Review Article

Association between Periodontitis and Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease which significantly increases with age. Its onset can be either early or late. AD is characterized by the salient inflammatory features, microglial activation, and increased levels of proinflammatory cytokines which contribute to the inflammatory status of the central nervous system (CNS). Whereas, periodontitis is a common oral infection associated with the gram negative anaerobic bacteria. Periodontitis can be marked as a "low-grade systemic disease" by release of proinflammatory cytokines into systemic circulation and elevation of C-reactive protein (CRP). Inflammation is known to play a pivotal role in both the disease process serving as a connecting link between periodontitis and AD. The present review throws a light on possible enigmatic link between AD and periodontitis. This review is designed by collecting data from PubMed database using key words like "Alzheimer's disease", "inflammation", "periodontitis", and "proinflammatory cytokines".

Keywords: Alzheimer's disease, Inflammation, Periodontitis, Proinflammatory cytokines

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Introduction

Alzheimer's disease (AD) is a fatal neurodegenerative disease associated with elderly age group and a major health problem in the geriatric subject's worldwide. The incidence of AD significantly increases with age, reaching almost 50% in subjects aged 85 years.[1] As the population ages and life span increases, the prevalence of AD will increase even further and is expected to affect around 14 million people in the next 50 years. A decrease in the prevalence of AD can be achieved by switching to newer treatment approaches which can be effective against probable risk factors for AD and can also delay the onset.[2]

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AD could be either early or late onset. Early onset AD is thought to be genetically determined; whereas late onset or sporadic AD, which includes the majority of patients, is believed to be a result of interaction between genetic and environmental factors. Age is a major risk factor for AD. Other risk factors for late onset AD include family history, education, high fat diet, hypertension, diabetes, history of head trauma, and susceptibility genes such as apolipoprotein E (APOE). Among all these risk factors; age, family history, and APOE 4 allele are considered to be accepted risk factors. Periodontitis is also considered to be one of the probable risk factors for AD. It is a chronic inflammation of the tissue surrounding the teeth which is due to complex bacterial interaction, resulting in breakdown and loss of supporting structures around the teeth. The present review elucidates the enigmatic link between AD and periodontitis, showcasing the pathophysiology and possible implications of the association.

AD is characterized by the formation of extracellular amyloid β-peptide (AβP) plaques and intraneuronal neurofibrillary tangles (NFTs) of hyperphosphorylated

tau protein, leading to gradual loss of neuronal synapses and ultimately neuronal degeneration with diminution of essential neurotransmitters.[3] Genetic aberration causes increased expression of the amyloid precursor protein (APP) gene which could be a risk factor for late-onset of AD. It is also likely that APOE epsilon 4 (APOEε4) allele is genetically linked to majority of the AD cases.[4]

Pathogenesis of AD

AD has the tendency to induce inflammation, including Aβ-amyloid 1-42 peptide (Aβ42) found in senile plaques, hyperphosphorylated tau protein (P-Tau) comprising the NFTs, or components of degenerated neurons.[3] These pathologic changes in turn are likely to stimulate microglial cells. These microglial cells are protective in nature at low levels (concentration). They help in maintaining a homeostasis in the brain by acting as mononuclear phagocytes against any noxious injury within the central nervous system (CNS). In healthy individuals, microglial cells play a neuroprotective function by clearing the AβP plaques.[5] With advancing age and genetic predisposition, the normal neuroprotective capability of the microglial cells is compromised, resulting in persistence of chronic inflammatory response within the CNS.[6,7] This results in microglial cells of the brain to direct their phenotypes to produce neurotoxic substances when they are exposed to the systemic inflammatory signals. Such response of the microglial cells contributes to the pathogenesis of AD instead of providing with a protective response to the systemic inflammatory signals. The induced microglial cells now referred to as "activated microglial cells" alters its morphology and secrete cell antigens, which in turn results in uncontrolled expression of proinflammatory factors. This uncontrolled expression of factor levels as in AD can induce neurodegeneration, suggesting that the expression of inflammatory molecules will contribute to the progression of the AD.[8]

Microglial cells in AD

The function of microglial cell is like a "double-edged sword" being either damaging or protective depending on the situation.[9-11] Stimulated/activated microglial cells produce proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and C-reactive protein (CRP). These elevated proinflammatory cytokines and CRP might then act via paracrine and/or autocrine pathways to stimulate glial cells to further produce additional Aβ42, P-Tau, and proinflammatory molecules. Thus, leading to a pathway where inflammatory mediators play a dual role by both stimulating glial cells and activating molecular pathways, resulting in neurodegeneration.[12] Senile plaques are associated with reactive astrocytes and activated microglial cells which react with antibodies against TNF-α, IL-1β, IL-6, CRP, and complement proteins.[3] TNF-α, IL-1β, and IL-6 are capable of stimulating the synthesis of Aβ42 and the phosphorylation of tau protein, and Aβ42 and P-Tau can in turn stimulate the production of TNF-α, IL-1α, and IL-6 by glial cells.[12-14]

Research studies have revealed the correlation between value of CRP and other systemic inflammatory markers in the onset of AD. Elevated levels of CRP increase the risk of developing AD in various populations.[15,16] A case-control study of 1,050 subjects reported that higher levels of CRP increased the risk of developing AD 25 years later.[17,18] The presence of a composite genotype characterized by the presence of IL-1α-889 and IL-1β + 3953 polymorphisms conferred an almost 11-fold increased risk of developing AD, presumably as a result of increased IL-1 levels.[19]

Mechanisms involved in spread of inflammation to brain

There are two mechanisms involved in the brain which causes an increase in proinflammatory molecules, that is, via systemic circulation and/or neural pathways. In the systemic circulation, proinflammatory molecules enter brain through areas which lack blood brain barrier (BBB). Alternatively these inflammatory molecules can also enter areas in brain with blood brain barrier through:

(a) Fenestrated capillaries of the BBB,
(b) Using cytokine-specific transporters,
(c) Increasing the permeability of BBB, or
(d) Endothelial cells of the brain are activated to produce cytokine-inducing signaling molecules such as nitric oxide or prostanoids.

As the proinflammatory molecules enter the brain, it leads to increase in the local proinflammatory cytokine pool or stimulation of glial cells to synthesize additional proinflammatory cytokines. Alternative pathway through which the cytokines derived from peripheral inflammatory sources might affect the brain is through neuronal pathway.[20] Peripheral cytokines have the capability to stimulate afferent fibers of peripheral nerves, resulting in increased levels of brain cytokines; similarly they can also utilize channels or compartments associated with peripheral nerves to enter the brain.

Other mechanism include the presence of receptors for CD14 present in the brain which can get activated by LPS derived from invasive bacteria or AD AβP, which in turn will activate CD14 cells. These CD14 cells are exposed to systemic circulation such as leptomeninges, circumventricular areas, and choroid plexus; thus increasing further brain cytokines and hypothetically contributing to the inflammatory burden of AD.

Microbiota in AD

The role of bacteria in the pathogenesis of AD is thought to be due to *Chlamydia pneumoniae* and spirochetes which is emphasized by certain studies conducted. The presence of *Borrelia burgdorferi* spirochetes were found in the blood and cerebrospinal fluid of patients with AD, and it was also observed that glial and neuronal cells exposed to *B. burgdorferi* synthesized βAPP and P-taus.[21]

Spirochetes and *Treponema denticola* are commonly isolated microorganisms in moderate to severe periodontitis.[22] These organisms are also detected in patients with AD suggesting that periodontopathic bacteria can invade the brain by systemic circulation as well as peripheral nerve pathways. Invasion of microorganisms through neuronal pathways is supported by presence of oral treponemas in the trigeminal ganglia.[23,24] The presence of oral bacteria in systemic circulation is usually expected when heavy bacterial plaques are present. AβP, the main component of amyloid plaques is derived from APP by proteolytic cleavage. Studies support the hypothesis that APP and AβP are instrumental in the pathogenesis of AD.[25]

The stability of microtubules in neurons is maintained by associated tau protein. But hyperphosphorylation of tau takes place as a result of inflammation, oxidative stress, upregulation of tau kinases, and downregulation of phosphatases.[26] This hyperphosphorylated tau is insoluble with low affinity for microtubules, disrupting the microtubule stabilization, thus conducing to synaptic dysfunction and neurodegeneration.

AD was thought to be a disorder related to synthesis and decline in the degradation of AβP. But, with the introduction of "amyloid cascade hypothesis" impaired clearance of AβP is also stated as a cofactor with APP playing a pivotal role.[27]

Studies have shown that, chronic lipopolysaccharide (LPS)-induced neuroinflammation ensues in the elevated levels of intraneuronal AβP in transgenic mice. This may contribute to the deterioration of AD-affected brain.[28-30]

Periodontal Disease: As a low-grade systemic disease

Periodontal disease (PD) is a condition that causes inflammation and destruction of the gingiva (gums), alveolar bone, and other structures that support the teeth. The etiology of PD is complex involving the presence of pathogenic bacteria found in dental plaque evoking host immune response. PD is a common source of chronic systemic inflammation and immune reactions that result in loss of bone and soft tissue that supports teeth in the jaws.[31]

Periodontitis which is primarily a result of plaque exists in the form of biofilm and consists of numerous microorganisms. Characteristic features of periodontitis include, bleeding and purulent discharge from the gums, progressive deepening of gingival sulcus (referred as pocket formation), oral halitosis, spacing between the teeth, and mobility of teeth in advanced stages. The predominant periodontal pathogens involved in periodontitis are *Aggregatibacter actinomycetemcomitans* (Aa), *Porphyromonas gingivalis* (Pg), *Prevotella intermedia* (Pi), *Fusobacterium nucleatum* (Fn), *Tannerella forsythensis* (Tf), *Eikenella corrodens* (Ec), and *Treponema denticola* (Td).[32,33]

The inflammatory process in periodontitis extends from the gingiva (gums) into deeper connective tissues, resulting in the loss of connective tissue and bone mainly through the activation of host-derived osteoclasts and matrix metalloproteinases (MMP). The connective tissue adjacent to the pocket epithelium is infiltrated with intense inflammatory cells consisting of polymorphonuclear leukocytes, monocyte/macrophages, T- and B-cells mediated by a multitude of cytokines and chemokines, and most of them produced by the inflammatory cells themselves.[34] This low grade inflammation is conceived to perturb the general systemic health and exasperate other systemic disorders. Therefore, chronic periodontitis can be a significant source of covert peripheral inflammation within the general population.[35] Thus, periodontitis can be marked as a "low-grade systemic disease".

Periodontitis is basically a result of inflammation caused due to wide array of pathogenic microorganisms [Figure 1]. These microorganisms release numerous proteolytic enzymes, resulting in destruction of soft and hard tissues supporting the teeth. Release of LPSs from the gram negative bacteria results in the expression of proinflammatory factors/cytokines like IL-1α and

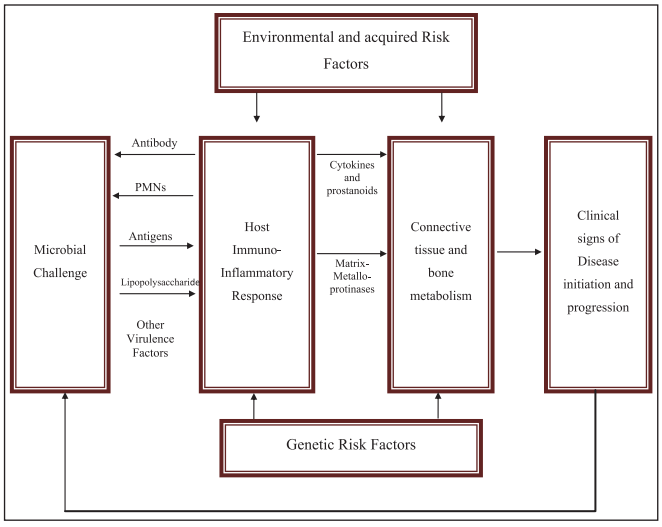

Figure 1: Pathogenesis of periodontitis

-1β, IL-6, TNF-α, prostanoids, MMP, and by the host tissue cells (neutrophils and monocytes); ultimately paving way to more destruction of periodontal tissues. Hence, host response plays a role of diabolical "dual role" leading to self-destruction, due to the exaggerated expression of tissue proteolytic enzymes.[36]

Microorganisms involved in periodontitis can elicit systemic effects through various mechanisms [Figure 2].

- Periodontal bacteria and their products could be aspirated, which could induce pulmonary pathology.
- Periodontal pathogens have the capability to gain access to systemic circulation and subsequently colonize different distant anatomic sites in the body. For example, periodontal bacteria have been implicated in several systemic diseases including endocarditis and brain abscesses [Figure 3].
- Periodontal bacteria and their products can disseminate through systemic circulation in pregnant woman inducing inflammatory changes and resulting in preterm low birth weight infants.
- Chronic adult periodontitis has been associated with several conditions including increased risk of atherosclerotic complications, myocardial infarction, stroke, poorly controlled diabetes mellitus, and possibly with AD.[37]
- The host response also plays a vital role in inducing systemic effects by producing a multitude of inflammatory mediators including cytokines (against the periodontal microbiota) that gain access to the systemic circulation.

The isolation of periodontal microbiota from various samples obtained from respiratory tract, atheromatous plaque in the heart, brain, vaginal smears, and also from patients suffering from rheumatoid arthritis reveals a possible association of periodontitis with systemic diseases.

AD and periodontitis — A correlation

Inflammation is known to play a pivotal role in this process. It is proposed that periodontitis can lead to progression of AD by two probable mechanisms.

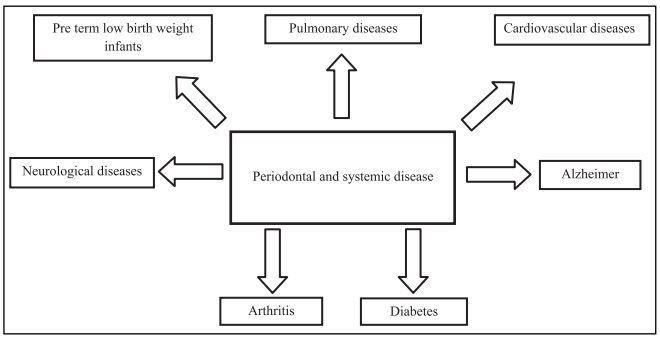

Figure 2: Systemic outcomes due to periodontal diseases

Two mechanisms have been put forth to explain the association of periodontitis and AD.

a. According to the first mechanism, periodontopathic microorganisms and the host response cause an increase in the levels of proinflammatory cytokines. This results in an array of cytokines and pro-inflammatory agents that are spurted out in systemic circulation leading to systemic inflammatory burden resulting in a state of systemic/peripheral inflammation. These proinflammatory molecules are capable of compromising the BBB and entering the cerebral regions. This leads to priming/activation of microglial cells and the adverse repercussions leading to neuronal damage.
b. The second mechanism is thought to be due to invasion of brain by microorganisms present in the dental plaque biofilm. The microorganisms in the dental plaque can enter brain either through blood stream or via peripheral nerves. These microorganisms and their products elicit an inflammatory mechanism within the CNS. It is generally accepted with appreciable evidence that presence of inflammation in the CNS results in cognitive impairment, such as that seen in AD. This inflammatory impairment is attributed to cytokine arbitrated interactions between neurons and glial cells. Cytokines released due to inflammation include IL family, TNF-α, transforming growth factor-β, and chemokines (monocyte chemotactic protein, IL-8, macrophage migration inhibitory factor, and monokine induced by γ-interferon) that have also been implicated as serum and plasma biomarkers for pathogenesis of AD.[38] Cytokines which are released (especially TNF-α) during inflammation play a

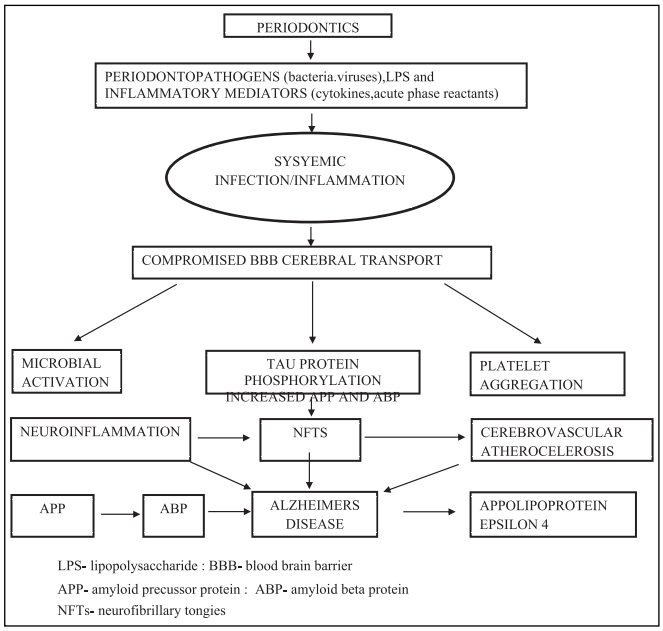

Figure 3: Possible pathway between periodontal infection and AD

major role in neurodegenerative disease. TNF-α exaggerates the inflammatory process resulting in gliosis, demyelination, BBB deterioration, and cell death. Thus, TNF-α plays a very important role in the neurodegenerative process.[39,40] Anti-inflammatory agents indicated during any inflammatory conditions markedly reduce the effects of these cytokines and other proinflammatory molecules. Studies conducted on mice models have revealed salutary effects of anti-inflammatory agents in the amelioration of neuroinflammation and amyloid plaque deposition. Alongside, there is also a significant reduction in the levels of IL-1β and glial fibrillary acidic protein levels in mice treated with nonsteroidal anti-inflammatory agent.[41,42]

The role of anti-inflammatory agents has been studied by Alzheimer's disease Anti-inflammatory Prevention Trial (ADAPT) and hypothesized that the beneficial effect of anti-inflammatory drugs is evident only in the early, asymptomatic, phases of the disease. In individuals with AD, elevated IL-1β predicted rates of cognitive decline.[43] Patients with elevated markers preceding a baseline levels showed a greater rate of cognitive decline over a 2-month follow-up period than those who did not have elevated levels prior to baseline. Similarly, dementia is also considered to be a complex disorder associated with an interaction between genetics and diseases related to systemic inflammation. Elevated blood inflammatory markers predict risk for dementia and incidence of cognitive impairment. Cross-sectional and longitudinal studies have revealed dementia in subjects with poor oral health. Thus, Periodontitis which leads to the presence of inflammatory molecules in systemic circulation is thought to be a definite risk factor for developing a variety of systemic diseases including AD.[42]

Conclusion

Inflammation could serve as a connecting link between periodontitis and AD. However; in the literature, there are no animal studies specifically addressing the causal relationship of periodontal inflammation to AD. Since periodontitis has a tendency to infiltrate the systemic circulation with inflammatory mediators and result in systemic disease outcome; thus, it would always be advisable and better option to prevent periodontal disease progression to prevent further systemic outcomes.

References

1. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, *et al.,* Alzheimer's Disease International. Global prevalence of dementia: A Delphi consensus study. Lancet 2005;366:2112-7.
2. Kamer AR, Craig RG, Dasanayake AP, Brys M, Glodzik-Sobanskad L, de Leon MJ. Inflammation and Alzheimer's disease: Possible role of periodontal diseases. Alzheimers Dement 2008;4:242-50.
3. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, *et al.* Inflammation and Alzheimer's disease. Neurobiol Aging 2000;21:383-421.
4. Bertram L, Lill CM, Tanzi RE. The genetics of Alzheimer disease: Back to the future. Neuron 2010;68:270-81.
5. Fetler L, Amigorena S. Neuroscience. Brain under surveillance: The microglia patrol. Science 2005;309:392-3.
6. Schram MT, Euser SM, de Craen AJ, Witteman JC, Frolich M, Hofman A, *et al.* Systemic markers of inflammation and cognitive decline in old age. J Am Geriatr Soc 2007;55: 708-16.
7. Arosio B, Trabattoni D, Galimberti L, Bucciarelli P, Fasano F, Calabresi C, *et al.* Interleukin-10 and interleukin-6 gene polymorphisms as risk factors for Alzheimer's disease. Neurobiol Aging 2004;25:1009-15.
8. von Bernhardi R, Eugenin J. Microglial reactivity to beta-amyloid is modulated by astrocytes and proinflammatory factors. Brain Res 2004;1025:186-93.
9. Weitz TM, Town T. Microglia in Alzheimer's disease: It's all about context. Int J Alzheimers Dis 2012;2012:314185.
10. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. Nat Rev Immunol 2007;7:161-7.
11. Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM. Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. J Neurosci 2005;25:8843-53.
12. McGeer PL, McGeer EG. Inflammation, autotoxicity and Alzheimer disease. Neurobiol Aging 2001;22:799-809.
13. Konsman JP, Drukarch B, Van Dam AM. (Peri) vascular production and action of pro-inflammatory cytokines in brain pathology. Clin Sci (Lond) 2007;112:1-25.
14. Gosselin D, Rivest S. Role of IL-1 and TNF in the brain: Twenty years of progress on a Dr. Jekyll/Mr Hyde duality of the innate immune system. Brain Behav Immun 2007;21:281-9.
15. Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, *et al.* Inflammatory proteins in plasma and the risk of dementia: The rotterdam study. Arch Neurol 2004;61:668-72.
16. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, *et al.* The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004;292:2237-42.
17. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol 2002;52:168-74.
18. Kalman J, Juhasz A, Laird G, Dickens P, Jardanhazy T, Rimanóczy A, *et al.* Serum interleukin-6 levels correlate with the severity of dementia in Down syndrome and in Alzheimer's disease. Acta Neurol Scand 1997;96:236-40.
19. Nicoll JA, Mrak RE, Graham DI, Stewart J, Wilcock G, MacGowan S, *et al.* Association of interleukin-1 gene polymorphisms with Alzheimer's disease. Ann Neurol 2000;47:365-8.
20. Dantzer R, Konsman JP, Bluthe RM, Kelley KW. Neural and humoral pathways of communication from the immune system to the brain: Parallel or convergent? Auton Neurosci 2000;85:60-5.

21. Miklossy J, Kis A, Radenovic A, Miller L, Forro L, Martins R, *et al.* Beta-amyloid deposition and Alzheimer's type changes induced by Borrelia spirochetes. Neurobiol Aging 2006;27:228-36.
22. Ellen RP, Galimanas VB. Spirochetes at the forefront of periodontal infections. Periodontol 2000. 2005;38:13-32.
23. Riviere GR, Riviere KH, Smith KS. Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer's disease. Oral Microbiol Immunol 2002;17:113-8.
24. Foschi F, Izard J, Sasaki H, Sambri V, Prati C, Muller R, *et al.* Treponema denticola in disseminating endodontic infections. J Dent Res 2006;85:761-5.
25. Galimberti D, Scarpini E. Progress in Alzheimer's disease. J Neurol 2012;259:201-11.
26. Lee YJ, Han SB, Nam SY, Oh KW, Hong JT. Inflammation and Alzheimer's disease. Arch Pharm Res 2010;33:1539-56.
27. Claeysen S, Cochet M, Donneger R, Dumuis A, Bockaert J, Giannoni P. Alzheimer culprits: Cellular crossroads and interplay. Cell Signal 2012;24:1831-40.
28. Miller AJ, Luheshi GN, Rothwell NJ, Hopkins SJ. Local cytokine induction by LPS in the rat air pouch and its relationship to the febrile response. Am J Physiol 1997;272:R857-61.
29. Lee JW, Lee YK, Yuk DY, Choi DY, Ban SB, Oh KW, *et al.* Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. J Neuroinflammation 2008;5:37.
30. Tan ZS, Seshadri S. Inflammation in the Alzheimer's disease cascade: Culprit or innocent bystander? Alzheimers Res Ther 2010;2:6.
31. Garcia RI, Henshaw MM, Krall EA. Relationship between periodontal disease and systemic health. Periodontol 2000. 2001;25:21-36.
32. Socransky SS, Haffajee AD. Periodontal microbial ecology. Periodontol 2000. 2005;38:135-87.
33. Filoche S, Wong L, Sissons CH. Oral biofilms: Emerging concepts in microbial ecology. J Dent Res 2010;89:8-18.
34. Taubman MA, Valverde P, Han X, Kawai T. Immune response: The key to bone resorption in periodontal disease. J Periodontol 2005;76:2033-41.
35. D'Aiuto F, Graziani F, Tetè S, Gabriele M, Tonetti MS. Periodontitis: From local infection to systemic diseases. Int J Immunopathol Pharmacol 2005;18:1-11.
36. Preshaw PM, Taylor JJ. How has research into cytokine interactions and their role in driving immune responses impacted our understanding of periodontitis? J Clin Periodontol 2011;38:60-84.
37. Gatz M, Mortimer JA, Fratiglioni L, Johansson B, Berg S, Reynolds CA, *et al.* Potentially modifiable risk factors for dementia in identical twins. Alzheimers Dement 2006;2: 110-7.
38. Lee KS, Chung JH, Choi TK, Suh SY, Oh BH, Hong CH. Peripheral cytokines and chemokines in Alzheimer's disease. Dement Geriatr Cogn Disord 2009;28:281-7.
39. Park KM, Bowers WJ. Tumor necrosis factor-alpha mediated signaling in neuronal homeostasis and dysfunction. Cell Signal 2010;22:977-83.
40. Montgomery SL, Bowers WJ. Tumor necrosis factor-alpha and the roles it plays in homeostatic and degenerative processes within the central nervous system. J Neuroimmune Pharmacol 2012;7:42-59.
41. Yan Q, Zhang J, Liu H, Babu-Khan S, Vassar R, Biere AL, *et al.* Anti-inflammatory drug therapy alters beta-amyloid processing and deposition in an animal model of Alzheimer's disease. J Neurosci 2003;23:7504-9.
42. Heneka MT, Sastre M, Dumitrescu-Ozimek L, Hanke A, Dewachter I, Kuiperi C, *et al.* Acute treatment with the PPARgamma agonist pioglitazone and ibuprofen reduces glial inflammation and Abeta1-42 levels in APPV717I transgenic mice. Brain 2005;128:1442-53.
43. Holmes C, El-Okl M, Williams AL, Cunningham C, Wilcockson D, Perry VH. Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2003;74:788-9.

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