Original Article

Evidence of corelation between periodontal pathogens and alzheimers disease. A Systematic review

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Abstract

Alzheimer's disease (AD) seen in the aging population worldwide, is the most frequent type of dementia characterized by a progressive decline in memory.
This systematic review was conducted based on the indications of the Prisma protocol.
The formulation of the PICO question was as follows; what is the etiopathogenetic role of periodontal disease and periodontal bacteria in the onset and progression of Alzheimer's disease compared to unaffffected patients? After an initial selection phase of the records identifified from the databases, the potentially eligible articles were qualitatively evaluated to investigate the role of periodontal disease bacteria.
The literature search was conducted on the search engines PubMed, Scopus and Web of science between 10.09.2000 and 02.09.2022. With the application of the eligibility criteria, there were 397 articles. There were 89 articles that discussed the role of periodontal bacteria in the onset and progression of Alzheimer's disease; there were 28 articles after eliminating overlaps. After applying the inclusion and exclusion criteria, the result was a total of 7 articles for the qualitative analysis. Although the host–pathogen interaction appears to be a key factor in the pathogenicity of periodontitis, as to how periodontal disease can impact or translocate to the brain remains poorly understood.

1. INTRODUCTION

Alzheimer's disease (AD) seen in the aging population worldwide, is the most frequent type of dementia characterized by a progressive decline in memory, thinking, language and learning capacity, which ultimately ends in death. More than 37 million people are affected by it globally, with the highest prevalence in the elderly aged ≥65 years. (1,2) It has been speculated that with the increasing life expectancy and lifestyle changes, one in 85 people would be living with AD by the year 2050.

Although Alzheimer's disease is an age associated complex neurodegenerative disorder with multiple etiologies for initiation and progression, till date there is no confirmed or accepted model which can provide optimal explanation for the complex pathophysiology of this desolating disorder. The most significant hallmark of this disorder is the formation of extracellular amyloid β-peptide (AβP) plaques and intraneuronal neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein, followed by consequent loss of neuronal synapses and neuronal degeneration. This leads to diminution of essential neurotransmitters. (1) Enhanced expression of the amyloid precursor protein (APP) gene caused because of genetic aberration may be a risk factor for late-onset AD. Apolipoprotein epsilon4 (APOEε4) allele is genetically linked to majority of the AD cases. (2) AβP, the main component of amyloid plaques is derived from APP by proteolytic cleavage. Studies corroborate the hypothesis that APP and AβP are instrumental in the pathogenesis of AD. (3)

The NFTs are constituted of hyperphosphorylated forms of the microtubule-associated protein tau. The microtubule-associated tau protein is responsible for the stability of microtubules in neurons. Hyperphosphorylated tau is insoluble with low affinity for microtubules, jeopardizing the microtubule stabilization, thus conducing to synaptic dysfunction and neurodegeneration. Hyperphosphorylation of tau takes place because of inflammation, oxidative stress, up-regulation of tau kinases and down-regulation of phosphatases. (4) However, studies have revealed the interplay of other factors apart from the characteristic AβP plaques and intraneuronal NFTs for the complete evolution of AD. AβP exerts detrimental effects on the neurovascular endothelial cells, either by direct action or causing local inflammation.

Inflammation leads to AβP formation in the cerebral microvasculature and AβP, in turn, stimulates the release of pro-inflammatory mediators. Initially, AD was conceived as a disorder related to the augmentation in the synthesis and decline in the degradation of AβP. Now, impaired clearance is also stated as a co-factor. This hypothesis has been proposed as the "amyloid cascade hypothesis" of AD, with APP playing a pivotal role.
In AD, the neuroinflammation is significantly exaggerated. It is hypothesized that neuroinflammation may be a result of pro-inflammatory cytokines, reactive oxygen and nitrogen species, instrumental in activation of microglia and abetting the formation of NFTs.

Microglia cells are mononuclear phagocytes present in the brain, committed to thwart any noxious injury within the central nervous system and achieve brain homeostasis. In health, microglial cells maintain a neuroprotective function by clearing the AβP plaques.12 They also express several neurotrophic factors, such as insulin-like growth factor (IGF)-1, brain-derived neurotrophic factor, transforming growth factor-β and nerve growth factor. In states of peripheral or systemic inflammation, the molecular and cellular components extend the inflammatory signals to the brain via different pathways. Under normal conditions, the inflammatory response is suitably regulated to avoid uncontrolled inflammatory damage However, the normal regulatory mechanisms may become deficient with aging and genetic predisposition. Thus, a sustained inflammatory response persists. During these states, the microglial cells in the brain are programmed to switch their phenotypes to produce neurotoxic substances in event of exposure to the systemic inflammatory signals. Thus, instead of confronting with a protective response to these systemic inflammatory signals an exaggerated response is elicited by the diseased microglia, contributing to the pathogenesis of AD. The "fired up" microglia change its morphology and releases a number of cell antigens. These are referred to as 'activated microglia'. Activation of microglia results in expression of various pro-inflammatory factors. The uncontrolled release of these factors can induce neural damage. The microglial function may be likened to a "double-edged sword" being either damaging or protective depending on the context. (5) Chronic inflammation and cytokine up-regulation conduces to tau hyperphosphorylation in experimental mice model of AD. It has been observed 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.(6)

2. MATERIALS AND METHODS

This systematic review was conducted based on the indications of the Prisma protocol. The study was constructed on the PICO question: Population (patients with Alzheimer's disease), Intervention (periodontal disease and periodontal bacteria), Control (patients who do not suffffer from Alzheimer's disease), and Outcome (the role of periodontal bacteria and inflflammation induced by periodontal disease in the onset and progression of Alzheimer's disease). The formulation of the PICO question was as follows; what is the etiopathogenetic role of periodontal disease and periodontal bacteria in the onset and progression of Alzheimer's disease compared to unaffffected patients? After an initial selection phase of the records identifified from the databases, the potentially eligible articles were qualitatively evaluated to investigate the role of periodontal disease bacteria (Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, and Treponema denticola).

Eligibility Criteria

The works taken into consideration were systematic reviews, concerning the role of periodontal disease and bacteria in the onset and progression of Alzheimer's disease; we particularly considered articles investigating the role of bacteria such as Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Fusobacterium nucleatum, and Treponema denticola in association with Alzheimer's disease that were conducted recently and published in English. We focused on articles from the last 20 years because the investigation of a possible association between periodontal disease and Alzheimer's disease has only been undertaken in the last 20 years. The articles considered to be potentially eligible were those reporting on the association between periodontal disease and Alzheimer's disease, excluding articles published more than 20 years ago and that did not present an abstract in English. The potentially eligible articles were fifinally subjected to a full text analysis to verify their use for qualitative analysis. The inclusion and exclusion criteria applied in the full text analysis were the following.
• To include all those studies describing the association between Alzheimer's disease and periodontal disease.
• To include all articles describing the role of bacteria such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum and *Treponema denticola* in the onset and progression of the Alzheimer's disease.
• To exclude all studies that were not written in English and were published before 2000. • To exclude non-systematic literature reviews.

Research Methodology

Studies have been identifified through bibliographic research on electronic databases. The literature search was conducted on the search engines PubMed, Scopus and Web of science between 01.01.2000 and 02.09.2022.

Screening Methodology

The records obtained were subsequently examined by two independent reviewers and a third reviewer acted as a decision-maker in situations of doubt. The screening included the analysis of the title and the abstract to eliminate the records not related to the topics of the review. Specifically, the identifification of the articles related to the secondary

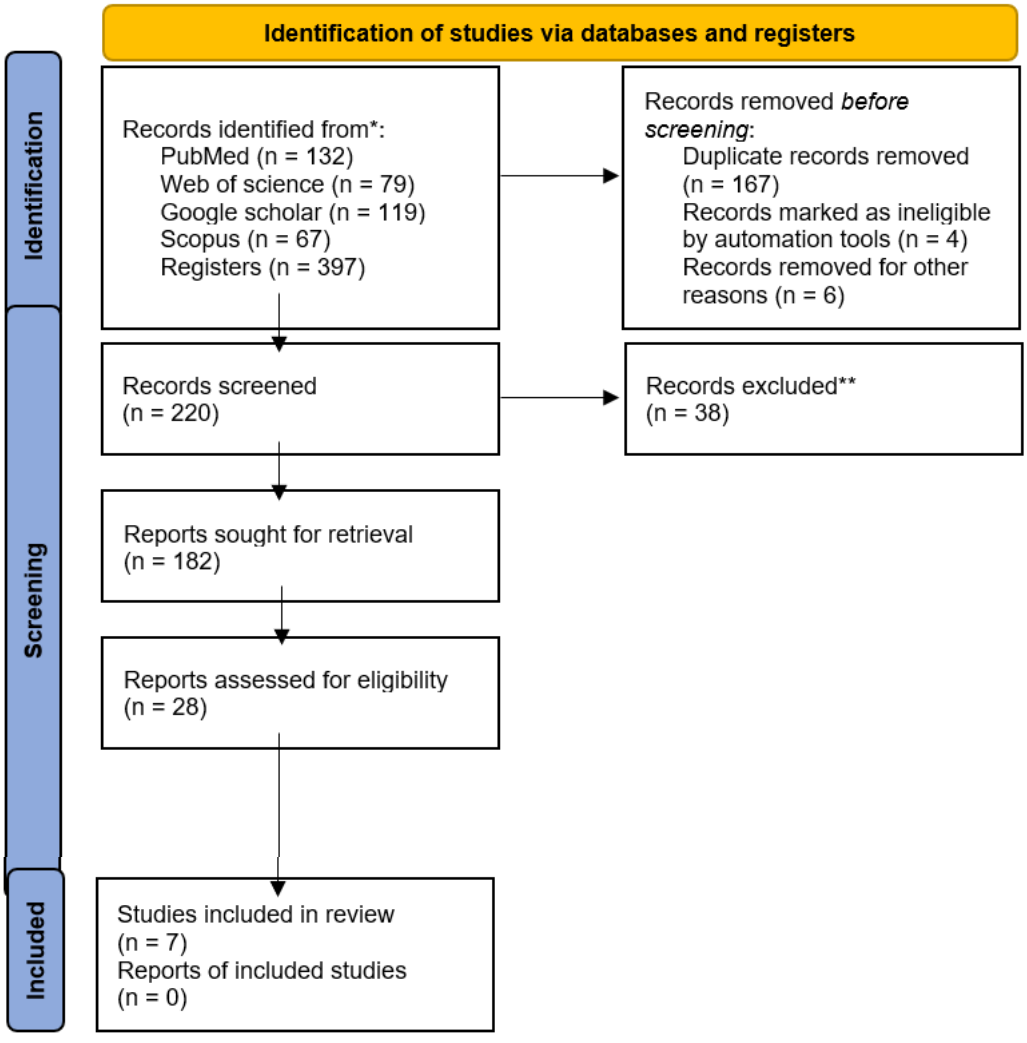
outcome topics was made for each key word analyzing the title; the abstract; and, in doubtful cases, the full text. The various articles, selected from each keyword, were grouped and subject to overlap removal. The choice to manually and subsequently remove only the screening phase was made to facilitate the manual removal procedure. After the screening phase, the overlaps were removed, and the complete texts of the articles were analyzed to identify those eligible for qualitative analysis.

The results sought by the two reviewers were as follows. (1) Primary outcome: associations between periodontitis and Alzheimer's disease. (2) Secondary outcome: associations between bacteria involved in the pathogenesis of periodontal disease and Alzheimer's disease.

RESULTS

With the application of the eligibility criteria (studies dealing with the topic of Alzheimer's disease in relation to oral inflflammatory processes and bacteria), there were 397 articles. There were 89 articles that discussed the role of periodontal bacteria in the onset and progression of Alzheimer's disease; there were 28 articles after eliminating overlaps. After applying the inclusion and exclusion criteria, the result was a total of 7 articles for the qualitative analysis. (Table 1)

Table 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



DISCUSSION

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:

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. (7)

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 includes 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.

Microbiology of Alzheimers Disease

The role of bacteria in the pathogenesis of Alzheimers disease is thought to be due to Chlamydia pneumoniae and spirochetes which is emphasized by certain studies. 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. (8) Spirochetes and Treponema denticola are commonly isolated microorganisms in moderate to severe periodontitis. (9) 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. (10) 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. The stability of microtubules in neurons is maintained by associated tau protein. But hyperphosphorylation of tau takes place because of inflammation, oxidative stress, upregulation of tau kinases, and downregulation of phosphatases. 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. 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. (11,12,13)

Periodontal Disease:

As a low-grade systemic disease periodontal disease (PD) is a condition that causes inflammation and destruction of the gingiva, 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. 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 (pocket formation), oral halitosis, spacing between the teeth, and mobility of teeth in advanced stages. The predominant periodontal pathogens involved in periodontitis are Aggregatibacteractinomycetemcomitans (Aa), Porphyromonas gingivalis (Pg), Prevotellaintermedia (Pi), Fusobacteriumnucleatum (Fn), Tannerellaforsythensis (Tf), Eikenellacorrodens (Ec),and Treponemadenticola (Td).(14)

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. 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. 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. 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 -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.

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. 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.[15]

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.

Alzheimers disease and periodontitis – Corelation

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. Two mechanisms have been put forth to explain the association of periodontitis and AD. 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 can compromise the BBB and entering the cerebral regions. This leads to priming/activation of microglial cells and the adverse repercussions leading to neuronal damage.

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. (16) Cytokines which are released (especially TNF-α) during inflammation play a 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. (17,18,19) 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. (20,21)

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. (22) Patients with elevated markers preceding a baseline level 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. (23,24)

Table 2- Summary of selected articles

Author	*Article*	*Type of study*	*Investigated microorganisms*	*Conclusion*
Ide, Mark, et al. (25)	*"Periodontitis and cognitive decline in Alzheimer's disease." PloS one 11.3 (2016): e0151081.*	*Observational cohort*	*P Gingivalis*	*Study shows direct relation between periodontitis and cognitive decline*
Ishida, Naoyuki, et al. (26)	*"Periodontitis induced by bacterial infection exacerbates features of Alzheimer's disease in transgenic mice." npj Aging and Mechanisms of Disease 3.1 (2017): 1-7.*	*Experimental study on Mice*	*P Gingivalis*	*Concludes that periodontitis is a risk factor for Alzheimers Disease*
Dominy, Stephen S., et al. (27)	*"Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors." Science advances 5.1 (2019): eaau3333.*	*Prospective pilot study*		*P Gingivalis and gingipains in the brain play a vital role in pathogenesis of AD*
Stein, Pamela Sparks, et al(28)	*. "Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease." Alzheimer's & Dementia 8.3 (2012): 196-203.*	*Longitudinal study*	*P Gingivalis, P Rectus*	*Possible association between antibody levels and onset and progression of AD*
Carter, Chris J., et al(29)	*. "The Porphyromonas gingivalis/host interactome shows enrichment in GWASdb genes related to Alzheimer's disease, diabetes and cardiovascular diseases." Frontiers in aging neuroscience 9 (2017): 408.*	*Bioinformatics study on databases*	*P Gingivalis*	*Supports many documented relationships between P. gingivalis infection and AD or its comorbidconditions*
Díaz-Zúñiga, J., et al. (30)	*"Serotype b of Aggregatibacter actinomycetemcomitans triggers pro-inflammatory responses and amyloid beta secretion in hippocampal cells: a novel link between periodontitis and Alzheimer´ s disease?." Journal of oral microbiology 11.1 (2019): 1586423.*	*Experimenatl study on cell line rat*	*A Actinomycemcomitans*	*Probable association between aparodontal disease sustained by Aggregatibacter and AD etiopathology*
Fujino, T., et al. (31)	*"Effects of plasmalogen on patients with mild cognitive impairment: a randomized, placebo-controlled trial in Japan." J Alzheimers Dis Parkinsonism 8.419 (2018): 2161-0460.*	*Clinical study*	*P Gingivalis T Denticola T forsythia*	*The data does not support an associative hypothesis*

CONCLUSION

The relationship between AD and periodontitis may be mediated through inflammation. However, there are no studies on animals that specifically address the causal relationship between AD and periodontal infection. Although the host–pathogen interaction appears to be a key factor in the pathogenicity of periodontitis, as to how periodontal disease can impact or translocate to the brain remains poorly understood. To completely understand the functional link between periodontitis and Alzheimer's disease and to develop timely therapies for the prevention and/or slowing of the disease, future combined clinical research in dentistry, immunology, and neuroscience will be essential.

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