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Mini Review

The role of Microbiota in the Pathogenesis of Alzheimer's Disease

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Abstract

The World Health Organization has reported that in 2020 approximately 55 million people live with dementia worldwide with 10 million new cases every year. Alzheimer's disease (AD) is the most common form of dementia and contributes to 60-70% of dementia cases. The role of gut microbiota with host metabolic regulation that acts as a bridge between the food lipids and the health of AD individuals has become of major concern. Microbiome composition has been linked to neurodegenerative disease and plays a critical role in the gut and brain axis. Microbial fermentation may release short-chain fatty acids such as butyric acid that have a major influence on the gut-brain axis with effects on brain amyloid beta levels and plaque deposition. Butyric acid is involved in brain histone acetylation and deacetylation plays an important role in metabolic regulation, brain amyloidosis and the pathogenesis of AD. Several mechanistic studies are required to determine the underlying mechanisms for effective and safe probiotic treatment for AD and the relevance of gut dysbiosis may be the cause of the induction of the pathogenesis of AD. The safety of probiotic therapy for AD patients requires investigation with relevance to the induction of dyslipidemia and the release of bacterial lipopolysaccharides and amyloid beta from gram-negative bacteria needs to be controlled in these probiotic formulations. In this review, we will summarize the knowledge of the characteristics of the gut microbiota and the communication pathways of the microbiota-gut-brain axis, analyse the role of dysbiosis of the gut microbiota in the pathogenesis of AD, and highlight the modification of gut microbiota composition as a preventive or therapeutic approach for AD) and the benefits, limitations and safety of gut microbiota and probiotics on the metabolic regulation by LPS and lipids are required to delay or reverse the pathogenesis of Alzheimer's disease.

Keywords: Alzheimer's Disease; Probiotic; Short Chain Fatty Acid (SCFA); Lipopolysaccharide (LPS)

Abbreviations

SCFA: Short Chain Fatty Acids; LPS: Lipopolysaccharide; AD DISEASE: Alzheimer's Disease; GI: Gastrointestinal; NFTs: Neurofibrillary Tangles; GBA: Gut Brain Axis; CSF: Cerebrospinal fluid; HPA-Hypothalamic-pituitary-adrenal; BBB: Blood Brain Barrier; GABA: Gamma-aminobutyric acid; ENS: Enteric Nervous System; TMP: Traditional Persian Medicine; MD: Mediterranean Diet; CNS: Central Nervous System; ANS: Autonomic Nervous System; HPA: Hypothalamic-Pituitary-Adrenal

Introduction

The human body is inhabited by a wide variety of commensal microorganisms called microbiota. Many microbes colonize the skin and mucosal cavities (nasal, oral, pulmonary, and vaginal) but the gastrointestinal tract (GI) has trillions of bacteria, fungi, and viruses in symbiosis with the host [1,2]. According to recent research, the gut microbiota is not limited to the intestinal tract. There is a strong correlation between GI tract communication and central nervous system communication. Microbiota-gut-brain axis concepts have been developed as a result of research showing that gut microbiota has a major influence on brain processing [3,4].

A significant component of this crosstalk is the biochemical messengers produced by the microbiota. Different mechanisms can be used to facilitate bidirectional communication between the microbiota and its mammalian host. Short chain fatty acids (SCFAs) produced by the intestinal microbiota affect CNS development and homeostasis, immune response, host metabolism and gastrointestinal physiology [5]. An optimum state of microbiota is indispensable for homeostasis with SCFA important in the regulation of body weight, glucose metabolism, neurotropism, immunomodulation, hypersensitivity, inflammation, and in regulating normal growth and development. Genetic susceptibility and resistance to diseases are determined by the composition of bacteria in individuals.

Through their interaction with the gut-brain axis gut microbiota is thought to influence cognitive processes through the hypothalamic-pituitary-adrenal (HPA) axis, the central stress response system and immunogenic mechanisms [6]. Microbiota-host interactions have markedly improved in recent years but we still need to better understand gut-brain-microbiota interactions. New therapeutic targets may be developed by understanding the precise roles that these metabolites play in gut-brain interactions. SCFAs have the ability to directly and indirectly regulate CNS processes which in turn affect behavior and cognition for the treatment of CNS disorders [7]. These metabolites affect the growth and maintenance of healthy brain function and can also be used as dietary therapies. This current review gives information with relevance to gut-microbiota-brain interactions and Alzheimer's disease.

Food and nutrition guidelines for handling and processing of dairy probiotic products, fresh fruit, bread, meat and vegetables are essential and many food products may require cold preservation procedures to prevent minimal bacterial contamination. Bacterial contaminations with gram negative bacteria is associated with the generation of toxic lipopolysaccharides (LPS) structures that cause inflammation, hypercholesterolemia and amyloid beta aggregation [8,9] with relevance to neurodegeneration. There have been several publications on probiotics and the beneficial effects on delaying the progression for Alzheimer's disease (3-5). Probiotics have recently been suggested as potential therapeutic options for AD due to the close relationship between gut microbiota and AD. A probiotic is defined as a live microorganism that confers health benefits to the host when administered in adequate amounts. The presence of gram positive and gram-negative bacteria in probiotic products [10-15] such as dairy products (yogurt, cheese, etc.) to correct intestinal microflora and dysbiosis is now of major research interest. This mini-review discusses the role of microbiota, short chain fatty acids and LPS (gram negative bacteria) with relevance to the pathogenesis of Alzheimer's disease.

Microbiota-gut-brain axis

The majority of intestinal microbes are bacteria [16]. The three major phyla of gastrointestinal microbiota are Firmicutes, Bacteroidetes, and Actinobacteria [17]. There is a unique gut microbiota profile for each individual. Several nutrients and metabolites are extracted, absorbed and synthesized by the gut microbiota (bile acids, lipids, amino acids, vitamins, and SCFAs). Extensive study has focused on the immunoregulatory influence of the commensal gut microbiota on the both innate and adaptive immune systems [18]. Over the past decade significant research has been conducted on gut microbiota and gut-brain communication. A gut-brain axis (GBA) involves bidirectional communication between the central nervous system and the enteric nervous system both of which influence gut microbiota interaction [19]. In-depth research is now being performed on the microbiota-gut-brain axis which involves two-way communication mechanisms including cytokines, immunological responses, hormonal responses and neuronal signals [20]. Through humoral action the gut microbiome can affect brain activity via the vagus nerve. Consequently gut microbiota dysbiosis could result in cerebral malfunction [21].

Inflammatory metabolites and cytokines released by gut dysbiosis affect the blood-brain barrier (BBB) and the size of the brain. BBB permeability is controlled by innate immune cells such as mast cells and microglia and is sensitive to pro-inflammatory mediators, increased BBB permeability may make it easier for immune cells or mediators to enter the brain accelerating neuroinflammation [22].The gut and brain are bidirectionally connected through the central nervous system (CNS), autonomic nervous system (ANS), hypothalamic pituitary adrenal axis (HPA) and enteric nervous system (ENS) [23]as shown in Figure 1. The gut contains 500 million neurons that connect the gut with the brain. The vagus nerve is one of the largest nerves that connects the gut with the brain in a bidirectional manner [24,25].

A surprising number of neurotransmitters are produced by our gut cells as well as by microbes. Serotonin is produced by the gut to promote optimism, happiness and satisfaction [26] as is gamma-aminobutyric acid (GABA) a neurotransmitter that controls feelings of fear and anxiety [27]. Trillions of microbes residing in our gut produce various chemicals that affect the brain [28]. Gut microbiota also metabolize bile acids and amino acids to produce other chemicals that affect the brain [29]. There is a connection between the gut-brain axis and inflammation through the immune system. Inflammatory toxins produced by gram negative microbes such as LPS can cause various brain disorders like dementia, Alzheimer's disease and Schizophrenia [30].

The interactions between the gut microbiota and the CNS has been discussed in several research studies [31-33]. Research in animals has shown a close association between the hippocampus with the gut microbiota and probiotic bacteria [34]. The impact of microbiota on the hippocampus has been reported in aged mice [35]. The results from these experiments show that age-associated shifts of the microbiota have an impact on protein expression and key functions of the CNS. These finding are of importance to the gut brain axis in ageing and may provide future therapies to restore a young-like microbiota to improve cognitive functions by modulation of hippocampal synaptic plasticity and improve the quality of life in the elderly [36]. In other studies the effects of the age related changes in composition of gut microbiota is associated with the increased content of Gram-negative bacteria like Enterobacteriaceae. The release of LPS from these Gram-negative bacteria acts as endotoxin with the level of SCFAs (acetate, butyrate, and propionate) in the intestine of aged people reduced compared to young people [37].

Figure 1: Schematic diagram illustrating the gut-brain axis. Through the Central Nervous System (CNS), Autonomic Nervous System (ANS), Hypothalamic Pituitary Adrenal Axis (HPA),Immune System and Enteric Nervous System (ENS), the gut and brain are bidirectionally linked. Our gut microbiota metabolizes bile acids, amino acids, gut hormones, to produce other chemicals that affect the brain. There is a connection between the gut-brain axis (GBA) and inflammation through the immune system. Inflammatory toxins produced by microbes such as Lipopolysaccharide (LPS) can cause various brain disorders like dementia, Alzheimer's disease, Tumors, Schizophrenia, several Neurodevelopmental and Neuropsychiatric disorders.

Gut microbiota and metabolites on brain function

Microbes live in the gut of humans in complex communities and there are numerous metabolites produced by gut bacteria that may cause encephalotoxicity. In various bacteria, GABA, serotonin (5-HT), histamine, and dopamine are produced. These compounds function as neurotransmitters and neurotransmitter precursors in mood, behaviour and cognition [38]. The host and its gut microbiota produce a variety of metabolites including SCFAs that are crucial for the host's health. Acetate, propionate and butyrate are the most common SCFAs that function through G protein-coupled receptors or histone deacetylases [39].

Short chain fatty acids

SCFAs are organic monocarboxylic acids with up to six carbon atoms and are the major metabolites produced by bacterial fermentation of dietary fiber in the gastrointestinal tract. SCFA play a critical role in the microbiota-gut brain axis as most of them contain acetate (C2), propionate (C3), and butyrate (C4) [40-42]. Monocarboxylate transporters (MCTs) are responsible for absorbing SCFAs into the colon by H+-dependent or sodium-dependent monocarboxylate transporters [43]. The effects of SCFAs on gut health range from maintaining intestinal barrier integrity, mucus production and protection against inflammation to reduce the risk of cancer [44].

Despite the paucity of studies on physiological concentrations of SCFAs in the brain, the three metabolites are all measurable in cerebrospinal fluid (CSF), typically in the range of 0-171 M for acetate, 0-6 M for propionate, and 0-2 M for butyrate. Research conducted indicates [45], the high expression of MCTs in endothelial cells may promote SCFA crossing of the blood brain barrier (BBB). As reported by these studies [46], human brain tissue had average concentrations of 17.0 butyrate and 18.8 propionates pmol/mg. The SCFAs appear to be crucial to BBB function but also for maintaining its integrity which is closely connected with the careful regulation of the flow of molecules and nutrients from the bloodstream to the brain and plays a crucial role in brain development. Based on the experiment conducted by Germ-free mice showed decreased expression of tight junction proteins including claudin and occludin which resulted in a more permeable BBB from infancy through adulthood supporting the hypothesis that SCFAs affect BBB function [47].

Short chain fatty acids and the blood brain barrier

The BBB plays a crucial role to maintain the central nervous system's homeostasis [48]. In addition to endothelial cells and pericytes the BBB is composed of glial cells (oligodendrocytes, microglia, and astrocytes) as well as smooth muscle cells. The disruption of the BBB plays a crucial role in the onset and progression of

AD causing microglial activation to speed up neuroinflammation, oxidative stress and neuronal death. The GPR41 receptor for SCFAs has been found on endothelial cells. In addition to develop a healthy BBB SCFAs aid in the defence and repair of the BBB during diseases. The BBB permeability can be decreased in germ-free animals with sodium butyrate therapy [49]. NF-B nuclear translocation is inhibited by valproic acid, tight-junction proteins are destroyed and matrix metalloproteinase-9 is induced thereby reducing BBB breakdown and brain edema caused by middle cerebral artery blockage. SCFAs have been shown to adversely affect the BBB in AD as demonstrated in figure 2 and further research is required [50].

Figure 2: An overview of SCFAs' impact on Alzheimer's.

SCFAs from the gut microbiota passes the blood-brain barrier to reach the CNS and activates the CREB/BDNF signalling pathway and expressing memory-consolidation genes, they work on neurons to promote neuronal repair and regeneration. Additionally, by blocking the MAPK, NF-B, and other proinflammatory pathways in disease-related microglia and astrocytes, inflammatory factor release is decreased. Additionally, SCFAs take role in the pathogenic control of the Aβ and tau proteins, which ultimately lessens cognitive decline in AD. NF-B stands for nuclear factor-B, CREB for cyclic-AMP response element binding protein, BDNF for brain-derived neurotrophic factor, and MAPK for mitogen-activated protein kinase.

Gut microbiota dysbiosis linking Alzheimers disease

Diet, infectious agents, antibiotics and xenobiotics are constantly exposed to the gut's unique and dynamic microbiome [51,52]. Gut microbiota (GM) play many important roles in a healthy body including protecting against pathogenic organisms. During colonocyte differentiation and regeneration short-chain fatty acids (SCFAs) are produced by the microbiota by fermenting complex plant carbohydrates [53]. In addition to synthesize essential vitamins and amino acids GM also regulates fat metabolism and plays a role in immune system and its development [54,55].

Multiple factors can contribute to the instability of GM including infections, diet, exercise, sleep patterns, antibiotic exposure and multimorbidity. Dysbiosis of the gut microbiota is defined as an imbalance associated with poor outcomes [56] in which necessary microbial input is lost or ineffective and pathogenic microbes are spread. Multiple disease states result from dysbiosis and its pro-inflammatory effects [57]. GM dysbiosis has been associated with various immune-mediated disorders. There are a variety of chronic inflammatory diseases that can occur in the body. A few examples include inflammatory bowel disease (IBD) [58], rheumatoid arthritis [59], type 1 diabetes [60], multiple sclerosis [61], and systemic lupus erythematosus (SLE)as well as other neurological diseases such as Parkinson's disease, Alzheimer's disease and multiple sclerosis [62].

The role of lipopolysaccharide in health and disease

In gram negative bacteria LPS is a structural component of the cell wall. Polysaccharides are covalently connected to lipids. A dense network of these chains forms a gelatinous layer that protects bacteria by forming a shield on their surface. LPS is produced by enzymes and it keeps the outer surface of bacteria moist and slightly negatively charged. Several diseases have been linked to bacterial LPS also known as endotoxin [63] and include liver damage, neurodegeneration, chronic inflammation of the gut and diabetes [64]. Gut dysbiosis is associated with neuroinflammation a crucial aspect of AD pathophysiology. LPS and Gram-negative bacteria can transfer to the blood of older people because the intestinal epithelium becomes more permeable [65].

Figure 3: Gut dysbiosis producing LPS, Bacterial amyloid, Trimethylamine N-oxide (TMAO) and Alzheimer's Disease.

LPS in the pathophysiology of AD. The key contributing factors to the development of AD include amyloid plaques and intracellular NFTs, neuroinflammation, mitochondrial dysfunction, OS, IR, and chronic cerebral hypoperfusion. These elements are either directly or indirectly related to one another. Cerebral hypoperfusion brought on by severe atherosclerosis or endothelial dysfunction, IR, and mitochondrial dysfunction causes an increase in ROS levels, which in turn causes APP to be overexpressed and processed more quickly, tau to be hyperphosphorylated, and NFT pathology to develop, all of which contribute to neuronal death. A few of the variables that can cause inflammation include A, TBI, and infections. APP amyloid precursor protein, IR insulin resistance, NFT neurofibrillary tangle, OS oxidative stress, ROS reactive oxygen species, TBI traumatic brain injury are acronyms used in this article.

The impact of lipopolysaccharide on Alzheimer's disease

Research suggests bacterial endotoxins may contribute to amyloidosis and Alzheimer's disease by the deposition of amyloid beta plaques. The prolonged administration of bacterial LPS an outer cell wall component of Gram-negative bacteria mimics many of the degenerative and inflammatory characteristics of AD patients' brains. Among the characteristics of AD and LPS containing E.coli is the ability of amyloid-peptide (Aβ) to aggregate into fibrils which serve as the primary component of amyloid plaques. Certainly the ability of amyloid-peptide (Aβ) to form fibrils among brain cells is one of the characteristics of AD and LPS containing E. coli bacteria can form extracellular amyloid [66,67]. The results of [68] experiments suggest that celastrol can decrease NF-B, COX-2, and GSK-3 expression, as well as oxidative stress, in order to minimize LPS-induced cell death. Additionally these results suggest Gram-negative E. *coli bacteria are capable of synthesizing extracellular amyloid.* As a result of binding to the TLR4/CD14 complex on peripheral monocytes/macrophages or brain microglia LPS activates NF-B and boosts the production of cytokines including IL1, IL6, and TNF [69-71]. LPS-induced increases in β -AβPP and Aβ may be partially explained by overexpression of BACE-1/PS-1 and downregulation

of ADAM10 by LPS [72]. In addition, LPS entails adverse effects on the blood-brain barrier and interferes with LDL receptor related protein (LRP) which is necessary for the removal of Aβ from the brain [73]. High doses of LPS can damage the BBB enabling LPS to enter the brain more easily. The LPS can also be absorbed by macrophages or monocytes. In addition to triggering cytokine release LPS binds to endothelial TLR4 [74]. Also, LPS stimulates tau hyperphosphorylation [76]. Figure 3 illustrates how LPS can contribute to amyloid plaques, myelin damage and hyperphosphorylated tau in AD. Due to the uncertainty regarding the origin of LPS and other bacterial compounds in the brain the debate regarding exogenous infections against internal or external sources must be resolved. The presence of LPS in AD brains suggests that additional infectious agent molecules may also be relevant in subgroups where they may be mediated by other Toll-like receptors [77].

Amyloid plaques, myelin damage, and tau hyperphosphorylation are believed to occur in the AD brain because of LPS among other variables. Since LPS has been demonstrated in numerous laboratories to be present in human AD brains, LPS, TLR4/CD14 receptors, and Gram-negative bacteria may all be useful therapeutic and preventative targets for sporadic AD [78].

LPS and cholesterol linked to the risk of Alzheimer's disease

The amyloid precursor protein (APP), which is processed proteolytically by β- and -γ secretases, yields Aβ. In contrast, α-secretase may also cleave APP within the Aβ domain, preventing the subsequent generation of Aβ. The three secretases, including APP, are membrane-integral proteins that move via secretory and endocytic trafficking routes. Therefore, the membrane lipid composition may be crucial to the movement and metabolism of proteins linked to Alzheimer's disease [79]. Numerous studies demonstrate that the gut microbiota through its function in bile acid metabolism and the production of microbial products has the ability to change the blood lipid composition such as cholesterol [80,81]. A disturbance in cholesterol formation has numerous negative effects that controls many physiological processes including the generation of BA and the regulation of hormones [82]. Hypercholesterolemia has been associated with amyloid beta-peptide (Aβ) deposition and accelerates the AD-related pathology. In several studies the CNS had considerably higher quantities of formic acid-extractable Aβ peptides after diet-induced hypercholesterolemia and a direct correlation between total Aβ levels and total cholesterol levels in the plasma and CNS was found [83-85]. The role of LPS on hypercholesterolemia and amyloid beta aggregation is a possible culprit with relevance to AD pathology. LPS has been shown to induce NAFLD with disturbed sphingolipid, cholesterol and ceramide synthesis that may accelerate the pathogenesis of AD [86]. The hypercholesterolemic diet has been shown to increase beta-amyloid burden by increasing both the quantity and size of the deposits. Probiotic diets that contain gram negative bacteria release LPS that induce excessive cholesterol levels and worsens AD-related pathology accelerating Aβ buildup. In order to reduce the risk of AD it is thus suggested that a therapeutic probiotic diet should be implemented [87]. This therapeutic probiotic diet needs to activate the gut-liver-brain axis to reverse hypercholesterolemia and amyloid beta aggregation in AD individuals.

Potential Theurapeutics for Alzheimer's disease

Alterations in the gut microbiota's composition and diversity due to ageing, infections, unhealthful eating patterns and lifestyle choices may initiate the beginning and development of neurodegenerative diseases such as AD as changes in intestinal permeability, BBB dysfunction, and neuroinflammatory processes are all tightly associated with dysbiosis [88,89]. In order to treat AD cognitive symptoms only a small number of medications such as AChEIs galantamine, tacrine, and donepezil have received FDA approval [90]. Traditional Persian Medicine (TPM) recommends several dietary changes to prevent and treat dementia. The microbiome's composition is influenced by dietary choices and a meat- and dairy-based diet increased the abundance of Bacteriodes while decreasing the abundance of Firmicutes. Studies reveal that plant-based diet high in grains, legumes, fruits and vegetables led to a rise in the number of Firmicutes that digest fibre including Eubacteria and Roseburia which raises the level of short-chain fatty acids [91].

No extensive research has been conducted on the possible impact of nutrition on AD development. In some cases dietary habits can prevent the development of neurodegenerative diseases such as the Mediterranean diet and vitamin supplements but the effects of dietary changes on AD therapy remain unclear [92,93]. In addition to the considerable evidence linking high-carbohydrate diets to AD altered glucose metabolism has also been suggested as a possible contributing factor. As a result of persistently high levels of dietary sugars AD has been linked to insulin resistance [94]. There is no effective therapeutic agent for AD and novel therapeutic approaches have attracted attention in recent years. Probiotics have recently been suggested as potential therapeutic options for AD due to the close relationship between gut microbiota and AD. Although most studies support the beneficial effects of probiotic supplementation on AD in many aspects such as cognitive deficit and related histological parameters [95].

Probiotics should be used more rationally to treat AD with more effort and intensive research required [96]. Although oxidative and inflammatory pathways have been implicated in the effects of probiotics on AD there are likely to be other pathways which need to be clarified. Several studies have indicated alterations in gut microbiota are associated with AD-related behavioral and histologi-

cal symptoms [97]. Hence microbiota targeted interventions may represent a promising therapeutic strategy for AD [98,99]. Beneficial bacteria known as probiotics modulate intestinal microbiota composition and function, facilitate digestion and nutrient absorption and may modulate the epithelial and immune responses of the host. As a result they are vital to maintaining immune homeostasis [100]. Studies with piglets showed that the lactic acid bacteria, *Enterococcus faecium (E. faecium)* decreased levels of IL-1β, IL-6, IL-8 and IL-12 in jejunal and ileal mucosa and upregulated IL-10 expression resulting in anti-inflammatory responses [101]. Furthermore, probiotics like E. faecium possess antioxidant properties since they reduce ROS levels in the hippocampus when supplemented *in vivo* [102-103]. To treat diabetic rats a mixture of probiotics (Lactobacillus acidophilus, Bifidobacterium lactis and Lactobacillus fermentum) was administered.

Conclusion

Therapeutics such as probiotics exert a beneficial effect on host gut microbiota after consumption and may be capable to prevent several diseases such as AD. Fermented dairy foods, cheese whey and buttermilk whey offer suitable matrices for the growth and viability of probiotic microorganisms and are potential sources for the development of probiotic dairy-based beverages. The literature shows that the heterogeneous food matrices of non-dairy food carriers are the major constraints for the survival of the probiotics and the use of antioxidants in yogurt manufacture. Dairy consumption such as sour/fermented milk, yogurt, cheese, butter/cream, ice cream, and infant formula need to be assessed for the content of microbial diversity. The role of fermentation, freezing/thawing, room temperature modification and probiotic shelf life may have a critical effect on the generation of LPS from gram negative bacteria that may lead to dysbiosis. The association between high fat/high cholesterol diets have been shown to be linked to the increased incidence for Alzheimer's disease (AD). The literature shows strong evidence with relevance to changes in cholesterol metabolism and transport that is associated with AD pathogenic processes. The understanding of the role of gut microbiota and the metabolic regulation of food lipids is now important to the induction of AD. Diets that contain low, medium and high fat have been shown to influence gut microbiota and functional foods and probiotics exert a beneficial effect on host gut microbiota and may be capable to prevent several diseases such as AD. Probiotics in food determine the composition of gut bacteria with dysbiosis that now are connected to the generation of LPS and toxic lipids from the liver such as sphingolipids and ceramides. The gut-brain-microbiota interactions may induce abnormal liver lipid metabolism and hypercholesterolemia that may accelerate AD with LPS and toxic lipids shown to be involved with accelerated brain amyloidosis with increased risk of AD. The use of beneficial probiotics in therapeutics may improve lipid metabolism and reverse hypercholesterolemia that is connected to amyloidosis and Alzheimer's disease.

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