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Erratum

A prior version of the article was initially published. This is the most recent and up-to-date version of the article.

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BACKGROUND

Alzheimer's Disease (AD) is a progressive neurodegenerative disease generally characterized by loss of memory, disorientation, and mood/behavioral changes. Advanced cases of AD may also include difficulty performing basic motor skills such as speaking and walking. There are two types of AD that lead to these devastating symptoms. Familial AD has an early onset and is linked to deterministic mutations in amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes [16]. On the other hand, sporadic AD has a late onset and is associated to both the apolipoprotein E (APOE) gene and environmental causes. Examples of environmental factors include exposure to pollution/asbestos, diet, tobacco usage, and exercise [26]. Prolonged neuroinflammation leads to the formation and prolonged presence of beta-amyloid plaques and neurofibrillary tangles (comprised of hyperphosphorylated tau proteins) that prevent normal neurological functioning; the two formations are key criteria necessary for official diagnosis of both familial and sporadic forms of the disease [24,41].

AD currently has no means of therapeutic intervention despite extensive molecular research, emphasizing the vast complexity of the disease. As a result, scientists expanded their prospects towards other potential therapeutic targets, taking large interest in the human flora. Though this flora is largely populated by bacteria, other organisms like archaea, protozoa, fungi, and viruses are also present in several systems of the body. This review article will focus on evidence published by various researchers that suggests microbial involvement plays a large role in the development and progression of AD.

Beta-Amyloid Plaques

APP, one of the proteins linked to familial AD, is responsible for synaptic stability and neuronal protection [9]. Normally, it is processed by α-secretase and γ-secretase to form soluble APPα [9]. Beta amyloid plaques are formed by accumulation of Aß40 and Aß42 peptides following aberrant processing of APP by ß- and γ-secretases [33]. Aß42 specifically is toxic and susceptible to aggregation compared to its counterpart, Aß40 [27]. Both frequent pathogen colonization and/or failure to remove these peptides via exocytosis to form soluble oligomers following appropriate use can lead to over-accumulation between the neuronal spaces [35]. This agglomeration leads to the formation of plaques that are responsible for deteriorating nigh brain tissue through the interception of cell function. Duplications of the protein-coding APP gene can also result in excessive proliferation of APP, leading to Aß build-up [9].

Conversely, recent research has proposed that Aß accumulations display antimicrobial properties, which supports the idea of plaque formation occurring as a response to microbial colonization. In a study comparing Aß activity against twelve microorganisms, Aß was reported to thwart further microbial growth [43]. These findings suggest amyloid plaques may be present as a result of defensive responses against pathogen colonization. Further research, however, has not yet been published quantifying healthy versus excessive amounts of the peptide in question. One of the major hypotheses in the development of AD suggests Aß protein to be the causative agent of Alzheimer's with subsequent hyperphosphorylation of tau proteins leading to cell loss and vascular damage [39].

Neurofibrillary Tangles

Tau, the main component of neurofibrillary tangles, is a protein that normally binds tightly to microtubules within the brain for functional stabilization [40]. Ordinarily, phosphorylated and non-phosphorylated tau proteins are present and regulated by tau kinases and phosphatases [31]. In the AD-inflicted brain, however, this balance is disrupted and the regulatory mechanism is impaired, causing tau to detach from their associated microtubules and attach to other tau proteins instead. This results in the hyperphosphorylation of tau proteins that assemble as tangles [41]. As a consequence, operations like axonal and dendritic transport are disabled.

Neuroinflammation

Cytokines, which are responsible for the regulation of immunity and inflammatory responses, have been found to have significantly elevated concentrations in the AD brain compared to baseline [44]. For this reason, increased neuroinflammation, plaques, and tangles are thought to work in a cyclic manner regarding brain tissue deterioration. Amyloid plaques, neurofibrillary tangles and prolonged inflammation lead to tissue damage, but

neuroinflammation also facilitates further formation of these debilitating structures [44].

Microglial cells are strongly associated with Aß buildup and enhanced inflammation of brain tissue. Microglial cells are the major cell type regarding immune responses. Upon activation, these cells produce cytokines as a defensive mechanism against pathogen and tissue damage [51]. Unfortunately, microglial cell activity is highly associated with neurotoxicity despite its intentionally helpful function [6]. When repeatedly stimulated, activation of these cells causes loss of ability to phagocytose Aß with continued output of cytokines [32], leading to swift increases in quantity of Aß present.

MICROBES

Microbes, in the eye of the general public, receive a bad reputation. In reality, the presence and exposure to an array of microbes can heavily improve the efficiency of the immune system and help regulate bodily functions [45]. The human microbiota is constituted by millions of diverse microbes. These microbes reside in nearly all regions of the body, but especially large aggregates are found in the gastrointestinal (GI) tract, skin, oral cavity, and respiratory tract.

Microbial Gut-Brain Axis

The gut-brain axis (GBA) is a bidirectional communication system between the central (CNS) and enteric nervous system (ENS). The CNS encompasses the brain and spinal cord; the ENS is a division of the autonomic nervous system that detects and maintains the physiological conditions of the GI tract and coordinates intestinal processes like motility, digestion, and barrier defense [17]. The appropriate development of both systems is reliant on the optimal balance of intestinal microbiota, affecting neurotransmitter expression and turnover rates [10]. In eubiosis, this communication system relays to the hypothalamic pituitary (HPA) axis, which acts as the core stress efferent axis and is responsible for coordination of adaptive responses within the organism [10]. Moreover, as part of the limbic system, the HPA axis is involved with memory and emotional response.

It is known that environmental stressors may activate this communication system, but recent research has pinpointed evidence of gut microbiota acting as a signaling component as well [5]. Study results involving communication between the vagal nerve and GI tract have found that gut microbes can indirectly stimulate the ENS via creation of neurotransmitters, short chain fatty acids, and/or bacterial metabolites [7]. These communications may also be introduced through bacteria that induce a similar effect to host hormones. Naturally, since gut microbes hold a large role in the regulation of the GI environment, it makes sense that dysbiosis may impede fine-tuned processes.

Gut Microbiota

The GI tract is home to over 10^{14} microorganisms that aid in metabolic and homeostatic responses such as enzyme synthesis, nutrient absorption, and production of short-chain fatty acids [10]. Though the intestinal flora accumulates during infancy and remains relatively consistent throughout an individual's life, patients with AD showed decreased richness and diversity of microbes in comparison to non-afflicted individuals of the same age [49]. Under this principle, it has been established that obesity has a complex but major role in the residential phyla of the gut. Multiple studies have compared the relationship between BMI and present flora to find that mid-life increases in BMI are correlated with phyla alteration that ultimately leads to greater risk for AD development [3,18]. Interestingly, the same studies discovered that late life increases of BMI protect against the progression of AD [3,18]. A low-power piloted study found Actinobacteria to be most abundant in postmortem AD brain samples, though this must be implemented on a multi-regional level to better understand the universality of this finding [52]. Irritable bowel syndrome (IBS) also has a strong correlation with the development of dementia secondary to hypothesized gut dysbiosis [12]. Both IBS and gastroenteritis (a great risk factor for development of IBS) have shown to be associated with a multitude of parasitic pathogens and their overgrowth.

There are few GI-involved pathogens specifically connected to AD. In a study involving AD association with infectious burden from viruses and bacteria, *Helicobacter pylori* was one of five pathogens to implement higher levels of serum Aß40 and Aß42, which interferes with synaptic function, compared to those uninfected [8,19]. It is suggested that *H. pylori*, which is typically responsible for gastritis and peptic ulcers through elevation of pH, also alters cognitive efficiency through neuroinflammation. Another study exploring the effects of *H. pylori* infection found the pathogen to be responsible for hyperphosphorylation of tau proteins which are fundamental for neurofibrillary tangles as mentioned before [50].

Though the causative role of dysbiosis needs further workup, evaluating the effects of antimicrobial properties have supported the idea of pathogen-influenced physiological changes. In a study of transgenic AD mice raised under germ-free conditions, less cerebral amyloid depositions were present in comparison to mice exposed to microbes [21]. Intriguingly, antibiotic treatment is associated with a decrease in fibril formation and an increase in cognitive function [46]. It is important to note that antibiotics vary in terms of ability to cross the blood

brain barrier (BBB) [34]. Rifampicin, a compound with penetrative potential, has shown a decrease in Aß toxicity and aggregation. A study involving mice has also shown broad-spectrum antibiotics to decrease tau phosphorylation [47]. Despite these findings, absence of microbiota did not equate to complete elimination of plaque development.

Oral Microbiota

Roughly 700 different microorganisms colonize the mouth to make up the oral microbiota [25]. While these microbes are responsible for medical issues such as dental caries, periodontal disease, and edentulism, they also have a strong association with AD [36]. Attachment of microcolonies in the form of biofilms, commonly known as dental plaques, can result in increased virulence of pathogens; buildup of dental plaque is commonly resolved by daily brushing of teeth but may reside if hygienic practices are not consistent or efficient [28]. Unless gingival ulcers are present, the routine brushing of teeth poses little to no risk for bacteremia to travel through the blood stream and colonize the heart and brain [4,22].

Pathogens that lead to periodontitis may colonize the oral cavity and form toxins that decay the teeth and nearby issue, which further increase the probability of spread [23,42]. *Porphyromonas gingivalis* is considered one the major infectious agents found in the brain of AD patients [15]. *P. gingivalis* may access the brain upon oral infection through several pathways, including monocytes, endothelial cells pertaining to the BBB, and/or cranial nerves [15]. Upon entering the brain, it is suggested that the bacteria are spread via the same mechanism through which it invades vascular tissue: it travels through connected pathways to reach an abundance of neurons [42]. In patients with active chronic periodontitis (CP) caused by *P. gingivalis*, a notable decline in cognition was reported in comparison to those demented without CP [23]. *P. gingivalis* infection can work in conjunction with genetic factors that pose increased risk of AD development, such as apolipoprotein E4 (APOE4) and triggering receptors expressed on myeloid cells (TREM1/TREM2). With a study involving *Apoe*$^{-/-}$ mice, three different bacterial oral infections were induced [38]. Only those infected by *P. gingivalis* showed infection of the brain and activation of complement pathways. A similar study with transgenic mice that overexpressed mutated human-APP were orally infected by *P. gingivalis*. Upon examination of their brains, cognitive function was deemed impaired and there arose an increase in deposition of plaques like those in AD patients [42].

Gingipains, the major virulence factor produced by *P. gingivalis*, are cysteine proteases made up of lysine-gingipain (Kgp), arginine-gingipain A (RgpA) and arginine-gingipain B (RgpB) [30]. Gingipains suppress interleukin-2 (IL-2) secretion, which is an extremely important humoral immune response to invasion [37]. This ultimately leads an inflammatory cascade to the brain that modifies the clonal formation of T helper 17 (Th17) cells, resulting in an immune cell population imbalance that works in favor of *P. gingivalis* [37]. These cysteine proteases may induce proteolysis of tau proteins to which the host attempts to compensate for, increasing production rates to maintain homeostasis [40]. With APOE4, the apolipoprotein itself is a large target for gingipain proteolysis which may result in the generation of neurotoxic fragments [30]. TREM2, which normally regulates inflammatory responses, serves as a phagocytic receptor for bacteria [16]. TREM1, with structural homology to TREM2, has also been linked with AD as *P. gingivalis* has proved to increase expression of the allele that is already a target for gingipain proteolysis (by Rgp) and degradation (by Kgp) [16]. These actions have a correlation with neuroinflammation following infection.

A study evaluating herpes virus simplex 1 (HSV 1) was also linked to increased risk for the development of AD. Multiple logistic regressions found that APOE4 frequency was much higher in those affected by both HSV1 and AD, signifying a strong risk factor when paired [8]. Though recurrence of HSV1 symptoms lessen with age, the connection between the virus and APOE4 may determine the extent of damage. Both the virus and apolipoproteins bind to heparin sulphate proteoglycans in cell plasma membranes which affects the number of cells infected. The mechanism of HSV1 as a vector, however, must be further investigated.

Respiratory Microbiota

The respiratory tract, with lower components previously thought to be sterile, actually harbors a large array of microorganisms that aid in resistance of pathogen colonization [13,14]. Acutely responsible for community-acquired pneumonia and asthmatic bronchitis, recent studies have pinpointed *Chlamydia pneumoniae* infection as a potential trigger for AD. Mice inoculated with *C. pneumoniae* demonstrated Aß42 deposits that steadily increased in number over the course of 1-3 months [29]. This microorganism has demonstrated elicitation of extreme inflammatory responses, which are characteristic in the AD brain [20]. With higher bacterial burden showed extremely high levels of tissue and cellular damage within the brains of AD patients. Data also suggests the load has a positive correlation with the presence of the APOE4 allele, though the role in neuropathogenesis is unclear [20].

Mycobiota

Fungal microbial flora makes up less than 1% of the human flora [48]. Fungi is most typically found either on

the skin or within the mucosal membranes of the human body. However, recent examination of brain tissue has unveiled the presence of fungal DNA and proteins in patients with AD [2] as well as fungal residues within neurons [37], all of which were not observed in control patients. Cerebrospinal fluid (CSF) may tell a lot about fungal contribution to AD. Within the CSF of those positive for Alzheimer's, chitin (the major component of fungal cell walls) has been identified [11].

Candida albicans is one of the major fungal organisms found in CSF. Candidemia, caused by *C. albicans*, proves the ability of fungi to cross the BBB via mucosal colonization [51]. Recent studies have shown *C. albicans* to increase activation of both interleukins and tumor necrosis factors, indicating the fungi can cause extensive neuroinflammation upon seepage into the BBB [51]. The presence of the fungus within the BBB additionally leads to enhancement of the development of Aß plaques due to their antimicrobial properties [43,51]. It is therefore plausible that formation occurs as a defensive response against *C. albicans*. Another cytoplasmic experiment has found AD brain tissue to have abnormally high amounts of tau when fungal infection has come into the equation, though this finding has not been verified through separate studies [37].

CONCLUSION

Though microbes are not considered to be the sole drivers in development and progress, there is paramount evidence supporting the association between dysbiosis and AD. Further research to understand exact mechanisms of pathogenesis and roles of individual microorganisms is imperative if there is any hope for a treatment or cure for AD. Although fungi has remarkable associations with AD, significance of the results are limited due to low quantity of animal studies. This is especially important considering the conceptual confliction with the amyloid cascade hypothesis.

It is known that genes like TREM1, TREM2, and especially APOE4 have a crucial role in the development of amyloid plaques and neurofibrillary tangles. It would appear that the presence of the APOE4 allele supports or promotes pathogenesis of several harmful microbes [20]. These genetic risks impose facilitation of pathogens through the BBB where they may induce neuroinflammation and/or development of neurologically debilitating structures.

Given limited understanding of AD, there is no guaranteed safety from the disease. However, there are several preventative measures indicated when considering aforementioned findings. For example, those with a higher genetic predisposition to AD yield better protection when they complete their full antibiotic course prescribed for common infections they may come across in their lifetime. Whether the antimicrobial treatment is in place for upper respiratory or oral infections, finishing the full course of these medications minimizes the risk of bacterial allocation and/or resistance by limiting the activation of microglia that leads to inflammation [6]. Proper oral hygiene may also serve as a pertinent step in prevention of oral-associated infections. Daily removal of plaques prevents aggregation of *P.* gingivalis bacteria responsible for gum disease [28]. Regarding the gut microbiome, weight maintenance, health-conscious diet and the consumption of probiotics help prevent the likelihood of gut dysbiosis by maintaining microbial diversity [1]. Since genetic changes may not be plausible, being proactively well-rounded in maintenance of one's health is thought to be a supportive factor in keeping distance from AD.

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