiota was obtained. The antibiotic treatment of first choice was amoxicillin and metronidazole, due to their effectiveness against pathogens when Aggregatibacter actinomycetemcomitans (Aa) is present, but wasn´t succeed in eradicating the pathogen, Akrivopoulou found 100% resistant to penicillin and metronidazole, therefore azithromycin 500 mg was indicated. Azithromycin has proven effective against Aa, reaching high concentrations in the gingival and intraepithelial fluids which could favor the elimination of this pathogen, capable of invading epithelial cells. On the other side, it has been observed that azithromycin would have an additional benefit for having anti-inflammatory characteristics, reducing the volume of gingival fluid and the pro-inflammatory cytokines (IL-1β, IL-8 and TNF-α) [8-20].

At the radiographic level, bone loss was stopped and corticalization was observed, thus indicating that a tissue healing process is occurring.

After periodontal therapy, the Neutrophils blood count had a significant increase which led his hematologist to lower the daily dose of Neupogen®. This could be related to the improvement in his periodontal health, since the requirement for neutrophils would decrease. Gouschin et al 2000 demonstrated, in his report, that periodontal treatment may restore circulating neutrophil levels in patients with neutropenia treated with rhG-CSF. On the other hand, the use of G-CSF increases the risk of having Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML). This risk increases in patients using G-CSF at doses above 8 g/kg per day1. It has been suggested that the pathogenesis of SCN and its progression to secondary malignancies, may involve an underlying genomic instability. Pharmacological doses of G-CSF could potentially stimulate the stepwise acquisition of genetic changes in bone marrow cells in these patients with the potential proliferation of a malignant cells clone [20].

Conclusion

If the periodontal treatment leads to improvements in the immune system of these patients and it is possible to reduce the drug dosage, the risk of suffering from leukemia could also be reduced. Further studies are necessary in order to ensure that periodontal treatment achieves improvements at the immune system level in these patients and possible therapies with antimicrobial peptides. Kostmann syndrome is a congenital condition characterized by severe neutropenia. Patients with this condition take a benefit from the use of human recombinant Granulocyte Colony-Stimulating Factor (G-CSF), Neupogen®, which increases the number of neutrophils circulating in the bloodstream.

References

1. Rosenberg, Philip S Blanche Alter, Audrey Bolyard and Mary Ann Bonilla. "The Incidence of Leukemia and Mortality from Sepsis in Patients with Severe Congenital Neutropenia Receiving Long-Term G-CSF Therapy." *Blood* 107(2006): 4628-4635.
2. Carlsson and Fasth. "Infantile Genetic Agranulocytosis, Morbus Kostmann: Presentation of Six Cases from the Original 'Kostmann Family' and a Review." *Acta Paediatr* 2001(90): 757-764.
3. Göran, Carlsson, Ylva-Britt Wahlin, Anders Johansson and Anders Olsson, et al. "Periodontal Disease in Patients from the Original Kostmann Family with Severe Congenital Neutropenia." *J Periodontol* 77(2006): 744-751.
4. Jonathan, Spoor, Hamid Farajifard and Nima Rezaei. Congenital Neutropenia and Primary Immunodeficiency Diseases. *Crit Rev Oncol Hematol* 133(2019):149-162.
5. Suzuki, Park, and Falker. "Immunologie Profile of Juvenile Periodontitis I. Lymphocyte Blastogenesis and the Autologous Mixed Lymphocyte Response." *J Periodontol* 55(1984): 453-460.
6. Bellanne´-Chantelot, Clauin and Leblanc. "Mutations in the Ela2 Gene Correlate with More Severe Expression of Neutropenia: A Study of 81 Patients from the French Neutropenia Registry." *Blood* 103(2004): 4119-4125.
7. Germeshausen, Deerberg, Peter and Reimer, et al. "The Spectrum of ELANE Mutations and their Implications in Severe Congenital and Cyclic Neutropenia". *Hum Mutat* 34(2013): 905-914.
8. Belaaouaj, McCarthy, Baumann and Gao, et al. "Mice Lacking Neutrophil Elastase Reveal Impaired Host Defense Against Gram Negative Bacterial Sepsis." *Nat Med* 4(1998):615-618.
9. Sekhar, Culbert, Hoots and Klein, et al. "Severe Osteopenia in a Young Boy with Kostmann's Congenital Neutropenia Treated with Granulocyte Colony-Stimulating Factor: Suggested Therapeutic Approach." *Pediatrics* 108(2001): E54.
10. Reddy, Morgan. "Decreased Bone Mineral Density and Periodontal Management." *Periodontol* 61(2000): 195-21.
11. Harrel and Nunn. "The Association of Occlusal Contacts with the Presence of Increased Periodontal Probing Depth." *J Clin Periodontol* 36(2009):1035-1042.
12. Branschofsky, Beikler, Schäfer and Flemming, et al. "Secondary Trauma from Occlusion and Periodontitis." Quintessence Int 42(2011):515-522.
13. Pin-Chuang, Lai, Weiting Ho, Nidhi Jain and John. "Azithromycin Concentrations in Blood and Gingival Crevicular Fluid after Systemic Administration." *J Periodontol* 82(2011): 1582–1586.
14. Pin-Chuang, Lai and John. "Azithromycin Kills Invasive Aggregatibacter actinomycetemcomitans in Gingival Epithelial Cells." *Antimicrob Agents Chemother* 57(2013): 1347-1351.
15. Teughels, Feres and Oud Martín Matesanz. "Adjunctive Effect of Systemic Antimicrobials in Periodontitis Therapy." *J Clin Periodontol* 29(2020).
16. Jourdain, Marie-Laure, Velard Frédéric, Pierrard Loïc and Sergheraert Johan, et al. "Cationic Antimicrobial Peptides and Periodontal Physiopathology: A Systematic Review." *J Periodontal Res* 54(2019):589-600.
17. Ye, Carlsson and Wondimu. "Mutations in the ELANE Gene are Associated with Development of Periodontitis in Patients with Severe Congenital Neutropenia." *J Clin Immunol* 31(2011):936-945
18. Mysak, Podzimek, and Sommerova. "Porphyromonas gingivalis: Major Periodontopathic Pathogen Overview." J Immunol Res (2014).
19. Feres, Retamal-Valdes and Mestnik. "The Ideal Time of Systemic Metronidazole and Amoxicillin Administration in the Treatment of Severe Periodontitis: Study Protocol for a Randomized Controlled Trial." *Trials* 19(2018):201.
20. Akrivopoulou, Green, Donos and Nair et al. "Aggregatibacter Actinomycetemcomitans Serotype Prevalence and Antibiotic Resistance in A UK Population with Periodontitis." *J Glob Antimicrob Resist* 10(2017): 54-58.

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