The Prevention and Treatment of Neural Arterial Gingival Simplex

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Abstract
Neural Arterial Gingival Simplex is a common systemic disease linked to an invasive periodontal pathogen, Porphyromonas gingivalis as the key initiator. Instead of considering separate pathologic conditions as separate diseases, the health community should view this disease as a single entity, to diagnose and treat accordingly. We discuss the evidence for this hypothesis and the need for definitive research. A strategy to maintain a healthy, resilient microbiome with adjunctive support by probiotics and polyols is warranted. Newer diagnostic and monitoring technologies along with many possible therapeutic agents and protocols are readily available to prevent and treat Neural Arterial Gingival Simplex.

Keywords: Neural arterial gingival simplex, Porphyromonas gingivalis, Alzheimer’s disease, Polyols.

Introduction
The importance of re-establishing a normal microbiome cannot be overemphasized [1,2]. Modern diet and the overuse of antimicrobials have resulted with a tremendous increase in autoimmune diseases that were virtually unheard of in the past [3-5]. This shift in diet occurred first in the Neolithic period, followed by another shift in the Industrial Era, and finally now with the combined effects of fast food and antimicrobials [6]. Even a number of common food preservatives and additives have been shown to exert negative health effects [7]. As a result, it is estimated that almost half of all middle-aged Americans have metabolic syndrome [8-10]. In short, the costs of western diet and life style have been significant, and unless a paradigm shift urgently occurs, we could be a society devoted only to extending the life span of the chronically ill, incapable of achieving the accomplishments of prior generations [11,12]. Fortunately, advances in scientific study of the microbiome provide hope that wellness can be restored and productive health span increased.

The connection of oral health to systemic health is now well established [13]. Indeed, there is no isolated disease such as periodontal disease; it is simply a symptom of a systemic disease that may best be described as Neural Arterial Gingival Simplex (NAGS). Porphyromonas gingivalis has been found to be a causative agent of periodontal disease, arteriosclerosis and inflammatory Alzheimer’s [14-16]. Because P. gingivalis can be considered the foremost or “keystone” initiator of periodontal disease, it is reasonable to describe P. gingivalis as a causal agent of NAGS, a single disease with all of its downstream comorbidities [17]. Such is the case for any other disease, for instance, viral acute gastroenteritis due to rotavirus may cause fever, chills, muscle aches, fatigue and nausea, and each component is not considered a separate disease [19,20].

Addressing the microbiome may very well become the preventive technique of choice. Oral and systemic preventive protocols would include probiotic supplementation, possibly with overlapping beneficial bacterial, archaeon, viral or yeast probiotics. For example, it may be stated that an historical precedent for use of a viral “probioctic” would be the cowpox inoculation by Jenner to prevent the mortality seen with the scourge of smallpox [21]. In this sense, cowpox may be considered a viral probiotic as it contributed to the health and even survivability of the individual.

Evolution Guerilla Tactics
P. gingivalis has been called a “guerilla” for its notable tactics of slowly subverting the host’s defense mechanisms [22]. The host’s immunity is bypassed by the ability of P. gingivalis fimbriae to attach to host cells, such as gingival epithelial cells or endothelial cells, and then to invade the cell itself [23]. The ability of P. gingivalis to shift genomes in different strains to specifically target different host cells makes it particularly virulent [24]. In addition, the epigenetic influence of P. gingivalis allows it to open the tight junctions between cells and to modulate the immune response [25]. All told, P. gingivalis subverts a massive host immune response, and does not normally overwhelm the host because that would effectively limit the spread of the pathogen. A dead host does not propagate a pathogen.

P. gingivalis is a perfect pathogen. It spreads from the older members of the host population to the younger members [26]. P. gingivalis is seen in children as young as 7-8 years of age, however, gingival pathology is not usually detected until age 17 [27,28]. The majority of young adults already have more than a millimeter of attachment loss [29]. It should be noted that in autopsy studies 20% of 2-15 year old children demonstrate atherosclerosis, and by age 21 50% will have
calcified aortic deposits [30-32]. This too perfectly coincides with the development of “periodontal disease”. In addition, research at Northwestern University revealed that in their early 20’s subjects were already developing beta amyloid plaque and tau protein deposits [33]. With recent publications demonstrating the correlation between gingipain from P. gingivalis and Alzheimer’s disease, this should not be the least surprising [14].

With the new concept of P. gingivalis infection causing a single disease with multiple symptoms, it is now easy to understand the modes involved. The oral component is the initial infection where the immune system is alerted and subverted, creating an inflammatory environment. Circulating leukocytes carry P. gingivalis and associated Lipo Poly Saccharide (LPS), affecting the endothelial cells of arteries, and passing into the neural component, eventually reducing the cognitive ability of the host, which would reduce the oral hygiene of the host, further spreading the pathogen amongst all contacts [34].

**Prevention**

The key to prevention will always lie with having the healthiest microbiome [35]. A “healthy non-western microbiome” will trigger the innate robust response to pathogens that the least autoimmune in consequences. Unfortunately for the civilized world, we have brought upon ourselves the epidemic of autoimmune disease, while decreasing our innate response to common pathogens [36]. Much has been said of the hygiene hypothesis, and of us all being “too clean” [37]. But it is extremely doubtful that as a society, we will all return to our hunter-gatherer roots (barring some natural catastrophe). Probiotic supplementation appears to be the essential to re-establish a healthy resilient microbiome [38-42]. This option alone, without appropriate diet and lifestyle modification, is severely limited [43]. The appropriate diet is necessary to provide the required prebiotics that beneficial organisms need to thrive and to favorably influence the entire microbiome [44]. The microbiome metabolites then exert an epigenetic effect upon the host, either producing health, or illness [45]. Dysbiosis not only directly produces disease, but also the metabolites of the microbiome are messengers to the brain and the rest of the body [46]. The immune system responds, as does the behavior of the host [47]. Depression has been linked to the presence of a specific bacterial species, and also the lack of one species [48,49]. Schizophrenia is also an epigenetic disease and Autism Spectrum Disorder (ASD) has been linked to propionic acid producing bacterial species, such as, Clostridia botaleae and Clostridia histolyticum [50-54]. Conversely the presence of Clostridia sporogenes could help protect against ASD by combining propionic acid with indole to produce 3-Indole Propionate, a neural protective metabolite, thereby neutralizing the epigenetic effect of propionic acid [55,56]. It has been theorized that the absence of C. sporogenes is related to the use of glyphosate, known by the trade name Roundup [57]. Possibly the increase risk of non-Hodgkin’s Lymphoma seen in chronic exposure to individuals exposed to Roundup is due to its effect on the host’s microbiome, by removing or reducing the level of a protective bacterial species.

With dysbiosis, the existence of disease always means not just an increase in the presence of a pathogen, but normally always a decrease in the level of commensals, allowing the pathogen to generate the pathological response [58]. In a perfectly balanced system, the host should always survive, at least long enough to pass the pathogen on to subsequent generations. The host should, by evolution, develop a robust response to the pathogen, increasing the chance of the host species survival [59]. If this does not happen, the host species will disappear and the pathogen can only survive by becoming a zoonotic disease pathogen, jumping species, such as, bird flu or swine flu [60]. There is a canine version of P. gingivalis, Porphyromonas cangingivalis, and periodontal pathogns typically seen in human hosts have been detected in canines [61-62]. Whether this is by co-evolution or zoonotic origin is of interest, as it should explain the disease process with greater clarity.

Gingipain-deficient mutant P. gingivalis may prove to be a precursor to an Alzheimer’s preventive probiotic. After all, this mutant strain could and should compete with the “wild type” strains producing gingipain. A further example of this would be the strains of Fusobacterium nucleatum that do not have the FADA gene. These strains could occupy that ecological niche of F. nucleatum and possibly decrease miscarriages (spontaneous abortions) and colorectal cancer. Development of these less virulent strains is similar to Jeffrey Hillman’s research into a low or non-lactic acid producing strain of Streptococcus mutans [63]. Colonization of the population with this safe probiotic could greatly decrease the most common disease of childhood, dental caries. It is estimated that over 98% of the human population suffers from dental caries, a totally preventable disease that is strictly due to dietary habits and dysbiosis [64]. Oddly enough, dentistry totally ignores this and concentrates only on fluoridation, limiting the effectiveness of prevention programs [65-72].

**Treatment**

Erythritol and xylitol are polyols that have been extensively researched and demonstrated to have notable anti-cariogenic and anti-periodontal disease properties [73]. Polyols (particularly the non-hexitol alditols or “sugar alcohols” erythritol and xylitol) have been found effective in inhibiting the transition to and maturation of biofilms from planktonic cells [74]. Xylitol clearly inhibited the formation of mixed species biofilms, which included P. gingivalis in vitro [75]. Erythritol suppressed the maturation of gingivitis biofilms, and contributed to a healthier oral ecosystem [76].

P. gingivalis takes advantage of early colonizers (Streptococci and Candida) to provide attachment and protection within the biofilm matrix. Polyols can reduce extracellular polysaccharide production and interfere with biofilm matrix elaboration, thereby reducing adherence and biofilm development [77-79].

Streptococci and Candida utilize common dietary sugars sucrose and D-glucose for preferred energy sources, as well as for polysaccharide production. Higher glucose concentrations stimulate Candida growth. Compared with common D-sugars, xylitol induced the lowest adhesion and biofilm formation on either S. mutans or Candida albicans [80].

Candida facilitates the colonization and proliferation of periapical biofilm by co-aggregating with P. gingivalis and adhering to epithelial cells [81]. Patients with severe periodontitis have a higher rate of Candida colonization [82]. In diabetics, high levels of glucose in the gingival sulcus coupled with immunosuppression enhance Candida growth [83]. Glucose, fructose and mannose are the preferred sugars used for energy and biosynthesis by Candida, whereas polyols such as xylitol are poorly utilized. Sugar sensing drives virulence attributes, including adhesion, oxidative stress resistance, biofilm formation, morphogenesis, invasion, and antifungal drug tolerance in fungal pathogens [84,85]. In dual species biofilm Candida helps provide P. gingivalis adherence and protection against oxygen, allowing it to organize in shallower gingival pockets [86].

The hydroxyl groups of polyols may interfere with the hydrogen bonding between hydroxyl groups of polysaccharides and allow greater penetration of antimicrobials. Polyols, especially erythritol, enhanced the fungicidal effect of benzenthonium chloride toward in vitro candidal biofilms [87]. Xylitol and sorbitol at the concentrations used in commercial oral health care products had some levels of candidacidal activity [88]. Polyols can penetrate biofilms to deliver probiotics [89]. Erythritol delivered zinc chloride deeper into the protective three-dimensional matrix of extracellular polymeric substances of mature biofilm [90].

Although P. gingivalis utilizes peptides for its main energy source, sugars are used by P. gingivalis for biosynthesis of macromolecules.

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Polys can interfere with these processes. As a result, polys reduce the growth and the virulence factors of P. gingivalis. Xylitol was found to inhibit the inflammatory cytokine expression provoked by LPS remnants of P. gingivalis [92]. Further, xylitol interferes with P. gingivalis phagocytosis by macrophages. In macrophages that are infected with live P. gingivalis, xylitol significantly decreased the production of cytokines, NO and chemokines such as TNF-α, IL-1β, IL-12p40, eotaxin, IP-10, MCP-1, and MIP-1α. Such potent anti-inflammatory activities recommend use of polys for prevention and mitigation of periodontal conditions [93]. Plaque grown in the presence of polys has consistently been shown to be less inflammatory and less irritating to tissues than sucrose-grown plaque [94-99].

Polys can suppress the growth and virulence expression of mixed bacterial biofilms. Erythritol was the most effective polys in suppressing the growth and organization of P. gingivalis grown on a Streptococcus gordonii biofilm. Erythritol exerted inhibitory effects on several pathways-reduced growths through DNA and RNA depletion, attenuated extracellular matrix production, and alterations of dipetide acquisition and amino acid metabolism [100].

Recognition of NAGS corresponds with newer enhancements in the diagnosis, prevention and treatment of periodontal diseases. Periodontal diagnosis goes beyond gross visual, radiographic and mechanical probing to include Polymerase Chain Reaction (PCR), DNA determination of specific pathogenic entities and quantities-the oral microbiome. Genetic and other tools have also been included to help construct an overall assessment of individual patient risk and assign targeted treatment plans. Improved salivary and inflammatory diagnostics can help with monitoring treatment progress in achieving and maintaining therapeutic end points.

Awareness of NAGS likewise calls for prevention, treatment and maintenance that extend beyond localized mechanical strategies. Presence of P. gingivalis is not limited to those with bleeding gums and deep pockets [101]. P. gingivalis in dental biofilms is associated with expression of virulence factors leading to progression of periodontal disease [102]. P. gingivalis biofilms are not easily controlled by purely mechanical means and are more resistant to antimicrobials than planktonic cells [74]. Treatment of Periodontal disease and the prevention of dental caries should include a very strong antimicrobials than planktonic cells [74]. This theory would not only prevent the oral disease, but should also help prevent the development of systemic disease, atherosclerosis and the scourge of the elderly, Alzheimer’s disease [109,110]. Certainly, it would be advantageous to prevent NAGS, as the cost to society is enormous, and the cost to the individual can be devastating. Polys are available in many forms such as tabletop sweeteners and as ingredients in commercial foods and beverages. More direct “polyol delivery systems” for oral care include toothpaste, lozenges, chewing gum, mouth rinses and oral sprays. Further research is warranted and necessary to reduce the burden of this devastating disease on modern society. We should first perform a number of retrospective review of patients who have been diligent users of polyol products, especially the reviewing the children’s health records of those that were subjects in the early Finnish studies of xylitol and erythritol supplements. Unfortunately, this may be difficult due to human subject privacy rules. On a positive note, there are apparently studies that have already been started that are long term in scope, such as the Pussinen et al study [111]. Prospective studies could take many decades to irreutably prove the long term positive effects of polyol and probiotic supplementation. Due to the documented early onset of atherosclerosis in children, newer diagnostic technologies should be utilized to identify and monitor risk. With the now available non-invasive testing for the presence of P. gingivalis and use of ultrasound for atherosclerosis detection, the research may be accomplished sooner rather than later.

Conclusion

A disease of neural, arterial and gingival involvement resulting from an infection by P. gingivalis has since prehistoric times inflicted severe pathological effects on the homo genus. The disease is now of an epidemic nature and should be prevented by probiotic therapy, dietary changes, and life style adjustments. Treatment should include supplemental polyol support.

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