American Journal of Medicine and Medical Sciences 2017, 7(5): 221-228
DOI: 10.5923/j.ajmms.20170705.03

Alzheimer and Helicobacter Pylori; Should We Fight and Kill or Save H. Pylori!! We Should Save H. Pylori

Abdullah M. Nasrat[1,*], Randa M. Nasrat[2], Mohammad M. Nasrat[3]

[1]General Surgeon, Zytona Center, Medina, KSA
[2]Department of Internal Medcine, Helwan General Hospital, Helwan, Egypt

Abstract This review study aimed at assessment of the bacterium ***Helicobacter pylori*** whether it is guilty, not guilty or innocent towards the brain and Alzheimer disease (AD). AD is a chronic age-related degenerative disease characterized by loss of cognitive and memory functions. A genetic theory was suggested while the amyloid hypothesis is the most accepted. There are many medical pathologies that could contribute to Alzheimer such as diabetes, hypertension and dyslipidemia. Other factors like toxic elements, air pollution and nutrition are also under consideration. A lot of controversy entails the influence of systemic ammonia and the endothelial-liberated nitric oxide (NO) on the pathogenesis of the amyloid disease and in turn on the onset and progress of Alzheimer disease. Elevated levels of ammonia is toxic and is associated with progress of the amyloid disease and dementia symptoms. Excess NO is involved in nitro-oxidative stress sequels resulting in endothelial and neuronal degeneration. Meanwhile, the normal level of ammonia could help to maintain the neuro-protective function of NO via its endothelial liberation due to the effect of shear stress. Accordingly, the normal-behavior ***H. pylori*** strains in the stomach could be biologic and healthy towards Alzheimer and the brain while the colonic ***H. pylori*** strains could be considered pathologic and toxic to the brain and dementia symptoms. AD remains a disease without real cure or prevention because of permanent degeneration of some areas of the brain; therefore, attempts to delay the onset and symptoms of Alzheimer constitute intelligent and practical strategies. Eradication of colonic ***H. pylori*** strains via natural colon clear might be the most effective measure among these strategies as it eliminates the main pathologic source with its greater toxic influence in addition to amelioration of other factors contributing to AD such as diabetes, hypertension and dyslipidemia. On conclusion, ***H. pylori***-produced ammonia in accordance could constitute at the mean time a cure and a poison towards Alzheimer while the natural existence of the bacterium ***H. pylori*** is biologic and protective; hence, it should be saved not killed.

Keywords Alzheimer, Dementia, Helicobacter pylori, Senna purge, Vinegar

1. Aim

The aim of this review study of the literature is attempting to approach a conclusion whether the bacterium ***Helicobacter pylori*** is healthy or toxic to the brain and whether it is biologic or pathologic as concerns the onset and progress of Alzheimer disease (AD) in addition to assessing the observational findings concerning the association between the colonic ***H. pylori*** strains and the frequency of Alzheimer during late decades.

2. Introduction

AD is a chronic, progressive and prevalent neuro-degenerative disease characterized by loss of higher cognitive functions with an associated memory loss. Alzheimer is the most common age-related degenerative disease. It should be admittedly that a lot is not known about Alzheimer's. More than 100 years after its discovery, it is still not exactly known what causes this neuro-degenerative disease and an exact cure is still not known. However, it is important not to lose sight of how far what has been achieved since the unique symptoms of the disease were first noticed; the interest and hope in realizing fundamental cure should not be lost. AD was first described in 1906 in a female patient who experienced memory loss, paranoia and psychological changes. Autopsy revealed shrinkage in and around nerve cells in her brain. Cognitive measurement scales were created in 1968 which allowed researchers to investigate degree of impairment and estimate the volume of damaged brain tissue. A National Alzheimer's Disease Genetic Study started in 2003 to hopefully identify risk genes for the disease. In 2010, Alzheimer's was considered the sixth leading cause of death in the United States [1, 2]. There still a lot of work ahead is needed to find a cure or at least control of the challenge of Alzheimer's.

* Corresponding author:
abdullahnasrat@hotmail.com (Abdullah M. Nasrat)
Published online at http://journal.sapub.org/ajmms

Dementia is defined as a clinical syndrome characterized by variety of symptoms and signs manifested by difficulties in memory or memory loss, disturbances in language and cognitive functions, changes in behaviors and impairments in activities of daily life. AD is the most common cause of dementia accounting for up to 75 % of dementia cases, AD is a progressive and challenging neuro-degenerative disorder. During the last few decades, epidemiological study of the disease has noticed tremendous progress in its researches and marked increase in the disease incidence [3].

Alzheimer's disease represents an increasing challenge to public health and the health care system which has had tremendous impact on both the individual and societal levels. Epidemiologic researches have provided sufficient evidence that vascular risk factors in middle-aged and older adults play a significant role in the development and progression of dementia and AD whereas extensive social network and active engagement in mental, social, and physical activities may postpone the onset of dementia. Multi-domain community intervention trials are warranted to determine to what extent preventive strategies toward optimal control of multiple vascular factors and disorders as well as the maintenance of an active lifestyle are effective against dementia and AD [1, 3].

Population aging has become a worldwide universal phenomenon. The number of older people (65+ years) in the world is expected to increase with the proportion of older people being increased from 7% to 12%. Developing countries will see the largest increase in absolute numbers of older persons. As the occurrence of AD is strongly associated with increasing age, it is anticipated that the disorders of dementia will pose huge challenges to public health and elderly care systems in all countries all over the world [3].

Concerning prevalence, the pooled data of population-based studies in Europe suggests that the age-standardized prevalence in people 65+ years old is 6.4 % for dementia and 4.4 % for AD. In the US, the study of a national representative sample of people aged >70 years yielded a prevalence for AD of 9.7 %. Worldwide, the global prevalence of dementia was estimated to be 3.9 % in people aged 60+ years. More than 25 million people in the world who are currently affected by dementia are mostly suffering from AD with around 5 million new cases occurring every year. The number of people with dementia is anticipated to double every 20 years. The age-specific prevalence of AD almost doubles every 5 years after the age of 65 [1, 2, 4-6].

The pooled incidence rate of AD among people 65+ years of age in Europe was 19.4 per 1000 person-years. The pooled incidence of population aged 65+ years in US yielded an incidence rate for AD of 13.0 in males and 16.9 in females per 1000 person-years. The incidence rate of AD increases almost exponentially with increasing age until 85 years of age [7-9].

Alzheimer's dementia is a multi-factorial disease in which old age is the strongest risk factor suggesting that the aging-related biological processes may be implicated in the pathogenesis of the disease. Furthermore, the strong association of AD with increasing age may partially reflect the cumulative effect of different risk and protective factors over the lifespan including the effect of complex interactions of genetic susceptibility, psycho-social factors, biological factors and environmental exposures over the life. Various etiologic hypothetical studies support the role of genetic, vascular, and psycho-social factors in the development of AD whereas evidence for the etiologic role of other factors such as dietary or nutritional factors, occupational exposures and inflammation is insufficient [10].

AD significantly shortens life expectancy and is one of the principal causes of physical disability and impaired quality of life. Epidemiologic studies have confirmed that AD is associated with increased risk of death for older people in a similar extent to that of malignant tumors. Several follow-up studies showed that AD was associated with a two to five-fold increased risk of death. The years of survival for people with newly diagnosed AD ranges from 3 to 6 years [11, 12].

3. Review

The genetic hypothesis of the disease which accounts for only about 2 to 5 % of all Alzheimer patients emphasizes that early-onset familial AD is often caused by autosomal dominant mutations such as mutations in amyloid precursor protein [13]. According to the vascular hypothesis moderate to strong evidence from multidisciplinary research works has emerged supporting the concept that vascular risk factors such as smoking, alcohol consumption, obesity and high total cholesterol together with vascular morbidity factors such as hypertension, diabetes, silent brain infarcts and white matter lesions are associated with an increased impact on the risk of dementia including AD [14-26].

Silent strokes or small spots of dead brain cells were found linked to memory loss in the elderly people in a rate about one out of four. Both hippocampal volume and brain infarcts independently contribute to low memory performance in elderly individuals. A group of 658 people aged 65 and older were studied by MRI for silent strokes and hippocampal shrinkage; 174 of them were found having silent strokes and they scored worse on memory tests. A small hippocampus, which is the memory center of the brain, related to silent strokes was considered a new clue as regards why some older people lose their memory leading to the development of a new intervention for prevention of Alzheimer via stroke prevention as a mean for staving off memory problems [27].

Air pollution may contribute to white matter loss in the brain; long-term exposure to air pollution may pose risk to brain structure and cognitive functions among middle-aged and older adults. It was found that air pollution over long periods could have impact on brain shrinkage with time and other risks including stroke and dementia. On the other way, having a purpose in life, physical or simple modified aerobic activities and mental activities might improve health of aging

brain [28-31].

Other factors that could have an impact on the development of Alzheimer's include nutritional or dietary pattern, educational and economic status, social engagement, physical or mental activity and traumatic head injury. Further important factors include inflammation, toxic exposure and pathogens [31].

The emerging roles of pathogens in leading to Alzheimer via causing slowly progressive dementia, cortical atrophy and amyloid deposition have supported a hypothetical research concept that dementia might be prevented by the combined effect of antibiotic, antiviral and anti-inflammatory therapies. A possible link of the influence of the abnormal-behavior ***Helicobacter pylori*** strains in AD has been documented in literature. An association was found between ***H. pylori*** and AD but the contribution of ***H. pylori*** in the neuro-inflammatory process in Alzheimer was not confirmed or denied [32]. AD is associated with amyloid beta peptide deposition that could lead ultimately to neuro-degeneration. An infectious hypothesis is suggesting an alteration of the blood-brain barriers (BBB) and activation of a neuro-inflammation in the brain which could play a role in AD especially in the presence of decreased amyloid beta peptide clearance. Several viral or bacterial agents have been incriminated including ***H. pylori***; ***H. pylori*** can induce systemic inflammation and increase homocysteine levels contributing to worsen AD [33, 34]. Homocysteine levels and amyloid beta peptide levels were found elevated in association with Alzheimer and ***H. pylori***. AD patients associated with existence of ***H. pylori*** tend to show more cognitive impairment [35, 36].

As concerns the role of ***H. pylori*** in neurological diseases such as Alzheimer's, since the latest decade several studies have reported on the link between chronic ***H. pylori*** infection and a variety of extra-gastric manifestations including dementia. A recent longitudinal population-based cohort study found that after 20 years of follow-up, 28.9% of ***H. pylori***-positive versus 21.1% of ***H. pylori***-negative subjects developed dementia. Existence of ***H. pylori*** usually persists throughout life resulting in a chronic inflammatory response with local secretion of numerous inflammatory mediators including chemokines such as interleukin and cytokines such as tumor necrosis factor and interferon which can pass into the circulation and have a systemic effect. The persistence of detectable systemic and local concentrations of inflammatory mediators is likely to alter the outcome of neurological diseases. These pro-inflammatory factors can induce brain inflammation, death of neurons and could eventually be involved in the development of AD. Although most neurological diseases are the result of a combination of multiple factors, yet the systemic inflammatory response is a common component and determinant in the onset, evolution, and outcome of diseases in general. However, a sufficient understanding of the mechanism by which the inflammatory response generated by ***H. pylori*** affects neurological diseases is still required [37-39].

The pathologic behavior of the abnormal-attitude ***H. pylori*** strains includes its migration or being forced to migrate to the colon under the influence of antibiotic violence. ***H. pylori*** in the colon will continue producing ammonia for a reason or no reason, unopposed or buffered by any acidity, leading to accumulation of profuse toxic amounts of ammonia, ammonia is neuro-toxic and toxic to the brain; hepatic ammonia encephalopathy is a frank example. The elevation of ammonia concentrations progressively leads to impaired mental status as concerns cognitive and memory functions. It has been also shown that exposure of rat hippocampal slices to high ammonia concentrations compromised the neuro-receptors. It was found that elevated levels of ammonia impairs memory and cognition in animals [40-44].

The amyloid hypothesis is the classical theory explaining AD pathogenesis and hence is currently targeted for drug development; Alzheimer's is marked by progressive accumulation of beta amyloid peptide which appears to trigger neuro-toxic and inflammatory sequels. The hypothesis signifies that certain cellular proteins which are normally soluble in the living organisms, under certain conditions change behavior to form aggregates with a specific structure called beta amyloid. These intra or extra-cellular insoluble aggregates whether fibers or plaques constitute marks of many neuro-degenerative pathologies including AD. Amyloidoses are widespread disorders in the elderly human population showing rapid demographic expand in many global population. Increasing age is the most significant risk for these degenerative diseases associated with amyloid deposition. Role of amyloidosis in the pathogenesis of AD and dementia development has been significantly and adequately confirmed in literature [45-47]. Beta amyloid peptides exert pro-oxidant or anti-oxidant effects based on the metal ion concentrations that it sequesters, at low metal ion concentrations it is an anti-oxidant whereas at relatively higher concentration it is a pro-oxidant. Therefore; increased oxidative stress in the human brain includes accumulating evidences that could be a key causative factor for AD and treatment strategies could be hence largely based on beta amyloid clearance [48].

Does ammonia play an essential role in amyloid disease of the CNS!! The excessive formation of ammonia in the brain of AD patients has been demonstrated and it has been also shown that AD patients exhibit elevated serum ammonia levels. The formation of amyloid plaques is currently considered as the key event of AD. The histological hallmarks of the disease include formation of fibrillary tangles and astrocytosis in some cortical areas of the brain. Among the toxic factors which have been considered to contribute to the symptoms and progression of AD, ammonia deserves special interest for many reasons; 1. Ammonia is formed in nearly all tissues and organs of the vertebrates and it is the most common endogenous neuro-toxic compound, 2. Several symptoms and histological sequels of hepatic ammonia encephalopathy caused by impairment of ammonia detoxification resemble those of AD, 3. Ammonia is the most important natural modulator of lysosomal protein

processing and there are sufficient evidences for the involvement of aberrant lysosomal processing of beta-amyloid precursor protein in the formation of amyloid deposits, 4. Ammonia is able to affect the characteristic functions of microglia such as endocytosis and cytokine production whereas inflammatory processes and activation of microglia are widely believed to be implicated in the pathology of AD. It has been further reported that elevated level of serum ammonia causes biochemical and cellular dysfunctions in the brain which can be found in the brain of dementia and AD patients. Experimental attempts were made to demonstrate evidences in favor of the idea that ammonia plays a definite role in dementia of the Alzheimer type. Astrocytosis and impairment of neuro-transmission with net increase in excitability and glutamate release were considered among these evidences. Derangement of lysosomal processing of proteins is another potential site of ammonia action which is especially important in view of the growing evidence for the role of the endosomal-lysosomal system in the formation of amyloidogenic fragments from beta-amyloid precursor protein. Based on these facts, an ammonia hypothesis of AD has been first suggested in 1993 which is in support of the findings that ammonia is a factor able to produce symptoms of AD and to affect the progression of the disease [48-50].

All living organisms produce ammonia as a by-product of cellular metabolism, ammonia is the major end product of cellular amino acid metabolism. Ammonia is a highly toxic material in animals at even sub-millimolar concentrations. At high concentrations, ammonia is toxic and can cause adverse effects to the cell. Effects include disruption of cellular energy metabolism, mitochondrial dysfunction, modulation of inflammatory responses and neuro-transmission in neurons. Existing evidences suggest that accumulation of ammonia in the brain affects neuronal function and may lead to several neurological abnormalities [51-55]. In mammalian brains, ammonia is derived mostly from protein metabolism. In the brain, ammonia is derived from two main pathways; endogenous and exogenous sources. Endogenous sources of brain ammonia involve hydrolysis of proteins and degradation of amino acids [49, 50, 56]. Exogenous sources produce large quantities of ammonia in the gastro-intestinal tract resulting from bacterial splitting of urea and de-amination of amino acids. Bacterial infections in the gut are major causes of accumulation of ammonia in the brain [54, 57]. In addition to the fact that ammonia can diffuse BBB due to its small size and uncharged state leading to major toxic damage in the brain. Elevated ammonia could also dissociate changes in BBB morphology and permeability allowing other toxins to diffuse with all expected bad sequels [54, 58, 59]. In most animal species, including mammals, the ammonia concentration of body fluids is typically low, high concentrations are usually toxic to mammalian cells [55, 60]. The elevation of ammonia concentrations progressively leads to impaired mental status as concerns cognitive, learning, and memory functions. It has been shown that exposure of rat hippocampal slices to high ammonia concentrations compromised the neuro-receptors. It was found that elevated levels of ammonia impairs memory or conditioned learning in animals [43, 44]. In most species, including mammals, ammonia concentrations exceeding 1 mmol/L are usually toxic to mammalian cells. Because of its toxicity an effective ammonia detoxification or excretion system is crucial to maintain cellular and body fluid ammonia levels within a tolerable range to ensure normal systemic functions [48, 54, 61].

Nitric oxide (NO) is an intelligent molecule produced by neurons and endothelial cells in the brain. The endothelial NO is essential for the integrity of the micro-capillary vasculature and it acts in the neurons as a neuro-transmitter. It is consistent that NO has got a significant neuro-protective role. NO is a specific micro-capillary vasodilator, the challenge and intelligence in NO is its specific production in response to particular requirements and its approach to a specific targeted pathological site such as in Alzheimer's. Unlike medicinal preparations like Viagra, NO could include toxic side-effects on the heart, blood pressure or the retina because of lack of specificity [48, 62, 63]. NO deficiency is associated with progression of AD and abscence of NO synthase 3 increases beta amyloid disease pathology in mice; it has been reported that fibrillary beta-amyloid deposits are closely associated with atrophic nitric oxide synthase [63-65]. Whereas NO can be scavenged in a rapid reaction with superoxide (O2-) to generate peroxynitrite (ONOO-) which is a potent oxidant and the primary component of nitro-oxidative stress. At high concentrations ONOO- can undergo homolytic or heterolytic cleavage to produce highly reactive oxidative components and secondary components of nitro-oxidative stress. This high nitro-oxidative stress can initiate a cascade of reactions that can trigger and evoke neuronal and endothelial degeneration similar to what is observed in AD. The role of oxidative stress and nitro-oxidative stress associated with increased systemic ammonia in AD has been sufficiently emphasized in literature. The vast accumulating evidences that increased oxidative stress in the human brain is a key causative factor for Alzheimer have attracted the treatment strategies towards this field [48, 63]. Accordingly, NO could constitute a cure and a poison at the mean time in AD.

The natural biological behavior of the bacterium ***H. pylori*** includes its existence under the shelter of the gastric mucus layer. ***H. pylori*** colonized the stomach since an immemorial time as if both the gastric wall and the bacterium used to live together in peace harmless to each other. The bacterium does not exist in the gastric lumen during presence of food where it stays settling on the gastric mucosa protected from any acidity reaching adjacent to the gastric wall by the ammonia produced at its immediate vicinity, protecting in turn the gastric mucosa from its acid if it goes in excess. The bacterium gains nutrition from food remnants after travel of the meal from the stomach and drop of the acid to a minimum in a blink-like momentum protected by a shield of ammonia and leaving some scattered ammonia after it in the

gastric lumen. This scattered ammonia excites the gastric wall to secrete its acid to buffer the ammonia; ***H. pylori*** in this way protects from absence of the defensive role of the gastric acid during absence of food [41, 42, 66]. Hence; this biological balance between ammonia of ***H. pylori*** and gastric acid is constant life-long round the clock ensuring a residual level of ammonia that could further account for a constant systemic serum ammonia level. Systemic ammonia derived from the natural biological behavior of ***H. pylori*** could therefore have a healthy effect on the cerebral micro-capillary circulation via ensuring an endothelial-derived NO liberation due to the effect of shear stress [48, 60, 61, 67]. NO is neuro-protective; hence, normal levels of serum ammonia could be protective towards the brain and Alzheimer. According to a population based study, it has been reported that eradication of ***H. pylori*** was associated with progression of dementia [68]. Whereas excess systemic ammonia constitutes a potential neuro-toxic factor in AD [69]. Similarly then, ammonia is a cure and a poison at the mean time in AD; as if ammonia or NO or both of them function as a cure and a poison at the same situation in Dementia and Alzheimer's.

4. Motive of the Review

As Alzheimer is a degenerative disease, treatment and prevention remain until current time a great challenge. Delaying the onset of Alzheimer could be a logic attempt. Many investigators have followed the policy of delaying the symptoms or onset of the disease relying mainly on early detection of symptoms because if not early detected, improvement might not be expected [1, 3]. Revision of the records of the research investigators of this review study since 2011 revealed the medical information of eleven elderly patients with newly-discovered symptoms of dementia of Alzheimer who have undergone follow up for the purpose of evaluating the role of colon clear in delaying the symptoms of the disease. Those patients were actually referred by their relatives to do blood-let out cupping therapy for them in order to improve memory functions. Cupping therapy was not done for them but they were investigated for existence of colonic ***H. pylori*** strains and tested for serum ammonia level. Age of patients ranged between 71 and 99 years, they were seven males and four females. All patients were positive for existence of colonic ***H. pylori*** strains according to a specific test (***H. pylori*** fecal antigen test) [40]. Serum ammonia was elevated in all patients which ranged between 113-147 umol/L. All patients underwent colon clear employing the natural senna leaves extract purge for eradication of colonic ***H. pylori*** strains. After colon clear, they followed a vinegar therapy in the form of a vinegar-mixed salad amidst of principal meals once or twice daily, 3-5 days/week for six months. Vinegar therapy should be given in the middle of a meal in order to fight the abnormal-behavior ***H. pylori*** strains only that exist in the gastric lumen while presence of food whereas the normal-behavior strains are sheltered under the gastric mucus layer during presence of food where no violence can defeat them even the strongest antibiotics except forcing them to migrate to the colon particularly those antibiotics given in excess mal-use on empty stomach with consequent loss of the protective function of ***H. pylori*** at least in the stomach [41, 66]. Colon clear was repeated after further one month and after two months later if required. Patients were followed up for every 3 years survival with adequate observation of recurrence of dementia symptoms throughout the life of the patient. Three patients showed mild improvement and four patients showed moderate improvement of memory functions after undergoing colon clear three times whereas two patients showed marked recovery of memory after the first colon clear and two patients did not show any improvement in spite of revision of colon clear two times. Five patients developed recurrence of dementia symptoms after 1-3 years but they recovered their previous memory level after colon clear while six patients died after 2-2.5 years in peace for a reason un-related to Alzheimer without developing any recurrent symptoms of dementia. The case of one female patient was amazingly interesting, she was seen in year 2011 for early dementia symptoms, she was from Yemen living in Gizan in the Southern region of Saudi Arabia, her age that time was 96 years, she improved completely after colon clear, three years later (in 2014) at age of 99 she developed marked loss of memory to the extent that she could not recognize her sons and daughters or distinguish her grand kids, suddenly she went into coma and developed diabetes, she was severely constipated, ***H. pylori*** fecal antigen test was strongly positive, level of serum ammonia was 146 umol/L, random blood sugar was 334 mg/dL and she was put on insulin therapy, she recovered completely from coma after colon clear, her diabetic condition was also corrected and insulin therapy was discontinued, most importantly she recovered her memory even relatives were astonished that she was able to recognize and distinguish perfectly her sons, daughters and grand kids again after recovery from coma, she died two years later in year 2016 without developing any dementia symptoms. Her coma and memory loss were attributed to the toxic effect of ammonia on the brain while her diabetic condition was considered a potential condition of toxic pancreatitis due to a biological toxic stress caused by accumulation of profuse toxic amounts of ammonia in the colon [66, 70]. The sequence of events of this patient was actually the motive for the research team to review the influence of ***H. pylori***-produced ammonia on cognitive and memory functions.

Ammonia is not considered the only primary factor of the AD. However, since elevated levels of serum ammonia and the release of ammonia from the brains of AD patients is well supported by observational findings, ammonia could be taken into account as a factor that contributes to manifestations and the progression of AD [50]. Therefore; traditional therapeutic strategies that can help elimination of excess ammonia such as colon clear can lead to the

amelioration of symptoms and progression of AD. The abnormal-behavior colonic ***H. pylori*** strains contribute also in different ways in leading to some medical problems that could further contribute in the pathogenesis of AD such as diabetes mellitus, hypertension and dyslipidemia [10, 40, 41, 70-72]. Hence, elimination of these colonic ***H. pylori*** strains via colon clear employing natural measures (the senna leaves extract purge) could constitute the most effective strategy to improve or improve and delay the symptoms of Alzheimer when newly detected.

Accordingly, a normal-behavior of ***H. pylori*** seems to be useful to the cerebral micro-capillary circulation as it is responsible for maintaining a normal residual systemic ammonia level which contributes to ensure the endothelial-derived NO liberation via the effect of shear stress; NO is an intelligent neuro-protective and an essential element to maintain the integrity of the cerebral micro-capillary circulation. While the abnormal colonic ***H. pylori*** strains are the reason for accumulation of profuse toxic amounts of ammonia in the colon which is leading to increased systemic serum ammonia level with consequent ammonia toxicity and NO toxicity in turn; elevated systemic ammonia is a major reason in the pathogenesis and progression of amyloid disease of the brain whereas high nitro-oxidative stress can evoke cytotoxic effects in neuronal and endothelial degeneration observed in Alzheimer [48, 62, 67-69]. Therefore; it might be safely suggested that both ammonia and NO resemble a cure and a poison at the same time for Alzheimer and dementia.

5. Summary

In Summary, It seems that the strategy of delaying the onset and symptoms of Alzheimer constitutes a practical solution for a medical challenge that does not currently have any fundamental treatment or prevention. It might be also considered that elimination of the potential source of excess toxic amounts of ammonia via natural eradication of the abnormal colonic ***H. pylori*** stains is the most effective measure among these strategies in order to delay or postpone symptoms and the onset of AD [43, 44, 48, 50]. In spite of that all scientific efforts should continue persevere attempts to achieve real cure or prevention of Alzheimer by means of investigating all fields and factors contributing to the disease.

6. Conclusions

The natural structure and existence of the normal-behavior ***H. pylori*** strains contributing to maintain a normal residual systemic ammonia level is healthy to the brain as it supports the endothelial-derived NO liberation which is a neuro-protective element via maintaining the integrity of the cerebral micro-capillary circulation. Preservation of the natural structure and existence of the normal behavior-***H. pylori*** strains could delay the onset of Alzheimer and dementia symptoms. Therefore; we should not fight and kill but we should save ***H. pylori*** for the sake of brain health and for delaying the onset and symptoms of Alzheimer disease for many elderly people.

Alzheimer's is still until now a non-curable/ non-preventable degenerative disease; hence, attempts to delay the onset of the disease upon early detection of symptoms constitute an effective practical strategy. Accordingly, elimination of the abnormal colonic ***H. pylori*** strains responsible for the profuse colonic ammonia toxicity might be the most effective measure among these strategies. In addition, observational findings indicating that eradication of the colonic ***H. pylori*** strains could help improving other factors contributing to Alzheimer such as diabetes, hypertension and dyslipidemia may further support the natural strategy of ***H. pylori*** eradication as a measure to delay Alzheimer and dementia symptoms.

REFERENCES

[1] Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. *Neurology 2000; 54: S4-S9.*

[2] Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology 2007; 29: 125-132.*

[3] Kalaria RN., Maestre GE., Arizaga R., et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol 2008; 7: 812-826.*

[4] Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet 2005; 366: 2112-2117.*

[5] Wimo A, Winblad B, Agüero-Torres H, et al. The magnitude of dementia occurrence in the world. *Alzheimer Dis Assoc Disord 2003; 17: 63-67.*

[6] Brookmeyer R, Johnson E, Ziegler-Graham K, et al. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement 2007; 3: 186-191.*

[7] Fratiglioni L, Launer LJ, Andersen K, et al. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. *Neurology 2000; 54: S10-S15.*

[8] Kawas C, Gray S, Brookmeyer R, Fozard J, et al. Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. *Neurology 2000; 54: 2072-2077.*

[9] Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol 2002; 59: 1737-1746.*

[10] Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *Lancet 2006; 368: 387-403.*

[11] Helzner EP, Scarmeas N, Cosentino S, et al. Survival in Alzheimer disease: a multiethnic, population-based study of incident cases. *Neurology 2008; 71: 1489-1495.*

[12] Mehta KM, Yaffe K, Pérez-Stable EJ, et al. Race/ethnic differences in AD survival in US Alzheimer's Disease Centers. *Neurology 2008; 70: 1163-1170.*

[13] Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. *Lancet 2006; 368: 387–403.*

[14] Aggarwal NT, Bienias JL, Bennett DA, et al. The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. *Neuroepidemiology 2006; 26: 140–146.*

[15] Anstey KJ, von Sanden C, Salim A, et al. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol 2007; 166:367–378.*

[16] Ding J, Eigenbrodt ML, Mosley T H Jr, et al. Alcohol intake and cerebral abnormalities on magnetic resonance imaging in a community-based population of middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke 2004; 35: 16–21.*

[17] Paul CA, Au R, Fredman L, et al. Association of alcohol consumption with brain volume in the Framingham study. *Arch Neurol 2008; 65: 1363–1367.*

[18] Rosengren A, Skoog I, Gustafson D, et al. Body mass index, other cardiovascular risk factors, and hospitalization for dementia. *Arch Intern Med 2005; 165: 321–326.*

[19] Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol 2009;66: 336–342.*

[20] Kivipelto M, Helkala EL, Laakso MP, et al. Apolipoprotein E Â4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. *Ann Intern Med 2002; 137: 149–155*.

[21] Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging. 2000; 21: 49–55.*

[22] Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ 2001; 322: 1447–1451.*

[23] Arvanitakis Z, Wilson RS, Bienias JL, et al. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol 2004; 61: 661–666.*

[24] Irie F, Fitzpatrick AL, Lopez OL, et al. Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE e4: the Cardiovascular Health Study Cognition Study. *.Arch Neurol. 2008; 65: 89–93.*

[25] Vermeer SE, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med 2003; 348: 1215–1222.*

[26] Honig LS, Tang MX, Albert S, et al. Stroke and the risk of Alzheimer disease. *Arch Neurol 2003; 60: 1707–1712.*

[27] Blum S, Luchsinger JA, Manly JJ, et al. Memory after silent stroke: hippocampus and infarcts both matter. *Neurology 2012 Jan 3; 78 (1): 38-46.*

[28] WU YC, Lin YC, YU HL, et al. Association between air pollutants and dementia risk in the elderly. *Alzheimers Dement (Amst) 2015 May 14; 1 (2): 220-8.*

[29] Calderón-Garcidueñas L, Calderón-Garcidueñas A, Torres-Jardón R, et al. Air pollution and your brain: what do you need to know right now. *Prim Health Care Res Dev 2015 Jul; 16 (4): 329-45.*

[30] Weuve J. Invited commentary: how exposure to air pollution may shape dementia risk, and what epidemiology can say about it. *Am J Epidemiol 2014 Aug 15; 180 (4): 367-71.*

[31] Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin Neurosci 2009; 11 (2): 111-28. Review.*

[32] Miklossy J. Emerging roles of pathogens in Alzheimer disease. *Expert Rev Mol Med 2011 Sep 20; 13: e30. doi: 10.1017/S1462399411002006.*

[33] Malaguarnera M, Bella R, Alagona G, et al. Helicobacter pylori and Alzheimer's disease: a possible link. *Eur J Int Med 2004 Oct; 15 (6): 381-386.*

[34] Roubaud Baudron C, Varon C, Mégraud F, et al. Alzheimer's disease and Helicobacter pylori infection: a possible link? . *Geriatr Psychol Neuropsychiatr Vieil 2016 Mar; 14 (1): 86-94.*

[35] Roubaud Baudron C, Krolak-Salmon P, Quadrio I, et al. Impact of chronic Helicobacter pylori infection on Alzheimer's disease: preliminary results. *Neurobiol Aging 2012 May; 33 (5): 1009. e11-9.*
doi: 10.1016/j.neurobiolaging.2011.10.021. Epub 2011 Dec 1.

[36] Roubaud Baudron C, Varon C, Mégraud F, et al. Alzheimer's disease: the infectious hypothesis. *Geriatr Psychol Neuropsychiatr Vieil 2015 Dec; 13 (4): 418-24.*

[37] Adriani A, Fagoonee S, De Angelis C, et al. Helicobacter pylori infection and dementia: can actual data reinforce the hypothesis of a causal association? *Panminerva Med 2014 Sep; 56 (3): 195-9.*

[38] Roubaud Baudron C, Letenneur L, Langlais A, et al. Does Helicobacter pylori infection increase incidence of dementia? The Personnes Agées QUID Study. *J Am Geriatr Soc 2013 Jan; 61 (1): 74-8.*

[39] Alvarez-Arellano L, Maldonado-Bernal C. Helicobacter pylori and neurological diseases: Married by the laws of inflammation. *World J Gastrointest Pathophysiol 2014 Nov 15; 5 (4): 400-4.*

[40] Farinha P, Gascoyne RD. Helicobacter pylori and MALT Lymphoma. *Gastroenterology 2005 May; 128 (6): 1579-605.*

[41] Nasrat AM, Nasrat SAM, Nasrat RM, et al. Misconception and misbehavior towards Helicobacter pylori is leading to major spread of illness. *GM 2015; S1 (002).* [Open Access]

[42] Butterworth RF. Pathophysiology of hepatic encephalopathy: a new look at ammonia. *Metab Brain Dis 2002 Dec; 17 (4): 221-7.*

[43] Albert MS. Cognitive and neurobiologic markers of early Alzheimer disease. *Proc Natl Acad Sci U S A 1996 Nov 26; 93 (24): 13547-51.*

[44] Aguilar MA, Minarro J, Felipo V. Chronic moderate hyperammonemia impairs active and passive avoidance behavior and conditional discrimination learning in rats. *Exp Neurol 2000; 161: 704-713.*

[45] Shukla M, Boontem P, Reiter RJ, et al. Mechanisms of melatonin in alleviating Alzheimer's disease. *Curr Neuropharmacol 2017 Mar 13.*
doi: 10.2174/1570159X15666170313123454.
[Epub ahead of print]

[46] Andreeva TV, Lukiw WJ, Rogaev EI. Biological Basis for Amyloidogenesis in Alzheimer's Disease. *Biochemistry (Mosc) 2017 Feb; 82 (2): 122-139.*

[47] Cahill MK, Huang EJ. Testing the Amyloid Hypothesis with a Humanized AD Mouse Model. *Neuron 2017 Mar 8; 93 (5): 987-989.*

[48] Kosenko EA, Solomadin IN, Tikhonova LA, et al. Pathogenesis of Alzheimer disease: role of oxidative stress, amyloid-β peptides, systemicammonia and erythrocyte energy metabolism. *CNS Neurol Disord Drug Targets 2014 Feb; 13 (1): 112-9.*

[49] Seiler N. Ammonia and Alzheimer's disease. *Neurochem Int 2002 Aug-Sep; 41 (2-3): 189-207.*

[50] Seiler N. Is ammonia a pathogenetic factor in Alzheimer's disease? *Neurochem Res 1993 Mar; 18 (3): 235-45.*

[51] Wright PA. Nitrogen excretion: three end products, many physiological roles. *J Exp Biol 1995; 198 (2): 273-281.*

[52] Marcaida G, Felipo V, Hermenegildo C, et al. Acute ammonia toxicity is mediated by the NMDA type of glutamate receptors. *FEBS Lett 1992 Jan 13; 296 (1): 67-8.*

[53] Britto DT, Kronzucker HJ. NH4+ toxicity in higher plants: a critical review. J *Plant Physiol 2002; 159 (6): 567-584.*

[54] Adlimoghaddam A, Sabbir MG, Albensi BC. Ammonia as a Potential Neurotoxic Factor in Alzheimer's Disease. *Front Mol Neurosci 2016 Aug 8; 9: 57.*
doi: 10.3389/fnmol.2016.00057.

[55] Cooper AJ, Plum F. Biochemistry and physiology of brain ammonia. *Physiol Rev 1987; 67: 440-519.*

[56] Seglen PO. Inhibitors of lysosomal function. *Meth Enzymol 1983; 96: 737-764.*

[57] Marcaggi P, Coles JA. Ammonium in nervous tissue: transport across cell membranes, fluxes from neurons to glial cells, and role in signalling. *Prog Neurobiol 2001; 64: 157-183.*

[58] Laursen H, Diemer NH. Morphometric studies of rat glial cell ultrastructure after urease-induced hyperammonaemia. *Neuropathol Appl Neurobiol 1979; 5: 345-362.*

[59] Fiorentino M, Sapone A, Senger S, et al. Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. *Mol Autism 2016 Nov 29; 7: 49. eCollection 2016.*

[60] Hrnjez BJ, Song JC, Prasad M, et al. Ammonia blockade of intestinal epithelial K+ conductance. *Am J Physiol 1999; 277 (3): 521-532.*

[61] Sumii T, Nakano Y, Abe T, et al. The Effect of Nitric Oxide on Ammonia Decomposition in Co-cultures of Hepatocytes and Hepatic Stellate Cells. *In Vitro Cell Dev Biol Anim 2016 Jun; 52 (6): 625-31.*

[62] Nasrat AM, El-Sayed SM, Shabaka AA, et al. Male pelvic congestion and erectile dysfunction; obscure reasons for an obvious phenomenon among the young. *GM 2016; S1 (1).* [Open Access]

[63] Malinski T. Nitric oxide and nitroxidative stress in Alzheimer's disease. *J Alzheimers Dis 2007 May; 11 (2): 207-18.*

[64] Hartlage-Rübsamen M, Apelt J, Schliebs R. Fibrillary beta-amyloid deposits are closely associated with atrophic nitric oxide synthase (NOS)-expressing neurons but do not upregulate the inducible NOS in transgenic Tg2576 mouse brain with Alzheimer pathology. *Neurosci Lett 2001 Apr 20; 302 (2-3): 73-6.*

[65] Hu ZI, Kotarba AM, Van Nostrand WE. Absence of Nitric Oxide Synthase 3 Increases Amyloid βProtein Pathology in Tg-5xFAD Mice. *Neurosci Med 2013 Jun; 4 (2): 84-91.*

[66] Nasrat AM. The world misconception and misbehavior towards Helicobacter pylori is leading to major spread of illness. *The 7th Anti-Aging Medicine World Congress, Monte-Carlo, Monaco, 2009 Mar.* Available from URL, www.euromedicom.com

[67] Cooper AJ, Plum F. Biochemistry and physiology of brain ammonia. *Physiol Rev 1987; 67: 440-519.*

[68] Chang YP, Chiu GF, Kuo FC, et al. Eradication of Helicobacter pylori is associated with the progression of dementia: A population-based study. *Gastroenterol Res Pract 2013; 2013: 175729.* doi: org/10.1155/2013/175729. Epub 2013 Nov 25.

[69] Adlimoghaddam A, Sabbir MG, Albensi BC. Ammonia as a potential neurotoxic factor in Alzheimer's disease. *Front Mol Neurosci 2016 Aug 8; 9: 57.* doi: 10.3389/fnmol.2016.00057. eCollection 2016.

[70] Nasrat SAM, Nasrat RM, Nasrat MN, et al. The dramatic spread of diabetes mellitus worldwide and influence of Helicobacter pylori. *General Med. 2015; 3 (1) : 159-62.*

[71] Nasrat SAM, Nasrat AM. An alternative approach for the rising challenge of hypertensive illness via Helicobacter pylori eradication. *Cardiol Res. 2015.* [Open Access] doi: org/10.14740/cr382e

[72] Aksoy H, Sebin SO. H. pylori and cardiovascular diseases. *General Med. 2015; S1: 1.* [Open Access]
doi: org/10.4172/2327-5146.1000S1-007