ACTA SCIENTIFIC MEDICAL SCIENCES
Volume 2 Issue 2 May 2018
Review Article

Alzheimer's Disease: Multiple Causes Requiring Multiple Therapies

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Received: March 09, 2018; **Published**: April 16, 2018

Abstract

Despite years of testing for an effective Alzheimer's therapy, no means to stop the inexorable cognitive decline characterizing Alzheimer's patients has been found. A new approach to achieving this goal is urgently required.

Changes should start by recognizing that late onset Alzheimer's Disease (AD) is a disease of multiple etiologies. These require a combination of therapies directed against the major causative pathologies of the disease rather than the current standard of treating one or another of the disease etiologies with a single mono-therapy. The test end point should be whether or not treatment completely stops progressive dementia. This would have two major advantages. Most important is that an effectively treated patient will no longer show a cognitive decline. They may in fact show a lessening of dementia in time, a result infinitely better than only slowing progressive cognitive decline. This article presents the methods and rationale for effecting these changes.

Keywords: Combination Therapy; Alzheimer's Dementia; Drug Therapy; Off-Label Drugs

Introduction

It is obvious that past and current research toward finding an effective treatment for Alzheimer's Disease (AD) was, is and will likely remain an abject failure. It has been reported that between 2004 to 2014 only one drug of 244 tested has been approved for clinical use in the United States [1]. That decades worth of testing probably involved over 100,000 patients and estimated over a billion dollars. The specific aim of this failed research has been to find a drug that slows the rate at which dementia progresses in AD. This aim is itself inadequate, e.g. Aricept. Dementia continues its inexorable progression despite the possible slowing in its rate of development. Patients still lose cognitive function. What is required is a means to completely stop progressive dementia. This would be ideal, perhaps as close to finding a "cure" for AD as can be achieved. To reach this goal, the effort must be made toward achieving that end.

Although universally unsuccessful, the 243 failed treatments of AD all had evidence of effectiveness from the preliminary evaluations done in the course of their development. The reason for these disappointing trials can be logically attributed to the fact that AD is a disease of multiple etiologies, together all acting to destroy neurons with their combined effects which overwhelm any benefit of individual drugs acting against one or the other of the individual pathologic processes. There is compelling evidence for multiple etiologies causing AD in the medical literature.

Multiple Etiologies

Multiple etiologies for late onset AD are here listed and classified into four major types. These types, documented in table 1, are:

(I) Mitochondria metabolic dysfunction with an inadequate ATP production and excessive release of reactive oxygen species (ROS) [2].

(II) Misfolded protein pathology, characteristically amyloid beta (Ab) protein pathology [3], but also tau pathology [4], both of which are present in all AD patients, Lewy bodies found in 50% of AD patient [5] and TDP-43, present in 50% of AD patients [6], will also lead to primary and secondary neuronal destruction.

(III) Oxidative stress [7], particularly from protein glycation and secondary release of ROS, greatly increased in Alzheimer's [8]. Free radicals from iron toxicity [9], can also produce structural damage to neurons.

(IV) Pro-inflammatory effects [10], with failure of microglia [11] or dysfunction of microglia and astrocytic functions, the latter otherwise protecting neurons [12].

Two minor etiologies that are possibly important are ApoE-4, present in 60% of AD patients [13] and a question of Chlamydophila pneumoniae bacterial infection, reported present in 90% of AD patients [14].

Supporting the arguments for the four etiologies causing AD are definitive pathologic studies from autopsy specimens from the brains of Alzheimer's patients. Electron-microscopic studies of mitochondria from AD brains show significant reduction in the number of mitochondria with significant morphologic changes in these organelles as well [15].

I. Mitochondrial Dysfunction	1	Secondary to DNA mutations (hereditary or aging)
	2	Associated with inadequate cerebral circulation
	3	Associated with insulin metabolic dysfunction
	4	Metabolic dysfunction resulting in decreased ATP, affecting cellular function
	5	Metabolic dysfunction producing increased ROS
II. Abnormal Protein Inclusion Deposition	1	APP/amyloid (100%)
	2	Lewy body deposition (50%)
	3	TDP-43 (50%)
	4	Neurofibrillary tangles made up of pathologic tau proteins found in later stages of the disease (100%)
III. Oxidative Stress	1	Secondary to inadequate protective function of antioxidant moieties
	2	ROS reaction with ferric iron to produce a destructive hydroxyl radical
	3	APP/AB promoting oxidative stress
	4	Advanced glycation (AGE) occurring with aging may have a greatly accelerated free-radical production
	5	Direct effect of oxidative stress on neurons, microglia and astrocytes of the brain
IV. Immune Deficiency	1	Microglial or astrocytic dysfunction from excessive activity or inappropriate functioning of these cells
	2	Release of pro-inflammatory cytokines (e.g. IL-1, TNF alpha)
	3	Dystrophic/aberrant morphology, microglia shown in Alzheimer's brains
	4	Immune deficiencies promoting neurodegeneration including a stimulation of late tau pathology
	5	Resulting presence of chlamydia pneumoniae
Presence of Pathologic ApoE-4		Approximately 60% of Alzheimer's patients

Table 1: Alzheimer's etiologies divided into 4 major categories.
Legend: ROS: reactive oxygen species; APP: amyloid precursor protein; TDP-43: transactivation DNA-binding protein; AGE: advanced glycation end products

The histologic changes in Ab precursor proteins/Ab and tau deposition are accepted. In addition, evidence of TDP-43 Lewy bodies, referenced previously, have been shown in AD brains.

Lipid, DNA, and protein oxidation have been reported as elevated in AD brains [16]. Microglia and astrocytic phenotypic changes associated with activation of these cells have been shown [17] as well as dystrophic microglia cells associated with tau pathology [11]. The latter has been shown proceeding neuro degeneration in Alzheimer's brains.

Specific References for the Four Major Etiologies Causing AD:

Mitochondrial Dysfunction

Mitochondrial dysfunction is manifested primarily in two ways. Energy metabolism is reduced, with a reduction of ATP, which in turn negatively effects all cellular functions [2]. The second effect results in an excessive release electrons and the production of reactive oxygen species [2]. These in turn produce oxidative stress if compensatory mechanisms are inadequate to neutralize the increased quantities of reactive oxygen species and free radical production [18]. Oxidative stress can be destructive to all structural elements of the cell, including the mitochondria [19].

The pathologic process producing mitochondrial dysfunction appears to be associated with aging, from maternally transmitted mitochondria DNA mutations or spontaneous genetic mutations [2]. Cerebrovascular hypoprefusion [20] inadequate glucose metabolism possible associated with insulin deficiencies [21] appear to be important causes for the mitochondria dysfunction. Damaging effects on mitochondria status has been suggested as an effect of Ab precursor proteins/Ab pathology [22].

Ab Precursor Proteins/Ab Pathology and Other Misfolded Protein Inclusions

Amyloid pathology is complicated but definitely associated with the progression of AD [23]. Hereditary mutations effecting critical regions of Ab Precursor Proteins are observed in familial AD [24] and dramatically increased in late onset AD may be due to genetic abnormalities associated with mutations of aging or heredity [25]. The increased production of Ab ultimately coalesce and form senile plaques deposited in the brains of those with AD. There is a large literature describing the damaging effects of amyloid deposition on the neurons, microglia, and astrocytes of the brain. The amyloid protein inclusions can result in destructive free radicals effecting mitochondria [22]. There are toxic effects of prion receptors of Ab oligomers [26]. Ab may induce oxidative stress by engaging binding sites on the membrane surfaces of cells such as the receptor for advanced glycation end products [27].

Other misfolded protein inclusions are present in the brains of Alzheimer's patients. They presumably have similar pathologic effects as they do in other neuro degenerative diseases such as fronto-temporal degeneration, Parkinson's dementia, ALS, and chronic traumatic encephalopathy. Neurofibrillary tangles, made up of pathologic tau proteins, are found in all later stages of the disease [4].

Oxidative Stress

Oxidation can be destructive to any structures whose components are oxidizable. It is exactly iron rust. Structures and component elements of cells, including membranes, organelles and DNA can be oxidized and in the process lose their structural integrity and physiologic function [28]. Such a process in tissues is called oxidative stress. Oxidative stress occurs when reactive oxygen species are not neutralized by anti-oxidant moieties [18]. This can occur when reactive oxygen species are increased and overwhelm the defensive elements or when there is a decrease in the latter, as with aging. Mitochondria dysfunction results in oxidative stress [2]. Ab pathology promotes oxidative stress by various pathways [29]. Advanced glycation end products and deposition by cellular receptors is a process seen in aging, but is shown in AD to a much greater degree than in unaffected individuals [8]. The effect from this glycation of proteins results in significantly increased, perhaps by 50x, production of reactive oxygen species with significant secondary increase in oxidative stress processes [30]. Ultimately oxidative stress is destructive to neurons, microglia and astrocytes of the brain.

Neuroinflammation

Neuroinflammation can occur in association with microglia or astrocyte dysfunction [31]. This may be a result of excessive activity [12], inadequate functioning [11] or inappropriate functioning of these cells [10]. The abnormalities may be created by release of pro-inflammatory immune cytokines (e.g. IL-1, TNFa) [10]. Streit and associates have clearly shown dystrophic (aberrant morphology) microglia in the Alzheimer's brain, possibly due to oxidative stress [11]. It seems obvious that this cellular abnormality is associated with immunological deficiencies promoting neuro degeneration. This may include a stimulation of late tau pathology. Griffin suggests activation of microglia (rather than dystrophy) begins a cascade of events leading to destructive inflammatory processes [10]. She hypothesizes that this cascade is mediated at first by the pro-inflammatory interleukin-1 overexpressed by activated microglia. Neuronal death ensues, activating more microglia, destroying more neurons. Fuller, Steele and Munch suggest that astrocytic conversion into inflammatory cells results in the neglect of their supportive roles, making neurons vulnerable to neuro toxin [12].

Therapeutic Considerations

In order to treat multiple pathologic processes causing a disease, the ideal would be to treat each of these etiologies together with a combination therapy. Using three to five drugs is feasible in treatment protocols. This number can be effective in treating the four major causes of AD. Side effects are modulated if drugs selected are used for other clinical conditions.

Alzheimer's patients have a steady and measurable increase in dementia throughout the course of their disease. This progression has been measured, using the Dementia Severity Rating Scale, in a seven year study of 702 Alzheimer's patients reported by Xie., *et al* [32].

Based on their work, one should accept that a treatment that completely stops the progressive dementia in any single AD patient, must, for that patient, be a fully effective therapy. As with all AD patients, without treatment, that patient would continue to decline. It is presumed that other AD patients, whose etiologic pattern of pathology matches that of an effectively treated patient, would also have their progressive dementia halted by the same treatment. Partial diminution in the usual level of DSRS measured dementia increase would not be counted as an effective therapy, although a possible benefit of the combination used might be noted for treatment. . Results would either be positive or negative for each test therapy. If dementia was stopped in only a verified 10% of patients tested, that therapy could conceivable stop the cognitive decline of five hundred thousand of the 5 million AD patients in the United States.

Available Therapies That Should Be Considered for Combination Treatments

It is suggested that three, four, or five drugs should be combined in a test protocol. This should be practical for trials treating the four major etiologies. Combining the combination's benefits with the body's natural defenses may in fact stop AD progression. Table 2 lists therapies that might be considered for combined therapy studies. Many of these are drugs have been used for other medical conditions and have been shown to have positive benefits as AD treatments in animal, clinical, or autopsy studies. Table 2 divides the drugs into the four pathology groups, each drug, with evidence in referenced articles, as being effective for treating one or another of the disease etiologies. Several are suggested for inhibiting more than one process, making them of particular interest. The lead investigators responsible for selecting drugs to use for combination protocols can choose from these listed or from hundreds tried in prior test experiments, drugs suggested in the literature, or new compounds as they become available. The fact that there are a very large number of combinations to choose from for testing does not mean that the selection of a therapy is random, and does not preclude the selection of a successful combination where knowledgeable and careful choices are made from the possible therapies.

Drug	Original Use	Alzheimer's Treatment Purpose
Drugs Preserving Mitochondrial Function		
Beta blockers	Anti-hypertensives	Preserves circulation to brain
White L, Gelber R, Launer L, Zarow C, Sonnen J, Uyehara-Lock J, et al. (2013) Beta Blocker Treatment of hypertensive older persons ameliorates the brain lesions of dementia measured at autopsy: The Honolulu-Asia Aging Study. American Academy of Neurology 2013 Annual Meeting, Abstract 2171.		
Pentoxifylline (Trental]	Enhances cerebral circulation	Enhances cerebral circulation
European Pentoxifylline Multi-Infarct Dementia Study (1996) European Neurology 36(5), 315-21.		
Nicergoline	Enhances cerebral circulation	Enhances cerebral circulation
Winblad B, Floravanti M, Dolezal T, Logina I, Milanov IG, Popescu DC, Solomon A (2008) Therapeutic use of nicergoline. Clinical Drug Investigation 28(9), 533-52.		
Methylene blue	Rx methglobinemia	Improves mitochondria) metabolism, Methylene blue Rx methglobinemia decreasing formation ROS
Kumar R, Atamna H. (2011) Therapeutic approaches to delay the onset of Alzheimer's disease. Journal of Aging Research doi: 10.4061/2011/820903.		
Medium chain triglycerides	Coconut oil dietary agent	Alternate energy source to glucose for brain metabolism
Henderson ST. (2008) Ketone bodies as a therapeutic for Alzheimer's disease. Neurotherapeutics 5(3), 470-80.		
Pyruvate	Dietary agent	Supports Krebs cycle
Owen L, Sunram-Lea SI. (2011) Metabolic agents that enhance ATP can improve cognitive functioning: a review of the evidence for glucose oxygen pyruvate, creatine, and I-carnatine. Nutrients 3(8), 735-55.		
Drugs inhibiting APP/AB pathology and other misfolded protein inclusions		
Nilotinib	Chemotherapeutic drug	Stimulates formation of parkin
Lonskaya I, Hebron M, Desforges N, Schacter J, Moussa C. Nilotinib-induced autophagic changes increase endogenous parkin level and ubiquitination, leading to amyloid clearance. J Mol Med (Berl) 2014;92(4):373-86.		
Angiotensin II receptor antagonists	Hypertension, CHF, Diabetic	Inhibits amyloid deposition nephropathy
Hajjar I, Brown L., Mack WJ, Chui H (2012) Impact of angiotensin receptor blockers on Alzheimer disease neuropathology in a large brain autopsy series. Archives of Neurology 69(12),1632-8.		
Chlorpromazine	Anti-psychotic	Inhibits APP prion interaction
Orru CD, Cannas MD, Vascellari S, Angius F, Cocco P, Norfo C, et al. (2010) In vitro synergistic anti-prion effect of cholesterol ester modulators in combination with chlorpromazine and quinacrine. Open Life Sciences 5(2),151-65.		
Methylene blue	Rx methglobinemia	Blocks tau-tau binding interaction
Wischik CM, Edwards PC, Lai RY, Roth M, Harrington CR. (1996) Selective inhibition of Alzheimer disease-like tau aggression by phenothiazines. Proceedings of the National Academy of Sciences in the linked States 93(20), 11213-8.		
Lithium	Rx bipolar disorder	Induces autophagy (clears inclusions)
Sarkar 5, Floto RA, Berger 2, Imarisio S, Cordenier A, Pasco M, eta (2005) Lithium induces autophagy by inhibiting inositol monophosphatase. The Journal of Cell Biology 170(7),1101-11.		
Bexarotene [Targrentin]	Anti-neoplastic	Reduces amyloid plaque
Cramer PE, Cirrito JR, Wesson DW, Lee CY, Karlo IC, Zinn AE, et al (2012) ApoE-directed therapeutics rapidly dear -Am loid and reverse deficits in AD mouse models. Science 335 607 1503-6.		

Table 2: Potentially effective drugs.

Two previous articles have presented a combination of drugs from those listed and used clinically. This selection is felt to be a promising therapy for AD [33,34]. This protocol includes Trental, nicergoline, and methylene blue which suppress multiple etiologies. Making a five drug combination is provided with nilotinib and pyridoxamine (B6 vitomer). This combination of four drugs and one vitamin inhibits all four of the primary etiologies. An arrest of the expected outcome among AD patients tested with such a therapy would be expected within in a year. Determining treatment effect is not difficult, as the cognition of AD patients would otherwise always show a decline in a year [32].

Summary and Conclusion

The goal of finding an effective therapy for AD, despite great effort, has thus far not been achieved. This report offers an approach which has the promise of reaching this goal. It is based on significant evidence presented here, that AD is a disease caused by multiple pathologic processes. Accepting this, it is concluded that the most effective therapy for the disease requires treating all the different causes together with a combination therapy. Three to five of the agents listed and currently available can be combined in a treatment protocol. A promising example of such a combination is presented, which should be tested.

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